The ACCeRT Study

Auckland's Cancer Cachexia evaluating Resistance Training Study

A randomised feasibility study of EPA and Cox-2 inhibitor (Celecoxib) versus EPA, Cox-2 inhibitor (Celecoxib), Progressive Resistance Training followed by ingestion of essential amino acids high in leucine in NSCLC cachectic participants

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Abstract

Background: Cancer cachexia is a common problem in Non-Small Cell Lung Cancer (NSCLC). In cancer cachexia there is a significant loss of adipose tissue and skeletal muscle mass. There is a need to utilise a multi-targeted approach to decrease the inflammation process and stimulate the skeletal anabolic pathways with the use of progressive resistance training (PRT) and Essential Amino Acids (EAA).

Methods: ACCeRT is a randomised controlled feasibility, open-label study, investigating the acceptability, trends in efficacy and safety of a multi-targeted approach in end-stage NSCLC cachectic patients, over 20 weeks. Participants were randomised in a 1:2 ratio to Eicosapentaenoic acid (EPA) and celecoxib (Arm A), versus EPA, celecoxib, two sessions of supervised PRT per week, followed by 20g EAA over 3 days (Arm B).

Results: Twenty participants enrolled in the study, seven in Arm A, and 13 in Arm B. The mean age at entry was 68.2 years and 7.95% weight loss. Acceptability scored high on an acceptability questionnaire, with 100% for EPA and celecoxib within both Arms, and 100% for PRT sessions and EAA within Arm B. Compliance was also high with 99.6% (Arm A) and 86.8% (Arm B) for EPA, 60.7% (Arm A) and 100% (Arm B) for celecoxib, 94.4% for PRT sessions and 76.5% for EAA, all at week 20. Results showed a net gain in BIA FFM of +1.3kg, n=2 (Arm A), compared with +0.7kg, n=7 (Arm B) at week 12, and -1.5kg, n=2 (Arm A), compared with -1.7kg, n=4 (Arm B) at week 20. Trends in efficacy in terms of improvement and stability in cachexia markers were seen within BIA FFM and weight, IL-6 and TNF-α levels, albumin and CRP levels, MRI, FAACT-PWB and MFSI-SF-Total scores within both Arms. There were no exercise-related adverse events, with one possible related AE of asymptomatic atrial fibrillation in one participant within Arm A.

Conclusion: The above trends in efficacy in a number of cachexia markers within both Arms, and the minimal toxicity support further evaluation of this regimen within a larger phase II study. These data can serve as a baseline for future refractory cachexia studies.

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Glossary

1RM	One-repetition maximum
6MWT	6 Minute Walk Test
AA	Amino Acids
ACCeRT	Auckland's Cancer Cachexia evaluating Resistance Training
ACS	Anorexia/Cachexia Symptoms
AEs	Adverse Events
AF	Atrial Fibrillation
AIDS	Acquired Immune Deficiency Syndrome
ATP	Adenosine Triphosphate
b.d.s.	Bis Die Sumendum Latin: two times a day
BCP	Bromcresol Purple
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
CACS	Cancer Anorexia/Cachexia Syndrome
CAMRI	Centre for Advanced Magnetic Resonance Imaging
CHF	Congestive Heart Failure
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
COX-1	Cyclo-oxygenase-1
COX-2	Cyclo-oxygenase-2
CRP	C-Reactive Protein
CSA	Cross Sectional Area
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DEXA	Dual-Energy X-ray Absorptiometry
DHA	Docosahexaenoic Acid
EAA	Essential Amino Acids
ECG	Electrocardiogram
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EPA	Eicosapentaenoic Acid
ESAS	Edmonton Symptom Assessment Scale
EWB	Emotional Well-Being
FAACT	Functional Assessment of Anorexia Cachexia Treatment
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT-G	Functional Assessment of Cancer Therapy-General
FAS	Full Analysis Set
FFM	Fat Free Mass
FM	Fat Mass
FSR	Fractional Synthesis Rate
FWB	Functional Well-Being
GI	Gastrointestinal
GPS	Glasgow Prognostic Score
HADS	Hospital Anxiety and Depression Scale
HMB	β-Hydroxyl β-Methyl Butyrate
HGS	Hand-Grip Strength
HRQOL	Health Related Quality Of Life

IFN-γ	Interferon-gamma
IGF-1	Insulin Growth Factor-1
IL-1β	Interleukin-1 beta
IL-x	Interleukin -x
ITT	Intent To Treat
kN	Kilo Newton
KS	Karnofsky Performance Status
LBM	Lean Body Mass
LMF	Lipid Mobilising Factor
LSM	Least Squares Means
MA	Megestrol acetate
MAA	Mixed Amino Acids
MF-BIA	Multi Frequency Bioelectrical Impedance Analysis
MFSI-SF	Multidimensional Fatigue Symptom Inventory-Short Form
mGPS	modified Glasgow Prognostic Score
mITT	modified Intent To Treat
MPA	Medroxyprogesterone acetate
MRI	Magnetic Resonance Imaging
MVC	Maximum Voluntary Contraction
N	Newton
NF-κB	Nuclear transcription factor- kappaB
NSAIDs	Non-Steroid-Anti-Inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
o.d.	Omni Die - Latin once daily
PEG	Percutaneous endoscopic gastrostomy
PRO	Patient Reported Outcomes
PRT	Progressive Resistance Training
PSR	Performance Status Rating
PUFA	Polyunsaturated Fatty Acids
PWB	Physical Well-Being
QOL	Quality Of Life
RA	Rheumatoid Arthritis
RECIST	Response Evaluation Criteria In Solid Tumours
REE	Resting Energy Expenditure
ROS	Reactive Oxygen Species
RPE	Rate of Perceived Exertion
SAEs	Serious Adverse Events
SCP	Stair Climbing Power
SF-36	Short Form-36
SF-BIA	Single Frequency Bioelectrical Impedance Analysis
SR	Sustained-Release
SWB	Social Well-Being
t.d.s.	Ter Die Sumendum Latin: three times daily
TEE	Total Energy Expenditure
THC	delta-9-tetrahydrocannabinol/delta-9-THC
TNF	Tumour Necrosis Factor
TNF-α	Tumour Necrosis Factor - alpha
TPN	Total Parenteral Nutrition
ULN	Upper Limits of Normal

VAS	Visual Analogue Scale
WHOQOL-BREF	World Health Organization Quality of Life-Brief
ZAG/ZA2G	Zinc-α2-glycoprotein

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Joanna Stewart	Responsible for the statistical planning of the study
Stephen P Bird	Provided general oversight of aspects of nutrition and revision of the manuscript
Justin W L Keogh	Participated in the design of the study, advice on aspects of progressive resistance training and revision of the manuscript

Certification by Co-Authors

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
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1 Background

1.1 Definition

The word cachexia comes from the Greek words kakos and hexis, which translates to mean 'bad condition' (Inui, 2002). The definition of cancer cachexia has developed over a number of years. Back in 1977 it was defined as a "syndrome of emaciation, debilitation, and malnutrition" (Brennan, 1977, p. 2359). This was then followed by the addition of anorexia by Tisdale et al. in 1997 (Tisdale, 1997), and then "Anorexia, involuntary weight loss, tissue wasting, poor performance, and ultimately death" by Inui et al. in 2002 (Inui, 2002, p. 72).

It has recently been defined as a "multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" (Fearon et al., 2011, p. 1), and now incorporates the development of the stages of cachexia including pre-cachexia, cachexia and refractory cachexia (Fearon et al., 2011).

Cachexia is not unique to just cancer and occurs in other conditions including AIDS (Acquired Immune Deficiency Syndrome), tuberculosis, chronic heart failure, rheumatoid arthritis, and also in the elderly (Kotler, 2000).

Cancer cachexia is a syndrome of progressive weight loss, anorexia, and persistent reduction of body cell mass in response to a malignant tumour and is somewhat different from simple starvation or conditions such as anorexia nervosa. In cancer cachexia, there is the extensive loss of adipose tissue and equal amounts of skeletal muscle mass when compared to simple starvation where lean body mass is spared and approximately three quarters is from body fat (Brennan, 1977; Tisdale, 1997). More importantly, simple starvation can be reversed by feeding (Kotler, 2000).

1.2 Incidence

The incidence of cachexia is type of tumour and site dependent and can range from 30% to 80% of all cancer patients, with a low incidence in Non-Hodgkin Lymphoma, breast cancer and sarcomas and up to 83% in pancreatic cancer patients and over 85% in patients with gastric cancer. Small-Cell and Non-Small Cell Lung Cancer (NSCLC) patients also experience a high incidence of cachexia, 57% and 61% respectively (Dewys et al., 1980; Tisdale, 2009). It is estimated that cachexia is present in up to 80% of cancer patients at time of death (Inui, 2002).

Cancer cachexia is associated with a deterioration of functional status and quality of life and is also associated with poor survival (Inui, 2002). Cachectic cancer patients have also been associated with/documented to have lower response rates to chemotherapy and shorter median

survival (Dewys et al., 1980). This has been attributed to a number of factors. Firstly, because chemotherapy dosage is based on body surface area, thinner patients receive a lower dose of chemotherapy. Secondly, treatment breaks due to chemotherapy toxicities are higher in this population of patients (Andreyev, Norman, Oates, & Cunningham, 1998). Thirdly, previous chemotherapy treatments and concurrent multi-modality treatments (e.g. surgery and radiotherapy) will also affect nutritional status, which confounds the condition. Lastly, psychosocial issues including depression, anxiety, financial hardship and disability have been shown to have a profound affect (Schmale, 1979). While the majority of the weight loss is from adipose tissue, it has been suggested that it is the loss of muscle mass that accounts for the mortality and morbidity (McMillan, 2008), with the muscle wasting as the main cause of impaired function, leading to respiratory complications and fatigue (Muscaritoli, Bossola, Aversa, Bellantone, & Rossi-Fanelli, 2006).

Unintentional total body weight loss of 5% or 10% at presentation is associated with a higher mortality and morbidity, along with a decrease in tolerance to treatment, performance status and overall quality of life (Andreyev et al., 1998; Dewys et al., 1980). The most reliable predictor of outcome is the severity and rapidity of this weight loss (Brennan, 1977), although stabilisation along with an increase in weight is associated with a significant increase in survival (Andreyev et al., 1998). Patients can lose up to 85% of body fat with a total body weight loss of 30% (Muscaritoli et al., 2006).

1.3 Pathogenesis

Cachexia pathogenesis is an unknown multi-factorial process, consisting of three main factors. Firstly, the metabolic changes with raised or normal metabolic rate, altered fat, carbohydrate and protein metabolism. Current biological evidence suggests that host inflammatory cytokines are involved e.g. tumour necrosis factor (TNF)/cachectin and interleukins, 1, 2, 4 and 6 (IL-1, IL-2, IL-4 and IL-6), which lead to the above altered metabolism. Secondly, anorexia, and lastly reduced dietary intake due to the disease process. This could be due to bowel obstruction secondary to ovarian cancer, nausea and vomiting secondary to raised intracranial pressure and dysphagia due to tumour compression of the oesophagus (Bosaeus, Daneryd, & Lundholm, 2002).

Cachexia can be directly and indirectly related to treatment. All anti-cancer treatments, including surgery, radiotherapy and chemotherapy, can affect the nutritional status of a patient. Development of a number of side effects from these treatments can lead to a reduction in food intake (Ottery, 1995). The direct effects of the chemotherapy agents can cause nausea and

vomiting, along with the micronutrient imbalances due to platinum-containing chemotherapy, which causes a loss of magnesium. Lastly, most chemotherapy agents will affect the surface of the intestinal villi resulting in malabsorption and diarrhoea (Brighton & Wood, 2005). The indirect effects of receiving chemotherapy agents include, fatigue, taste changes, dry mouth, food aversion, stomatitis, constipation, infection and anorexia (Brighton & Wood, 2005).

Currently there is no way of reversing the cachectic process apart from the complete removal of the tumour itself (Brighton & Wood, 2005). Although a lot can be done by addressing and acknowledging all the above co-factors i.e. anorexia, loss of appetite, nausea and vomiting, xerostomia, food aversions, taste changes, stomatitis, mucositis, diarrhoea, malabsorption and constipation (Brighton & Wood, 2005).

1.4 Pathophysiology

It has been documented that patients experiencing cancer cachexia have increased resting energy expenditure (REE). This is most likely to be from an imbalance of the proinflammatory cytokines; TNF-α (Tumour Necrosis Factor-alpha), IL-1, IL-6 and IFN-γ (Interferon-gamma) and anti-inflammatory cytokines; IL-4, IL-12 and IL-15. This view has recently changed as some patients have shown hypo- while others show hyper-metabolism (Muscaritoli et al., 2006). It has also been documented that cancer cachectic patients have abnormalities in carbohydrate, protein and lipid metabolism. With the tumours requiring glucose and amino acids for protein synthesis and energy, decreased circulating levels of glucose and amino acid substrates have been seen. In an attempt to replete the amino acids there is an increase in hepatic gluconeogenesis, and an increase in the catabolism of muscle (Bartlett, Torosian, & Charland, 1994).

1.5 Carbohydrate metabolism

Most solid tumours produce lactate in large amounts; this is then converted back into glucose via the Cori cycle in the liver. This is a futile cycle that uses ATP (Adenosine Triphosphate) and is very energy inefficient for the patient. This may be part of the reason for increased energy expenditure. An increase in hepatic glucose production of up to 40% has been seen in cancer patients who lose weight (Inui, 2002).

1.6 Lipid metabolism

In a healthy adult, fat constitutes 90% of fuel reserves. In cancer cachexia, there is decreased lipogenesis and enhanced lipid mobilisation, along with decreased activity of the lipoprotein

lipase which is involved in the triglyceride clearance from the plasma (Inui, 2002). Cytokines are known to be strong lipolytic factors. In cancer cachexia, the increased lipid mobilisation is due to an alpha-2 glycoprotein tumour catabolic factor known as lipid mobilising factor. This factor was found to be the same as the plasma zinc-α2-glycoprotein (ZAG) (Sanders & Tisdale, 2004). LMF/ZAG acts directly on the adipocytes resulting in the release of glycerol and free fatty acids (Topkan, Yavuz, & Ozyilkan, 2007). These fat metabolism alterations result in the decreased fat storage (Inui, 2002). A recent review on cancer cachexia pathways states that this loss of fat is occurring more rapidly than lean tissue (Fearon, Glass, & Guttridge, 2012).

1.7 Muscle metabolism

The progressive loss of muscle mass is by far the most prominent stereotypic feature of cancer cachexia. Under normal physiological conditions, there is a balance between rates of muscle protein synthesis (anabolism) and breakdown (catabolism). It has been suggested that the loss of muscle is from increased protein catabolism and reduced muscle anabolism, or a combination of both (Fearon et al., 2012; Muscaritoli et al., 2006). There are three main proteolytic systems in skeletal muscle, the lysosomal, the non-lysosomal calcium-dependent proteases (calpains), and finally the predominant ATP-dependent ubiquitin-proteasome proteolytic pathway. In animal tumour-bearing models, the activation of the calcium-dependent proteases is essential for the initial degradation of myofibrillar proteins to release myosin and actin; this then allows them to be further degraded. Cytokines have been proven to be involved in the hyperactivation of the calpains, where pharmacological cytokine blockade has effectively reduced calpain activity, and prevented muscle depletion (Muscaritoli et al., 2006). Proinflammatory cytokines e.g. TWEAK, IL-1 and TNFα have also been shown to cause the activation of the nuclear transcription factor-κappaB (NF-κB). This then leads to the inhibition of muscle protein synthesis, and the reduction of the transcription factor MyoD, which principally modulates the muscle development signalling pathway (Fearon et al., 2012; Topkan et al., 2007).

2 Management

2.1 Overall management

The optimal treatment for cancer cachexia is the complete removal and cure of the cancer; unfortunately, in many advanced solid tumours this is unachievable. The next best options are to increase nutritional intake to counteract the weight loss, address the anorexia and inflammation, along with the metabolic alterations i.e. loss of body fat and addressing the skeletal muscle wasting (Inui, 2002; Murphy & Lynch, 2009).

There has been a recent change in the consideration of cachexia from a 'very late change' and inescapable event to 'an early phenomenon' with signs of cachexia present upon primary cancer diagnosis even if weight loss has not yet occurred. This has led to a recent shift in developing effective treatments aimed at preventing rather than reversing the symptoms (Muscaritoli et al., 2006).

2.2 Increasing nutritional intake

Cancer cachexia is different from simple starvation in that either parenteral and enteral nutrition support has only limited value (Kufe et al., 2006). Maintaining body composition, function and quality of life is the underlying goal of nutritional support and needs to be addressed early if it is to be successful (Bloch, 2000). Nutritional support is unable to correct advanced cachexia but can prevent further deterioration (Muscaritoli et al., 2006). Nutritional support improves weight, calorie intake, appetite, and immune parameters. Nutrition support should be via the oral route; if inadequate calories cannot be consumed, alternative nutrition support will need to be considered (Nixon, 1986). Nutritional counselling has been proven to be of benefit in a prospective, randomised controlled study involving colorectal patients undergoing radiotherapy. Patients were randomised to supplements versus dietary counselling versus ad libitum intake. Dietary counselling showed either an improvement or maintenance of symptoms and function when compared to the other group. It was also the only group to maintain a significant impact on patient outcomes at three months after radiotherapy (Ravasco, Monteiro-Grillo, Vidal, & Camilo, 2005).

2.2.1 Enteral nutrition

Nutritional support via enteral feeding has documented benefits and is recommended whenever possible. Atrophy of the microvilli lining of the intestinal wall can be prevented, along with maintaining normal gut flora and histology, stimulating bile flow and preventing cholestasis (Arbogast, 2002). For short term access nasoenteric tubes are advised. The advantage being that

the feedings are exposed to pancreatic enzymes, bile acid and gastric secretions before passing into the jejunum, maximising nutrient absorption. Disadvantages include misplaced feeding tubes, perforation of the gastrointestinal (GI) tract (Arbogast, 2002), and is not recommended for any patient who has oesophageal and oral ulcers as it leads to further irritation and can be uncomfortable as well as interfering with body image (Bloch, 2000).

For longer term feeding of several weeks, percutaneous endoscopic gastrostomy (PEG) or jejunostomy tubes are advised. Advantages of PEG are that they are easily inserted in the outpatient setting and have lower complication rates and higher success rates, and are generally well tolerated by the patients (Piquet et al., 2002). After a few weeks flat devices called 'buttons' are inserted allowing patients to take showers, wear fitted clothes, and provides a more positive self-image (Bloch, 2000). The jejunum is an alternative location site if placement in the stomach is contraindicated. Feedings via jejunostomies have the disadvantage of not being exposed to enzymes and gastric secretions, as they access directly into the small bowel (Bloch, 2000).

2.2.2 Parenteral nutrition

Parenteral nutrition can be used if the enteral route is unavailable. Careful assessment should be made before embarking on this method. There are many complications associated with parenteral feeding including infection, hypo- and hyperglycaemia, venous thrombosis and air embolism. Total Parenteral Nutrition (TPN) in some studies has led to an improvement via a decreased rate of infection, improved wound healing and a decrease in major complications and postoperative mortality. While other studies have found no advantage, one study found that there was an increase in postoperative complications (Detsky, Baker, O'Rourke, & Goel, 1987). A systematic review looked at 28 prospective controlled trials looking at the benefit of TPN. It was concluded that the use of TPN in cancer patients is only useful in selective groups i.e. patients undergoing surgery. In patients receiving chemotherapy, there was no benefit in treatment toxicity or tolerance, tumour response and overall survival (Klein, Simes, & Blackburn, 1986). This was then followed by a published meta-analysis that showed parenteral nutrition in patients undergoing chemotherapy had a detrimental effect, with decreased survival and poorer tumour response. It was concluded that trials were required in specific patient groups (McGeer, Detsky, & O'Rourke, 1990). The European Society for Parenteral and Enteral Nutrition has produced guidelines on parenteral nutrition in surgical (Braga et al., 2009) and non-surgical oncology patients (Bozzetti et al., 2009). Interestingly, a recent narrative review looked at providing nutritional support and tumour growth in humans. The review reported that seven out of the twelve studies showed

increased tumour growth when compared to patients without nutritional support. It was still concluded that nutritional support should be provided with the overall aim of maintenance of nutritional status, and allowing compliance with anti-cancer treatment (Bozzetti & Mori, 2009).

2.3 Pharmacological agents and support

Over the last few decades, a number of pharmacological agents and methods of support have been investigated to address the following three main areas of cancer cachexia. Firstly, addressing anorexia via appetite stimulation; secondly, addressing alterations in energy and substrate metabolism, and lastly addressing skeletal muscle loss via targeting the anabolic and catabolic pathways (Fearon et al., 2012; Muscaritoli et al., 2006).

3 Review of human clinical studies

A literature search was conducted on PubMed (includes MEDLINE), Embase (through OvidSP) Cochrane Central Register of Controlled Trials (CENTRAL), and Clinicialtrials.gov website over a time frame ranging from each database set-up date to December 2010. Key words included; cancer-cachexia, human, clinical studies, and trials. For the purpose of thesis, only randomised controlled studies with a study period of more than four weeks are included as per Table 1. Study period of more than weeks was chosen as weight gain has been shown at this time frame (Fearon et al., 2003; Gordon et al., 2005). Only studies with published full-text in peer review journals were included. For the purpose of the table, the term *'late cachexia'* is used to define participants with weight loss and deemed end-stage and not appropriate to receive any form of anti-cancer treatment, while the term *'cachexia'* is used to define participants with weight loss and receiving anti-cancer treatment.

Figure 1 Flow diagram of reviewed human cancer cachexia studies pre ACCeRT

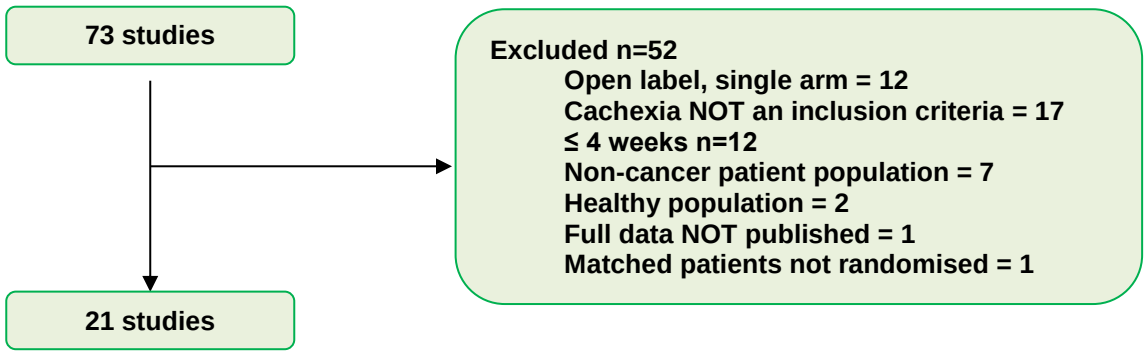


Table 1 Reviewed randomised studies pre ACCeRT study

Patients				Study design			Main results		
Author, year	**Total No of pts**	**Patients characteristics**	**Criterion of cachexia, probable cachexia stage**	**Interventions**	**Duration of intervention (weeks)**	**Outcomes**	**Other**	**Side effects**	**Effect on weight**
Corticosteroids									
Moertel 1974 (Moertel, Schutt, Reitemeier, & Hahn, 1974)	116	Advanced GI patients (adenocarcinoma). Estimated survival of less than two months.	Poor nutritional intake. *Late cachexia*	**Randomised, double-blind, placebo-controlled** 1. Placebo (40%) 2. Dexamethasone 0.75 mg QDS (30%) 3. Dexamethasone 1.5 mg QDS (30%)	0 to 30	1. X 2. X 3. 4. X 5. X	NS difference in survival. Results at 2 weeks similar between groups in appetite & strength. Results at 4 weeks, dexamethasone showed a significant difference in appetite and strength. Put down to euphoria. No difference between different dexamethasone dosages.	1 patient GI haemorrhage (placebo). 36% of patients treated with dexamethasone had onset of oedema or increase in pre-existing oedema vs. 30% of patients on placebo	Not published
Metz Or Popiela 1989 (Metz, Popiela, Lucchi, & Giongo, 1989)	173	Female advanced cancer. Chemotherapy NOT permitted.	Cachexia on LASA scale. *Late cachexia.*	**Randomised, double-blind, placebo controlled** 1. IV MPSS 125 mg daily for 56 days. 2. IV Placebo.	8	1. X 2. 3. 4. 5. X	<u>Attrition - completed study (51%):</u> MMPS, 44% Placebo, 57% <u>NS difference in survival –death;</u> MMPS, 38% Placebo, 30% QOL (LASA scales). NS difference in pain or sleep. Significant difference in improved appetite, nausea, anxiety and sense of well-being across time in MPSS group.	Infectious complications comparable between groups. <u>Significant differences in GI AE</u> MPSS, 10.6% Placebo, 2.2% (p<0.05).	No change
Loprinzi 1999 (Loprinzi et al., 1999)	496	Advanced cancer. Chemotherapy and RT permitted.	Weight loss of 5 Lbs over previous 2 months. Daily caloric intake of less than 20cal/kg. *Cachexia.*	**Randomised controlled open-label** 1. Megestrol acetate 800 mg OD (Control) 2. Dexamethasone 0.75 mg QDS. 3. Fluoxymesterone 10 mg BD.	Monthly up to 20 months	1. X 2. 3. 4. 5. X	<u>Attrition – completed 4 weeks:</u> 66% NS difference in survival. Similar stimulation in appetite with dexamethasone and megestrol acetate, but different toxicities.	<u>Dexamethasone group:</u> Myopathy, 18% (p=0.0006) Cushingoid, 6% (p=0.0008) Peptic ulcer, 3% (p=0.04) Insomnia, 4% (p=0.005) <u>MA group:</u> DVT, 5% (p=0.06)	NS difference in weight. Trends favouring megestrol acetate.

MPA / MA									
Simons 1996 (Simons et al., 1996)	206	Advanced non-hormone sensitive cancer. Chemotherapy permitted. KS >60.	Appetite and weight. *Cachexia.*	**Randomised, double-blind, placebo-controlled** 1. MPA 500 mg BDS 2. Placebo	12	1. X 2. X 3. 4. 5. X	<u>Attrition - completed 6 weeks (65%);</u> MPA, 66% Placebo, 64% <u>Completed 12 weeks (48%);</u> MPA, 51% Placebo, 44% <u>Death/physical deterioration</u>; MPA, 27% Placebo, 38% Significant improvement in appetite at both 6 (p=0.008) and 12 (p=0.01) weeks. NS trend in improvement in appetite loss, nausea & vomiting for MPA.	<u>Mechanical obstruction;</u> MPA, 4 <u>Sigmoid perforation and peritonitis;</u> MPA, 1 MPA attrition due to painful breasts, headache, heart failure, abdominal discomfort with nausea & vomiting, and fatal lung embolism.	<u>Significant difference in weight gain (kg) at 12 weeks;</u> MPA, +0.6 ± 4.4 Placebo, -1.4 ± 4.6 Difference of +2.0 kg (p=0.04).
Cannabinoids									
Jatoi 2002 (Jatoi et al., 2002)	469	Advanced cancer. Chemotherapy and RT permitted. Life expectancy ≥ 3 months. ECOG PS 0-2.	Self-reported weight loss of 5 Lbs over previous 2 months. Daily caloric intake of less than 20cal/kg. *Cachexia.*	**Double-blind, randomised controlled** 1. Megestrol acetate 800 mg OD + placebo (Standard/Control). 2. Dronabinol 2.5 mg BDS + placebo. 3. Megestrol acetate 800 mg OD + dronabinol 2.5 mg BDS (Combination).	0 to 11	1. X 2. X 3. 4. 5. X	<u>Attrition – completed 4 weeks;</u> 45% <u>Patient refusal and/or toxicity;</u> Control, 45% Dronabinol, 58% Combination, 41% <u>NS difference in death;</u> Control, 22% Dronabinol, 15% Combination, 26% <u>NS difference in increased appetite;</u> Control, 75% Dronabinol, 49% Combination, 66%	NS difference in toxicity. Although 18% of male participants reported impotence.	<u>Home weight change of ≥10% from baseline;</u> Control, 10% Dronabinol, 3% Combination, 8%. <u>Physician weight change of ≥10% from baseline;</u> Control, 14% Dronabinol, 5% Combination, 11%.

Strasser 2006 (Strasser et al., 2006)	289	Advanced cancer. Chemotherapy permitted. ECOG PS 0-2.	CACS weight loss ≥5% over 6 months. *Cachexia.*	**Randomised, double-blind, placebo-controlled** Randomised 2:2:1. 1. THC 2.5 mg BD + cannabidiol 1 mg BDS (CE). 2. THC 2.5 mg BDS (THC). 3. Placebo BDS (Placebo).	6	1. X 2. X 3. X 4. 5. X	<u>Attrition - completed 6 weeks (68%);</u> CE, 69% THC, 67% Placebo, 69% <u>NS difference in reported increased appetite;</u> CE, 73% THC, 58% Placebo, 69% NS difference in QOL, mood and nausea in all groups. Study supports placebo effect.	NS difference in toxicity in all groups.	No change in weight.
Thalidomide									
Gordon 2005 (Gordon et al., 2005)	50	Advanced pancreatic cancer. Chemotherapy and RT **NOT** permitted. Life expectancy ≥ 6 weeks.	≥10% weight loss over 6 months. *Late cachexia.*	**Randomised, double-blind, placebo-controlled** 1. Thalidomide 200 mg OD. 2. Placebo	24	1. X 2. X 3. X 4. X 5. X	<u>Attrition – completed 4 weeks (70%);</u> Thalidomide, 74% Placebo, 67% <u>Completed 8 weeks (43%);</u> Thalidomide, 52% Placebo, 33% NS difference in QOL. Improvement in physical functioning correlates positively with weight gain (p=0.001). <u>Significant difference in bone free arm muscle mass (cm^3);</u> <u>Week 4,</u> Thalidomide, +1.0 Placebo, -4.6 (p=0.002). <u>Week 8,</u> Thalidomide, -0.5 Placebo, -8.4 (p=0.014). NS difference in grip strength.	<u>Thalidomide AE include;</u> Peripheral neuropathy (9%). Rash (9%). Daytime somnolence (17%). Constipation (week 4) p=0.04. Decreased insomnia (week 4) p=0.023.	<u>Significant difference in weight (kg);</u> <u>Week 4,</u> Thalidomide, +0.37 Placebo, -2.21 (p=0.005). <u>Week 8,</u> Thalidomide, -0.06 Placebo, -3.62 (p=0.034).

Melatonin									
Persson 2005 (Persson, Glimelius, Rönnelid, & Nygren, 2005)	24	Advanced GI cancer. Chemotherapy permitted. KS ≥60. Serum albumin ≤35 g/L.	Documented ≥10% weight loss over 6 months. *Cachexia.*	**Randomised, open-label study.** Dietary advice plus; 1. EPA 4.9 g + DHA 3.2 g per 30 mL/day (FO). 2. Melatonin 18 mg/day (MLT).	4 weeks single agent, followed by 4 weeks of combination.	1. X 2. X 3. X 4. 5. X	<u>Attrition- completed 4 weeks (84%);</u> FO, 85% MLT, 82% <u>Completed 8 weeks (66%);</u> FO then FO + MLT, 77% MLT then FO + MLT, 55% <u>Death/progressive disease;</u> <u>Week 4,</u> FO, 2 MLT, 2 <u>Week 8,</u> FO then FO + MLT, 1 MLT then FO + MLT, 3 NS difference in KS, overall survival, biochemical variables and cytokines.	<u>Week 4,</u> <u>Anorexia;</u> FO, 1 <u>Fatigue;</u> MLT, 1 <u>Week 8,</u> <u>Anorexia;</u> FO, 1 <u>Heartburn/belching;</u> FO, 1 <u>CNS;</u> MLT, 1 <u>Paraesthesia;</u> MLT, 1	<u>NS change in weight (kg);</u> <u>Week 4,</u> FO, -0.6 MLT, -1.8 <u>Week 8,</u> FO then FO + MLT, +0.2 MLT then FO + MLT, +0.8

Prostaglandins									
Lundholm 1994 (Lundholm et al., 1994)	135	Mixed advanced solid cancer, mainly GI cancer. Last cancer treatment 6 months prior. No other cancer treatment available. Life expectancy > 6 months.	Insidious or ongoing weight loss. *Late cachexia*	**Randomised, placebo-controlled study.** 1. Placebo 2. Prednisolone 10 mg BDS. 3. Indomethacin 50 mg BDS. Participant blinded to allocation	2 to 125	1. X 2. X 3. X 4. X 5. X	<u>Attrition;</u> Not stated. <u>Significant difference in survival (days);</u> Placebo, 250 ± 28 Indomethacin, 510 ± 28 days (p<0.05). Placebo, 274 ± 28 Prednisolone + indomethacin, 505 ± 65 (p<0.03). <u>Significant difference in AMC (cm) between placebo vs. prednisolone (p=0.001);</u> Placebo, 22.8 Prednisolone, 23.8 Indomethacin, 22.0 <u>KS significant lower in the placebo group when compared to both prednisolone and indomethacin (p=0.03);</u> Placebo, 66 ± 3 Prednisolone, 73 ± 2 Indomethacin, 75 ± 2 <u>HGS (kg) highest in prednisolone (p=0.001);</u> Placebo, 18.8 Prednisolone, 23.8 Indomethacin, 18.8 NS difference in CRP, albumin, creatinine, BP, and fatigue.	No serious complications	<u>Significant difference in body weight (kg) in prednisolone (p=0.003);</u> Placebo, 64.6 Prednisolone, 69.7 Indomethacin, 62.5

Amino acids HMB/Arg/Gln									
May 2002 (May, Barber, D'Olimpio, Hourihane, & Abumrad, 2002)	49	Advanced solid cancer, stage IV. Chemotherapy and RT permitted. Life expectancy ≥ 3 months.	≥ 5% documented weight loss. *Cachexia.*	**Double-blind, randomised Controlled** 1. Control isonitrogenous, isocaloric mixture. 11 g alanine 6.10 g glycine 4.22 g serine 1.75 g glutamic acid 30.52 g gelatin daily in two divided cases. 2. HMB/Arg/Gln (Juven). 3 g HMB 14 g arginine 14 g glutamine daily in two divided cases.	24	1. X 2. 3. X 4. 5. X	<u>Attrition - completed 4 weeks (66%);</u> Control, 56% HMB/Arg/Gln, 75% <u>Completed 24 weeks (19%);</u> Control, 8% HMB/Arg/Gln, 29% <u>Died;</u> Control, 4% HMB/Arg/Gln, 4% Increase in haemoglobin +2.2 g/dL in HMB/Arg/Gln group.	<u>HMB/Arg/Gln group;</u> Decreased physical well-being by Functional Assessment Health Survey. <u>12 weeks;</u> HMB/Arg/Gln, increased levels of BUN, uric acid, phosphorous and sodium. Control, decreased levels of above markers. NS difference in other safety assessments.	<u>Weight (kg) at 4 weeks;</u> Significant difference ($p<0.05$) HMB/Arg/Gln, +0.95 ± 0.66 Control, -0.26 ± 0.78 <u>FFM (kg) at 4 weeks;</u> Significant difference ($p=0.02$) HMB/Arg/Gln, +1.12 ± 0.68 Control, -1.34 ± 0.78 <u>FFM (kg) at 24 weeks;</u> NS difference HMB/Arg/Gln, +1.6 ± 0.94 Control, +0.48 ± 1.08
Berk 2008 (Berk et al., 2008)	472	Advanced solid cancer, stage III or IV. Chemotherapy permitted. Life expectancy ≥ 3 months. Zubrod PS 0-2.	2% to 10% weight loss over previous 3 months. *Cachexia.*	**Randomised, double-blind, placebo-controlled** 1. Placebo isonitrogenous, isocaloric mixture. 7.72 g *l*-alanine 4.28 g glycine 2.96 g *l*-serine 1.23 g *l*-glutamic acid 30.52 g gelatin BDS. 2. HMB/Arg/Gln 3 g HMB 14 g arginine 14 g glutamine BDS.	8	1. X 2. 3. 4. 5. X	<u>Attrition – completed 8 weeks (37%);</u> Placebo, 34% HMB/Arg/Gln, 40% <u>Discontinued due to death;</u> Placebo, 11% HMB/Arg/Gln, 9% <u>Discontinued due to patient preference, side effects, weight loss >5% at 4 weeks, and disease progression;</u> Placebo, 55% HMB/Arg/Gln, 48% <u>Chemotherapy (53%);</u> Placebo, 55% HMB/Arg/Gln, 47% <u>Compliance full 8 weeks;</u> Placebo, 34% HMB/Arg/Gln, 40% NS difference in fatigue and QOL.		<u>BIA LBM (kg);</u> NS change Placebo, -0.74 HMB/Arg/Gln, -0.215 <u>NS change in skin fold;</u> Placebo, +0.642 HMB/Arg/Gln, +0.541 <u>NS % change in weight (kg);</u> Placebo, +2.47 HMB/Arg/Gln, +2.23 <u>2% to 5% weight loss group;</u> 2.26% significant treatment difference in favour of HMB/Arg/Gln ($p=0.01$). <u>5% to 10% weight loss group;</u> NS difference ($p=0.38$). HMB/Arg/Gln showed strong trend towards higher BIA LBM and skin-fold.

Pentoxifylline									
Goldberg 1995 (Goldberg et al., 1995)	70	Advanced malignancy. Chemotherapy and RT permitted. Estimated life expectancy ≥3 months. ECOG PS 0-2.	≥5 lbs over previous 2 months or estimated caloric intake ≤20 kcal/kg/d. *Cachexia.*	**Randomised, double-blind, placebo-controlled** 1. Pentoxifylline 400 mg TDS. 2. Placebo	2 months for interim analysis.	1. X 2. X 3. 4. 5. X	<u>Attrition – completed 4 weeks (61%);</u> Pentoxifylline, 19% Placebo, 24% <u>Improved taste of food;</u> Pentoxifylline, 0% Placebo, 13% <u>Medication helped;</u> Pentoxifylline 21% Placebo, 35% Study supports placebo effect.	Similar toxicities between groups.	<u>>10% weight gain;</u> Pentoxifylline, 5.7% Placebo, 8.6% Pentoxifylline range -4.7% to +13.8%, median +0.6%. Placebo range -6.7% to +14.1%, median gain +1.8%.
Anti-TNF-α antibody									
Jatoi 2007 (Jatoi et al., 2007)	66	Incurable cancer (except brain). Chemotherapy and RT permitted. Life expectancy ≥ 3 months. ECOG PS 0-2.	Reported weight loss ≥2.27 kg over previous 2 months. Loss of appetite a concern. Daily caloric intake of less than 20cal/kg. *Cachexia.*	**Randomised, double-blind, placebo-controlled** 1. Placebo subcut twice weekly. 2. Etanercept 25 mg subcut twice weekly	24	1. X 2. 3. X 4. 5. X	<u>Attrition – completed 4 weeks (81%);</u> Placebo, 83% Etanercept, 79% <u>Completed 8 weeks (51%);</u> Placebo, 50% Etanercept, 52% <u>NS difference in median survival (days);</u> Placebo, 148 Etanercept, 175 <u>Declined further treatment and/or AE;</u> Placebo, 40% Etanercept, 32% <u>Progressive disease;</u> Placebo, 17% Etanercept, 12% <u>Death;</u> Placebo, 23% Etanercept, 13% NS difference in appetite and QOL. Study terminated early due to poor accrual.	<u>Rate of neurotoxicity;</u> Placebo, 0% Etanercept, 29% <u>Rate of anaemia;</u> Placebo, 19% Etanercept, 0% <u>Rate of thrombocytopenia;</u> Placebo, 14% Etanercept, 0% <u>Vomiting at week 4;</u> Placebo, 6% Etanercept, 32%	<u>0 to 4% weight gain;</u> Placebo, 3% Etanercept, 27% <u>5 to 9% weight gain;</u> Placebo, 9% Etanercept, 17% <u>NS median change at 4 weeks (kg);</u> Placebo, -1.4 (range -13.1 to +6.4) Etanercept +0.3 (range -6.3 to +6.4) <u>NS median change at 8 weeks (kg);</u> Placebo -0.4 (range -8.0 to +6.1) Etanercept +0.4 (range -8.0 to +4.3)

Wiedenmann 2008 (Wiedenmann et al., 2008)	89	Newly diagnosed pancreatic cancer stage II to IV. First line gemcitabine chemotherapy. Life expectancy ≥ 3 months. KS >70.	Documented weight loss ≥10% of pre-morbid weight or 5% within last 90 days. *Cachexia.*	**Randomised, double-blind, placebo-controlled** Randomised 1:1:1. Gemcitabine chemotherapy plus; 1. Placebo 2. Infliximab 3 mg/kg subcut twice weekly. 3. Infliximab 5 mg/kg subcut twice weekly.	24	1. X 2. 3. 4. X 5. X	<u>Attrition – completed 8 weeks (62%);</u> Placebo, 57% Infliximab 3 mg/kg, 50% Infliximab 5 mg/kg, 71% <u>Died (8 weeks);</u> Placebo, 6.7% Infliximab 3 mg/kg, 14% Infliximab 5 mg/kg, 3.6% <u>Died (24 weeks) (82%);</u> Placebo, 90% Infliximab 3 mg/kg, 82% Infliximab 5 mg/kg, 75% <u>NS difference in mOS (months);</u> Placebo, 7.4 Infliximab 3 mg/kg, 5.3 Infliximab 5 mg/kg, 7.3 <u>NS difference in mPFS (months);</u> Placebo, 3.5 Infliximab 3 mg/kg, 2.0 Infliximab 5 mg/kg, 3.9 <u>NS difference in KS decreased score by 20;</u> Placebo, 34% Infliximab 3 mg/kg, 50% Infliximab 5 mg/kg, 34% <u>NS difference in 6MWT metres (mean);</u> Placebo, -114.1 Infliximab 3 mg/kg, -157.5 Infliximab 5 mg/kg, -87.8 FACIT-F score (3 points=clinical meaningful. Significant difference (p=0.042) in Infliximab 5 mg/kg, 31% increased scores of 3. Mean score +2.3.	Well tolerated. <u>Infusion reactions (one or more);</u> Placebo, 0 Infliximab 3 mg/kg, 2 Infliximab 5 mg/kg, 4 Increased incidence of neutropenia, fever and thrombocytopenia with Infliximab 5 mg/kg.	<u>NS difference in mean LBM difference (kg) at 8 weeks;</u> Placebo, +0.4 Infliximab 3 mg/kg, +0.3 Infliximab 5 mg/kg, +1.7 <u>NS difference in median LBM difference (kg) at 8 weeks;</u> Placebo, +1.1 Infliximab 3 mg/kg, +0.2 Infliximab 5 mg/kg, +1.8

EPA									
Fearon 2003 (Fearon et al., 2003)	200	Unresectable pancreatic cancer. KS ≥60. Chemotherapy NOT permitted. Life expectancy > 2 months.	Weight loss of 5% of pre-illness stable weight over previous 6 months. *Late cachexia*	**Double-blind, randomised controlled** 1. Oral supplement 480 mL containing 32 g protein, 620 kcal, 12 g fat split into two daily (Control). 2. Oral supplement 480 mL containing 32 g protein, 620 kcal, 12 g fat plus 2.2 EPA and enriched antioxidants split into two daily (Experimental).	8	1. X 2. X 3. 4. 5. X	Attrition – completed 4 weeks (80%); Control, 80% Experimental, 80% Completed 8 weeks (60%); Control, 57% Experimental, 62% Compliance issue below recommended dose. Experimental correlated positively with QOL.		NS difference in weight at 4 weeks; Control, -0.37 kg/month Experimental, -0.25 kg/month NS difference in LBM at 4 weeks; Control, +0.12 kg/month Experimental, +0.27 kg/month
Jatoi 2004 (Jatoi et al., 2004)	421	Incurable malignancy (excluded breast, ovarian, prostate and endometrial). ECOG PS 0-2. Life expectancy ≥ 3 months. Chemotherapy and RT permitted.	Weight loss 5 lbs over 2 months or ≤ 20 cal/kg/d. *Cachexia.*	**Double-blind, randomised controlled** 1. Isocaloric, isonitrogenous oral supplement containing 600 kcal, 32 g protein, 2.18 g EPA, 0.92 g DHA + liquid placebo (EPA). 2. MA liquid suspension 600 mg/d plus above isocaloric, isonitrogenous oral supplement minus EPA. (MA) (Control) 3. EPA + MA (Combination).	Median 3 months.	1. X 2. 3. 4. 5. X	Attrition - withdrew; EPA, 54% MA, 52% Combination, 48% Died; EPA, 17% MA, 19% Combination, 16% NS difference in mOS Significant difference in FAACT appetite score at 4 weeks (p=0.004); EPA, 40 (n=85) MA, 55 (n=69) Combination, 55	Significant difference across group (p=0.0006) Impotence; EPA, 3% MA, 9% Combination, 19% Thromboembolic events; EPA, 6% MA, 8% Combination, 2% NS difference in patient reported nausea; EPA, 32% MA, 14% Combination, 16% NS difference in patient reported vomiting; EPA, 7% MA, 6% Combination, 9%	Max weight gain 0%; EPA, 63% MA, 61% Combination, 55% Max weight gain 1 to 4%; EPA, 22% MA, 11% Combination, 20% Max weight gain 5 to 9%; EPA, 9% MA, 10% Combination, 14% Significant difference in max weight gain ≥10% (p=0.01); EPA, 6% MA, 18% Combination, 11% Significant difference in mean weight change (kg) (p=0.008 EPA vs MA, p=0.03 across groups); EPA, -1.0 MA, +1.3 Combination, +0.1

Fearon 2006 (Fearon et al., 2006)	518	Advanced GI or Lung cancer. Life expectancy ≥2 months. KS ≥70. Chemotherapy and RT NOT permitted.	Weight loss. *Late cachexia.*	**Randomised, double-blind, placebo-controlled** 1. EPA 2 g. 2. EPA 4 g. 3. Placebo.	Primary objective at week 8. Total 24 weeks.	1. X 2. 3. X 4. 5. X	<u>Attrition – completed 4 weeks (72%);</u> EPA 2 g, 73% EPA 4 g, 72% Placebo, 70% <u>Completed 8 weeks (52%);</u> EPA 2 g, 54% EPA 4 g, 53% Placebo, 49% <u>Significant difference in physical function at 8 weeks:</u> EPA 2 g, +7% EPA 4 g, -5% (*p*=0.04) <u>NS difference in compliance of >80% over 4 weeks:</u> EPA 2 g, 68% EPA 4 g, 75% Placebo, 77% <u>NS difference in mOS (days);</u> EPA 2 g, 155 EPA 4 g, 142 Placebo, 140 NS differences in KS, CRP levels, and appetite.	Similar AE across groups.	<u>Weight difference from placebo at 4 weeks (kg);</u> EPA 2 g, +0.1 EPA 4 g, +0.2 <u>Weight difference from placebo at 8 weeks (kg);</u> EPA 2 g, +1.2 EPA 4 g, +0.3 <u>LBM difference from placebo at 4 weeks (kg);</u> EPA 2 g, -0.4 EPA 4 g, +0.9 <u>LBM difference from placebo at 8 weeks (kg);</u> EPA 2 g, -0.3 EPA 4 g, -0.1 <u>GI group weight change significant mean difference from placebo at 8 weeks (kg) (*p*=0.044);</u> EPA 2 g, +1.9 EPA 4 g, +1.3 <u>Lung group weight change NS mean difference from placebo at 8 weeks (kg) (*p*=0.230);</u> EPA 2 g, +0.5 EPA 4 g, -0.7

Atractylenolide									
Liu 2007 (Liu, Jia, Dong, Wang, & Qiu, 2007)	22	Advanced unresectable gastric cancer. Chemotherapy and RT NOT permitted. Life expectancy ≥2 months.	Low or absent appetite. *Late cachexia.*	**Randomised, controlled, open-label** 1. 1.32 g per day in 12 mL split into two doses, 30 minutes post meal (ATR). 2. 3.6 g per day fish oil enriched supplement split into two doses EPA + DHA 315 mg (FOE).(Control)	7 3 weeks on treatment, then 1 week rest, followed by additional 3 weeks on treatment	1. X 2. X 3. X 4. 5. X	Attrition – completed 7 weeks: ATR, 100% Control, 100%. Significant difference in rate of change of KS at 3 weeks (*p*=0.01); ATR, 0.47-0.73 FOE, 0.33-0.47 Significant difference in rate of change of KS at 7 weeks (*p*=0.01); ATR, 0.93-1.47 FOE, 0.6-1.00 Significant difference in rate of change of appetite at 3 weeks (*p*=0.01); ATR, 2.09-2.11 FOE, 1.16-1.43 Significant difference in rate of change of appetite at 7 weeks (*p*=0.01); ATR, 2.46-2.73 FOE, 2.13-2.27 NS difference in rate of change of MAMC at 3 weeks; ATR, 0.03-0.05 FOE, 0.02-0.04 NS difference in rate of change of MAMC at 7 weeks); ATR, 0.07-0.11 FOE, 0.10-0.12 Significant difference in IL-1, IL-6 and TNF levels at 3 weeks.	ATR group experienced bad taste. Nausea, 27% Dry mouth, 9%	NS difference in rate of weight loss at 3 weeks; ATR, 0.01-0.03 FOE, 0.02-0.04 NS difference in rate of weight loss at 7 weeks; ATR, -0.01-+0.01 FOE, -0.02-+0.00 Overall; Weight gain, 23% Stable weight, 45% Weight loss, 32%

Combinations									
McMillan 1999 (McMillan, O'Gorman, & McArdle, 1999)	73	Advanced or metastatic GI cancer. Supportive care only. Life expectancy ≥2 months. Chemotherapy and RT NOT permitted.	≥5% weight loss. *Late cachexia.*	**Randomised, double-blind, placebo-controlled** 1. MA 160 mg TDS + placebo (MA+ P). 2. MA 160 mg TDS + Ibuprofen 400 mg TDS (MA + IB). Please note MA + placebo considered a 'placebo-controlled' arm as MA ineffective in gastric patients.	12	1. X 2. X 3. X 4. 5. X	Attrition - completed 4-6 weeks (56%); MA + P, 50% MA + IB, 63% Completed 12 weeks (37%); MA + P, 29% MA + IB, 46% Significant decrease in CRP levels (p<0.05); MA + P, n=13. MA + IB, n=10. Significant increase in VAS appetite (p<0.05). Significant difference in change in mid-upper arm circumference (cm) at 4-6 weeks (p<0.01); MA + P, -0.6 (range -5.7 to +0.6). MA + IB, +0.1 (range -2.5 to +3.1). Significant difference in change in mid-upper arm circumference (cm) at 12 weeks (p<0.05); MA + P, -1.0 (range -5.7 to +0.4). MA + IB, +0.0 (range -5.4 to +3.0). Week 4-6; NS difference in appetite score, biceps and triceps skinfold thickness and albumin. Week 12; NS difference in appetite score, biceps and triceps skinfold thickness and albumin.	Thrombosis; MA + P, 1. MA + IB, 2. Upper GI bleeding; MA + P, 1. MA + IB, 2. Ascites; MA + P, 2. MA + IB, 3.	Significant difference in median weight (kg) at 4-6 weeks (p<0.01); MA + P, -1.5 (range -6.0 to +4.5). MA + IB, +1.0 (range -3.7 to +6.5). Significant difference in median weight (kg) at 12 weeks (p<0.001); MA + P, -2.8 (range -7.0 to +2.2). MA + IB, +2.3 (range -2.0 to +12.4).

Cerchietti 2007 (Cerchietti, Navigante, & Castro, 2007)	24	NSCLC. ECOG-PS 0-2. CRP ≥10 µg/mL. Chemotherapy and RT NOT permitted.	≥10% weight loss. Anorexia 5/10 VAS. *Late cachexia.*	**Randomised study.** Oral supplement containing 1.52 kcal/mL, 56.4% carbohydrates, 14.6% proteins, and 29% fat plus either; 1. Fish oil 2 g TDS + placebo (FO + P). 2. Fish oil 2 g TDS + celecoxib 200 mg BDS (FO + Cox). Assuming participant blinded to allocation	6	1. X 2. X 3. X 4. X 5. X	Attrition – completed 6 weeks; All Arms 100% Compliance high; FO + P, 96% FO + Cox, 98% Significant difference in hand-grip (p=0.002); FO + P, +1.16 FO + Cox, +3.12 Significant difference in CRP (µg/mL) (p=0.005); FO + P, -6.7 FO + Cox, -21.3 NS difference in fat mass, lean mass, body water, appetite and fatigue. Significant correlations		Significant difference in weight (kg) (p=0.05); FO + P, -1.4 FO + Cox, +1.5
Mantovani 2010 (Mantovani, Macciò, Madeddu, Serpe, Massa, et al., 2010)	322	Advanced cancer. Chemotherapy and hormone therapy permitted.	≥5% weight loss over 3 months. *Cachexia*	**Randomised, open-label** Basic polyphenols + antioxidants + vitamins plus either; Arm 1. MPA 500 mg/d or MA 320 mg/d. Arm 2. EPA 2.2 g/d x 2 (Prosure or Resource) or 2 g/d x 3 (Forticare). Arm 3. L-carnitine 4 g/d. Arm 4. Thalidomide 200 mg/d. Arm 5. All of the above.	≥16	1. X 2. X 3. X 4. X 5. X	First interim analysis (125 pts) Arm 2 terminated. Second interim analysis (204 pts) Arm 1 terminated. Attrition – completed 16 weeks; All Arms 100%. NS difference in any primary or secondary endpoints for Arm 1. Significant difference in REE (kcal/d) and fatigue score for Arm 2. Significant difference in GPS and ECOG-PS for Arm 3. Significant difference in IL-6, GPS and ECOG-PS for Arm 4. Significant difference in decreased REE, improved fatigue via MFSI-SF, increased VAS appetite, decreased IL-6, TNF-α, GPS and ECOG-PS.	Toxicity was negligible and comparable between arms.	Significant difference in LBM (kg) by DEXA (p=0.007); Arm 5, +2.1 ± 2.1. Arm 4, -0.8 ± 2.6. Arm 3, -0.7 ± 2.2. Significant difference in LBM (kg) by DEXA baseline to post treatment (p=0.015); Arm 5, 43.8 ± 9.4 to 44.9 ± 7.7 Significant difference in LBM (kg) by estimated L3-CT baseline to post treatment (p=0.001); Arm 5, 42.8 ± 8.1 to +45.4 ± 23.9. NS difference in LBM (kg) by BIA in all Arms.

Outcomes: 1. Weight/anthropometry (e.g. kg, BMI, LBM); 2. Anorexia and food intake (e.g. appetite on VAS, Likert scale, food diary); 3. Catabolic drive (e.g. inflammation markers and tumour activity; 4. Physical performance (e.g. hand-grip and 6 min walk test); 5. Function and psychosocial effect (e.g. Karnofsky, ADL and QOL parameters).

3.1 Pre ACCeRT PICOS summary

After reviewing the literature on published human clinical studies, there are a number of emerging themes, as per PICOS approach (Liberati, Altman, & Tetzlaff, 2009), within Table 1;

Populations

Participants enrolled onto the reviewed cancer cachexia studies were recruited from advanced cancer populations. Some studies chose to select either a single or double specific cancer population. Population numbers ranged from 22 (Liu et al., 2007) and 24 (Persson et al., 2005), and up to 518 (Fearon et al., 2006). Twelve of the studies permitted anti-cancer treatment and were defined as *'cachexia'* and nine restricted its use and defined as *'late cachexia'.*

Interventions

These varied widely addressing either appetite stimulants with corticosteroids, progestinal agents, cannabinoids, and thalidomide. Targeting proinflammatory cytokines with prostaglandins. Supporting protein synthesis with amino acids, and suppressing muscle loss with Eicosapentaenoic Acid (EPA).

Comparisons

Twenty-one of the reviewed studies were randomised and are included in table 1, while twelve studies were single-arm.

Outcomes

Generally the primary outcome/endpoint was the change in either body weight by scales or Lean Body Mass (LBM)/Fat Free Mass (FFM) by Bioelectrical Impedance Analysis (BIA) and later Dual-Energy X-ray Absorptiometry (DEXA) and Lumbar-3-Computed Tomography (L3-CT). Some of the included studies did not clarify the primary outcome, while some utilised change in appetite by Visual Analogue Scale (VAS).

Study design

Eligibility criteria included participants reported poor appetite and weight loss. Along with documented weight loss ranging from 5 lbs over previous two months, 2 to 10% over previous three months, or 5 or 10% weight loss over previous six months. Duration of the study period ranged from four (Persson et al., 2005) up to 125 weeks (Lundholm et al., 1994), with eight and twenty-four weeks being frequently used, with one study ranging from eight to twenty-four weeks

(Fearon et al., 2006). Interestingly two of the late cachexia studies designed a study period of twenty-four weeks (Fearon et al., 2006; Gordon et al., 2005).

Risk of bias

Four of the twenty-one studies did not publish the method for randomisation sequence generation. However, eighteen of the studies did not state how the allocation was concealed, while three studies utilised sealed envelopes. Within the randomised studies, eleven were double-blind, placebo-controlled, four were double-blind, controlled, one study stated participants were blinded therefore single-blind, placebo controlled, one study single blind, non-controlled, one open-label controlled study, and three open label non-controlled studies. Attrition was often seen in the reviewed cancer cachexia studies. Completion rates of eighteen studies ranged from 45 to 100% at 4-6 weeks, 37 to 100% at 7-8 weeks, 37 to 48% at 12 weeks, 100% at 16 weeks, and 18 to 19% at 24 weeks. Three studies did not formally define attrition/completion rates. When separated into cachexia studies, rates ranged from 45 to 81% at 4-6 weeks, 37 to 66% at 7-8 week, 48% at 12 weeks, 100% at 16 weeks and 18 to 19% at 24 weeks. However, rates for late cachexia were higher than the above cachexia rates, ranging from 56 to 100% at 4-6 weeks, 43 to 100% at 7-8 weeks, and 37% at 12 weeks. All studies stated outcome measures in the context of number of participants completing to various study time points.

3.2 Summary of outcomes

As per table 1 above, summary of outcomes were subdivided into the main components of cancer cachexia.

3.2.1 Weight/anthropometry

Examples included weight within fifteen studies, LBM by DEXA within one study, and FFM by BIA within eight studies.

3.2.2 Anorexia and food intake

Examples included appetite on VAS within six studies, food diary within two studies, and dietary and calories intake within one study.

3.2.3 Catabolic drive

Examples included tumour activity, and biomarkers of inflammation and nutritional states within eight studies.

3.2.4 Physical performance

Examples included the use of hand-grip within four studies; 6MWT and SenseWear both within one study each.

3.2.5 Function and psychosocial effect

Examples included KS and ECOG-PS. Interestingly eleven of the above reviewed studies assessed survival as a secondary outcome, with RECIST within one study. Summary of PRO used within the above reviewed studies include; EORTC QLQ-C30 used within eight studies. Five used Uniscale, with QOL LASA scales within one study. Global assessment of efficacy within one study, while two studies used SF-36. Spitzer QOL, FACIT-F and BPI were all used within one study.

The above summary shows a range of secondary outcomes utilised within the different cancer cachexia studies. Frequent outcomes utilised above were used in the design of the ACCeRT study, as discussed below.

4 Study design

After reviewing the literature and published clinical studies within chapter three, a number of factors were used in the designing of a pilot/phase I study.

4.1 Multi-targeted

It was decided to investigate a multi-targeted approach with agents that had shown some efficacy and safety, either in combination or as a single agent, from human clinical studies. This decision was based on that over the last few decades a number of pharmacological agents had been investigated showing either no or only limited benefit. It has also been documented and proposed that there is a need for a multi-modal approach to the management of cancer cachexia, involving the use of anti-inflammatory agents, improved food intake, especially protein, and exercise, to stabilise the cachectic patient (Fearon, 2008).

4.1.1 EPA

EPA is an omega-3 polyunsaturated fatty acid found in oily fish. It has been shown to have anti-tumour and anti-cachectic activity in animal cachexia models (Dagnelie et al., 1994; Tisdale & Dhesi, 1990). There have been a number of clinical studies investigating EPA. It was decided to administer EPA at approximately 2g/day. This decision was based on the data from an open-label, non-randomised study that explored EPA 2.18g/day (Barber, Ross, Voss, Tisdale, & Fearon, 1999), taken together with the data from two large randomised-controlled studies supporting a dose-response of improved lean body mass to EPA 2.2g/day (Fearon et al., 2003) and the suggested optimum dose of at least EPA 2g/day (Fearon et al., 2006).

It must be acknowledged that a systematic review of five studies including 587 patients was carried out to investigate the benefit of EPA in cachectic patients. It was concluded that there was insufficient data to establish if EPA was better than placebo and to define the optimal dose (Dewey, Baughan, Dean, Higgins, & Johnson, 2008). EPA was chosen as part of the treatment regimen due to its anti-inflammatory properties (Wigmore et al., 1996), and the proposed inhibition of production of the proinflammatory cytokines (Mantovani, Macciò, Madeddu, Serpe, Massa, et al., 2010).

4.1.2 COX-2

The use of Non-Steroid-Anti-Inflammatory Drugs (NSAIDs) in cancer patients is not widespread due to concerns regarding cyclo-oxygenase-1 (COX-1) inhibition, and the effect of

haematological tissue and gastrointestinal mucosal lining (Davis et al., 2004). The development of selective cyclo-oxygenase-2 (COX-2) inhibitors has led to the possibility of their use in reducing tumour-mediated prostaglandin levels safely and could help alleviate or control cancer cachexia (Davis et al., 2004). It was decided to administer celecoxib at 300mg/day based on the following data.

Celecoxib at a dose of 200mg b.d.s., (bis die sumendum-Latin two times a day) versus placebo for three weeks has been investigated in a placebo-controlled randomised-controlled study in head and neck and gastrointestinal cancer patients. Efficacy was shown in terms of weight, improved Quality Of Life (QOL) scores and increased Body Mass Index (BMI) scores, although these were not statistically significant, indicating that to target just inflammatory suppression may not be enough to produce a clinical effect in lean body mass. Results showed good compliance with no adverse events seen (Lai et al., 2008).

Recently, a phase II non-randomised prospective study investigated celecoxib at a dose of 300mg/day for four months in advanced cancer patients. Efficacy was show in terms of TNF-α levels and LBM, QOL, Eastern Cooperative Oncology Group Performance Status Performance Status (ECOG-PS), Glasgow Prognostic Score (GPS) and hand-grip strength (HGS). No grade 3 or 4 toxicities were noted. This study concluded that celecoxib was an effective single agent for cancer cachexia treatment (Mantovani, Macciò, Madeddu, Serpe, Antoni, et al., 2010). Celecoxib was chosen as part of the treatment regimen due to its anti-inflammatory properties that could potentially address the ‘acute-phase response’ induced from the tumour (Mantovani, Macciò, Madeddu, Serpe, Antoni, et al., 2010).

4.1.3 EPA plus COX-2

As summarised within table 1, the study by Cerchietti et al. investigated the combination of EPA and COX-2 inhibitor in NSCLC patients. Efficacy was shown in terms of body weight and LBM and within the hand-grip strength data. No toxicity or safety concerns were noted (Cerchietti et al., 2007). It must be noted that the total dose of EPA in this study was 1.08g per day, although other studies aimed for 2g per day (Barber et al., 1999; Fearon et al., 2006; Fearon et al., 2003; Wigmore, Barber, Ross, Tisdale, & Fearon, 2000). It was decided to utilise the combination of COX-2 inhibitor of 300mg celecoxib plus 2.09g of EPA per day as the best supportive care arm.

4.1.4 Exercise

Increased knowledge has been gained regarding the molecular pathways involved in the muscle wasting process component of cancer cachexia. Understanding the factors and pathways has opened the possibility of potential molecular therapeutic targets (Boddaert, Gerritsen, & Pinedo, 2006; Fearon et al., 2012). Muscle wasting is a combination and balance of the anabolic and catabolic pathways. The anabolic pathway involves the increased expression of Insulin Growth Factor-1 (IGF-1) followed by the binding of it to its receptor and the activation of the P13K/Akt and mTOR pathway (Muscaritoli et al., 2006). The catabolic pathway involves the proinflammatory activation of the calcium-dependent ubiquitin-proteolytic pathway and the ATP-dependent ubiquitin-proteolytic pathway, resulting in the degradation of muscle proteins to amino acids (Boddaert et al., 2006).

Progressive resistance exercise training (PRT) has been shown to be a potent stimulus for growth in muscle strength and mass. PRT may down-regulate proinflammatory activity and increase the phosphorylation of intramuscular amino acid signalling (Al-Majid & Waters, 2008).

PRT has been investigated in patients with well-controlled rheumatoid arthritis (RA) with cachexia. This phase II study showed that PRT, when used on average 2.5 times a week for 12 weeks, stimulated muscle growth. PRT seemed to be a safe and effective intervention with no exacerbation of the activity of the RA disease. The study compared RA patients receiving PRT with age-sex matched RA patients. Efficacy was shown in terms of significant increases in FFM and total body protein. This was associated with improvements in physical function measurements (Marcora, Lemmey, & Maddison, 2005).

In 2008, Carroll et al. published an abstract of results from a placebo-controlled, double-blind, randomised study that investigated the benefit of either placebo, acetaminophen or ibuprofen in older healthy adults undergoing resistance training (Carroll et al., 2008). Full results were published later in 2011 (Trappe et al., 2011). Efficacy was shown in terms of increased quadriceps muscle volume. It was concluded from this study that the concurrent use of acetaminophen or ibuprofen with resistance training results in an additional muscle hypertrophy of ~25 to 50% when compared to resistance training alone in older adults (Carroll et al., 2008; Trappe et al., 2011).

Exercise and progressive resistance training has become popular in the cancer community in recent years. There is now extensive literature supporting PRT as the most effective method for improving muscle function and strength, and improving the effects of sarcopenia in older adults (Galvao et al., 2006). Recently, a systematic review of 65 studies of aerobic or resistance training

exercise in cancer patients highlighted the acceptance of an exercise programme, with high levels of completion and adherence. Most of the studies were conducted in breast cancer patients, with only four studies restricted to lung cancer patients only. Of these four, one study was restricted to stage I-II lung cancer, two restricted to stage I-III lung cancer, and the final one stage was not reported (Maddocks, Mockett, & Wilcock, 2009).

A review has shown that resistance exercise and amino acids can independently stimulate skeletal muscle synthesis in humans via the mTORC1 signaling pathway. It has also shown that muscle synthesis is greatly increased if amino acids, especially leucine, are ingested after the resistance training exercise. Studies in older adults have confirmed that providing this nutrition after exercise increases the muscle synthesis, although over a slower time, to levels similar to younger adults. Utilising this strategy will maximise the synthesis of skeletal muscle in the older NSCLC cachectic cancer patients (Drummond, Dreyer, Fry, Glynn, & Rasmussen, 2009).

4.1.5 Amino acids +/- exercise

Intravenous and orally administered amino acids (AA) have been investigated in a number of settings in relation to muscle protein synthesis. Studies in healthy participants have shown that intravenous infusion of amino acids results in hyperaminoacidemia and increased protein synthesis at rest (Tipton, Ferrando, Phillips, Doyle, & Wolfe, 1999). Exercise has also been shown to have a profound effect on both muscle protein breakdown and protein synthesis. Studies have investigated the combination of both amino acid supplementation both pre and post exercise. Results showed that an increase in muscle synthesis and muscle protein breakdown was prevented if the infusion of amino acids was given post exercise with an overall anabolic effect on the muscle. Ingesting an oral amino acid solution is a more practical way of gaining these supplements. Research was lacking to determine if hyperaminoacidemia from orally administered amino acids was similar to an infusion solution. This theory was tested within the following study, which investigated whether an oral solution of essential amino acids (EAA) would be comparable to a mixed amino acids (MAA) solution post exercise in increasing muscle protein anabolism in six healthy participants (Tipton et al., 1999). Results showed that an oral amino acid ingested solution resulted in hyperaminoacidemia, with amino acids concentration levels similar to those from an amino acid intravenous infusion. This study showed that post exercise muscle protein is negative in the post absorptive condition. The addition of amino acids after exercise switches the muscle protein balance from negative to a positive i.e. an anabolic state. It was concluded, due to similar increase in muscle protein anabolism between the EAA and MAA groups, that non-

essential amino acids were not required to increase net muscle protein synthesis (Tipton et al., 1999). Between 2000 and 2008, a number of studies investigated the optimum regimen of exercise and/or EAA, at a single exposure in healthy young and older participants (Dreyer et al., 2008; Dreyer et al., 2006; Fujita et al., 2007; Katsanos, Kobayashi, Sheffield-Moore, Aarsland, & Wolfe, 2005, 2006; Paddon-Jones et al., 2004; Rasmussen, Tipton, Miller, Wolf, & Wolfe, 2000; Tipton, Borsheim, Wolf, Sanford, & Wolfe, 2003; Tipton et al., 2001).

All the above studies investigated a single exposure to the amino acid supplements. Efficacy and safety in repeated doses and longer-term exposure were then studied within the following populations. In 2008, Aquilani et al. published results from a randomised controlled study that investigated the benefit of oral supplement with 4g of amino acids b.d.s., versus placebo in exercise capacity in elderly patients experiencing chronic heart failure (CHF) for 30 days. This study contained no resistance exercise element, and patients were concurrently taking cardiac medication (Aquilani et al., 2008). Results showed efficacy in terms of exercise output intensity and duration and post exercise recovery was improved with a shorter time. No toxicity or safety concerns were stated (Aquilani et al., 2008).

Solerte et al. then followed this in 2008 with published results from a study that investigated forty-one elderly subjects experiencing sarcopenia with an open-label, crossover study investigating oral amino acid supplements over a period of eighteen months. Results showed efficacy in terms of a significant increase in BMI at 16 months post treatment. No toxicity or safety concerns were detected (Solerte et al., 2008).

Efficacy and safety within a cancer cachexia population was shown in a single-arm, open-label study that investigated the use of 4g of amino acids (AMINOTROFIC) b.d.s. for a period of eight weeks. Efficacy was shown in terms of a significant increase in grip strength and a decrease in Reactive Oxygen Species (ROS) and increase in albumin levels, along with a trend in decreasing C-Reactive Protein (CRP) and increasing leptin levels. Due to the non-significant increase in weight and LBM it was concluded that amino acid supplementation should be part of a multi-targeted combination approach. No toxicity and safety concerns were noted (Madeddu et al., 2010).

In 2011, Deutz et al. published results from a double-blind, randomised-controlled, study investigating a medical food containing 10% leucine in advanced cancer patients (Deutz et al., 2011). Patients were randomised to either the experimental group who ingested 40g of protein enriched with 10% free leucine, or the control groups who ingested 24g casein protein. This study contained no resistance exercise element. It can be concluded from this study that although the

cancer patients were not cachectic, it was possible to overcome anabolic resistance with a specially formulated nutritional supplement by stimulating an approximately 40% increase in Fractional Synthesis Rate (FSR). No toxicity or safety concerns noted (Deutz et al., 2011).

In summary, the above studies have shown increases in muscle protein synthesis to be approximately 50% in physiological hyper-insulinemia, 100% after resistance exercise, 150% with amino acid availability, and >200% with amino acid availability post resistance exercise. Along with increases of up to 400% with amino acid and carbohydrate availability, elevated insulin concentrations and resistance exercise (Rasmussen et al., 2000). The ingestion of the EAA leucine 41% resulted in both an improved muscle protein balance and muscle protein FSR in the elderly, when compared to leucine 26%, highlighting that the quantity of EAA and the composition is important when considering elderly patients (Katsanos et al., 2006). All the above clinical studies have shown that either amino acid supplementation or exercise as single agents or in combination can have different levels of efficacy. This was shown in both young and elderly healthy adults, adults with CHF, sarcopenia and cancer. Safety data has been gained from short term to longer-term studies between 1 to 16 months' exposure of amino acids, all with no major toxicity and/or safety concerns.

After reviewing oral essential amino acid composition studies as discussed above with doses ranging between 6.7g and 40g, it was decided to use the amino acid composition used within the studies of Fujita et al., (Fujita et al., 2007) and Dreyer et al., (Dreyer et al., 2008).

The efficacy and safety of a multi-targeted approach to address a multifactorial syndrome has been proven within the open-label study by Mantovani et al., in 2006 and randomised study in 2010 (Mantovani et al., 2006; Mantovani, Macciò, Madeddu, Serpe, Massa, et al., 2010). It was decided to utilise the regimen of combined EPA and COX-2 (Arm A, best supportive care) versus EPA and COX-2, plus PRT two sessions per week, followed by essential amino acids high in leucine (Arm B, experimental) within the ACCeRT study (Auckland's Cancer Cachexia evaluating Resistance Training).

4.2 Placebo arm

It must be acknowledged that there may be a placebo effect within cancer cachexia studies. As per Table 1, placebo-controlled studies have shown trends supporting a non-significant difference between arms. These include the cannabinoid study (Strasser et al., 2006) and the pentoxifylline study (Goldberg et al., 1995). The cannabinoid study showed a non-significant difference in appetite, QOL, mood and nausea in all groups. It must be noted that approximately 50% of

participants within all groups were permitted to continue to receive chemotherapy during the six week study period, along with a mixed cancer population, and this could have affected the results (Strasser et al., 2006). Interestingly, the pentoxifylline study showed higher rates of improved taste of food and participant rated that the medication helped within the placebo group. Again, 50% of participants within all groups were permitted to receive chemotherapy (Goldberg et al., 1995).

A placebo arm was not included because it was not considered ethical by the ACCeRT study team. As per Table 1, a number of interventions have shown benefit when compared to placebo within cancer cachexia populations receiving chemotherapy e.g. etanercept study by Jatoi et al. (Jatoi et al., 2007), and late cachexia population who did not receive concurrent anti-cancer treatment e.g. thalidomide study by Gordon et al. (Gordon et al., 2005). This aspect of a non-placebo controlled study design was also acknowledged and supported by the group who recently published the phase III 5 arm study (Mantovani, Macciò, Madeddu, Serpe, Massa, et al., 2010).

4.3 Single cancer population

It was decided to restrict the inclusion criteria to a single cancer population rather than the high number of previously published data in mixed cancer populations. This decision was based on the high incidence of cancer cachexia seen within different cancer populations. With high incidence in gastric, NSCLC and pancreatic cancer (Dewys et al., 1980; Tisdale, 2009). Six studies from Table 1 restricted inclusion criteria to a single cancer population, while one targeted two populations, all in the above mentioned high incidence cancer populations. NSCLC was chosen as the candidate has a special interest in this population. In addition, a degree of cachexia may have resulted from possible bowel obstruction and/or tumour compression within both the gastric and pancreatic populations.

4.4 End-stage/refractory cachexia population

It was decided to restrict the inclusion criteria to participants who were not undergoing active anti-cancer treatment but at the end-stage of their disease trajectory. The ACCeRT study was planned to be part of a program investigating the use of exercise within a multi-targeted approach in a number of NSCLC populations. These being concurrently and post first-line chemotherapy treatments, concurrently with targeted therapy e.g. erlotinib, gefitinib and ALK inhibitors, and end-stage cancer. It was decided by the study team to begin with the end-stage population study

first. If the regimen showed acceptability and safety within this population, this would support its investigation in early cachexia. It must be noted that this was against current international consensus, who believe that end-stage/refractory cachexia participants would not benefit from any interventions and therefore considered not appropriate to recruit to cancer cachexia studies (Fearon et al., 2011). As per Table 1, nine of the included studies were in the late cachexia populations. Results showed efficacy with significant differences in bone-free arm muscle mass (Gordon et al., 2005), physical functioning and weight (GI group) (Fearon et al., 2006), decreased CRP levels, increased appetite, mid upper arm circumference, body weight (McMillan et al., 1999), and difference in weight, hand-grip and decreased CRP levels (Cerchietti et al., 2007). As stated above, completion rates were similar to cachexia studies receiving anti-cancer treatments. This decision was also supported by current published literature in palliative care. This included an open-label study of twice-weekly exercise in palliative patients for six weeks. A total of 36% participants continued to receive ongoing anti-cancer treatments. Results showed efficacy and safety within this end-stage cancer population (Oldervoll et al., 2006). This was followed by a randomised controlled study investigating twice weekly exercise in palliative patients for eight weeks, however anti-cancer treatments continued for all participants within this study (Oldervoll et al., 2011). A recent systematic review and meta-analysis of 66 high quality studies supported emerging evidence and many benefits of exercise at various time points within the cancer journey, but as yet nothing in end-stage cancer patients (Speck, Courneya, Mâsse, Duval, & Schmitz, 2010). A recent systematic review investigated the views of palliative care patients and their relatives regarding participating within a palliative care research study (White & Hardy, 2010). Eight studies were identified, common themes identified include a desire to retain autonomy, altruism, and the potential for personal gain by participating in a research study, and patients were generally happy to participate and did want research studies to be offered (Kendall et al., 2007; Terry, Olson, Ravenscroft, Wilss, & Boulton-Lewis, 2006; White, Hardy, Gilshenan, Charles, & Pinkerton, 2008). All the above studies and factors assisted with the decision to proceed with a study in this population. Results from this study, including completion/attrition rates would assist in a future phase II study.

4.5 Study period

It was decided to use the study period of 20 weeks. This time period was based on the average of two previous studies by Mantovani et al., published in 2010 (Mantovani, Macciò, Madeddu, Serpe, Antoni, et al., 2010; Mantovani, Macciò, Madeddu, Serpe, Massa, et al., 2010), with study

periods of sixteen weeks, with high levels of completion (100% within both studies) and a number of studies over twenty-four weeks including one in late cachexia by Fearon et al., in 2006 (Fearon et al., 2006).

4.6 Cachexia definition for study entry

Cachexia definitions by Evans et al., (Evans et al., 2008) and Fearon et al., (Fearon et al., 2011) were reviewed. It was decided to utilise the definition by Evans et al., for a number of reasons. Firstly, the same definition could be utilised as an inclusion criteria for all the planned ACCeRT program of studies, allowing the weight loss to be over a period of up to twelve months. Secondly, it was easier to regularly monitor potential participants by assessing CRP levels, anaemia and serum albumin (Evans et al., 2008). Definition by Fearon et al., would require regular assessing skeletal muscle depletion either by mid upper-arm muscle area by anthropometry, appendicular skeletal muscle index by DEXA, lumbar skeletal muscle index by CT imaging, or whole body FFM by BIA (Fearon et al., 2011).

4.7 Study power

This was a feasibility study that investigated the acceptability and safety of a multi-targeted approach of supportive care in the above population, and was not powered to determine differences between groups. Therefore, the results are restricted to trends within both groups. Participants enrolled onto the ACCeRT research study were not stratified by any baseline factors.

4.8 Body composition

4.8.1 BIA

BIA for body composition was utilised within eight of the above reviewed studies as per Table 1. BIA form of body composition analysis was chosen due to the following four factors. Firstly, the study was originally designed to be carried out within a hospice setting, and required a portable analyser. Secondly, the nature of the study recruited participants at the end-stage of their disease trajectory and asking them to attend a central location, which had access to a DEXA machine, was considered an unnecessary burden. Thirdly, limited financial support for the study restricted the use of DEXA scan acquisition and analysis. Finally, that the study would be acquiring total quadriceps muscle volume data from a 3T MRI scanner to support BIA data.

BIA was utilised within the ACCeRT study for the reasons stated above. BIA has been demonstrated to show good short-term precision in terms of test-retest reliability in patients with advanced cancer and was close to 1% for repeated measures (Trutschnigg et al., 2008). Precision

error for FM and FFM from BIA has been found to be less than 2%, which has been shown to be similar to DEXA. BIA utilises predication equations that include age, gender, height and mass to convert the resistance to total body water and FFM values (Trutschnigg et al., 2008).

It must be noted that Multifrequency BIA (MF-BIA) and SF-BIA provide accurate body composition assessments with narrow limits of agreement and little bias. MF-BIA correlates closely with DEXA and provides a superior assessment when compared to SF-BIA. This was seen while investigating weight loss in overweight women (Thomson, Brinkworth, Buckley, Noakes, & Clifton, 2007). Due to restricted funding and the use of 3T MRI data, a SF-BIA machine was purchased and utilised within the study.

4.8.2 MRI

It was decided to improve body composition analysis in terms of 3T MRI (Magnetic Resonance Imaging) scanner data. This decision was based on the recent knowledge gained around the loss of skeletal muscle mass being the main component of cancer cachexia (Muscaritoli et al., 2006). This has led to the need to measure and quantify skeletal muscle, in terms of stabilisation or increase/loss in both skeletal muscle mass/volume and strength. Muscle strength and function can be inferred from the analysis of muscle volume, and measuring this over time is important in assessing changes during ageing, training and disease processes. The current 'gold standard' of measuring muscle volume involves utilising contiguous transverse MRI scans (Hudelmaier et al., 2010; Morse, Degens, & Jones, 2007). Additional benefits of MRI include the analysis of both muscle volume and cross-sectional area (CSA), along with morphologic features and distribution. MRI can characterise the loss of muscle quality, e.g. intra-muscular fat infiltration, fibrous connective tissue and oedema (Boutin, Yao, Canter, & Lenchik, 2015; Gray et al., 2011; Weber et al., 2009). This is becoming important as loss of mobility has been shown to be related to muscle strength and increased muscle lipid content, which can be quantified by both MRI and magnetic resonance spectroscopy (Boutin et al., 2015; Yip et al., 2015). Efficacy of utilising MRI data in an exercise study was shown in the placebo-controlled, double-blind, randomised study that investigated the benefit of either placebo, acetaminophen or ibuprofen in older healthy adults undergoing resistance training. Muscle volume of the knee extensor (quadriceps femoris) was measured by 1.5T MRI scanner. Manual planimetry utilising NIH image software was undertaken. The cross sectional area (cm^2) of the muscles of interest in each slice thickness was then multiplied to give muscle volume (cm^3), (Trappe, Lindquist, & Carrithers, 2001). At the time of designing the study, no other cancer cachexia studies had utilised MRI data.

It was decided to utilise images gained from a 3T MRI scanner due to the clinical benefits compared to a 1.5T scanner. The 3T scanner has a stronger field strength that results in the increased signal-to-noise ratio, which from a physics basis is twofold. Images are clearer and allow super high resolution studies (1024 x 1024) to be undertaken within a quicker time frame (Chao, 2007; Wong et al., 2009). The improved signal allows higher resolution and to cut thinner sections e.g. 2mm thick, and musculoskeletal studies have improved fat saturation and higher resolution (Chao, 2007). It was concluded that images from a 3T scanner provided improved diagnostic confidence and improved visualisation of anatomical structures by four independent radiologists from a study comparing images acquired from a 1.5T and 3T scanner images of the knee (Wong et al., 2009). A T1 weighted data was utilised in the analysis as this was considered the 'gold-standard' for morphological muscle measurements. Muscle strength and function can be represented by the analysis of muscle volume (Hudelmaier et al., 2010). The ACCeRT study is the first to utilise data acquired by a 3T MRI scanner within a cancer cachectic study.

4.9 Hand-grip strength

Four of the above reviewed studies utilised hand-grip strength as a form of physical functioning assessment (Cerchietti et al., 2007; Gordon et al., 2005; Lundholm et al., 1994; Mantovani, Macciò, Madeddu, Serpe, Massa, et al., 2010).

It was decided to use HGS as a measure of upper body strength, due to its simplicity of use, portability, low cost and minimal training. HGS has been associated with the prediction of mortality and morbidity, and has been shown to be highly reliable and valid within the advanced cancer population (Leong et al., 2016; Trutschnigg et al., 2008).

4.10 Leg strength

Leg strength testing has been utilised within various exercise studies within cancer populations (Adamsen et al., 2009; Battaglini et al., 2007; Baumann, Kraut, Schule, Bloch, & Fauser, 2009). At the time of designing the study, no current cancer cachexia studies were utilising leg strength analysis. It must be noted that there was concern around strength testing within patients who had bone metastasis. Leg grip strength was originally assessed by back/leg dynamometry if participants were bone metastasis free. This assessment was then changed to an isometric customised leg extension rig due to both participants and study team preference, along with its permitted use within participants with bone metastasis.

4.11 Biomarkers

Proinflammatory cytokines and CRP levels were assessed with the ACCeRT study as markers of inflammation, along with the regular assessment of nutrition by albumin levels.

4.12 PRO

4.12.1 FAACT

Five of the above reviewed studies utilised FAACT (Jatoi et al., 2007; Jatoi et al., 2004; Jatoi et al., 2002; Strasser et al., 2006; Wiedenmann et al., 2008). It was decided to utilise the FAACT, as it is a validated symptom-specific measure that investigates the Functional Assessment of Anorexia/Cachexia Treatment in cancer participants.

4.12.2 Fatigue/MFSI-SF

Fatigue was measured by either VAS, (Lundholm et al., 1994), MFSI-SF (Mantovani, Macciò, Madeddu, Serpe, Massa, et al., 2010) and Schwartz Fatigue Index (Berk et al., 2008). It was decided to use MFSI-SF as a validated symptom-specific measure that investigated fatigue over a period of the last 7 days. It has been used within a number of other non-randomised and open-label cancer cachexia studies and would allow comparison of results.

4.12.3 WHOQOL-BREF

WHOQOL-BREF has not been utilised within cancer cachexia studies. It was included within this study as an overall QOL questionnaire, and to compare detection of the subscales and symptoms including physical health, psychological health, social relationships and environment. It has the advantage of being translated into a number of languages.

4.13 Study summary

In summary, the ACCeRT study was designed as a feasibility study to determine the acceptability, trends in efficacy and the safety of a multi-targeted approach of supportive care in cachectic NSCLC participants. Participants were randomised in a 1:2 ratio to either EPA and COX-2 inhibitor (best supportive care, n=7) or EPA, COX-2 inhibitor, and PRT (2 sessions per week) plus EAA 20g high in leucine commencing 1 hour post exercise (treatment group, n=14) for the study period of twenty weeks. This combination was chosen to target and decrease the proinflammatory cytokines by using a cyclooxygenase-2 inhibitor (celecoxib) and EPA. The study aimed to increase muscle anabolism with PRT and EAA high in leucine post exercise, with

the overall goal of stabilising the effect of muscle catabolism/anabolism to a net gain in muscle mass.

The study planned to enroll twenty-one histologically diagnosed NSCLC participants who fulfilled the 'cachectic definition' as per Evans et al., (Evans et al., 2008) and who had received at least one line of either 'standard' chemotherapy or targeted therapy and had no further treatment options. All study visits were carried out at University of Auckland, Clinical Research Centre (UoA, CRC) with the option of attending the resistance training sessions at one of three locations, these being North Shore Hospice, Totara South Auckland Hospice or UoA, CRC. All exercise sessions were to be carried out under the supervision of an exercise physiologist. Primary endpoint of the acceptability of receiving EPA, COX-2 compared with the acceptability of receiving EPA, COX-2 and participating in two PRT sessions per week and 20g of EAA post exercise. Secondary outcomes included body composition by BIA, total volume of quadriceps muscle analysed by 3T MRI scanner, biomarkers of IL-6, Interleukin-1 beta (IL-1β), TNF-α, CRP and albumin, hand-grip and isometric leg strength analysis, compliance of EPA, COX-2, PRT sessions and EAA. Overall, cachexia symptoms were assessed by FAACT (Functional Assessment of Anorexia Cachexia Treatment), fatigue levels by MSFI-SF (Multidimensional Fatigue Symptom Inventory-Short Form) and overall quality of life by the WHOQOL-BREF (World Health Organization Quality of Life-Brief) questionnaires, GPS, KS and ECOG-PS, and serious adverse events. Along with the generation of a cachexia biobank of serum, plasma and urine samples for future research.

Results gained would be used to calculate the power and number of participants required, taking into account attrition rates for a future phase II study.

4.14 Guest participant

The ACCeRT study was utilising a number of new techniques, new members of the research team, along with a new research location. It was decided to invite a participant onto the study as a 'guest' to identify any potential scheduling and technique issues prior to recruiting to the main study. The guest participant was invited in April 2012, and completed the twenty week study, and a further twelve weeks under compassionate use, thereby supporting the chosen population and study period.

5 Review of published cachexia clinical studies while ACCeRT was in progress

Ongoing literature search was conducted on PubMed (includes MEDLINE), Embase (through OvidSP) Cochrane Central Register of Controlled Trials (CENTRAL), and Clinicialtrials.gov website over a time frame ranging from each database set-up date to December 2016. For the purpose of thesis, only randomised controlled studies, and study period of more than four weeks are included in Table 2.

During the recruitment period of the ACCeRT study, no agents or interventions were approved for the treatment of cancer cachexia, or cancer-associated muscle wasting. All the following studies either recruited from a different cancer population, or if NSCLC were not from a refractory cachexia i.e. omission of concomitant anti-cancer treatment during the study period. Therefore, the ACCeRT study was deemed still relevant and the results were still required in this population.

Figure 2 Flow diagram of reviewed human cancer cachexia studies during and post ACCeRT

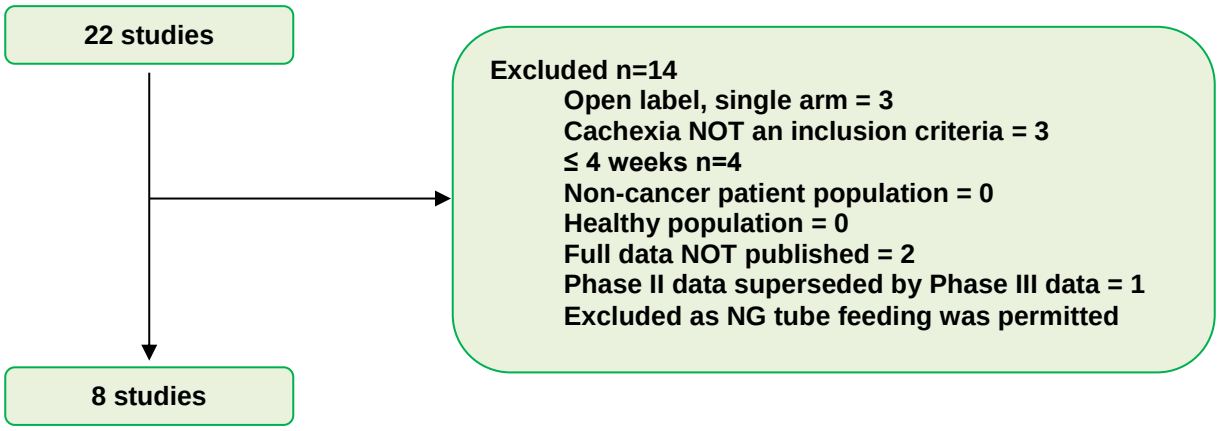


Table 2 Reviewed randomised studies during and post ACCeRT study

Patients				Study design			Main results		
Author, year	**Total No of pts**	**Patients characteristics**	**Criterion of cachexia, probable cachexia stage**	**Interventions**	**Duration of intervention (weeks)**	**Outcomes**	**Other**	**Side effects**	**Effect on weight**
Wen 2013 (Wen et al., 2013)	102	Advanced cancer. Chemotherapy permitted.	≥5% of pre-illness weight or ideal body weight over previous 3 months. *Cachexia.*	**Randomised, open-label** 1. MA 160 mg BDS + thalidomide 50 mg BDS (Trial group). 2. MA 160 mg BDS (Control group).	8	1. X 2. X 3. X 4. X 5. X	Attrition – completed 8 weeks (91%); Trial, 90% Control, 92% Significant change in all primary and secondary endpoints with trial group. Decrease in overall fatigue MFSI-SF score (p=0.01). Increase in EORTC QLQ-C30 score (p=0.02). Significant increase in VAS appetite (p=0.02) within the control group. Between group analysis showed significant difference in all primary and secondary endpoints except VAS appetite in favour of trial group.	Well tolerated. Grade 3-4 SAEs; Trial, 2 patients with somnolence. Control, 1 patient with oedema and 1 patient thromboembolism.	Significant increase in body weight within trial group from baseline to 12 weeks (p<0.01). Significant increase in body weight within control group from baseline to 12 weeks (p=0.02). Significant difference in body weight in favour of trial group (p=0.05); Trial, -2.27 ± 6.62 Control, -1.19 ± 2.57
Mehrzad 2016 (Mehrzad, Afshar, & Akbari, 2016)	70	Advanced cancer (except brain). Chemotherapy and RT permitted. Life expectancy ≥ 4 months.	Weight loss ≥ 5% of pre-illness or ideal body weight over previous 2 months. *Cachexia.*	**Randomised, double-blind, placebo-controlled** 1. Pentoxifylline 400 mg TDS (Case). 2. Placebo (Control).	8	1. X 2. 3. 4. 5. X	Attrition –completing 8 weeks (92%); Case, 94% Control, 89% NS difference in arm circumference within both groups. Significant difference in higher QOL scores in favour of case, at 4 weeks only (p=0.029); Case, 2129 ± 536 Control, 1850 ± 459.9	Adverse events in case group only; Tachycardia, 2 Nausea & vomiting, 1.	NS difference in body weight within both groups.

Temel 2016 ROMANA 1 and 2 (Temel et al., 2016)	484 (1) 323 (2)	NSCLC Chemotherapy and RT permitted.	Weight loss ≥ 5% over preceding 6 months. *Cachexia.*	**Randomised, double-blind, placebo-controlled** 2: 1 ratio. 1. Anamorelin 100 mg OD. 2. Placebo	12	1. X 2. 3. X 4. X 5. X	<u>ROMANA 1 Attrition – completed 12 weeks (74%);</u> <u>Primary efficacy;</u> Anamorelin, 88% Placebo, 88% <u>ROMANA 2 Attrition – completed 12 weeks (72%);</u> <u>Primary efficacy;</u> Anamorelin, 81% Placebo, 82% NS difference in 1 year median OS in ROMANA 1 and 2. NS difference in hand-grip strength between groups in ROMANA 1 and 2. Significant difference in FAACT-ACS scores between groups (p<0.0004) ROMANA 1 and (p<0.0016) ROMANA 2.	No treatment-related deaths. Low AE; 18 grade 3-4	LBM DEXA Significant difference in median LBM (p<0.0001) in ROMANA 1 and 2. Significant difference in LSM body weight between groups (p<0.0001) in ROMANA 1 and 2. Median LBM (kg) ROMANA 1, +0.99 ROMANA 2, +0.65
Takayama 2016 (Takayama et al., 2016)	181	Japanese NSCLC. Chemotherapy and RT permitted.	Weight loss ≥ 5% over preceding 6 months. *Cachexia.*	**Randomised, double-blind, placebo-controlled** 1:1:1 ratio. 1. Placebo. 2. Anamorelin 50 mg OD. 3. Anamorelin 100 mg OD.	12 with 2 week run-in.	1. X 2. 3. X 4. X 5. X	<u>Attrition – completed 12 weeks (64%);</u> Placebo, 70%. Anamorelin 50 mg, 64% Anamorelin 100 mg, 56% <u>Deaths;</u> Placebo, 20% Anamorelin 50 mg, 12% Anamorelin 100 mg, 11% NS difference in survival. NS difference in RECIST data. NS difference in grip strength.	<u>≥5% nausea;</u> Anamorelin 50 mg & 100 mg <u>Discontinued due to AE;</u> Placebo, 10%. Anamorelin 50 mg, 22% Anamorelin 100 mg, 24%	<u>Significant difference in LBM DEXA (kg) between 100 mg and placebo (p=0.0516);</u> Placebo, +0.55 ± 0.29 Anamorelin 50 mg, +1.15 ± 0.31 Anamorelin 100 mg, +0.85 ± 0.26 <u>Significant difference in body weight (kg) between 50 mg and placebo (p=0.0262) and 100 mg and placebo (p=0.0002);</u> Placebo, -0.93 Anamorelin 50 mg, +0.54 Anamorelin 100 mg, +1.77

Dobs 2013 (Dobs et al., 2013)	159	Cancer of NSCLC, colorectal, non-Hodgkin lymphoma, CLL or breast. Male >45 years or female, post-menopausal. Concurrent chemotherapy permitted. Life expectancy > 6 months. ECOG-PS 0-1.	BMI 35 kg/m^2 or less or, ≥2% weight loss in the previous 6 months. *Cachexia*	**Randomised, double-blind, placebo-controlled** 1:1:1 ratio. 1. Placebo. 2. Enobosarm 1 mg OD. 3. Enobosarm 3 mg OD.	16	1. X 2. 3. X 4. X 5. X	<u>Attrition – completed 16 weeks (67%);</u> Placebo, 73% Enobosarm 1 mg, 64% Enobosarm 3 mg, 63% <u>Died;</u> Placebo, 4% Enobosarm 1 mg, 8% Enobosarm 3 mg, 6% <u>Progression;</u> Placebo, 15% Enobosarm 1 mg, 9% Enobosarm 3 mg, 13% NS difference in HGS, hair growth, (female) or PSA (male) across groups. Significant increased stair climb power (watts) within Enobosarm 1 mg (p=0.0008) and Enobosarm 3 mg (p=0.0006) compared with placebo. Significant increased stair climb time (seconds) within Enobosarm 1 mg (p=0.0019) and Enobosarm 3 mg (p=0.0065) compared with placebo. Substantial clinical meaningful increase ≥10% in stair climb; Placebo, 39% Enobosarm 1 mg, 61% Enobosarm 3 mg, 61%	<u>Pneumonia;</u> Placebo, 4% Enobosarm 1 mg, 4% Enobosarm 3 mg, 6% <u>Febrile neutropenia;</u> Placebo, 6% Enobosarm 1 mg, 2% Enobosarm 3 mg, 0% No deaths were attributed to study drug.	LBM via DEXA. <u>Significant difference in median LBM (kg) (p=0.0012);</u> Enobosarm 1 mg, +1.5 (range -2.1 to +12.6). <u>Significant difference in median LBM (kg) (p=0.046);</u> Enobosarm 3 mg, +1.0 (range -4.8 to +11.5). <u>NS difference in median LBM (kg) (p=0.88);</u> Placebo, -0.02 (range -5.8 to +6.7).

Stewart Coats 2016 ACT-ONE (Stewart Coats et al., 2016)	87	Colorectal and NSCLC stage III or IV. Chemotherapy and RT permitted. ECOG-PS 0-2.	≥5% documented weight loss over 12 months. Subjective report of weight loss over 12 months and a recorded BMI <20 kg/m^2. Documented weight loss of ≥1 kg over 1 week. Prior to day 0, or 1.25 kg over 2 weeks, or 1.5 kg over 3-6 weeks and not more than BMI 25 kg/m^2. *Cachexia.*	**Randomised, double-blind, placebo-controlled** 3:2:1 ratio. 7 day placebo run-in. 1. High-dose, Espindolol 10 mg BD 2. Placebo 3. Low-dose, Espindolol 2.5 mg BD	16	1. X 2. 3. X 4. X 5. X	58 NSCLC, CRC 29. <u>≥80% compliance at week 4 mITT (77%);</u> High-dose, 71% Placebo, 81% Low-dose, 79% <u>Death;</u> High-dose, 26% Placebo, 10% Low-dose, 29% <u>NS difference in median OS (weeks);</u> High-dose, 61.0 Low-dose, 50.9 Placebo, 42.3 <u>Significant difference between high-dose/placebo (*p*=0.134) and low-dose/placebo (*p*=0.0006) in HGS mITT absolute change LSM;</u> High-dose/placebo, +2.36 Low-dose/placebo, +4.16 NS difference in Low-dose/high-dose, +1.8 NS difference in VAS, EQ-5D Index or 6MWT, SCP and SPPB. Although trend in favour of high-dose/placebo.	SAEs; High dose, 28.7% Placebo, 22.5% Low dose, 42.6%	Slope of absolute weight change over 16 weeks (DEXA). <u>Significant difference in slope of absolute weight change kg/ 4 weeks mITT (p<0.0001);</u> High-dose, +0.54 Placebo, -0.21 <u>Significant difference between high-dose and placebo (*p*=0.012) mITT median LBM (kg) at day 112;</u> High dose, +1.76 Placebo, +0.57 Low dose, +0.25 <u>Significant difference between high-dose and placebo (*p*=Not stated) mITT median weight (kg) at day 112;</u> High dose, +2.83 Placebo, -0.99 Low dose, +0.1 <u>Significant difference in slope of absolute weight change kg/ 4 weeks (DEXA) ITT (p<0.0001);</u> High-dose, +0.42 Placebo, -0.37 <u>Significant difference between high-dose and placebo (*p*=0.036) ITT median LBM (kg) at day 112;</u> Results not stated The difference in weight change between high-dose/placebo of +0.75 kg/4 weeks equals 3 kg/16-weeks. NS difference in either mITT or ITT between the high-dose and low-dose groups for the slope of weight change.

Madeddu 2012 (Madeddu et al., 2012)	60	Advanced cancer. Abnormal proinflammatory cytokines and/or CRP. Chemotherapy and hormonal therapy permitted. Life expectancy >4 months.	Weight loss ≥5% pre-illness or ideal body weight over 6 months. *Cachexia.*	**Randomised, open label, non-inferiority** Polyphenols 300 mg/d, lipoic acid 300 mg/d, carbocysteine 2.7 g/d, vitamin E 400 mg/d, vitamin A 30,000 IU/d, vitamin C 500 mg/d plus: Arm 1. L-carnitine 4 g/d and celecoxib 300 mg/d Arm 2. L-carnitine 4 g/d, celecoxib 300 mg/d, and MA 320 mg/d	16	1. X 2. 3. X 4. X 5. X	<u>Attrition – completed 16 weeks (94%);</u> Arm 1, 94% Arm 2, 93% <u>6MWT;</u> Significant difference in Arm 1 baseline to post treatment (p=0.015). Significant difference in Arm 2 baseline to post treatment (p=0.038). <u>MFSI-SF;</u> Significant difference in Arm 1 baseline to post treatment (p=0.036). Significant difference in Arm 2 baseline to post treatment (p=0.025). <u>GPS;</u> Significant difference in Arm 1 baseline to post treatment (p=0.003). Significant difference in Arm 2 baseline to post treatment (p=0.015).	Minimum toxicity. <u>Grade 3/4 Diarrhoea;</u> Arm 1, 1 Arm 2, 1 <u>Grade 1/2 epigastralgia;</u> Arm 2, 1	<u>LBM (kg) by DEXA;</u> Significant difference in Arm 1 baseline to post treatment (p=0.026). Significant difference in Arm 2 baseline to post treatment (p=0.036). <u>LBM (kg) by L3-CT;</u> Significant difference in Arm 1 baseline to post treatment (p=0.048). Significant difference in Arm 2 baseline to post treatment (p=0.041). NS difference in LBM (kg) by BIA. NS difference between Arms. <u>Body weight (kg);</u> NS difference in Arm 1 baseline to post treatment. Significant difference in Arm 2 baseline to post treatment (p=0.053).

Macciò 2012 (Macciò et al., 2012)	**104**	Gynaecological cancer. Progressive or recurrent disease after ≥ one line of chemotherapy. Restricted chemotherapy regimens permitted. Life expectancy ≥ 6 months.	Weight loss ≥5% pre-illness or ideal body weight over 3 months. *Cachexia.*	**Randomised, open label** Arm 1. L-carnitine 4 g/d, celecoxib 300 mg/d, MA 320 mg/d, lipoic acid 600 mg/d, and carbocysteine 2.7 g/d Arm 2. MA 320 mg/d	16	1. X 2. X 3. X 4. X 5. X	<u>Attrition – completed 16 weeks (87%);</u> Arm 1, 85% Arm 2, 88% <u>Death;</u> Arm 1, 11% Arm 2, 10% <u>NS difference in mOS (months);</u> Arm 1, 8 ± 4.2 Arm 2, 7.2 ± 3.4 <u>NS difference in mPFS (months);</u> Arm 1, 5.1 ± 2.1 Arm 2, 6.4 ± 3.2 Significant difference in REE (kcal/d) between Arms in favour of Arm 1. (*p*=0.046). Significant difference in EORTC QLQ-C30 between Arms in favour of Arm 1. (*p*=0.042). Significant difference in MFSI-SF between Arms in favour of Arm 1. (*p*=0.049). Significant difference in IL-6, TNF-α, and Leptin levels between Arms in favour of Arm 1. Significant difference in Arm 1 baseline to post treatment in LBM (DEXA), REE, EORTC, MFSI-SF, Appetite, IL-6, CRP, TNF-α, Leptin levels, GPS, ECOG-PS. NS difference in Arm 2 baseline to post treatment in all endpoints except for appetite and ECOG-PS.	Minimum toxicity. Arm 1 Grade 1/2 epigastralgia, 1. Arm 2, 1.	<u>LBM by DEXA;</u> Significant difference in Arm 1 baseline to post treatment (p=0.002). NS difference in Arm 2 baseline to post treatment (p=0.584). <u>Significant difference between Arms in favour of Arm 1. (*p*=0.032):</u> Arm 1, +4.65 (range +8.8 to -0.4) Arm 2, not stated

Outcomes: 1. Weight/anthropometry (e.g. kg, BMI, LBM); 2. Anorexia and food intake (e.g. appetite on VAS, Likert scale, food diary); 3. Catabolic drive (e.g. inflammation markers and tumour activity; 4. Physical performance (e.g. hand-grip and 6 min walk test); 5. Function and psychosocial effect (e.g. Karnofsky, ADL and QOL parameters).

5.1 During/post ACCeRT PICOS summary

After reviewing the literature on published human clinical studies during and post ACCeRT study, there are a number of emerging themes, as per PICOS approach (Liberati et al., 2009), within Table 2;

Populations

Participants enrolled onto reviewed cancer cachexia studies during/post ACCeRT were recruited from advanced cancer populations. Three studies chose to select a single population with one study from a double. Population numbers ranged from 60 (Macciò et al., 2012) to 323/484 in the ROMANA 1/2 studies (Temel et al., 2016). All eight of the studies permitted anti-cancer treatment and were defined as *'cachexia'*.

Interventions

These varied widely addressing either appetite stimulants with progestinal agents combined with thalidomide, or pentoxifylline, and ghrelin. Targeting muscle protein with selective androgen receptor modulators, or an anabolic/catabolic transforming agent. Along with a multi-targeted combination study.

Comparisons

Eight of the reviewed studies were randomised and are included in table 2, while three studies were single-arm.

Outcomes

The primary outcome/endpoint was the change in either body weight by scales or LBM/FFM by DEXA and L3-CT.

Study design

Eligibility criteria included participants with weight loss ranging from ≥5% of pre-illness or ideal body weight over previous three to six months, ≥2% over previous six months or BMI less than 35 mg/k^2. The study investigating espindolol included a comprehensive inclusion criteria of either ≥5% documented weight loss in the previous twelve months, or a subjective report of weight loss in the previous twelve months plus body mass index (BMI) less than 20 kg/m^2, or ongoing documented weight loss of at least 1 kg in the week prior to Day 0, or 1.25 kg in the 2 weeks prior to Day 0, or 1.5 kg in the 3 to 6 weeks prior to Day 0 provided that BMI was not more

than 25 kg/m^2 (Stewart Coats et al., 2016). Duration of the study period ranged from eight (Mehrzad et al., 2016; Wen et al., 2013) up to 16 weeks, with two studies utilising twelve weeks and four studies of sixteen weeks.

Risk of bias

All of the eight studies did publish the method for randomisation sequence generation. However, four of the studies did not state how the allocation was concealed, while three studies utilised sealed envelopes. Within the eight randomised studies, five were double-blind, placebo-controlled, and three were open-label controlled studies. Attrition was seen in the reviewed cancer cachexia studies. Completion rates of the eight studies ranged from 77% at 4 weeks, 91 to 92% at 8 weeks, 64 to 74% at 12 weeks, and 67 to 94% at 16 weeks. Completion rates were higher when compared with studies reviewed pre-ACCeRT. This was due to all of these studies permitted the use of anti-cancer treatment and therefore defined as cachexia. All studies stated outcome measures in the context of number of participants completing to various study time points.

5.2 Summary of outcomes

5.2.1 Weight/anthropometry

There has been a change in the analysis of body composition over time, with earlier studies utilising skin fold calculations, then BIA, more recently DEXA analysis, and L3-CT, which is now considered the 'gold-standard' of LBM analysis (Di Sebastiano & Mourtzakis, 2012). This trend was seen in the above reviewed studies with MUAC assessed within one study, body weight assessed by scales in six studies, body composition by BIA within two, DEXA by six, and L3-CT within one study.

5.2.2 Anorexia and food intake

Example included the use of appetite on VAS within two studies.

5.2.3 Catabolic drive

Example included the use of biomarkers within six studies.

5.2.4 Physical performance

Examples included the use of HGS within seven studies, stair-climb and power within one study, and SPBB within one. REE and 6MWT were both assessed each within one study, and ECOG-PS,

KS within three studies. Again, there was a high use of survival, which was assessed within six studies and RECIST within three studies.

5.2.5 Function and psychosocial effect

Examples included the use of MFSI SF within two studies, EORTC within three, and FAACT within two studies. FACIT was used within two studies, MDASI-J, EQ-5D and SF-36 all within one study.

The above summary shows again a range of secondary outcomes utilised within the different cancer cachexia studies. When comparing the reviewed cancer cachexia studies during and post ACCeRT recruitment the following main differences in study design and outcome measures were identified. The ACCeRT study was the only study targeting late cachexia/refractory cachexia. The study period had been reduced to eight to sixteen weeks compared to the ACCeRT study of twenty weeks. The ACCeRT study utilised BIA for body composition analysis compared with the majority of studies now utilising DEXA analysis. Similarities include the use of GPS, KS, ECOG-PS, both FAACT and MSFI-SF, along with the use of HGS as an assessment of strength analysis.

6 Study protocol/methods

The purpose of the study was to compare the acceptability of EPA, COX-2 inhibitor (Celecoxib) versus EPA, COX-2 inhibitor (Celecoxib), Progressive Resistance Training (PRT) 2 sessions per week followed by the ingestion of essential amino acids high in leucine in NSCLC cachectic participants. The secondary purpose was to assess the efficacy, safety and determination of an outcome to power a future study with the above combination in this population.

6.1 Outcomes

To undertake a feasibility study to test the acceptability, trends in efficacy and the safety of using a multi-targeted approach of supportive care (i.e. EPA, COX-2 inhibitor, PRT and essential amino acids high in leucine) in cachectic NSCLC participants.

6.1.1 Primary outcome - acceptability questionnaire

To determine the acceptability of a multi-targeted approach of supportive care in cachectic NSCLC participants.

6.1.2 Secondary outcome

- To assess the trends in efficacy of the above multi-targeted approach of supportive care in cachectic NSCLC participants.
- To assess the safety of the above multi-targeted approach of supportive care in cachectic NSCLC participants.
- To determine the most appropriate outcome measures to power a future study. This will be determined from the trend in difference of the following outcome measures at various study time points between the two groups (randomisation visit, week 1, 3, 6, 9, 12, 16 and 20).

Efficacy was assessed by comparison between the two groups using the following data.

1. Body composition by BIA; Fat-Free Mass, Weight and Fat Mass
2. 3T MRI total quadriceps muscle volume
3. Serum proinflammatory cytokine profiles
4. Hand-grip strength
5. Isometric leg strength
6. Compliance
7. FAACT questionnaire

8. MFSI-SF questionnaire
9. WHOQOL-BREF questionnaire
10. GPS, KS and ECOG-PS

Safety was assessed by comparison between the two groups using the following data.

1. Number of Serious Adverse Events (SAEs) and Adverse Events (AEs).

6.2 Study design

The study was named **ACCeRT: A**uckland's **C**ancer **C**achexia **e**valuating **R**esistance **T**raining study. ACCeRT was a prospective, randomised controlled feasibility study. Participants were randomised in a 1:2 ratio into one of the following two treatment arms: **A)** EPA and COX-2 inhibitor (international best supportive care) OR **B)** EPA, COX-2 inhibitor and PRT (2 sessions per week) plus 20g essential amino acids (EAA) high in leucine capsules over 3 days commencing 1 hour post exercise (treatment group). The study planned for 21 participants to be enrolled. All participants were to begin study treatment within 7 days from randomisation. Study treatment was administered for a maximum of 20 weeks. Study treatment was discontinued if unacceptable toxicity occurred, or consent was withdrawn. Participants who discontinued the study treatment were followed for 1 month (28 days). Following treatment completion, participants were followed until either death or the data cut-off date. No treatment arm crossover was permitted during the study. All participants completing the 20 week study, irrespective of which arm they were randomised to, were offered to continue to receive study medication/training sessions under compassionate use. Full study protocol version 2, dated August 2011, published by Rogers et al. (Rogers, MacLeod, Stewart, Bird, & Keogh, 2011).

6.2.1 Health and Disability Ethics Committee approvals.

6.2.1.1 ACCeRT Protocol version 2, dated 1st August 2011

Protocol was approved by the Northern X Regional Ethics Committee on the 2nd September 2011 (Reference NTY/11/06/064). Inclusion for all participants who had received at least a first line anti-cancer treatment e.g. surgery, chemotherapy and radiotherapy, and all study visits to be carried out at North Shore Hospice, Auckland.

6.2.1.2 ACCeRT Protocol version 3, dated 1st November 2012

Protocol was approved by the Northern X Regional Ethics Committee on the 29th November 2012 (Reference NTY/11/06/064). The protocol was amended to include all participants who had received at least a first line anti-cancer treatment e.g. surgery, chemotherapy, radiotherapy or a

targeted therapy (e.g. erlotinib or gefitinib and crizotinib), and all study visits were carried out at the Clinical Research Centre-University of Auckland, with training sessions at either North Shore Hospice, Clinical Research Centre-University of Auckland or Totara South Auckland Hospice. Measurement of leg strength was changed to an isometric customised leg extension rig with a 1kN (kilo Newton) load cell in series. Study drug adjustments were now permitted, but had to be documented.

6.3 Participants

Participants in this study all had a diagnosis of NSCLC and had received at least a first-line anti-cancer treatment e.g. surgery, chemotherapy, radiotherapy (version 2, dated August 2011) or a targeted therapy (i.e. gefitinib, erlotinib and crizotinib) (version 3, dated November 2012), and fulfilled the following cachexia definition as per Evans et al., 2008 (Evans et al., 2008).

Q1 Has lost 5% of oedema-free body weight in the previous 12 months or less

Q2 Mild >5%, Moderate >10%, Severe >15%

Q3 If no documented weight loss, is BMI of < 20 kg/m^2

Q4 At least 3 out of the following 5:

- Decreased muscle strength
- Fatigue either VO_2 max (maximal oxygen consumption) or reduced physical activity
- Anorexia
- Low fat-free mass index (low muscle mass)
- Abnormal biochemistry:

    CRP >5mg/L

    IL-6 >4pg/ml

    anaemia Hb <12g/dL

    hypoalbuminemia <3.2g/dL (32g/L)

6.3.1 Inclusion criteria

Participants were all

1. ≥18 years old.
2. histologically confirmed non-small cell carcinoma of the lung. (Histological or cytological specimens must be collected via surgical biopsy, brushing, washing or core needle aspiration of a defined lesion. Sputum cytology was not acceptable).

3. aware of their diagnosis of cancer.
4. able to give written informed consent obtained according to local guidelines.
5. fulfilled above 'cachectic definition'.
6. ECOG Performance Status 0, 1, 2 or 3 or a Karnofsky Score ≥60.
7. recently completed first-line platinum-based chemotherapy or targeted therapy.
8. laboratory values within range, as defined below, within 2 weeks of randomisation:
    - Absolute neutrophils count >2.0 x 10^9/L.
    - Platelets ≥100 x 10^9/L.
    - Haemoglobin ≥100 g/dL.
    - Serum creatinine ≤1.5 x ULN (upper limits of normal) (≤120 micro mol/L).
    - Serum bilirubin ≤1.5 x ULN (≤25 micro mol/L).
    - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5 x ULN (≤5 x ULN if liver metastases).
    - Electrolyte values (potassium, calcium, magnesium) within >1 x lower limits of normal and <1 x ULN.
9. female participants of child-bearing potential had a negative urine pregnancy test within 72 hours prior to initial dosing of study treatment.
10. life expectancy ≥20 weeks.

6.3.2 Exclusion criteria

Participants who

1. in the opinion of a doctor or nurse in the department, were unlikely to be suitable to participate by virtue of mental incapacity, severe current psychological or psychiatric disorder.
2. estimated prognosis of less than one month.
3. concurrently were using other investigational agents and participants who had received investigational agent's ≤4 weeks prior to randomisation.
4. concurrently were using other appetite stimulants e.g. Medroxyprogesterone acetate (MPA) or Megestrol acetate (MA) and 4mg o.d. (Omni Die - Latin once daily) dexamethasone or 30mg o.d. prednisolone.
5. systolic blood pressure >160 mmHG and/or diastolic > 90 mmHG.
6. pleural effusion that caused ≥CTCAE (Common Terminology Criteria for Adverse Events) grade 2 dyspnoea.

7. radiotherapy ≤2 weeks prior to randomisation. Participants had to have recovered from all radiotherapy-related toxicities.
8. a history of another primary malignancy ≤5 years with the exception of non-melanoma skin cancer or cervical cancer in situ.
9. Central Nervous System (CNS) metastases (participants having any clinical signs of CNS metastases had to have a CT or MRI of the brain performed to rule out CNS metastases in order to be eligible for study participation. Participants who had brain metastases surgically removed or irradiated with no residual disease confirmed by imaging were allowed).
10. recent haemoptysis associated with NSCLC (>1 teaspoon in a single episode within 4 weeks).
11. abnormal Baseline 12-lead ECG (Electrocardiogram).
12. concurrent severe and/or uncontrolled medical disease (i.e. uncontrolled diabetes, chronic renal failure, chronic liver disease).
13. were unwilling or unable to comply with the study protocol.

All participants were recruited from the medical oncology lung cancer clinic within Auckland District Health Board. All Auckland-based patients attend this clinic for their first specialist assessment visit, assessments before each cycle of chemotherapy treatment, and for post treatment follow up. As part of the clinic process, all patients were weighed on the same set of scales and data was recorded in their clinical notes. Each week of recruitment, the clinic was attended and all patients who were approaching 5% weight loss were identified. These patients were discussed with the medical team. If the outcome from the visit was for no further treatment/best supportive care, the ACCeRT study was discussed, and a Participant Information Sheet given and recorded in the CONSORT (Consolidated Standards of Reporting Trials) table. Please note that participants could receive a low dose of dexamethasone and ondansetron for antiemetic control during radiotherapy treatment to the spinal/gastrointestinal region.

6.4 Interventions

Participants were randomised in a 1:2 ratio into one of the following two treatment arms:

6.4.1 Arm A

2.09g EPA Ethical Nutrients Hi-Strength Liquid Fish Oil oral liquid (fruit punch flavour), 5.5mls per day, and 300mg of COX-2 inhibitor (Celecoxib) per day.

6.4.2 Arm B

2.09g EPA Ethical Nutrients Hi-Strength Liquid Fish Oil oral liquid (fruit punch flavour), 5.5mls per day, 300mg of COX-2 inhibitor (Celecoxib) per day, plus PRT (2 sessions per week) followed by 20g essential amino acids (Musashi) high in leucine capsules over 3 days commencing 1 hour post exercise.

6.4.3 Guest participant

The ACCeRT study was utilising a number of new techniques, new members of the research team, along with a new location. It was decided to invite a participant onto the study as a 'guest' to identify potential scheduling and technique problems before recruiting to the actual study. Participant 001 (guest) results are not presented within this thesis.

6.5 Sample size

Twenty-one participants were planned to be enrolled onto the study.

6.6 Participant numbering

Informed consent was obtained before performing and testing to determine a participant's eligibility. A 3-digit participant identification number uniquely identified each participant in the study. Once assigned to a participant, the participant number was not reused.

6.6.1 Randomisation/Treatment assignment

After participants completed the screening procedures at the **Screening Visit** and the principal investigator had confirmed that all inclusion/exclusion criteria had been met, all eligible participants were randomly assigned to a treatment arm.

6.6.2 Sequence generation

Simple randomisation by using a randomisation table created by computer software (i.e. computerised sequence generation).

6.6.3 Allocation concealment mechanism

Enclosed treatment assignments were serially numbered in opaque, sealed envelopes and opened sequentially after the participant's name and other details had been written on the appropriate envelope (Schulz, 1995).

6.7 Protocol Implementation

6.7.1 Visit schedule

As per following table 4 of schedule of events.

6.7.1.1 Treatment Phase Visits 2-6

Table 3 ACCeRT study treatment phase visits

Visit Number	Week Number	Days
Visit 2	Week 3	Day 21
Visit 3	Week 6	Day 42
Visit 4	Week 9	Day 63
Visit 5	Week 12	Day 84
Visit 6	Week 16	Day 112

	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Screening	Randomisation	Treatment phase						End of study visit
	- 7	0	+ 21	+ 42	+ 63	+ 84	+ 112	+ 140	Days
		Week 1	Week 3	Week 6	Week 9	Week 12	Week 16	Week 20	7 to 14 days
Informed consent	x								
Assign subject identification number	x								
Inclusion/exclusion criteria	x								
Fulfils cachexia definition		x							
Demographics	x								
Previous medical / surgical history	x								
Full Physical Exam	x					x			x
12 Lead ECG	x					x			x
Group B PRT 2 sessions per week		x	x	x	x	x	x	x	
Randomisation		x							
MRI	x	x						x	
Concomitant medications	x	x	x	x	x	x	x	x	
Clinical blood samples[a]	x	x	x	x	x	x	x	x	
Urine sample	x	x	x	x	x	x	x	x	
Hand-grip and Leg Dynamometry	x	x	x	x	x	x	x	x	
Vital signs[b]	x	x	x	x	x	x	x	x	x
Height and weight[c]	x	x	x	x	x	x	x	x	x
FAACT questionnaire	x	x	x	x	x	x	x	x	x
MFSI-SF and WHOQOL-BREF	x	x	x	x	x	x	x	x	x
Completed acceptability question						x			x
Adverse Events		x	x	x	x	x	x	x	x
[a] CRP, albumin, cytokines , routine									
[b] pulse rate, blood pressure, oxygen saturations and temp									
[c] percentage body fat, percentage lean mass by bioelectrical impedance									

Table 4 ACCeRT study schedule of events

6.8 Study Treatments

Prior to receiving study drug/intervention on each study visit, the participant must have met all of the following criteria:

1. No SAEs
2. AEs all checked by the principal investigator

6.8.1 Eicosapentaenoic Acid

2.09g EPA Ethical Nutrients Hi-Strength Liquid Fish Oil oral liquid (fruit punch flavour), 5.5mls per day.

6.8.2 COX-2 inhibitor

300mg/day of celecoxib (Pfizer, New Zealand).

6.8.3 Progressive Resistance Training

A tailored progressive resistance training (PRT) programme over 20 weeks was carried out under the supervision of trained exercise physiologists. All PRT sessions were carried out at one of the following locations nearest to the participant: North Shore Hospice, Clinical Research Centre-University of Auckland, or Totara Hospice South Auckland.

Each PRT session typically consisted of exercises that encompassed movements of the upper and lower body. PRT sessions were performed twice per week. Exercise resistance was provided in the form of rubber tubing (Theraband, USA), dumbbells, and body weight. The rubber tubing came in a variety of thicknesses, offering varying levels of elastic resistance. The tubing was colour coded from yellow (thinnest tubing) through to grey (thickest). Tube resistance could be manipulated by shortening the length of the tubing and/or by altering the amount of pre-tension (stretch) of the tube, which alters the force profile. Exercise intensity was prescribed and monitored using the Borg Rate of Perceived Exertion Scale (RPE) as per Table 5 (Borg, 1970). Prior to each exercise, the participant performed a warm-up set of the exercise movement with very light resistance. The participants started with low volume, low intensity training and progressed to moderate volume, moderate-high intensity training (Table 6). The intention was for all participants to progress to this moderate-high intensity training. Exercise physiologists were employed from another university to carry out the one-to one sessions, at any of the three locations as per participant's preference.

Table 5 Borg rating of perceived exertion

6	No exertion at all
7	
8	Very Light
9	
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Table 6 ACCeRT study progressive resistance training schedule

Phase	Exercise	Primary muscles	Loading form
1	Seated knee extension Seated knee curl Seated chest press Seated row	Quadriceps Hamstrings, calves Chest, shoulders, triceps Upper back, shoulders, biceps	Theraband Theraband Theraband Theraband
2	Seated knee extension Standing leg curl Supine chest press Bentover row	Quadriceps Hamstrings, calves Chest, shoulders, triceps Upper back, shoulders, biceps	Theraband Theraband Theraband Dumbbell
3	Sit to stand (squat) Seated knee extension Lying hip extension (bridge) Seated chest press Seated row	Quadriceps, hamstrings, buttocks Quadriceps Buttocks, hamstrings, lower back Chest, shoulders, triceps Upper back, shoulders, biceps	Body weight * Theraband Body weight * Theraband Theraband
4	Sit to stand (squat) Lying hip extension (bridge) Bentover row Supine chest press Upright row	Quadriceps, hamstrings, buttocks Buttocks, hamstrings, lower back Upper back, shoulders, biceps Chest, shoulders, triceps Shoulders, biceps	Body weight * Body weight * Dumbbell Dumbbell Dumbbell
5	Sit to stand (squat) Split squat Lying hip extension (bridge) Bentover row Supine chest press Upright row	Quadriceps, hamstrings, buttocks Quadriceps, hamstrings, buttocks Buttocks, hamstrings, lower back Upper back, shoulders, biceps Chest, shoulders, triceps Shoulders, biceps	Body weight * Body weight * Body weight * Dumbbell Dumbbell Dumbbell
***Body weight exercises, when they become too easy, can be progressed by adding dumbbells or theraband**			

6.8.4 Essential amino acids high in leucine

Originally, the study planned for 20g of the amino acid supplement (Musashi) to be taken as a bolus within a 250ml non-caffeinated, non-caloric soft drink. When delivery of the supplement arrived, it was determined that this was not possible due to its palatability and resulted in the capsulation (500mg per size '0' gelatin capsule.) by Douglas Pharmaceuticals. This resulted in 40 capsules to be ingested over 3 days commencing 1 hour post end of PRT session as per the following regimen depicted in Table 7. Within the ACCeRT study, dose modifications were permitted and capsules were taken in the afternoon and evening to allow the EPA and celecoxib to be taken mane. At each PRT session, participants received the following six doses in separate sealable bags with specific time point and participant study number on each bag:

Table 7 Essential amino acid schedule utilised within the ACCeRT study

EAA (g)	Number of capsules	Time point
4g	8	1 hour post exercise
4g	8	Evening post exercise
3g	6	Day 2 - afternoon
3g	6	Day 2 - evening
3g	6	Day 3 - afternoon
3g	6	Day 3 - evening

Table 8 Essential amino acid composition utilised within the ACCeRT study

Amino acids	g	%
Histidine	1.6	8
Isoleucine	1.6	8
Leucine	7	35
Lysine	2.4	12
Methionine	0.6	3
Phenylalanine	2.8	14
Threonine	2	10
Tryptophan		
Valine	2	10
Total	**20g**	**100%**

6.8.5 Preparation, storage and compliance

Study drug treatment cartons and drug packaging were dispensed at each study visit and used treatments were collected and recorded to verify drug accountability and compliance.

6.8.6 Study drug treatment dose adjustments

Study drug adjustments were permitted, but had to be documented.

6.9 RECIST/Tumour imaging assessment

Imaging for tumour assessment was not required as part of the study. Data was gained from any imaging each participant underwent during the study. Tumour assessment was based on RECIST criteria.

6.10 Generation of cachexia biomarker sample bank

At each study visit aliquots of serum, plasma and urine samples were stored at -80°C in a cachexia biomarker sample bank. The bank was generated with the possibility that additional biomarkers may be identified by results of external national and international research activities, during or post this study.

6.11 Safety

6.11.1 Serious Adverse Events and Adverse Events

Information about all adverse events, whether volunteered by the participant, or detected through physical examination, laboratory test or other means, were collected, recorded and followed as appropriate. All participants were followed for AEs and SAEs for 28 days following the last dose and/or last study visit. Safety was evaluated using assessment of AEs, SAEs and laboratory data. The assessment of safety was based mainly on the frequency of adverse events and on the number of abnormal laboratory values that were new or worsening based on the CTCAE grade. Other safety data was considered as appropriate. AEs and SAEs were categorised and summarised by the number of participants having an AEs/SAEs by system organ class and preferred term and treatment group, using the NIH/NCI CTCAE V3.0 (http://evs.nci.nih.gov/ftp1/CTCAE/About.html). Any other information collected (e.g. severity or relationship to study treatment) was listed and summarised by treatment group as appropriate. Data from other tests (e.g. vital signs, ECG) were listed along with any other information collected, as appropriate.

Serious Adverse Events:

To ensure participant safety, every SAE, regardless of suspected causality, occurring after the participant had provided informed consent and until 28 days after the participant had stopped study participation (defined as time of last dose of study drug taken or last visit, whichever was later) was recorded. Any SAEs experienced after this 4 week period were only reported if the investigator (Dr Rita Sasidharan) suspected a causal relationship to the study drug/intervention. The investigator (Dr Rita Sasidharan) assessed the relationship to study drug/intervention, completed the SAEs Report Form, and sent the completed, signed form by

fax within 24 hours to **Northern Y Regional Ethics Committee** (required only if a causal relationship to study drug/intervention was considered), and **Pfizer Safety New Zealand** (all SAEs irrespective of causality). For the purpose of the thesis, only SAE data is presented.

6.11.2 Concomitant medications

The participant was asked to notify the study team about any new medications he/she commenced 28 days prior to randomisation and after the start of the study drug/intervention. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered 28 days prior to randomisation and after the start of the study drug/intervention were recorded.

6.11.3 Physical examination

Physical examinations were performed according to the visit schedule. Physical examinations comprised a total body examination (general appearance, skin, neck, including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system) and carried out by a medically qualified person/member of the research team. Information about the physical examination was present in the source documentation at the study site. Significant findings that were present prior to the start of study treatment (i.e. Randomisation Visit) were included in the Relevant Medical History/Current Medical Condition Case Report Form. Significant findings made after the start of study treatment, which met the definition of an adverse event, were recorded.

6.11.4 Cardiac assessment (ECG)

All ECG evaluations were performed with the participant lying in the supine position. Participants received single ECG assessments at Screening Visit, week 12 and week 20/End of Trial visit.

6.11.5 Vital signs

Vital signs were collected according to the Visit Schedule (body temperature, blood pressure, pulse, oxygen saturations (on air).

6.11.6 Pregnancy test

For women of childbearing potential, a serum pregnancy test was performed at the Screening Visit and repeated with urine dipstick ≤72 hours prior to start of study treatment. To ensure participant safety, each pregnancy in a participant on study drug/intervention was reported to **Northern X Regional Ethics Committee**.

6.11.7 Laboratory evaluation

All clinical laboratory analyses were performed by LabPlus at Auckland City Hospital accredited laboratory according to the Visit Schedule. Laboratory data was summarised using NCI-NIH Common Terminology Criteria for Adverse Events version 3.0 grades (http://evs.nci.nih.gov/ftp1/CTCAE/About.html). Abnormal laboratory evaluations that were clinically significant (i.e. required dose interruption or delay of study drug, treatment for laboratory abnormality or treatment discontinuation) were recorded.

6.11.8 Routine safety bloods

At each study visit, a total of 20mls of blood was taken. 4mls of blood for serum analysis of CRP and albumin; 4mls of blood for plasma analysis of renal, hepatic function and electrolytes, 4mls of blood for EDTA analysis of full blood count with differential; 4mls of blood spun down and stored for serum cytokine analysis and cachexia biobank. 4mls of blood spun down and stored for plasma cachexia biobank. Samples were drawn in the following order: Serum x 2 tubes (Red) followed by Plasma x 2 tubes (Green) then EDTA x 2 tubes (Purple).

6.12 Data management

Data management was carried out to a standard of security and confidentiality consistent with Good Clinical Practice. Data was handled only by the research team and was held at the Faculty of Medical and Health Sciences, The University of Auckland.

6.12.1 Data Monitoring Committee

There was no Data Monitoring Committee for this feasibility study.

6.12.2 Database management and quality control

Data items were entered directly into the study database held at the Faculty of Medical and Health Sciences, The University of Auckland. Concomitant medications were entered into the database coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Coexistent disease and adverse events were coded using the Medical dictionary for regulatory activities (MedDRA) terminology. Laboratory samples were processed by LabPlus, Auckland City Hospital. Results were printed out from Concerto software. ECG readings were processed by the investigator, and then entered onto the database. After the database had been declared complete and accurate, it was locked for data analysis. Miss Elaine Rogers entered all data. Four random participant's data were verified by Professor Rod MacLeod (4/21 = 19%).

6.13 Statistical methods and data analysis

Statistical advice and guidance was sought from Ms Joanna Stewart – Bio-statistician, University of Auckland. Data was analysed using EXCEL 2013 software.

6.13.1 Populations for analysis

Analyses of primary and secondary efficacy outcomes were based on the Full Analysis Set (FAS) defined according to the Intent to Treat (ITT) principle. Safety analysis was performed for the safety analysis population. **FAS** consists of all participants who were randomised with a valid post-baseline assessment. Following the Intent to Treat principle, participants were analysed according to the treatment they were assigned to at randomisation. **Safety analysis population** consists of all participants who received at least one dose of any of the study drugs/intervention. Participants were analysed according to the treatment received.

6.13.2 Acceptability

Acceptability was assessed and analysed using data from the 'final acceptability questionnaire'. The questionnaire was given to participants at **week 12** and **Last** or **week 20/End of Trial visit**. Scores were analysed from six questions for participants randomised to Arm A, and nine questions for participants randomised to Arm B. High scores corresponded with high levels of acceptability. Please note that the brand name of Celebrex was utilised on the questionnaire to assist participants.

Table 9 ACCeRT acceptability questionnaire

Scoring	**5**	**4**	**3**	**2**	**1**
Both Groups Arm A and Arm B	Strongly agree	Tend to agree	Neither agree nor disagree	Tend to disagree	Strongly disagree
1 Overall did you find the taking the liquid EPA daily acceptable?	[ ]	[ ]	[ ]	[ ]	[ ]
2 Overall did you find taking the liquid EPA daily palatable?	[ ]	[ ]	[ ]	[ ]	[ ]
3 Overall did you find taking the tablets Celebrex daily acceptable?	[ ]	[ ]	[ ]	[ ]	[ ]
4 Overall did you find taking the tablets Celebrex daily palatable?	[ ]	[ ]	[ ]	[ ]	[ ]
5 Overall would you like to continue with the study medication?	[ ]	[ ]	[ ]	[ ]	[ ]
International Best Supportive Care Group only Arm A	Strongly agree	Tend to agree	Neither agree nor disagree	Tend to disagree	Strongly disagree
6 Overall would you like to commence the exercise and additional study treatment?	[ ]	[ ]	[ ]	[ ]	[ ]
Treatment Group Arm B	Strongly agree	Tend to agree	Neither agree nor disagree	Tend to disagree	Strongly disagree
7 Overall did you find participating in the resistance training programme acceptable?	[ ]	[ ]	[ ]	[ ]	[ ]
8 Overall did you find taking the essential amino acid capsules acceptable?	[ ]	[ ]	[ ]	[ ]	[ ]
9 Overall did you find taking the essential amino acid capsules palatable?	[ ]	[ ]	[ ]	[ ]	[ ]
10 Overall would you like to continue with the exercise and study medication?	[ ]	[ ]	[ ]	[ ]	[ ]

Results analysed by groups Arm A versus Arm B

mean (range) score in EPA acceptability

mean (range) score in COX-2 (Celecoxib) acceptability

mean (range) score in PRT acceptability

mean (range) score in EAA acceptability

mean (range) score in continuing PRT/medication (Arm B)

mean (range) score in commencing PRT/medication (Arm A)

Both Arm A and B; EPA acceptability, celecoxib acceptability, continue with medication,

Arm A only; commence exercise and medication.

Arm B only; PRT acceptability, EAA acceptability, continue with exercise and medication.

6.13.3 Body composition by Bioelectrical Impedance Analysis

Participants' body composition was performed and analysed at all study visits. Body composition was analysed by an 8-electrode BIA (Tanita BC-418 Segmental Body Composition Analyzer, Tanita). Results were gained in the 'Standard Male' or 'Standard Female' mode, set to kilograms (kg), and height was entered in centimetres (cm). Full printouts comprised of the following: **Height** (cm), **Weight** (kg), **BMI** with weight (kg) divided by height (m^2), **Basal Metabolic Rate (BMR)** total energy expended by the body to maintain normal function at rest for circulation and respiration, **Fat%:** The percentage of total body weight in the body that is fat. **Fat Mass:** Total weight of fat mass (in kg in the body). **Fat Free Mass** is comprised of muscle, bone, tissue, water, and all other fat free mass in the body. **Total Body Water** (**TBW)** is the amount of water (expressed as kg) retained in the body. TBW comprises between 50%-70% of total body weight. Generally, men tend to have higher water weight than women due to a greater amount of muscle. **Impedance:** Impedance reflects the body's inherent resistance to an electrical current. Muscle acts as a conductor of the electrical current, adipose tissue acts as a resistor. **Segmental analysis: Predicted Muscle Mass (PMS)** means bone-free lean tissue mass (LTM)

- Right Leg
- Left leg
- Right arm
- Left arm
- Trunk

Results analysed by groups Arm A versus Arm B

mean (range) change and percentage change from baseline to week 12 in Fat Free Mass (kg)

mean (range) change and percentage change from baseline to week 20 in Fat Free Mass (kg)

mean (range) change and percentage change from baseline to week 12 in Weight (kg)

mean (range) change and percentage change from baseline to week 20 in Weight (kg

mean (range) change and percentage change from baseline to week 12 in Fat Mass (kg)

mean (range) change and percentage change from baseline to week 20 in Fat Mass (kg)

6.13.4 MRI Total quadriceps muscle volume analysis

All participants attended the Centre for Advanced Magnetic Resonance Imaging (CAMRI) – The University of Auckland, at post **Screening visit/Randomisation visit** and **Last** or **week 20/End of Trial visit**.

Please note identical thigh for leg strength testing was used for the MRI scanning; right thigh analysis was preferred unless there was a contraindication.

MRI of the right/left thigh was performed as described (Weber et al., 2009). Briefly, MRI was performed in the supine position on the 3T Siemens Skyra scanner using the manufacturer's standard phased array coil for signal reception. Please note, slice thickness was set at 3mm and two acquisitions were gained with an overlap and then the two scans were then stitched together for analysis.

A T1 weighted data was utilised in the analysis as this was considered the 'gold-standard' for morphological muscle measurements. Muscle strength and function can be represented by the analysis of muscle volume (Hudelmaier et al., 2010).

Data were acquired with the following parameters: slice thickness 3mm (no gaps); acquisition matrix 512 x 512; (288 x 288 interpolated to 576), field of view 25 mm; echo time (TE) 2.46ms; repetition time (TR) 5.73ms; and flip angle 10°. Two acquisitions were obtained to improve the signal-to-noise ratio.

Total quadriceps muscle volume (mm^3) was performed utilising the 'ITK-SNAP' segmental software (Yushkevich et al., 2006). Briefly, using the Active Contour Segmentation Mode, a region of interest was centred over the anterior compartment of the thigh. The superior extent of the analysed volume was defined as the inferior aspect of the ischial tuberosity, and the inferior aspect of the volume was defined as the superior aspect of the patella. The tensor of the fascia lata and sartorius were excluded. The automatic segmentation feature of the software was then used to delineate the quadriceps muscle. Subsequently, each slice was individually analysed and refined using manual segmentation to ensure accuracy.

Thirty scans were analysed. All scans were anonymised and coded for randomisation. Both observers were 'blinded' to the identifying parameters such as the subject's name and clinical data. Observer one carried out all 30 analyses, with observer two carrying out three analyses (10%) for inter-observer rating. Observer one also carried out three analyses again 1 month later for intra-observer rating.

Results analysed by groups Arm A versus Arm B

mean (range) change from baseline to week 20/End of Trial visit total quadriceps muscle volume (mm^3)

Table 10 Definition of responses as per study by Greig et al., 2014

Moderate response	+2.1% to +4% increased change
Minor response	+0 to +2% increased change
Non-response	Any decline

6.13.5 Serum proinflammatory cytokine analysis

Participants' clinical blood samples were taken at all study visits. Serum Interleukin-1β (IL-1β), Interleukin-6 (IL-6) and Tumour Necrosis Factor-alpha (TNF-α) analysis was carried out in duplicate using the EMD Millipore's MILLIPLEX® MAP Human Cytokine/Chemokine Magnetic Bead Panel and the LUMINEX's laser based fluorescent analytical test instrumentation Luminex MAGPIX®. All samples were analysed in duplicate by the Auckland Cancer Society Research Centre, based within The University of Auckland.

Results analysed by groups Arm A versus Arm B

mean (range) change from baseline to week 12 in serum IL-6 levels (pg/ml)

mean (range) change from baseline to week 20 in serum IL-6 levels (pg/ml)

mean (range) change from baseline to week 12 in serum TNF-α levels (pg/ml)

mean (range) change from baseline to week 20 in serum TNF-α levels (pg/ml)

6.13.6 Hand-grip strength analysis

Participants' hand-grip strength (HGS) analysis was performed at all study visits. HGS was assessed by hand-grip dynamometry of the dominant hand, the highest of three attempts with a 1 minute rest between attempts utilising a Jammar® or TTM Smedlays dynamometer. Results recorded in kilograms (kg). Each participant was seated on a chair with the dominant arm placed at 90° on the armrest and both feet resting on the ground. The dominant arm was then

raised to shoulder level for each of the three maximal performances, each attempt was around 3 seconds with a 1 minute rest in-between.

Results analysed by groups Arm A versus Arm B

mean (range) change from baseline to week 12 in hand-grip strength (kg)

mean (range) change from baseline to week 20 in hand-grip strength (kg)

6.13.7 Isometric leg strength analysis

Participants' leg strength analysis was to be performed at all study visits. Leg strength was assessed by back/leg dynamometry of both legs, with the assessment repeated three times at 1 minute intervals (PE018 Back Dynamometer, Access Health) as per protocol version 2, dated 1st August 2016.

It was identified that the above back dynamometer was difficult to use by non-exercise physiologist staff and patients had commented on the unacceptability of this equipment. In addition, the safety of its use in participants with spinal bone metastases had not been previously investigated; therefore, the presence of bone metastases were an exclusion for this study assessment.

Results gained for guest (001), participant 002 are not included and 003, 004 and 005 were not tested.

Measurement of leg strength was then changed to an isometric customised leg extension rig (chair) with a 1kN (kilo Newton) load cell (Applied Measurement, Victoria, Australia) in series. Assessments were carried out by clinical exercise physiologists, repeated three times at 1-minute intervals, as per protocol version 3, dated 1st November 2012. (For participant 006 onwards).

The above testing was originally to be completed at the screening visit and Last or week 20/End of Trial visit only. From participant 016 onwards it was performed at each study visit due to the unpredictability of the population and that this could be the participant's last study visit.

Figure 3 Picture of a volunteer undergoing leg strength testing

Participants sat in the customised rig (chair) and velcro straps were placed across the pelvis/waist, thighs and chest to minimise movement from joints other than the knee. The starting knee position was set to 90° flexion, with participants crossing their arms across the chest during the testing.

Isometric force (strength) was assessed for either the right or left leg extensor (quadriceps femoris) muscle group. A comfortable padded cuff was placed around the lower leg, just above the malleolus, and attached to a chain in series with the load cell. The load cell output was amplified (RM044, Applied Measurement, Victoria, Australia) and sampled at 200 Hz (200 samples per second) by a 64-bit A–D converter (PCI-6035E, National Instruments, TX, USA) connected to a personal computer.

Maximum voluntary contraction (MVC) was assessed over a period of 10 seconds with considerable verbal encouragement by the clinical exercise physiologist. Contractions were repeated three times at 1 min intervals.

Load cell results gained initially in LabVIEW Measurement data (Labview, National Instruments, TX, USA) presented in Millivolts, kg and Newtons (N), and were converted into EXCEL software for analysis. Results were presented in Newtons with the highest of the three attempts at each study visit recorded as the MVC.

Results analysed by groups Arm A versus Arm B

mean (range) change from baseline to Last visit in isometric leg strength MVC (Newtons)

mean (range) change from baseline to week 20 in isometric leg strength MVC (Newtons)

6.13.8 Compliance

6.13.8.1 Progressive resistance training

The following data were recorded from the PRT sessions

- Attendance
- Participation
- Reason for non-attendance
- Reason for non-participation

6.13.8.2 EPA, Celecoxib and Essential Amino Acids

Study drug treatment cartons and drug packaging were dispensed at each study visit and used treatments were collected and recorded to verify drug accountability and compliance.

Results analysed by groups Arm A versus Arm B

mean percentage taken of total amount of EPA to week 12

mean percentage taken of total amount of EPA to week 20

mean percentage taken of total amount of celecoxib to week 12

mean percentage taken of total amount of celecoxib to week 20

mean percentage attendance of total PRT sessions to week 12

mean percentage attendance of total PRT sessions to week 20

mean percentage taken of total amount of EAA to week 12

mean percentage taken of total amount of EAA to week 20

Results were presented with individual participant data for EPA and celecoxib compliance, PRT attendance, PRT participation and EAA compliance for participants completing to week 12 and week 20.

6.13.9 Participant reported outcome

The FAACT, MFSI-SF and WHOQOL-BREF questionnaires were used to assess participant reported outcomes in all treatment groups. Participant reported outcomes (PRO) provide participants and physicians with valuable information about the impact of a given treatment on all facets of the participant's life. PRO measures for use in clinical studies assess symptoms, functioning, Health Related Quality Of Life (HRQOL) and QOL, or a combination of these outcomes. Questionnaires were administered at Screening Visit, Visits 1-7, and End of Trial visit. The questionnaires were administered under the following conditions: upon arrival to the clinic, before the participant had his/her evaluation visit with the treating doctor. The participant was given sufficient space and time to complete the questionnaires. The study

coordinator checked the questionnaire for completeness and encouraged the participant to complete any missing responses. The scoring of the questionnaires was handled as specified by the instrument developers. All HRQOL questionnaires were completed after checking for adverse events and change in concomitant medication and before either the physical examination by the study doctor (week 12 and week 20/End of Trial visit) or gaining the BIA data.

6.13.9.1 FAACT

FAACT is a validated symptom-specific measure that looks at the **Functional Assessment of Anorexia/Cachexia Treatment** in cancer participants. FAACT (version 4) comprised of seven questions for physical well-being, seven questions for social/family well-being, six questions for emotional well-being, seven questions for functional well-being and twelve questions for additional concerns; anorexia/cachexia. The re-validated version 4 questionnaire has been shortened from 18 items in the anorexia/cachexia subscale to 12 items (Ribaudo et al., 2000).

Administration time is usually around 10 to 15 minutes, with responses in the **last seven days**.

For all FACIT scales and symptom indices, the higher the score the better the QOL.

Handling missing items: If there are missing items, subscale scores can be prorated. This can be done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered. This can be done on the scoring guide or by using the formula below:

Prorated subscale score = [Sum of item scores] **x** [N of items in subscale] ÷ [N of items answered].

When there are missing data, prorating by subscale in this way is acceptable as long as **more than** 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc.). The total score is then calculated as the sum of the un-weighted subscale scores. The FACT scale is considered to be an acceptable indicator of patient quality of life as long as **overall item response rate** is greater than 80% (e.g., at least 22 of 27 items completed) of FACT-G (Functional Assessment of Cancer Therapy-General).

FAACT Scoring Guidelines (Version 4)

Instructions:

1. Record answers in "item response" column. If missing, mark with an X.
2. Perform reversals as indicated, and sum individual items to obtain a score.

3. Multiply the sum of the item scores by the number of items in the subscale, and then divide by the number of items answered. This produces the subscale score.

4. Add subscale scores to derive total scores (TOI, FACT-G & FAACT).

5. The higher the score, the better the QOL.

Subscale	Item Code	Reverse item?	Item response	Item Score
PHYSICAL *WELL-BEING (PWB)* *Score range:* 0-28	GP1	4	_____	=_____
	GP2	4	_____	=_____
	GP3	4	_____	=_____
	GP4	4	_____	=_____
	GP5	4	_____	=_____
	GP6	4	_____	=_____
	GP7	4	_____	=_____
	Sum individual item scores: _____			
	Multiply by 7: _____			
	Divide by number of items answered: _____ = **PWB subscale score**			
SOCIAL/FAMILY WELL-BEING (SWB) *Score range:* 0-28	GS1	0 +	_____	=_____
	GS2	0 +	_____	=_____
	GS3	0 +	_____	=_____
	GS4	0 +	_____	=_____
	GS5	0 +	_____	=_____
	GS6	0 +	_____	=_____
	GS7	0 +	_____	=_____
	Sum individual item scores: _____			
	Multiply by 7: _____			
	Divide by number of items answered: _____ **= SWB subscale score**			
EMOTIONAL WELL-BEING (EWB) *Score range:* 0-24	GE1	4 -	_____	=_____
	GE2	0 +	_____	=_____
	GE3	4 -	_____	=_____
	GE4	4 -	_____	=_____
	GE5	4 -	_____	=_____
	GE6	4 -	_____	=_____
	Sum individual item scores: _____			
	Multiply by 6: _____			
	Divide by number of items answered: _____ **= EWB subscale score**			

FUNCTIONAL WELL-BEING (FWB) *Score range:* 0-28	GF1	0	+	_____	=_____
	GF2	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____
	Sum individual item scores: **_____**				
	Multiply by 7: **_____**				
	Divide by number of items answered: **_____** = **FWB subscale score**				
ANOREXIA CACHEXIA (ACS) *Score range:* 0-48	C6	0	+		
	ACT1	0	+		
	ACT2	4	-		
	ACT3	4	-		
	ACT4	4	-		
	ACT6	4	-		
	ACT7	4	-		
	ACT9	4	-		
	O2	4	-		
	ACT10	4	-		
	ACT11	4	-		
	ACT13	0	+		
	Sum individual item scores:**_____**				
	Multiply by 12: **_____**				
	Divide by number of items answered: **_____** **= AC subscale score**				
FAACT Trial Outcome Index (TOI) *Score range:* 0-104	(**PWB** score) + (**FWB** score) + (**ACS** score) = **FAACT TOI**				
FACT-G total score *Score range:* 0-108	(**PWB** score) + (**SWB** score) + (**EWB** score) + (**FWB** score) = **FACT-G Total score**				
FAACT total score *Score range:* 0-156	(**PWB** score) + (**SWB** score) + (**EWB** score) + (**FWB** score) + (**ACS** score) = **FAACT Total score**				

Results analysed by groups Arm A versus Arm B

mean (range) change from baseline to week 12 in FAACT-ACS (48)

mean (range) change from baseline to week 20 in FAACT-ACS (48)

mean (range) change from baseline to week 12 in FAACT-PWB (28)

mean (range) change from baseline to week 20 in FAACT-PWB (28)

6.13.9.2 MFSI-SF

The **Multidimensional Fatigue Symptom Inventory- Short Form (MFSI-SF)** is a 30-item short form of the MFSI that yield scores only for the empirically derived subscales. Preliminary research suggests that it has acceptable psychometric properties and may be used as a substitute for the MFSI when time constraints and scale length are of concern (Stein, Jacobsen, Blanchard, & Thors, 2004; Stein, Martin, Hann, & Jacobsen, 1998).

Administration time is usually around 10 minutes, with responses in the **last seven days**. Higher scores indicate more fatigue.

MFSI-SF Scoring:

1) General scale = sum of items 10, 12, 14, 17, 18, and 28 (Total 24)

2) Physical scale = sum of items 2, 4, 6, 16, 19, and 26 (Total 24)

3) Emotional scale = sum of items 3, 8, 13, 21, 23, and 30 (Total 24)

4) Mental scale = sum of items 1, 11, 15, 20, 25, and 27 (Total 24)

5) Vigor scale = sum of items 5, 7, 9, 22, 24, and 29 (Total 24)

6) Total score = (General + Physical + Emotional + Mental) – Vigor (Total 96 – Total 24)

Handling missing items: Professor Paul Jacobsen recommended prorating if just one item was missing on any of the 6-item MFSI-SF subscales using the following approach.
Sum based on 5 items completed/5 = X/6. Solve for X and round to the nearest whole number to derive the score for the 6-item scale.

Results analysed by groups Arm A versus Arm B

mean (range) change from baseline to week 12 in MFSI-SF Total Score (96)

mean (range) change from baseline to week 20 in MFSI-SF Total Score (96)

6.13.9.3 WHOQOL-BREF

The WHOQOL-BREF was derived from data collected using the WHOQOL-100. It produces scores for four domains related to quality of life: physical health, psychological, social

relationships and environment. It also includes one facet on overall quality of life and general health (Skevington, Lotfy, & O'Connell, 2004; THE WHOQOL GROUP, 1998).

The WHOQOL-BREF is a self-reported questionnaire, comprising of two overall quality of life and general health questions, followed by 24 core questions, and five national questions.

Participants express how much they have experienced the items on a 5-point Likert scale ranging from:

1=very poor to 5=very good

1=very dissatisfied to 5=very satisfied

1=not at all to 5=an extreme amount

1=not at all to 5=extremely

1=never to 5=always

Administration time is usually around 10 to 15 minutes, with responses over **the last two weeks.** The questionnaire is available in English, Chinese, Czech, Farsi, Indonesian, Polish, Russian and Thai. All participants' response scores were entered onto an EXCEL spreadsheet. Three question's scores were reversed to produce the actual raw item score, Q3, Q4 and Q26. For each of the four domains, the sum of the actual raw item score through a simple algebraic summation as per Table 11 to produce the actual domain raw score.

Table 11 WHOQOL-BREF domain scoring

Domain 1 Physical Health: **Q3+Q4+Q10+Q15+Q16+Q17+Q18 = domain 1 raw score**
Domain 2 Psychological: **Q5+Q6+Q7+Q11+Q19+Q26 = domain 2 raw score**
Domain 3 Social Relationships: **Q20+Q21+Q22 = domain 3 raw score**
Domain 4 Environment: **Q8+Q9+Q12+Q13+Q14+Q23+Q24+Q25 = domain 4 raw score**

Once completed, the frequencies of each domain were checked to confirm that the scores were within the correct range as indicated below:

Domain 1 Physical Health: range 7-35

Domain 2 Psychological: range 6-30

Domain 3 Social relationships: range 3-15

Domain 4 Environment: range 8-40

Reliability: Intra-rater reliability is excellent for the total WHOQOL-BREF and its subscales, ICC range: 0.84-0.93. Inter-rater reliability is adequate to excellent for the total WHOQOL-BREF and its subscales, ICC range: 0.56-0.95. **Validity:** Correlation of the WHOQOL-BREF subscales with the Satisfaction with Well-Being Index is adequate to excellent. Psychological (Pearson's r=0.75), Physical (Pearson's r=0.63), Family/social (Pearson's r=0.45), Financial/environment (Pearson's r=0.59), Correlation of the WHOQOL-BREF subscales with the Chinese version of Quebec User Evaluation with Assistive Technology is adequate with Psychological (Pearson's r=0.344), Physical (Pearson's r=0.508), Family/social (Pearson's r=0.460) and Financial/environment (Pearson's r=0.567).

Handling missing items: Associate Professor Chris Krageloh recommended that if not more than half of the items in a particular domain were missing, i.e.

Physical = no more than 3

Psychological = no more than 3

Social = no more than 1

Environment = no more than 4

Impute the missing value with the average score of all the other items in that domain.

Results analysed by groups Arm A versus Arm B with raw item scores

mean (range) change from baseline to week 12 in WHOQOL-BREF Overall QOL Score (10)

mean (range) change from baseline to week 20 in WHOQOL-BREF Overall QOL Score (10)

mean (range) change from baseline to week 12 in WHOQOL-BREF Physical score (35)

mean (range) change from baseline to week 20 in WHOQOL-BREF Physical score (35)

6.13.10 Prognostic/performance status

6.13.10.1 Glasgow Prognostic Score

Participants' Glasgow Prognostic Score analysis was performed at all study visits. Samples for CRP and albumin were taken and analysed at LabPlus within the Auckland City Hospital. The method for albumin analysis changed from measuring albumin concentrations by dye binding with bromcresol green. This method lacks specificity towards albumin and can react with other serum proteins e.g. alpha-1 and alpha-2 globulins, resulting in the overestimation of albumin levels. With studies showing a mean bias of +1 to +5g/L when compared with the

immunochemical methods, especially at low albumin levels <30g/L (Doumas & Peters, 2009; Duly, Grimason, Grimason, Barnes, & Trinick, 2003; Pinnell & Northam, 1978). The method was changed to bromcresol purple (BCP) on the 25th August 2014. BCP is more accurate and specific for albumin. With 54% of accredited laboratories in the US utilising BCP (Doumas & Peters, 2009). Please note that the results on average would be lower by 4-5g/L with greater differences in patients with low albumin levels <30g/L.

The assessment of a patient's weight loss and performance status may be subjective. This led to the generation of a well-standardised, simple to measure prognostic score. An increased circulating concentration of the CRP has been shown to be a marker of a systemic inflammatory response and an independent prognostic factor in patients experiencing NSCLC. A new prognostic score was developed with the combination of hypoalbuminaemia. Prognostic scores and univariate survival analysis are shown as per Tables 12 and 13.

Table 12 Glasgow prognostic score from the study by Forrest et al., 2003

	Score
CRP ≤10mg L^{-1}	0
CRP >10mg L^{-1}	1
Albumin <35g L^{-1}	1
Albumin >35g L^{-1}	0

Table 13 Univariate survival analysis from the study by Forrest et al., 2003

Stage	***p*<0.05**
White cell count	***p* <0.01**
Tumour type	***p*<0.01**
CRP	***p*<0.01**
Performance status	***p*<0.001**
Albumin	***p*<0.001**
Stage and Performance status	***p*<0.006**
CRP and albumin	***p*<0.001**

Significant values in bold

Table 14 Glasgow Prognostic Score and survival from the study by Forrest et al., 2003

CRP	**Albumin**	**GPS Score**	**Survival (months)**
≤10mg L^{-1}	≥35g L^{-1}	0	17 (11.4 to 22.6)
≤10mg L^{-1}	<35g L^{-1}	1	8.9 (6.3 to 11.4)
>10mg L^{-1}	≥35g L^{-1}	1	
>10mg L^{-1}	<35g L^{-1}	2	3.9 (0.8 to 7.1)

Results showed that the systemic inflammatory response (increasing levels of CRP) combined with increased weight loss (decreasing levels of albumin) is related to outcome of survival in advanced NSCLC (Forrest, McMillan, McArdle, Angerson, & Dunlop, 2003).

The above prognostic score was then named Glasgow Prognostic Score (GPS) (Forrest, McMillan, McArdle, Angerson, & Dunlop, 2004). GPS has been shown to be a predicator of survival in NSCLC patients receiving platinum-based chemotherapy (Forrest et al., 2004) and has been validated in over 60 studies (McMillan, 2013).

GPS was then later changed to the modified Glasgow Prognostic Score (mGPS) (McMillan, Crozier, Canna, Angerson, & McArdle, 2007). The results of this study in patients with primary operable colorectal cancer were consistent with the prognostic value of the GPS previously reported in patients with advanced cancer. In those studies, more than 90% of patients with hypoalbuminaemia also had an elevated CRP concentration. In contrast, in the present study, only 70% of patients with hypoalbuminaemia also had an elevated CRP concentration. Moreover, those patients with hypoalbuminaemia alone had significantly better survival compared with those patients who had an elevated CRP concentration. Therefore, the GPS was modified such that patients without an elevated CRP concentration were assigned a score of zero regardless of the presence or absence of hypoalbuminaemia. Patients with an elevated CRP (>10mg/l) were assigned a score of 1 or 2 depending on whether or not they also had hypoalbuminaemia(<35g/L) (McMillan et al., 2007). Modified Glasgow Prognostic Score (mGPS) was scored as per Table 15:

Table 15 Modified Glasgow Prognostic Score

CRP	Albumin	mGPS Score
≤10mg L^{-1}	≥35 g L^{-1}	0
≤10mg L^{-1}	<35 g L^{-1}	0
>10mg L^{-1}	≥35 g L^{-1}	1
>10mg L^{-1}	<35 g L^{-1}	2

With 15 studies pointing to an increased GPS/mGPS being associated with increased weight and muscle loss (McMillan, 2013).

Results analysed by groups Arm A versus Arm B

mean (range) change from baseline week 12 in albumin (g/L) levels

mean (range) change from baseline to week 20 in albumin (g/L) levels

mean (range) change from baseline to week 12 in CRP (mg/L) levels

mean (range) change from baseline to week 20 in CRP (mg/L) levels

6.13.10.2 Karnofsky Score

Participants' Karnofsky Score was recorded at all study visits. The performance status was assessed according to the Karnofsky Performance Status (KS). The Karnofsky score runs from 100 to zero, where 100 is "perfect" health and zero is death (Table 16). Although the score has been described with intervals of 10, a practitioner may choose decimals if he or she feels a participant's situation holds somewhere between two marks (Schag, Heinrich, & Ganz, 1984).

Table 16 Table of Karnofsky Score

100%	normal, no complaints, no signs of disease
90%	capable of normal activity, few symptoms or signs of disease
80%	normal activity with some difficulty, some symptoms or signs
70%	caring for self, not capable of normal activity or work
60%	requiring some help, can take care of most personal requirements
50%	requires help often, requires frequent medical care
40%	disabled, requires special care and help
30%	severely disabled, hospital admission indicated but no risk of death
20%	very ill, urgently requiring admission, requires supportive measures or treatment
10%	moribund, rapidly progressive fatal disease processes
0%	death.

6.13.10.3 ECOG-PS

Participants' ECOG-PS was recorded at all study visits (Table 17). This describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.).

Table 17 Table of ECOG-PS

Grade	ECOG PERFORMANCE STATUS
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
5	Dead

6.13.11 Summary of candidate work on the study

The candidate was responsible for overall project/study management. This included the screening and recruiting potential participants, arranging for consent and all study visits. This included recording adverse events at each study visit, concomitant mediation records, and compliance, performing BIA, HGS, questionnaires, phlebotomy and processing samples to be stored at -80°C. CAMRI assisted with MRI scan acquisition and data analysis, and the candidate perfomed 10% of the analysis for interobserver data. Exercise physiologists carried out all supervised PRT sessions and the leg strength dynamometry and later the isometric leg strength analysis. The candidate carried out the cytokines analysis with the assistance of equipment from the Cancer Laboratories, The University of Auckland.

7 Results – main study

Please note, all results were entered into an EXCEL database and Professor Rod MacLeod verified total data for accuracy for four participants. Missing data was not imputed, except for the following questionnaires, FAACT, MFSI-SF and WHOQOL-BREF as per scoring manuals.

7.1 CONSORT statement

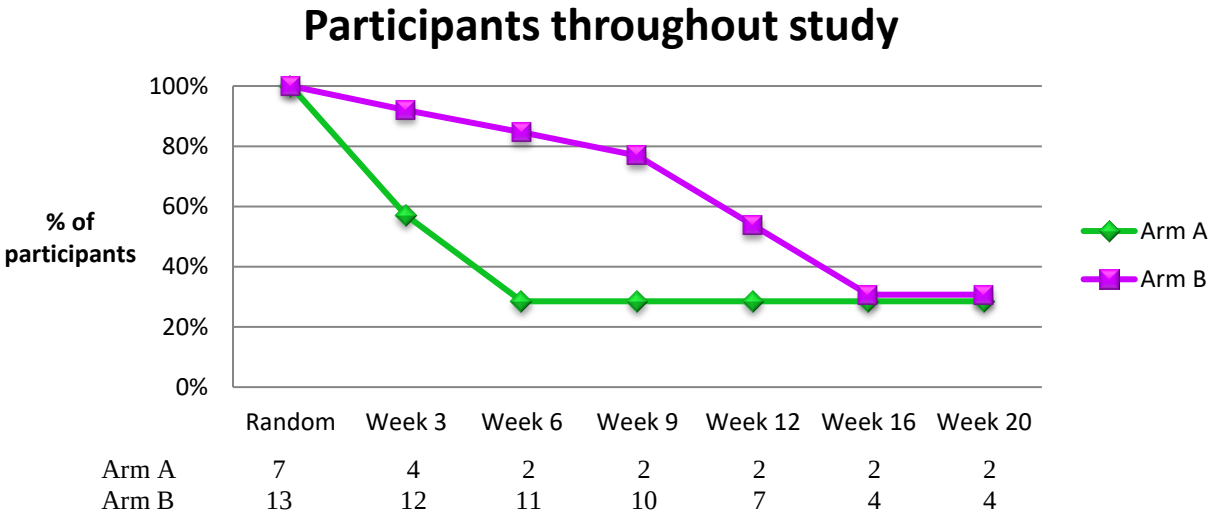
The ACCeRT clinical study was open to recruitment from April 2012 until the end of May 2015 (38 months). Sixty-nine patients were screened to be entered onto the study, with a consent rate of 30.4% (n=21/69) and randomisation rate of 28.9% (n=20/69). Participant 007 attended the consent/screening visit, but was then admitted to hospital for progression of NSCLC with infection and later died.

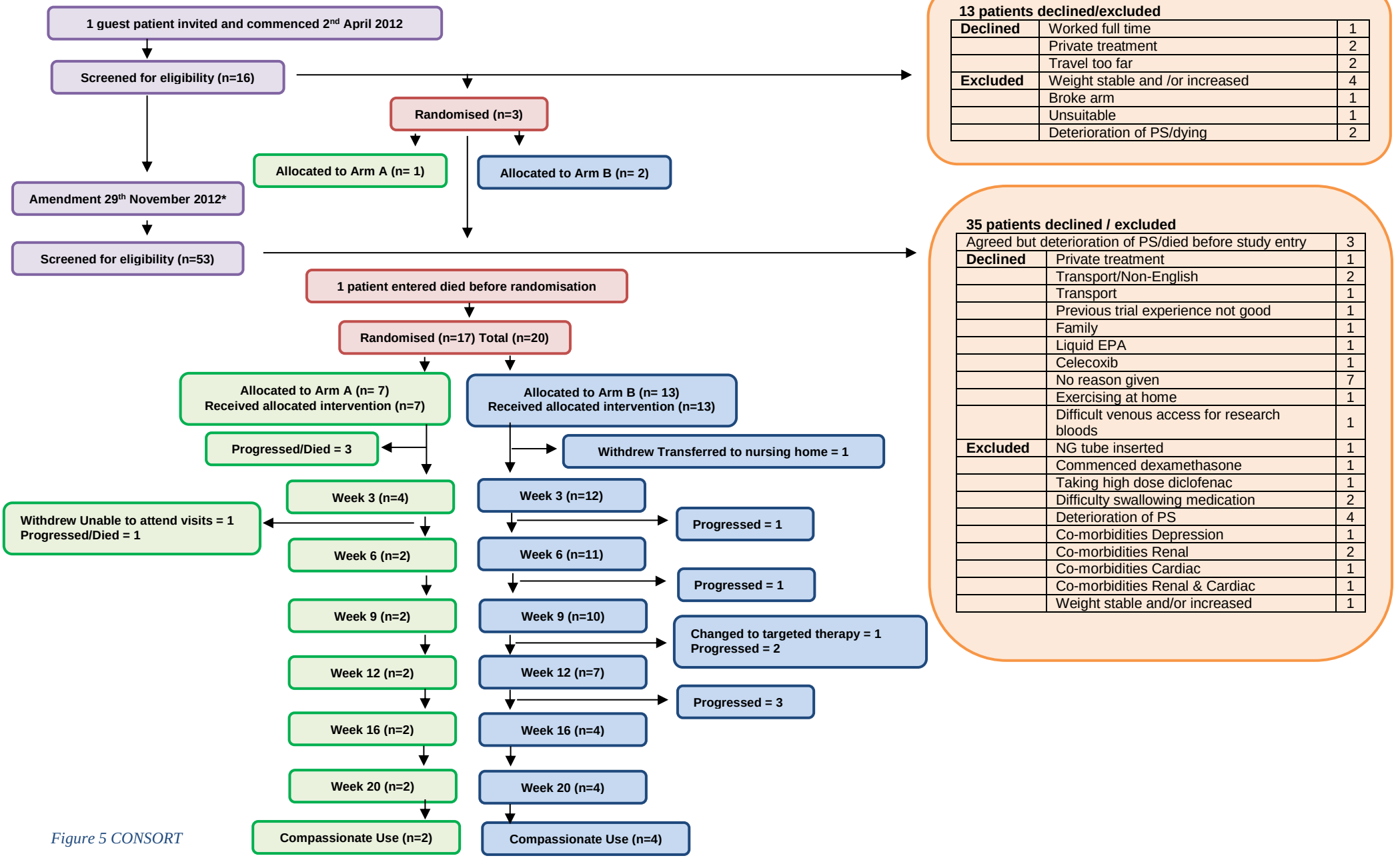
Approximately a third declined to participate or were excluded after further screening, 31.9% (n=22/69) and 33.3% (n=23/69) respectively, and a further 4.3% (n=3/69) agreed to participate but deteriorated before a screening visit could be arranged.

From the CONSORT diagram, total participants through the study dropped to 80% at week 3, 65% for week 6, 60% at week 9, 45% at week 12 and 30% both at weeks 16 and 20 (Figure 4 and 5).

All of the participants who completed the 20 week study (10% within Arm A and 20% within Arm B), agreed to continue to receive and participate with the medication and PRT sessions on a compassionate use basis. Both participants from Arm A commenced PRT sessions, with all Arm B participants continuing with their sessions.

Figure 4 Arm A and Arm B participants flow through the study





13 patients declined/excluded

Declined	Worked full time	1
	Private treatment	2
	Travel too far	2
Excluded	Weight stable and /or increased	4
	Broke arm	1
	Unsuitable	1
	Deterioration of PS/dying	2

35 patients declined / excluded

Agreed but deterioration of PS/died before study entry		3
Declined	Private treatment	1
	Transport/Non-English	2
	Transport	1
	Previous trial experience not good	1
	Family	1
	Liquid EPA	1
	Celecoxib	1
	No reason given	7
	Exercising at home	1
	Difficult venous access for research bloods	1
Excluded	NG tube inserted	1
	Commenced dexamethasone	1
	Taking high dose diclofenac	1
	Difficulty swallowing medication	2
	Deterioration of PS	4
	Co-morbidities Depression	1
	Co-morbidities Renal	2
	Co-morbidities Cardiac	1
	Co-morbidities Renal & Cardiac	1
	Weight stable and/or increased	1

Figure 5 CONSORT

*Please refer to section 6.2.1.2, protocol amendment version 3, dated 1st November 2012.

7.1 Baseline data/characteristics

Table 18 ACCeRT Baseline data/characteristics

	Total Mean (range) n=20	Arm A Mean (range) n=7	Arm B Mean (range) n=13
Age (years)	68.2 (47 to 87)	72.7 (64 to 81)	65.7 (47 to 87)
Race			
European	15	5	10
Maori	3	1	2
Asian	1	1	0
Filipino	1	0	1
Gender			
Male	13	5	8
Female	7	2	5
Body weight (kg) All	62.9 (42.2 to 89.0)	64.7 (45.6 to 89.0)	61.9 (42.2 to 79.0)
Male	67.9 (45.6 to 89.0)	67.6 (45.6 to 89.0)	68.0 (49.9 to 79.0)
Female	53.6 (42.2 to 78.6)	57.6 (52.7 to 62.4)	52.0 (42.2 to 78.6)
Weight loss at entry (%)	-8.0 (-5.0 to -20.2)	-7.1 (-5.6 to -9.8)	-8.4 (-5.0 to -20.2)
5 to 10%	16	6	10
10 to 15%	0	0	0
> 15%	1	0	1
Low BMI	3	1	2
Weight loss over days	83 (10 to 296)	117 (31 to 296)	65 (10 to 115)
Time since diagnosis (days)	603 (125 to 1328)	723 (140 to 1328)	538 (125 to 1181)
Diagnosis NSCLC			
Adenocarcinoma	14	4	10
Squamous	6	3	3
GPS			
Albumin g/L	37 (25 to 43)	37 (34 to 43)	37 (25 to 42)
CRP mg/L	72 (3 to 322)	98 (8 to 322)	60 (3 to 164)
GPS	1.1 (0 to 2)	1 (0 to 2)	1.2 (0 to 2)
Lines of previous treatment			
Total (excluding surgery)	2 (1 to 5)	1.6 (1 to 3)	2.2 (1 to 5)
Surgery	2	0	2
Targeted therapy (gefitinib/erlotinib)	11	3	8
Clinical study	4	1	3

Weight loss at study entry equals shortest time with documented date/weight from lung cancer clinic visit to date/weight at ACCeRT screening visit, which resulted in the minimum of 5% weight loss. BMI was calculated for any participant attending the clinic with a weight less than

50kg. If BMI was less than 18.5kg/m^2, participants were classed as underweight (National Institutes of Health) and BMI data was used at study entry. Please note two participants randomised to Arm A (142 days, approximately 4.5 months and 296 days, approximately 9.7 months) were on two-monthly and three-monthly follow up respectively, which resulted in a longer period (in days) between documented weight lost.

Seven patients were randomised onto Arm A, while thirteen participants were randomised onto Arm B. Baseline characteristics (Table 18) of the enrolled participants were the mean age of 68.2 years, with 13 males (65%) and 7 females (35%). Māori patients were well represented with 3 enrolled participants (15%). This reflects the current population experiencing NSCLC in New Zealand in terms of age, gender and ethnicity. With 49.5% of patients diagnosed at age 60 to 79 years, males 52.2%, females 47.8% and Māori at 19.7% of all patients registered during 2012 (Ministry of Health, 2015).

Study entry into ACCeRT was dependent on the cachexia definition by Evans et al. (Evans et al., 2008). Entry required oedema-free weight loss over the preceding 12 months or less at either 5 to 10% (mild), 10 to 15% (moderate), or greater than 15% (severe). Six and ten participants in Arm A and Arm B respectively had weight loss between 5 and 10%, with one participant experiencing severe weight loss within Arm B.

Participants with ≥5% weight loss within the preceding ninety days was high at 72.2%. Weight loss pre study entry was from documented date/weight from the lung cancer clinic visit to date/weight at ACCeRT screening visit. This involved weight data from two separate sets of scales. Participants could have documented ≥5% weight loss from data gained from the lung clinic scales, but then when attending for screening visit and weight performed on study BIA scales could result in the participant not reaching the minimum 5% threshold. An Arm A participant experienced a weight loss of 5.28% over 190 days on lung clinic scales, but then when they attended the screening visit 8 days later their weight of +0.9kg resulted in a 5% documented weight loss only if taken back to a previous weight/date of 296 days. This participant was on three to four monthly follow-up appointments, with documented weight only at these visits. All other participants had continued to lose weight as per BIA scales except for two participants within Arm B and two within Arm A who had an increase of +0.5kg, +0.2kg. +0.2kg and +0.3kg respectively. A second Arm A participant experienced 9.83% documented weight loss over 142 days due to three to four monthly follow-up appointments.

Participants within Arm B entered the study with an average reduced time from diagnosis. This suggests that this group was experiencing progression of their advanced cancer in a shorter period, with mean days from diagnosis to study entry of 538.3 versus 722.9 days

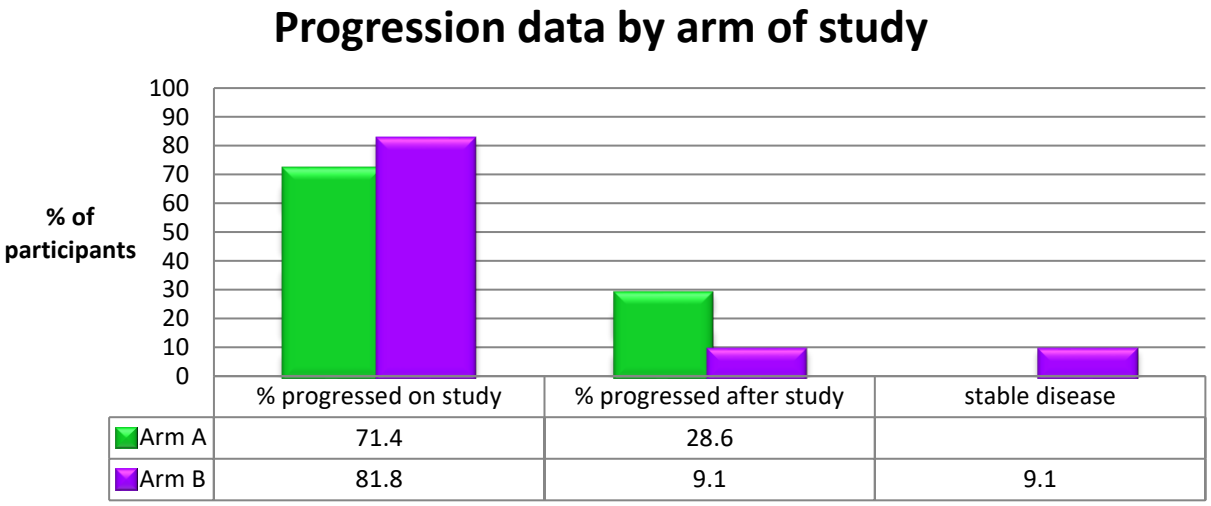
within Arm A. Participants within Arm B, also on average, had received a higher number of lines of chemotherapy treatments. This was due to higher number of participants with a histology of adenocarcinoma (n=10) versus four within Arm A, and receiving targeted therapy designed for this histological sub-group of NSCLC.

As per Table 18, mean and range of baseline outcomes was similar in both groups, except for the following. Participants randomised onto Arm B had a lower weight loss of -1.35%, lower FFM of -2.3kg, body weight of -1.8kg and MRI value of -35cm^3. Along with an increased level of CRP of +29.9mg/L, indicating a higher level of inflammation. Although this higher baseline level of CRP within Arm B, the mean and range of GPS was similar in both groups. Participants randomised onto Arm A had a lower mean HGS with a difference of -2.9kg.

In summary, all participants had demonstrated weight loss, and activation of the proinflammatory cytokines and similar range of QOL, cachexia symptoms and physical scores.

7.1.1 RECIST/tumour imaging assessment

Figure 6 ACCeRT participant progression data



As per above Figure 6 above, five (71.4%) and two participants (28.6%) had radiology imaging proving disease progression while on study and shortly post-study respectively within Arm A, giving an overall progression rate of 100%. Nine (81.8%) and one participant (9.1%) progressed while on study and shortly post-study respectively within Arm B, giving an overall progression rate of 90.9%. This data suggests that the population under testing was still experiencing progression of their end-stage disease and was in fact within the refractory cachexia period.

7.1.2 Numbers analysed

Full analysis set (FAS) consists of all participants who were randomised with a valid post-baseline assessment. Following the Intent to Treat principle, participants were analysed according to the treatment they were assigned to at randomisation. **Safety analysis population** consists of all participants who received at least one dose of any of the study drugs/intervention. Participants were analysed according to the treatment received.

Table 19 ACCeRT full analysis set and safety analysis population

Full analysis set		Safety analysis population	
Arm A	**Arm B**	**Arm A**	**Arm B**
4	12	7	13

Table 20 Number of participants data for each study assessment

	Total	Arm A	Arm B
1^0 objective			
Acceptability questionnaire	15	3	12
2^0 objectives – minimum of week 3 data			
LBM	16	4	12
MRI Total volume of quadriceps Baseline	19	7	12
MRI Total volume of quadriceps Pre/post	10	2	8
Proinflammatory cytokines	16	4	12
Hand-grip strength	16	4	12
Isometric leg strength (PE018)	1	0	1
Isometric leg strength (Load cell)	10	2	8
Participant Reported Outcome			
FAACT	15	3	12
MFSI-SF	15	3	12
WHOQOL-BREF	16	4	12
GPS/KS/ECOG-PS	16	4	12

Table 21 Arm A participants receiving radiotherapy on study

Individual participant*	Week 2	8 Gy	1#	Right rib

* participant did not complete to week 12

Table 22 Arm B participants receiving radiotherapy on study

Individual participant*	Week 7	20 Gy	5#	T5 - T9 spine
Individual participant	Week 11	8 Gy	1#	Left post ribs
Individual participant	Week 11	8 Gy	1#	Right ant ribs
Individual participant*	Week 11	12 Gy	6#	T6, T9, left ribs
Individual participant	Week 4	15 Gy	5#	L2 - L4 re-treat
Individual participant*	Week 2	30 Gy	10#	Right chest
Individual participant*	Week 2	20 Gy	5#	Right pelvis

* participant did not complete to week 12

As summarised above, one Arm A participant received RT during the study and did not complete to week 12, compared with five Arm B participants, with three not completing to week 12.

All results were presented with mean and range when number of participants >2, otherwise actual values presented if <2 participants.

7.2 Primary objective - acceptability questionnaire

Acceptability questionnaire was completed at a number of study time points. Results were presented at week 12 and week20/End of Trial visit. High scores correspond with high levels of acceptability. All participants randomised to Arm B completed the primary objective acceptability questionnaire at either the planned study visit or Last visit due to participants preference or study team withdrawal. Unfortunately, only three out of the seven participants randomised to Arm A completed the questionnaire. Three participants were admitted with an SAE from lung cancer progression and withdrawn from the study before the next study visit. It was not considered appropriate to contact/visit two of these participants for the primary endpoint data, due to confusion. One participant completed the questionnaire at the visit to assess the status of continuing with the study and was later withdrawn from the study. One participant attended the planned week 3 visit, but then later died before the next visit.

Table 23 ACCeRT mean (range) score in EPA acceptability for participants completing week 12 and 20

Mean (range) score in EPA acceptability				
	Arm A	**Score**	**Arm B**	**Score**
Week 12	n=2	5 (5, 5)	n=6*	3.8 (1 to 5)
Week 20	n=2	4.5 (5, 4)	n=4	5 (5)

*one Arm B participant stopped at week 10

Table 24 ACCeRT mean (range) score in celecoxib acceptability for participants completing week 12 and 20

Mean (range) score in celecoxib acceptability				
	Arm A	**Score**	**Arm B**	**Score**
Week 12	n=1*	5 (5)	n=7	3.7 (1 to 5)
Week 20	n=1*	5 (5)	n=4	5 (5)

*one Arm A participant stopped at week 5

Table 25 ACCeRT mean (range) score in PRT acceptability within Arm B participants completing week 12 and 20

Mean (range) score in PRT acceptability				
	Arm A	**Score**	**Arm B**	**Score**
Week 12			n=7	4.6 (4 to 5)
Week 20			n=4	4.8 (4 to 5)

Table 26 ACCeRT mean (range) score in EAA acceptability within Arm B participants completing week 12 and 20

Mean (range) score in EAA acceptability				
	Arm A	**Score**	**Arm B**	**Score**
Week 12			n=7	3.9 (1 to 5)
Week 20			n=4	4.5 (4 to 5)

Table 27 ACCeRT mean (range) score in continuing PRT and medication within Arm B participants completing week 12 and 20

Mean (range) score in continuing PRT and medication				
	Arm A	**Score**	**Arm B**	**Score**
Week 12			n=7	3.9 (1 to 5)
Week 20			n=4	4.5 (3 to 5)

Table 28 ACCeRT mean (range) score in commencing PRT and medication within Arm A participants completing week 12 and 20

Mean (range) score in commencing PRT and medication				
	Arm A	**Score**	**Arm B**	**Score**
Week 12	n=2	5 (5, 5)		
Week 20	n=2	5 (5, 5)		

7.2.1 Compliance table for participants completing week 12

Table 29 Compliance table for participants completing week 12

Percentage taken of the total study dose/sessions					
	EPA	**Celecoxib**	**PRT**	**EAA**	**Overall**
Arm A	100	37			68.5
Arm A	98.8	98.9			98.9
Mean	**99.4**	**67.9**			**83.7**
Arm B	100	85.7	87.5	18.8	73.0
Arm B	86.9	86.9	75	69.6	79.6
Arm B	50	50	91.7	54.2	61.0
Arm B	100	100	100	94.6	98.7
Arm B	100	100	95.8	91.6	96.9
Arm B	78.6	100	83	15.4	69.3
Arm B	100	100	100	99.0	99.8
Mean	**87.9**	**88.9**	**90.4**	**63.3**	**82.6**

Twelve weeks equals 84 doses of celecoxib and EPA, 24 PRT sessions, and 400g of EAA.

7.2.2 Compliance table for participants completing week 20

Table 30 Compliance table for participants completing week 20

Percentage taken of the total study dose/sessions					
	EPA	**Celecoxib**	**PRT**	**EAA**	**Overall**
Arm A	100	22.1			61.1
Arm A	99.2	99.2			99.2
Mean	**99.6**	**60.7**			**80.2**
Arm B	100	100	100	96.4	99.1
Arm B	100	100	97.5	95	98.1
Arm B	47.1	100	80	15.3	60.6
Arm B	100	100	100	99.4	99.9
Mean	**86.8**	**100**	**94.4**	**76.5**	**89.4**

Twenty weeks equals 140 doses of celecoxib and EPA, 40 PRT sessions, and 800g of EAA.

7.2.2.1.1 EPA

Table 23 depicts EPA acceptability data from Arm A and B participants completing to week 12 and 20. Compliance results as per Tables 29 and 30. Arm A data shows mean acceptability score of 5 (5, 5 n=2) ‘strongly agree’, and mean compliance of 99.4% (100%, 98.8%, n=2) at week 12. One participant had 98.8% compliance due to a missed dose during an in-patient admission.

Arm B data shows mean acceptability score of 3.8 (range 1 to 5, n=6) and mean compliance of 87.9% (50 to 100%, n=7) at week 12. All Arm B participants had compliance rates of 100%, except the following. One participant pre study entry was experiencing intermittent diarrhoea related to a previous clinical study involving ten cycles of concurrent docetaxel and the study medication ramucirumab within the REVEL study. Data from this study showed toxicity (any grade) of 32% of diarrhoea and 16% mucosal inflammation (Garon et al., 2014). This participant was still experiencing intermittent diarrhoea; therefore, the decision was made to withdraw all study medication at week 6 and to continue only with the PRT sessions. There was no change in the frequency of diarrhoea from pre study entry, to study entry with study medication and post study medication withdrawal, i.e. it was never resolved and was still experienced intermittently until the participant's death. This was attributed to the previous exposure to ramucirumab. This resulted in compliance of 50% at week 12. One participant who did not find the EPA acceptable or palatable stopped at week 10, with compliance of 78.6% at week 12. One participant stopped intermittently due to radiotherapy-induced nausea and vomiting, with compliance of 86.9% at week 12.

Overall, Arm A participants who 'tend to agree' and 'strongly agree' was 100% at week 12 and 20 with 99.4% and 99.6% compliance of EPA at weeks 12 and 20 respectively. With Arm B participants who 'tend to agree' and 'strongly agree' was 80.3% at week 12 and 100% at week 20 with 87.9% and 86.8% compliance of EPA at weeks 12 and 20 respectively. The above results conclude that on average, the administration of EPA at this dose and frequency was acceptable in this population.

7.2.2.1.2 Celecoxib

Table 24 depicts celecoxib acceptability data from Arm A and B participants completing to week 12 and 20. Compliance results as per Tables 29 and 30. Arm A data shows the acceptability score of 5 (n=1), and mean compliance of 67.9% (36.9%, 98.8%, n=2) at week 12. One participant was taking diclofenac 100mg SR (sustained-release) for bilateral hip osteoarthritis pre study entry. This medication was stopped and switched to the study medication of celecoxib 300mg o.d. The participant found the switch unacceptable and stopped the celecoxib and returned to diclofenac at week 5. This resulted in compliance of 36.9% at week 12, and they did not complete this item on the questionnaire. Diclofenac 100mg SR is considered a high dose and the comparable dose of celecoxib would be 200mg b.d.s. (Chou, McDonagh, Nakamoto, & Griffin, 2011). This study utilised a dose of 300mg o.d., therefore a lower dose than this participant was previously receiving. Future participants already receiving diclofenac at 100mg SR were not enrolled onto the study.

Arm B data shows mean acceptability score of 3.7 (range 1 to 5, n=7) and mean compliance of 88.9% (50 to 100%, n=7) at week 12. All participants had compliance rates of 100%, except the following. One participant stopped at week 6 as discussed above, with compliance of 50% at week 12. One participant stopped intermittently due to radiotherapy-induced nausea and vomiting, with compliance of 86.9% at week 12. One participant stopped at week 10, with compliance of 85.7% at week 12.

Overall, Arm A participants who 'tend to agree' and 'strongly agree' was 100% at week 12 and 20 with 67.9% and 60.7% compliance of celecoxib at weeks 12 and 20 respectively. With Arm B participants who 'tend to agree' and 'strongly agree' was 71.4% at week 12 and 100% at week 20 with 88.9% and 100% compliance of celecoxib at weeks 12 and 20 respectively. The above results conclude that on average, the administration of celecoxib at this dose and frequency was acceptable in this population.

7.2.2.1.3 Progressive resistance training

For the purpose of the study, a planned event, e.g. bone scan, blood transfusion, planned holiday and Christmas period with family, attending a family emergency, attending a funeral or cancelled by study team due to illness of exercise physiologists, were all classed as an attendance. Classification of non-attendance was for a participant or family member illness, or an in-patient admission.

Table 25 depicts PRT session acceptability data from Arm B participants completing to week 12 and 20. Compliance results as per Tables 29 and 30. Arm B data shows mean acceptability score of 4.6 (range 4 to 5, n=7), and mean attendance of 90.4% (range 75 to 100%, n=7) at week 12, and mean acceptability score of 4.8 (range 4 to 5, n=4) and mean attendance of 94.4% (range 80 to 100%, n=4) at week 20.

Arm B participants who 'tend to agree' and 'strongly agree' was 100% at week 12 and 20 with 90.4% (range 80 to 100%) and 94.4% attendance of PRT sessions at weeks 12 and 20 respectively.

Attendance was high in this population, although one participant only attended three out of six PRT sessions (50%) due to ill health. Followed by an admission to hospice for respite and then end of life care. One participant had 80% attendance. This participant was the youngest in age to be enrolled onto the study, and was the main caregiver for young children, and found it difficult at times to attend for family reasons. All other participants had family members who were willing to bring them to the twice-weekly sessions.

The above results conclude that on average, PRT sessions were acceptable in this population at this frequency. Interestingly, both participants from Arm A scored 5 'strongly agree' in wishing to commence the PRT sessions and EAA as per Table 28. Both Arm A

participants completed the 20 week study and commenced PRT sessions on a compassionate basis, while all four Arm B participants who completed the 20 week study also carried on with the PRT sessions.

7.2.2.1.4 EAA

Table 26 depicts EAA acceptability data from Arm B participants completing to week 12 and 20. Compliance results as per Tables 29 and 30. Arm B data shows mean acceptability score of 3.9 (range 1 to 5, n=7), and mean compliance of 63.3% (range 15.4 to 99%, n=7) at week 12. All participants had compliance over 90% except for the following. One participant found all the medication overwhelming and had dose reduction to 6g per session (12 capsules over the 3 days), with compliance of 15.4% at week 12. Another participant also had a dose reduction down to 6g per session, with compliance of 18.8% at week 12. One participant, as discussed above as per EPA and celecoxib data, stopped at week 6 with compliance of 54.2% at week 12. One participant stopped intermittently due to radiotherapy-induced nausea and vomiting, with compliance of 69.6% at week 12.

Arm B participants who ‘tend to agree’ and ‘strongly agree’ was 71.4% at week 12 and 100% at week 20 with 63.3% and 76.5% compliance of EAA at weeks 12 and 20 respectively. The above results conclude that on average, the administration of EAA at this dose and frequency was acceptable in this population.

7.3 Secondary objectives

7.3.1 Data for all secondary outcomes for participants at randomisation

Table 31 Data for all secondary outcomes for participants at randomisation

	Total Mean (range) n=20	Arm A Mean (range) n=7	Arm B Mean (range) n=13
FFM (kg)	47.7 (33.2 to 63.1)	49.1 (33.2 to 63.1)	46.8 (34.0 to 63.1) *[a] n=12
Weight (kg)	62.1 (42.6 to 89.1)	64 (46.3 to 89.1)	61 (42.6 to 79.5)
Fat mass (kg)	14.5 (1 to 31.4)	15 (1 to 26)	14.2 (5.9 to 31.4) *[a] n=12
MRI Total quadriceps muscle volume (cm^3)	902 (562 to 1361) n=18	925 (669 to 1353) *[b] n=6	890 (562 to 1361) *[c] n=12
Male	1011 (562 to 1361) n=11	968 (820 to 1353) n=4	1036 (562 to 1361) n=7
Female	730 (596 to 1011) n=7	840 (669, 1011) n=2	685 (596 to 771) n=5
IL-6 (pg/mL)	17.1 (3.4 to 38.2) *[d]n=19	18 (3.4 to 30.8)	16.6 (4.4 to 38.2) *[d] n=12
TNF-α (pg/mL)	20.6 (8.2 to 67.8)	19.2 (11.3 to 29.8)	21.4 (8.2 to 67.8)
HGS (kg)	20.9 (6.5 to 39.0)	19 (7 to 31.5)	21.9 (6.5 to 39)
FAACT ACS (0-48)	29.1 (19 to 43) *[e] n=19	27.8 (19 to 43) *[e] n=6	29.7 (19 to 41)
FAACT Physical Well-Being score (0-28)	20.3 (10 to 30.3) *[e] n=19	19.2 (10 to 27) *[e] n=6	20.9 (14 to 30.3)
MFSI-SF Total score (0-96)	20.6(-11 to 51) *[e] n=19	21 (-11 to 51) *[e] n=6	20.4 (-4 to 46)
WHOQOL-BREF Overall QOL (0-10)	5.6 (3 to 9)	6 (4 to 9)	5.4 (3 to 8)
WHOQOL-BREF Physical score (0-35)	20.8 (15 to 29)	21.9 (15 to 29)	20.2 (16 to 29)
Albumin (g/L)	36.7 (25 to 44)	34.7 (28 to 43)	37.8 (25 to 44)
CRP (mg/L)	64.6 (5 to 279)	45.1 (9 to 68)	75 (5 to 279)
GPS (0-2)	1.3 (0 to 2)	1.4 (0 to 2)	1.2 (0 to 2)

[a] No available BIA data for one Arm B participant
[b] Unable to perform analysis on MRI scan for one Arm A participant
[c] Unable to undergo MRI scan due to cochlear implant
[d] Level below detection level for one Arm B participant
[e] Questionnaires not available in Mandarin for one Arm A participant

7.3.2 Data for all secondary outcomes for participants completing to week 12

Table 32 Data for all secondary outcomes for participants completing to week 12

		Arm A Mean (n=2)	Arm B Mean (n=7)
FFM (kg)	Baseline	58.9	48.6
	12 weeks	60.2	49.3
	Difference	+1.3	+0.7
	% difference	+2.3	+0.3
Weight (kg)	Baseline	79.9	64.6
	12 weeks	80.6	63.8
	Difference	+0.7	-0.8
	% difference	+0.9	-2.2
Fat mass (kg)	Baseline	21.1	15.9
	12 weeks	20.5	14.5
	Difference	-0.6	-1.5
	% difference	-3.7	-5.9
IL-6 (pg/mL)	Baseline	7.8	8.5
	12 weeks	23.5	16.0
	Difference	+15.8	+8.7 (n=6)*[d]
	% difference	+356.4	+109.3
TNF-α (pg/mL)	Baseline	25.9	20.4
	12 weeks	21.4	24.6
	Difference	-4.5	+4.3
	% difference	-15.9	+31.3
HGS (kg)	Baseline	29.3	23.4
	12 weeks	29.5	21.4
	Difference	+0.3	-1.9
	% difference	+0.9	-9.5
FAACT ACS (0-48)	Baseline	37.5	31.4
	12 weeks	39.5	28.7
	Difference	+2	-2.7
	% difference	+5.5	-9.5
FAACT Physical Well-Being score (0-28)	Baseline	24	19.1
	12 weeks	23	17.4
	Difference	-1	-1.7
	% difference	-3.7	-2.1
MFSI-SF Total score (0-96)	Baseline	5.0	23.7
	12 weeks	1.5	30
	Difference	-3.5	+6.3
	% difference	-2.8	+91.6

WHOQOL-BREF Overall QOL (0-10)	Baseline	8.0	5.4
	12 weeks	8.5	4.7
	Difference	+0.5	-0.7
	% difference	+5.56	-10.24
WHOQOL-BREF Physical score (0-35)	Baseline	26.5	20.7
	12 weeks	27.5	18.1
	Difference	+1	-2.6
	% difference	+3.09	-9.8
Albumin (g/L)	Baseline	39.0	38.4
	12 weeks	35.0	35.7
	Difference	-4.0	-2.7
	% difference	-11.16	-6.48
CRP (mg/L)	Baseline	35.5	33.9
	12 weeks	95	54.0
	Difference	+59.5	+20.1
	% difference	+442.65	+61.2
GPS (0-2)	Baseline	0.5	1.0
	12 weeks	1.5	1.1
	Difference	+1	+0.14
	% difference	+100	0

[d] Level below detection level for one Arm B participant

The above table 32 shows overall difference and percentage difference in secondary outcomes for participants completing 12 weeks. Points of interest are the body composition data. These include at baseline the difference of -10.3kg in FFM, -15.3kg in weight and -5.2kg in fat mass between Arms. Arm B participants had consistently lower baseline values when compared with Arm A. Interestingly is that the levels of albumin and CRP were similar at baseline, with a lower percentage change in both albumin and CRP levels within Arm B at 12 weeks. This may be attributed to the addition of PRT and EAA within this arm.

7.3.3 Data for all secondary outcomes for participants completing to week 20

Table 33 Data for all secondary outcomes for participants completing to week 20

		Arm A Mean (n=2)	Arm B Mean (n=4)
FFM (kg)	Baseline	58.9	51.2
	20 weeks	57.4	49.5
	Difference	-1.5	-1.7
	% difference	-2.6	-2.9
Weight (kg)	Baseline	79.9	69.2
	20 weeks	78.0	65.6
	Difference	-2	-3.7
	% difference	-2.56	-4.3
Fat mass (kg)	Baseline	21.1	18.1
	20 weeks	20.6	16.1
	Difference	-0.5	-1.9
	% difference	-2.8	-5.2
MRI Total quadriceps muscle volume (cm^3)	Baseline	1093	1024.8
	20 weeks	1208	972.8
	Difference	+115	-52
	% difference	+12.5	-3.0
Male	Baseline	1093	1281
	20 weeks	1208	1145
	Difference	+115	-137
	% difference	+12.47	-10.15 (n=2)
Female	Baseline		769
	20 weeks		801
	Difference		+33
	% difference		+4.23 (n=2)
IL-6 (pg/mL)	Baseline	7.8	7.6
	20 weeks	10.8	23.7
	Difference	+3	+21
	% difference	+125.4	+228.2
TNF-α (pg/mL)	Baseline	25.9	19.2
	20 weeks	33.6	29.8
	Difference	+7.8	+10.7
	% difference	+31.4	+57.8
HGS (kg)	Baseline	29.3	21.6
	20 weeks	30.0	18.3
	Difference	+0.8	-3.4
	% difference	+2.8	-10.6

FAACT ACS (0-48)	Baseline	37.5	31.5
	20 weeks	38	28.0
	Difference	+0.5	-3.5
	% difference	+2.8	-12.6
FAACT Physical Well-Being score (0-28)	Baseline	24	18
	20 weeks	24	15.5
	Difference	+0	-2.5
	% difference	-1.6	-13.6
MFSI-SF Total score (0-96)	Baseline	5.0	30.8
	20 weeks	8.5	36.3
	Difference	+3.5	+5.5
	% difference	-24.9	+26.1
WHOQOL-BREF Overall QOL (0-10)	Baseline	8.0	5.3
	20 weeks	8.5	5.0
	Difference	+0.5	-0.3
	% difference	+5.6	-2.7
WHOQOL-BREF Physical score (0-35)	Baseline	26.5	20.0
	20 weeks	27.5	17.3
	Difference	+1	-2.8
	% difference	+3.1	-13.2
Albumin (g/L)	Baseline	39.0	36.8
	20 weeks	37.5	33.5
	Difference	-1.5	-3.3
	% difference	-3.5	-7.2
CRP (mg/L)	Baseline	35.5	39.0
	20 weeks	65.0	97.0
	Difference	+29.5	+58.0
	% difference	+61.8	+128.5
GPS (0-2)	Baseline	0.5	1.0
	20 weeks	1.0	1.3
	Difference	+0.5	+0.3
	% difference	+50	+25

The above table 33 shows overall difference and percentage difference in secondary outcomes for participants completing 20 weeks. Points of interest are again in the body composition data. These include at baseline the difference of -7.7kg in FFM, -11.7kg in weight and -3kg in fat mass between Arms. Arm B participants had consistently lower baseline values when compared with Arm A. Interestingly is that the levels of albumin and CRP were again similar at baseline, but with a higher percentage change in both albumin and CRP levels within Arm B

at 20 weeks. Thereby indicating the benefit gained between baseline and 12 weeks, had been lost.

7.3.4 Comparison of data for participants not completing to week 12

Table 34 Comparison data for all secondary outcomes for participants not completing or completing to week 12

	All participants NOT completing week 12 Mean (range) n=8*	All participants completing week 12 Mean (range) n=9
FFM (kg)	45.6 (33.2 to 55.7)	50.9 (34 to 63.1)
Weight (kg)	59.5 (49.8 to 72.1)	68 (46.2 to 89.1)
Fat mass (kg)	13.9 (7.3 to 19.2)	17.1 (5.9 to 31.4)
MRI Total quadriceps muscle volume (cm3)	798 (562 to 1037)	1001 (673 to 1361)
IL-6 (pg/mL)	23.9 (6.4 to 47.6)	8.35 (3.4 to 12.8)
TNF-α (pg/mL)	22.6 (8.2 to 67.8)	21.6 (11.8 to 30.6)
HGS (kg)	17.6 (7 to 25)	24.7 (6.5 to 39)
FAACT ACS (0-48)	24.4 (19 to 35)	32.8 (29 to 43)
FAACT Physical Well-Being score (0-28)	20.4 (0 to 30.3)	20.2 (14 to 27)
MFSI-SF Total score (0-96)	24.5 (-3 to 51)	19.6 (-11 to 43)
WHOQOL-BREF Overall QOL (0-10)	5.5 (4 to 8)	6 (3 to 9)
WHOQOL-BREF Physical score (0-35)	20.5 (16 to 26)	22 (13 to 29)
Albumin (g/L)	35.4 (32 to 41)	38.6 (25 to 44)
CRP (mg/L)	100 (30 to 279)	34.2 (5 to 62)
GPS (0-2)	1.8 (1 to 2)	0.9 (0 to 2)

*One participant Arm A, and two participants Arm B withdrew from the study and not included.

The above table 34 compares the baseline secondary outcome for participants not completing to 12 weeks (n=8/11), with participants completing. Results indicate that for participants not completing had on average lower body composition and strength values from BIA, MRI and HGS data. Higher levels of proinflammatory cytokines, anorexia/cachexia symptoms and fatigue are also seen. Lower albumin levels and higher CRP levels resulting in a higher mean GPS. The above data can be utilised to generate possible ranges for inclusion criteria for future studies.

7.3.5 Body composition by Bioelectrical Impedance Analysis

All participants' body composition was assessed utilising single-frequency bioelectrical impedance analysis (SF-BIA), at all study visits. Please note input errors were discovered for one participant within Arm B at week 6 visit and another participant within Arm B at randomisation visit, with height at 160 inputted instead of 167cm, and the height inputted at 165 instead of 166cm; therefore, FFM and fat mass results were not utilised for these study visits.

Results presented were percentage change in fat free mass (FFM), total weight and fat mass (FM) for individual participants completing to week 12 and week 20, and mean change over time within Arm A and Arm B participants completing to week 12 and week 20. ≥-0.51kg change defined as net loss, between -0.5 to +0.5kg change defined as stable, and ≥+0.51kg change defined as net gain, estimated by study team.

7.3.5.1 Fat Free Mass

Figure 7 Waterfall plot of percentage change in fat free mass from baseline to week 12

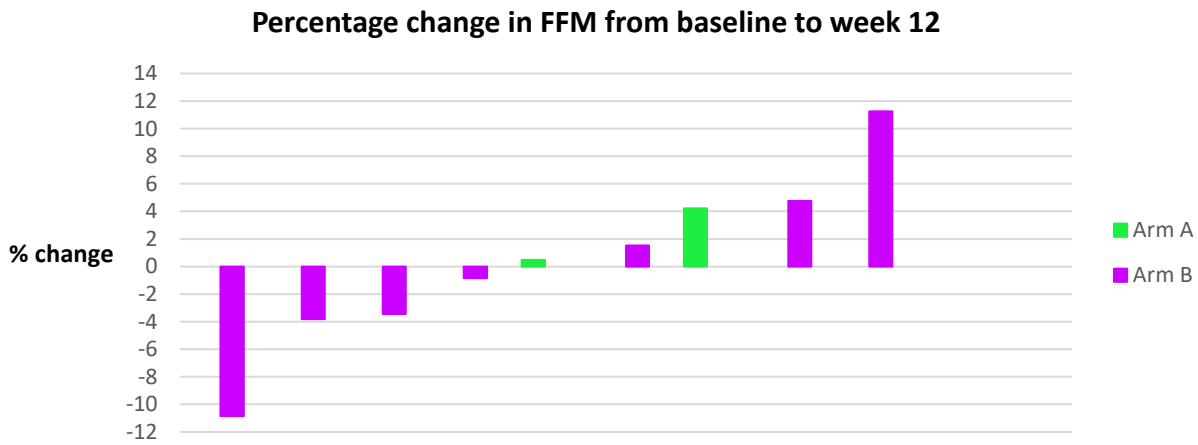


Figure 8 ACCeRT mean change over time in fat free mass for participants completing week 12

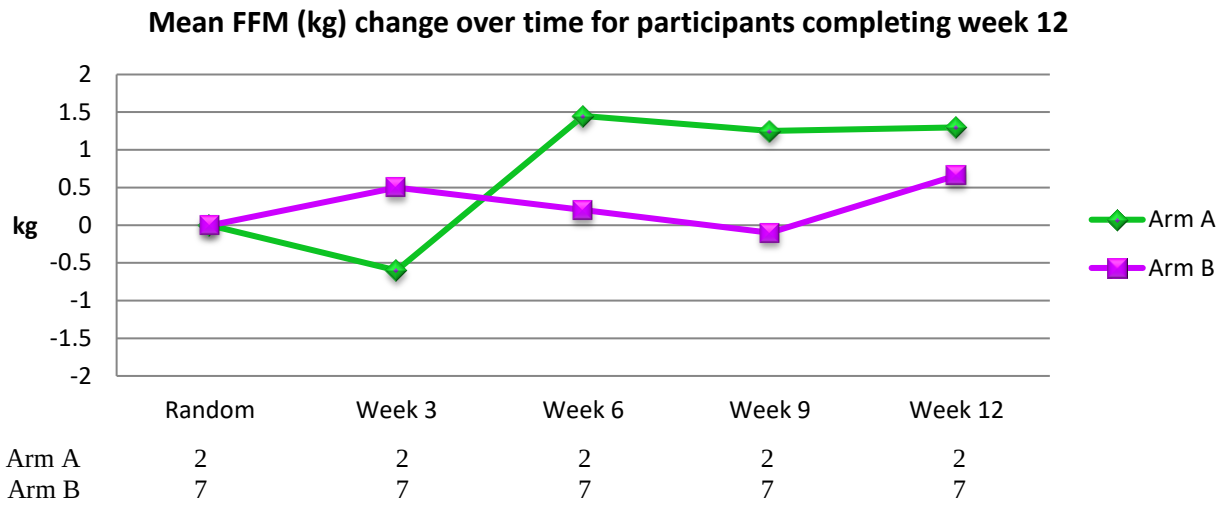


Figure 7 depicts percentage change in FFM from baseline to week 12. Data shows one net gain and one stable value within Arm A participants compared with three net gains, one stable and three net losses within Arm B participants. The mean change at week 12 was +1.3kg (+0.3, +2.3kg) within Arm A compared with +0.7kg (range -4.2 to +6.8kg, n=7) within Arm B, as depicted in Figure 8. This indicates the reversal and stability of FFM loss within some participants at week 12.

Figure 9 Waterfall plot of percentage change in fat free mass from baseline to week 20

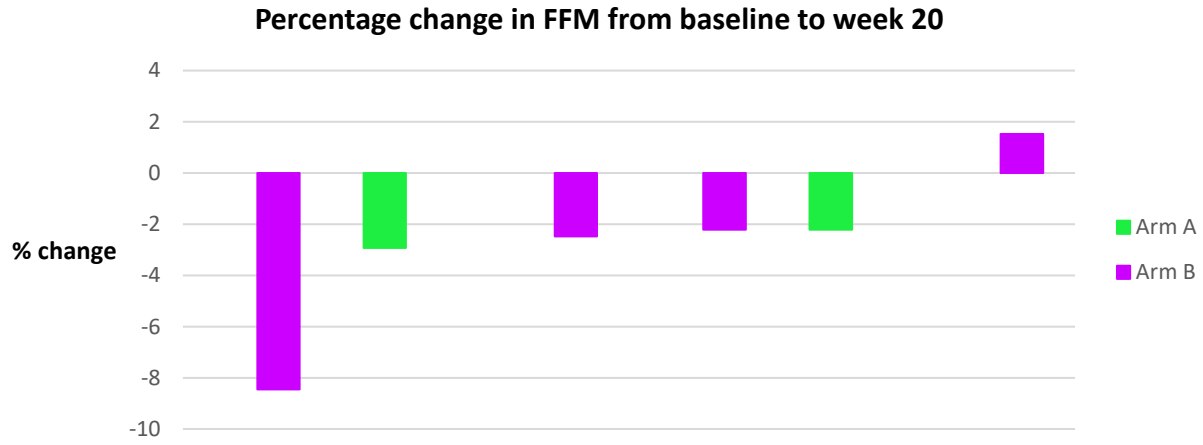
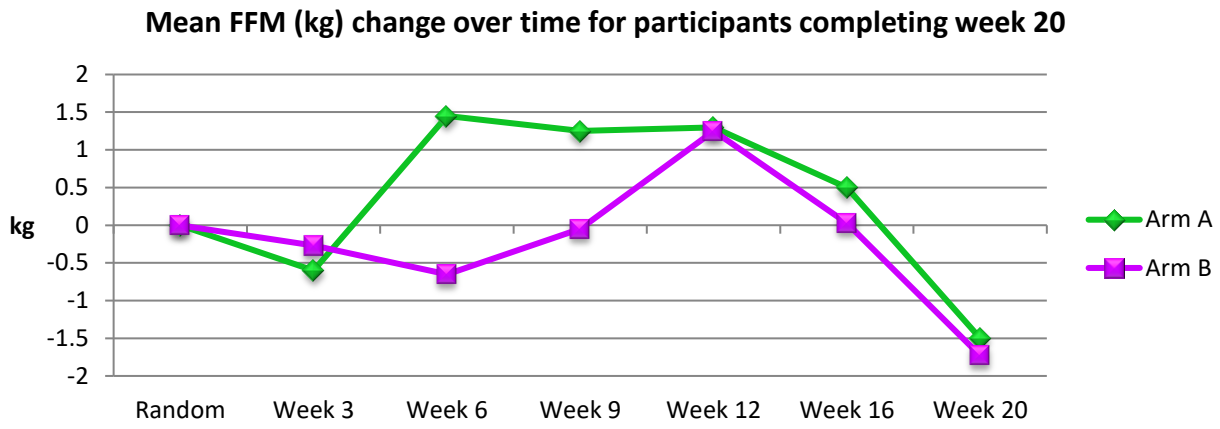


Figure 10 ACCeRT mean change over time in fat free mass for participants completing week 20



Arm A	2	2	2	2	2	2	2
Arm B	4	4	4	4	4	4	4

Figure 9 depicts percentage change in FFM from baseline to week 20. Data shows two net loss values within Arm A participants compared with one net gain, and three net losses within Arm B participants. The mean change at week 20 was -1.5kg (-1.4kg, -1.6kg) within Arm A compared with -1.7kg (range -4.9 to +0.6kg, n=4) within Arm B, as depicted in Figure 10. This indicates the reversal of FFM loss within one Arm B participant at week 20.

7.3.5.2 Weight

Figure 11 Waterfall plot of percentage change in weight from baseline to week 12

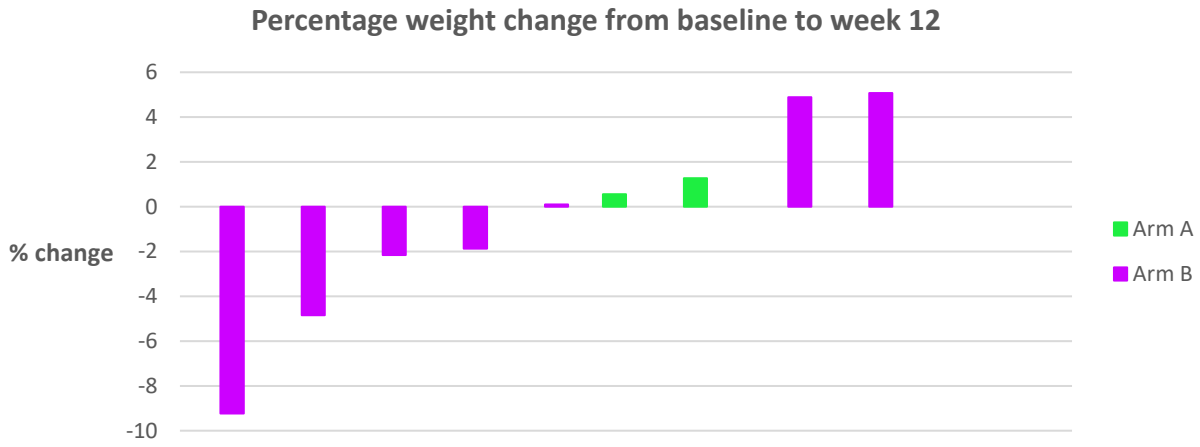


Figure 12 ACCeRT mean change over time in weight for participants completing week 12

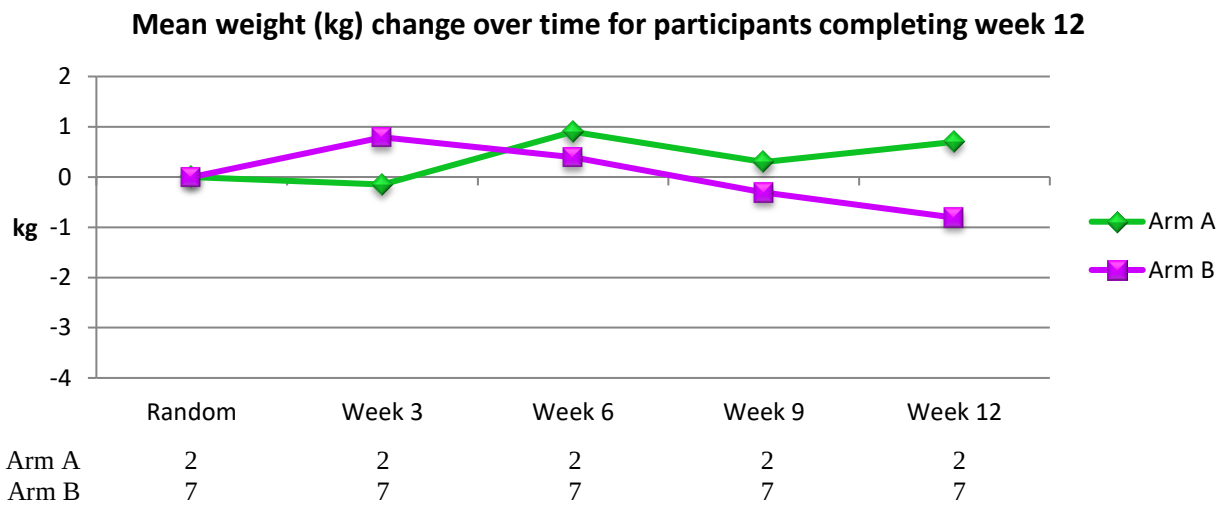


Figure 11 depicts percentage change in total body weight data from baseline to week 12. Data shows one net gain and one stable value within Arm A participants compared with two net gains, one stable and four net losses within Arm B participants. The mean change at week 12 was +0.7kg (+0.5kg, +0.9kg) within Arm A compared with -0.8kg (range -4.9 to +4kg, n=7) within Arm B, as depicted in Figure 12. This indicates the reversal and stability of weight loss within some participants at week 12.

Figure 13 Waterfall plot of percentage change in weight from baseline to week 20

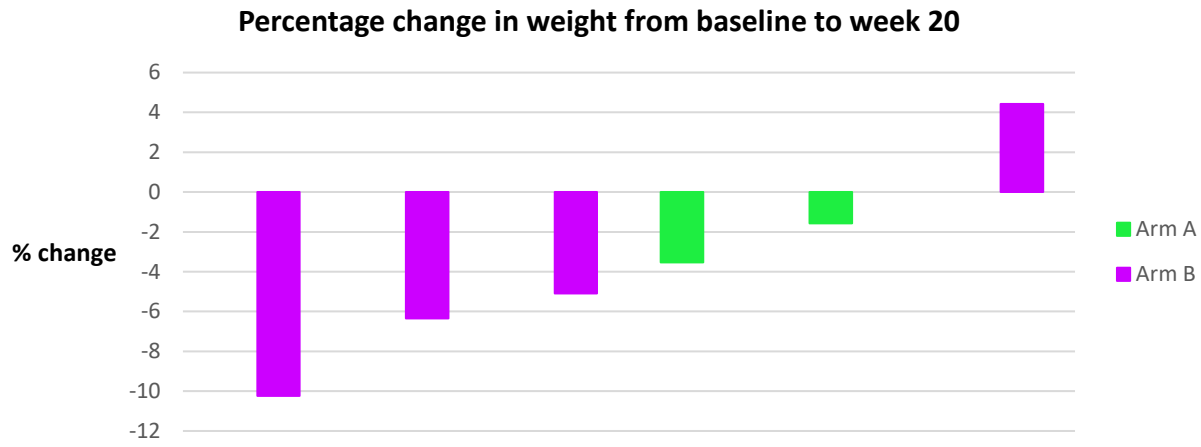
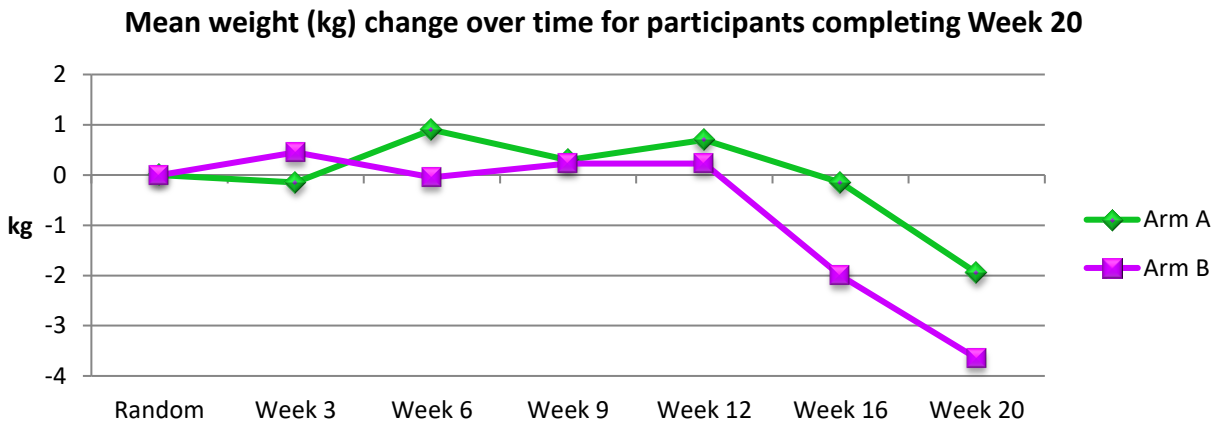


Figure 14 ACCeRT mean change over time in weight for participants completing week 20



Arm A	2	2	2	2	2	2	2
Arm B	4	4	4	4	4	4	4

Figure 13 depicts percentage change in total body weight data from baseline to week 20. Data shows two net loss values within Arm A participants compared with one net gain, and three net losses within Arm B participants. The mean change at week 20 was -2kg (-1.4kg, -2.5kg) within Arm A compared with -3.7kg (range -7.6 to +2kg, n=4) within Arm B, as depicted in Figure 14. This indicates the reversal of weight loss within one Arm B participant at week 20.

7.3.5.3 Fat Mass

Figure 15 Waterfall plot of percentage change in fat mass from baseline to week 12

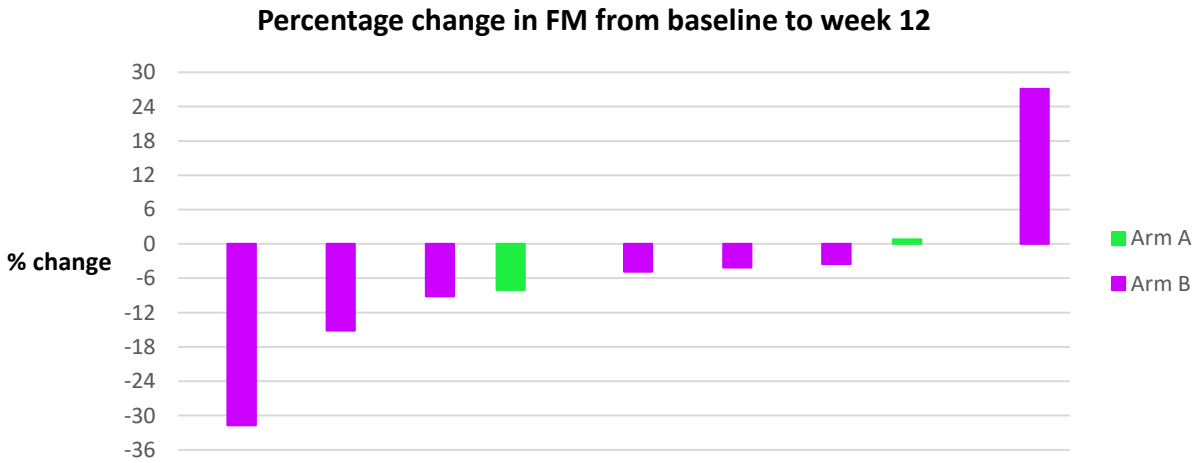


Figure 16 ACCeRT mean change over time in fat mass for participants completing week 12

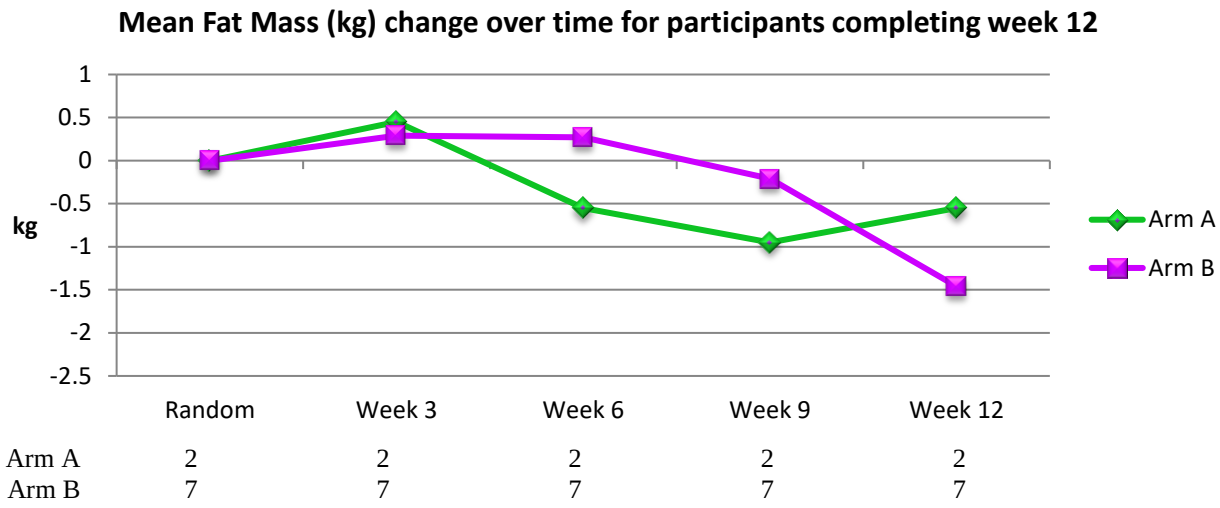


Figure 15 depicts percentage change in FM from baseline to week 12. Data shows one stable and one net loss values within Arm A participants compared with one net gain, one stable and five net losses within Arm B participants. The mean change at week 12 was -0.6kg (+0.2kg, -1.3kg) within Arm A compared with -1.5kg (range -5.2 to +1.6kg, n=7) within Arm B, as depicted in Figure 16. This indicates the reversal and stability of FM loss within some participants at week 12.

Figure 17 Waterfall plot of percentage change in fat mass from baseline to week 20

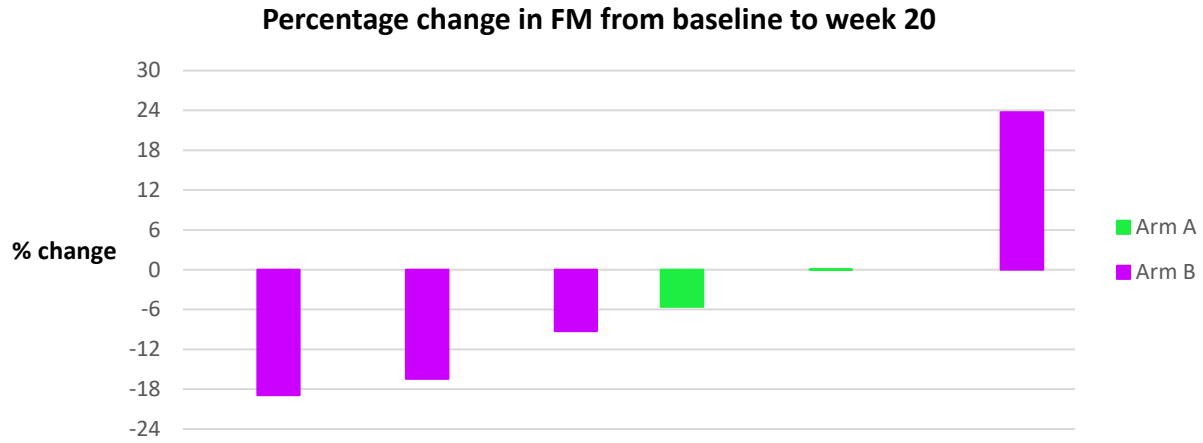
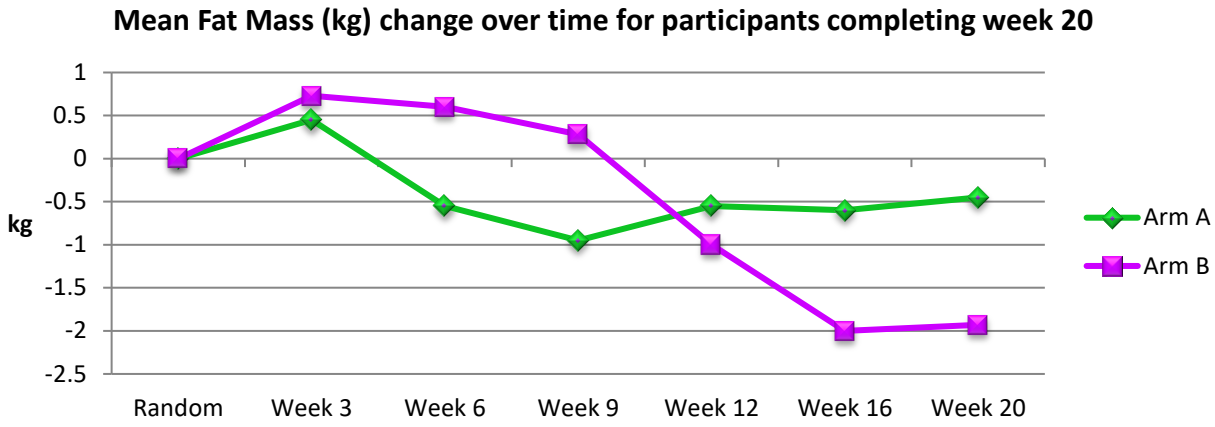


Figure 18 ACCeRT mean change over time in fat mass for participants completing week 20



	Random	Week 3	Week 6	Week 9	Week 12	Week 16	Week 20
Arm A	2	2	2	2	2	2	2
Arm B	4	4	4	4	4	4	4

Figure 17 depicts percentage change in FM from baseline to week 20. Data shows one stable and one net loss values within Arm A participants compared with one net gain, and three net losses within Arm B participants. The mean change at week 20 was -0.5kg (+0kg, -0.9kg) within Arm A compared with -1.9kg (range -3.5 to +1.4kg, n=4) within Arm B, as depicted in Figure 18. This indicates the reversal of FM loss within one Arm B participant and the stability within one Arm A participant at week 20.

Overall there was a gain of +1.3kg (FFM) and +0.7kg (weight) in Arm A, compared with +0.7kg (FFM) and -0.8kg (weight) in Arm B at 12 weeks. This then changed to a loss of -1.5kg (FFM) and -2kg (weight) compared with -1.7kg (FFM) and -3.7kg (weight) in Arm B at 20 weeks. These results indicate that within Arm A, there was an increase in FFM in the context of increasing weight at week 12. While there was an increase in FFM within Arm B, this occurred in the context of stable and/or decreasing total body weight. The two participants within Arm A had consistently higher FFM values at weeks 6 to 20 when compared with the mean values within both Arm B analysis. Although, in the Arm B week 20 analysis, mean values were similar from week 12 onwards. This trend in FFM was possibly due to the low numbers remaining within Arm A, and that both participants entered the study with the longest time period for 5% weight loss with 142 and 296 days respectively, and were maybe at an earlier stage in the refractory cachexia period. Test-retest reliability in patients with advanced cancer was close to 1% (Trutschnigg et al., 2008) and precision error for FM and FFM from BIA less than 2%. All participants had percentage change in weight greater than +2%/-2% except three at 12 weeks, and one at 20 weeks. Greater than +2%/-2% percentage change in FFM except two at 12 weeks, and two at 20 weeks. Trends supported stable results within all these participants.

Total body weight results indicate, on average, a net gain in weight at week 12 then weight loss returned within Arm A. For Arm B participants completing week 12, weight loss returned at week 9 onwards, while for participants completing week 20, weight loss was delayed and returned at week 16 onwards. Interestingly, for Arm B participants completing week 20 while the total body weight was stable, the FFM was increasing up to week 12, which could be attributed to the addition of PRT sessions and/or EAA and the potential stimulation of the anabolic pathway.

7.3.6 MRI total quadriceps muscle volume analysis

All participants underwent a 3T MRI scan at baseline and Last or week 20/End of Trial visit, except one Arm B participant who had a cochlear implant and therefore was unable to undergo this study assessment. Please note 10.0 E+05 mm^3 = $1000cm^3$

Table 35 ACCeRT MRI total quadriceps muscle volume analysis

Total quadriceps muscle volume (cm^3)		
Arm A	**Pre**	**Post**
Baseline only	669	
Baseline only	1011	
Baseline only	820	
Baseline only	865	
Week 20	1353	1411
Week 20	833	1005
Arm A (mean)	**925**	**1208**
Arm B		
Baseline only	562	
Baseline only	1252	
Baseline only	621	
Baseline only	596	
Week 9	1042	775
Week 9	1037	877
Week 12	673	620
Week 12	798	627
Week 20	1201	1177
Week 20	771	799
Week 20	1361	1112
Week 20	766	803
Arm B (mean)	**890**	**849**

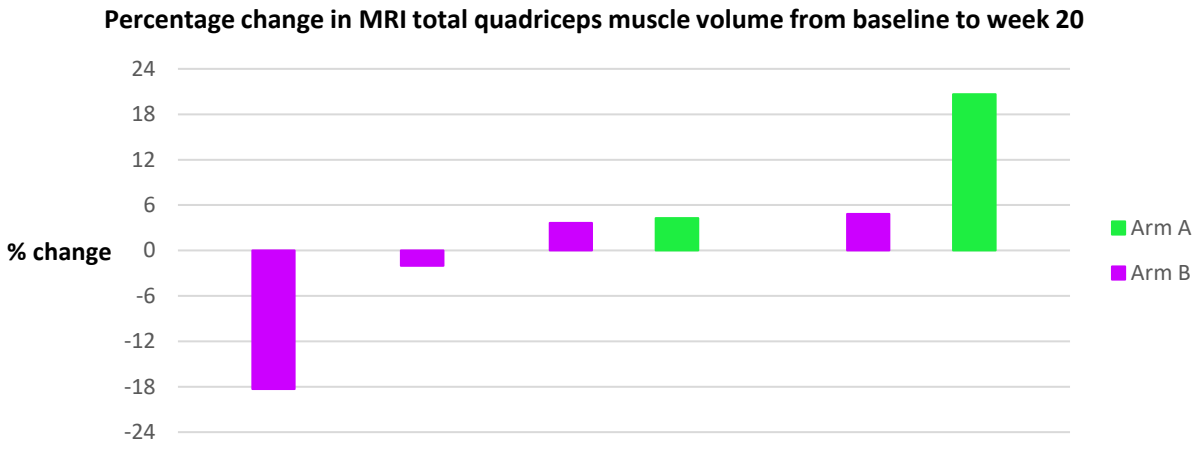
One Arm A participant underwent the scan, but unfortunately, the images were unable to be analysed as standardised for all the other images due to the significant deficiency of adipose tissue. There was no objective difference in the signal intensities between the muscle and

surrounding tissue, resulting in an inability to automatically segment and therefore assess the volumes, as per the study protocol. An adjustment in the degree of fat saturation at the time of acquisition may have been beneficial; however, this was probably unlikely due to the deficiency of adiposity. This corresponded with BIA data of 1.1kg FM (2.5%) at the screening visit. Due to attrition of participants as discussed earlier, pre and post treatment scan data was only available for two participants allocated to Arm A, and eight allocated to Arm B, as per Table 35.

Table 36 ACCeRT mean (range) change over time in total quadriceps muscle volume (cm3) for participants completing week 20.

Mean change (range) from baseline to Week 20 visit total quadriceps muscle volume (cm^3)						
	Arm A	**cm^3**	**% difference**	**Arm B**	**cm^3**	**% difference**
Week 20	n=2	+115 (+58, +172)	+12.5 (+4.3, +20.7)	n=4	-52 (-249 to +37)	-3 (-18.3 to +4.8)

Figure 19 Waterfall plot of percentage change in MRI total quadriceps muscle volume from baseline to week 20



Data from Table 36 shows the mean MRI total quadriceps muscle volume change from baseline to week 20 of +12.47% (+4.29%, +20.65%) within Arm A, compared with -2.96% (range -18.30 to +4.83%, n=4) within Arm B. Figure 19 depicts percentage change in muscle volume from baseline to week 20. Data shows two net gains within both Arm A participants compared with two net gain, and two net losses within Arm B participants. These results indicate, on average, a net gain of total quadriceps muscle volume for participants within Arm A, compared with a slight net loss within Arm B.

There is a difference in results between genders, with the baseline mean value for females of 730cm^3 (range 596 to 1011cm^3, n=7), and males of 1011cm^3 (range 562 to 1361cm^3, n=11). When analysing data between genders, the net percentage change of +4.23%

within females (n=2) compared with net percentage change of -10.15% (n=2) within males for Arm B participants completing week 20 visit as per Table 33.

If taking the pre-defined definition of response (Table 10), for the ACCeRT study, individual data within Arm A shows two major responses with the net change of +4.29% and +20.65%, both over 20 weeks. Within Arm B, there was one major and one minor responder with a net change of +4.83% and +3.63% respectively, and two non-responses with -2% and -18.3% over 20 weeks. Within Arm B, there were two non-responses of -25.62% and -15.43% at week 9 and two non-responses of -7.88% and -21.43% at week 12.

Both Arm A participants experienced weight loss over the longest time period and were maybe at an earlier stage in the refractory cachexia period. However, these results suggest that the use of EPA and celecoxib could potentially preserve muscle volume during this early refractory cachexia stage. The four participants within Arm B who completed the 20 week study had a mean percentage muscle volume loss of -2.96%. These data suggest that the use of EPA and celecoxib +/- PRT and EAA could potentially preserve muscle volume loss during the refractory cachexia stage.

Table 37 Intra-observer results for 3T MRI analysis for the ACCeRT study

	Intra-observer (cm^3)			
	Observer 1	**Observer 1**	**difference**	**% difference**
Scan 02	1112	1123	+11	+0.99
Scan 03	1011	987	-24	-2.37
Scan 05	766	765	-1	-0.13
Mean			**-4.67**	**-0.51**

Table 38 Inter-observer results for 3T MRI analysis for the ACCeRT study

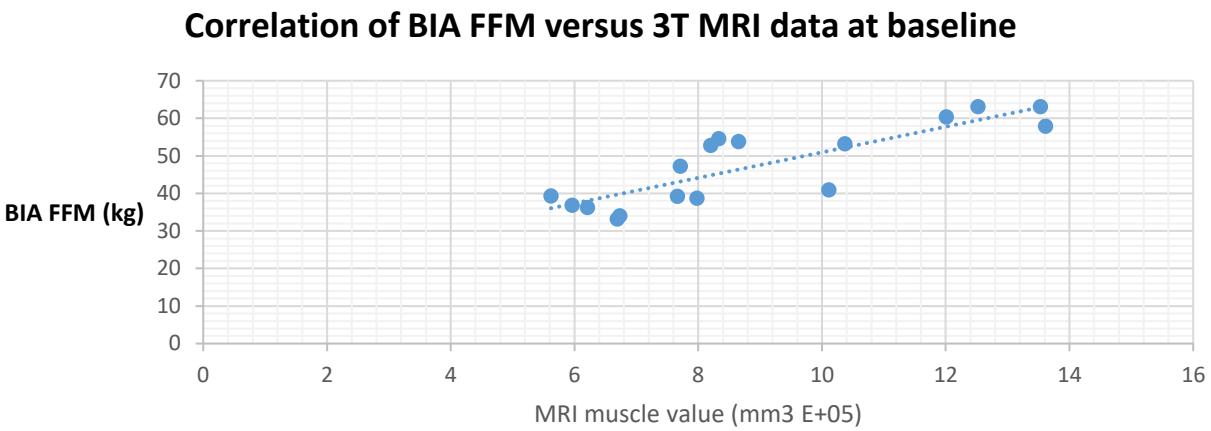
	Inter-observer (cm^3)			
	Observer 1	**Observer 2**	**difference**	**% difference**
Scan 01	1042	1038	-4	-0.38
Scan 04	1252	1247	-5	-0.40
Scan 05	766	766	+0	0
Mean			**-3**	**-0.26**

MRI scanning and analysis are dependent on the observer who performs the combined computerised and manual segmentation of each muscle within each slice. In the ACCeRT study, both observers agreed the start and end slice number on each scan, then independently performed the analysis. All scans were coded and blinded to treatment allocation. There was intra-observer agreement for three scans (10% of the total 30 scans analysed) with a mean

difference of -4.67cm^3 and -0.51% difference, and the inter-observer difference of -3cm^3 and -0.26% difference, all showing good correlation.

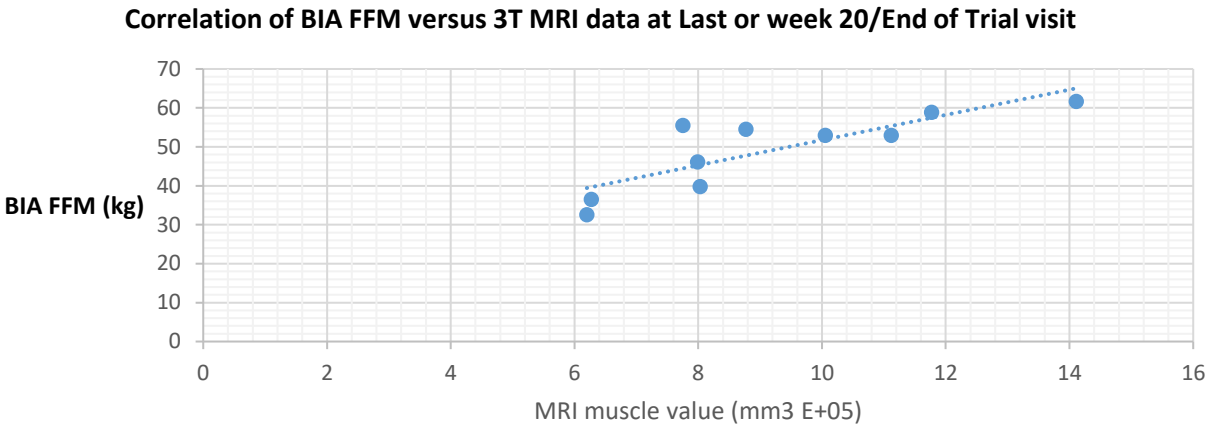
The average number of slices scanned was 98, which took approximately 60 minutes for each analysis. Interestingly, an abstract published from the eighth International Conference on Cachexia, Sarcopenia and Muscle Wasting, in Paris, France during December 2015, discussed a fast segmentation software that integrated the efficient interactive Random Walker segmentation algorithm into a convenient graphical user interface. A comparison was made between observers who performed a manual segmentation of the quadriceps volumes that required more than 5 hours, with observers producing similar volumes in less than 10 minutes with the presented software tool, thereby cutting down the above analysis time. At the time of thesis presentation this study is awaiting full publication (Baudin, Azzabou, & Carlier, 2015). Please note that most centres are already utilising a semi-automated software for muscle analysis.

Figure 20 Graph of correlation of BIA FFM versus 3T MRI data at baseline



Graph of correlation at baseline for six participants within Arm A and eleven within Arm B. Correlation=0.845.

Figure 21 Graph of correlation of BIA FFM versus 3T MRI data at Last or week 20/End of Trial visit



Graph of correlation at Last or week 20/End of Trial visit for two participants within Arm A and eight within Arm B. Correlation=0.828.

Both the above MRI total quadriceps muscle volume data and BIA FFM data correlated well at both baseline and Last or week 20/End of Trial visit with correlation of 0.845 (Figure 20) at baseline and of 0.828 (Figure 21) at Last or week 20/End of Trial visit. This supports the trends seen within the BIA results.

7.3.7 Serum proinflammatory cytokine analysis

All participants underwent proinflammatory cytokine testing at each study visit. Because the participants were at the end-stage of their disease trajectory and were already having difficulties with appetite, it was decided not to ask the participants to fast before sampling. Due to the nature and timing of the study visits all blood samples were taken between 9:15 a.m. and 3:30 p.m. All samples were centrifuged and then aliquoted out and stored at -80°C to form the ACCeRT biobank. Samples were removed from storage and kept on ice on the day of analysis.

One hundred and seven samples were analysed from the ACCeRT study, these included all screening visit, guest participant (001), non-randomised (007), and participants not included in the FAS. Interestingly, only 17 samples had detectable IL-1β levels, with two of these under the analysis kit detection level, giving an overall detection percentage rate of 14% (n=15/107). Detectable levels for IL-6 was present except for four samples, giving an overall detection percentage rate of 96.2% (n=103/107) and 100% detectable levels for TNF-α levels. Minimum detectable concentration of IL-1β =0.8pg/ml, IL-6 =0.9pg/ml and for TNF-α=0.7pg/ml. Detectable levels were not included in the analysis below. Results for IL-6 and TNF-α ≥-5.1pg/ml change defined as net decrease, between -5 to +5pg/ml change defined as stable, and ≥+5.1pg/ml change defined as net increase, estimated by study team. Inter-assay coefficient of variation; IL-1β = 6.7%, IL-6 = 18.3% and TNF-α = 13.0%. Intra-assay coefficient of variation; IL-1β = 2.3%, IL-6 = 2.0% and TNF-α = 2.5%. All values increased/decreased from random visit were above these thresholds, or remained stable.

7.3.7.1 IL-6 Levels

Figure 22 ACCeRT change over time in IL-6 levels for individual participants completing week 12

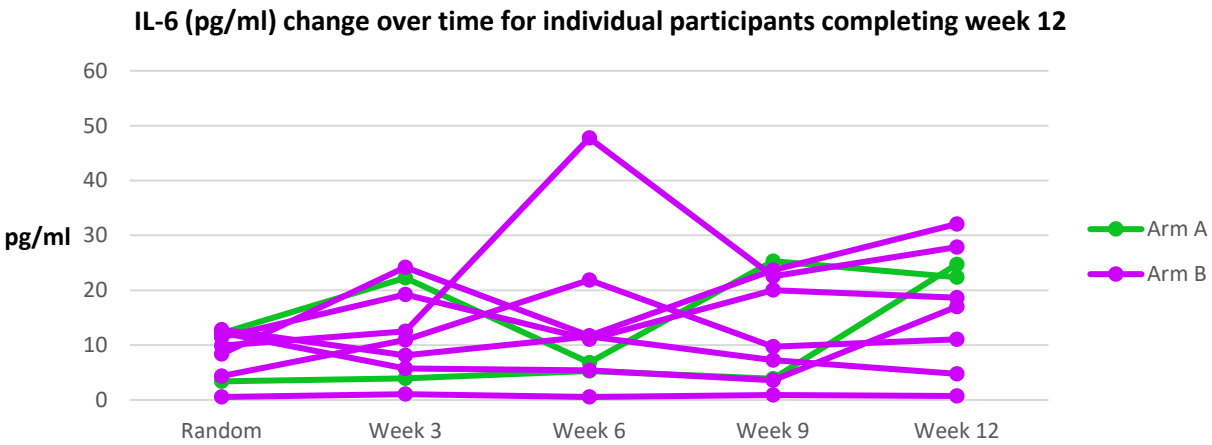


Figure 23 ACCeRT mean change over time in IL-6 levels for participants completing week 12

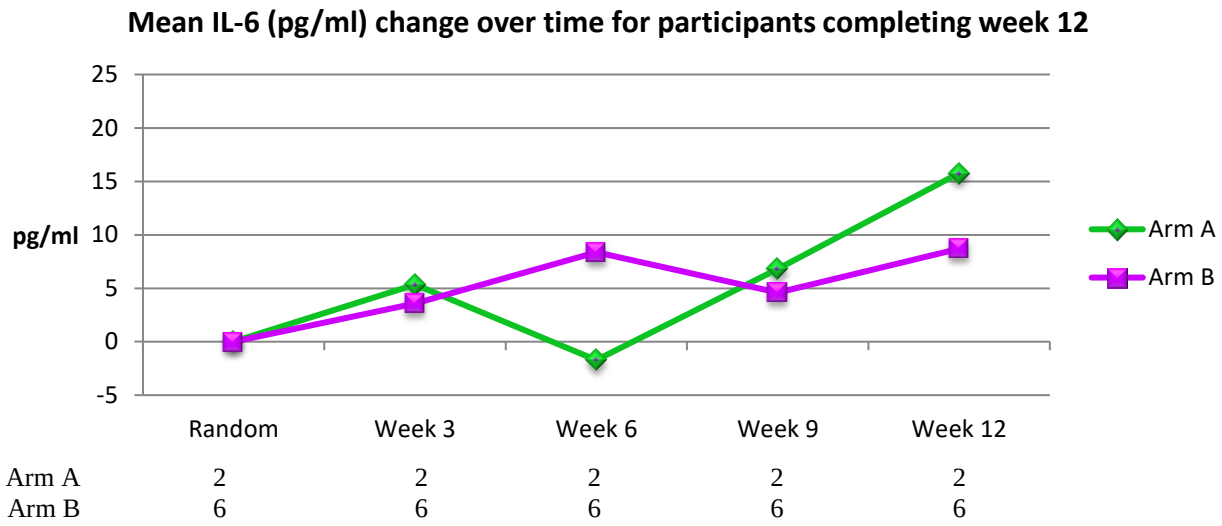


Figure 22 depicts IL-6 level data from Arm A and B participants completing week 12. Data shows two net increased levels within Arm A participants compared with one undetectable, one net decrease, and five net increases within Arm B participants. The mean change at week 12 was +15.8pg/ml (+10.2pg/ml, +21.3pg/ml) within Arm A compared with +8.7pg/ml (range -8.1 to +23.7pg/ml, n=6) within Arm B, as depicted in Figure 23. This indicates the reduction in IL-6 levels within one Arm B participant at week 12.

Figure 24 ACCeRT change over time in IL-6 levels for individual participants completing week 20

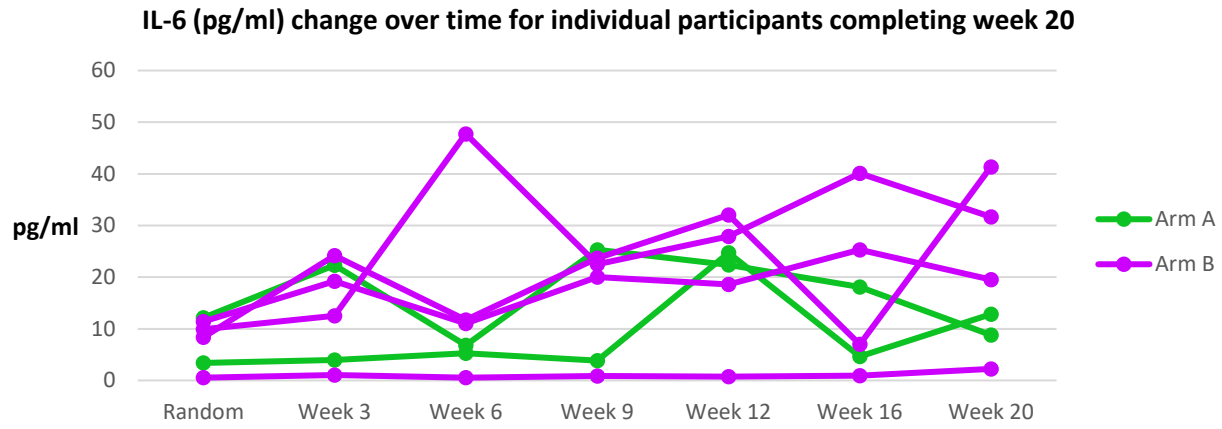


Figure 25 ACCeRT mean change over time in IL-6 levels for participants completing week 20

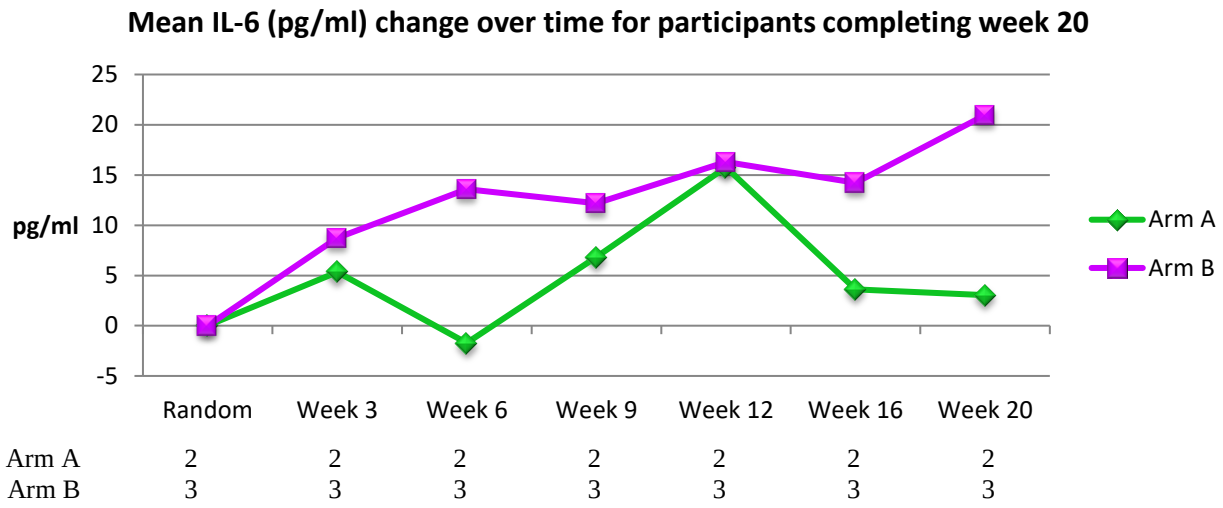


Figure 24 depicts IL-6 level data from Arm A and B participants completing week 20. Data shows one net increase and one net decreased levels within Arm A participants compared with one undetectable, and three net increases within Arm B participants. One Arm A participant experienced dyspnoea and commenced antibiotics and low dose prednisone for a pulmonary/upper respiratory infection around week 12; this could have resulted in the reduced levels at week 16 to week 20. The mean change at week 20 was +3pg/ml (-3.4pg/ml, +9.4pg/ml) within Arm A compared with +21pg/ml (range +8.1 to +33pg/ml, n=3) within Arm B, as depicted in Figure 25. This indicates increased proinflammatory activation of IL-6 levels within most participants and the reduction in IL-6 level within one Arm A participant at week 20. There were similar trends between Arm B participants completing week 12 and week 20.

7.3.7.2 TNF-α Levels

Figure 26 ACCeRT change over time in TNF-α levels for individual participants completing week 12

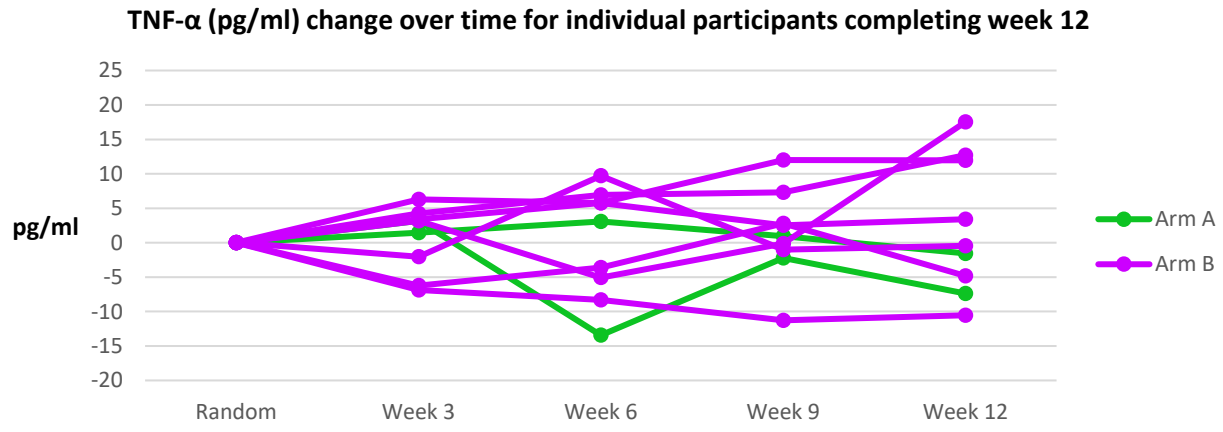


Figure 27 ACCeRT mean change over time in TNF-α levels for participants completing week 12

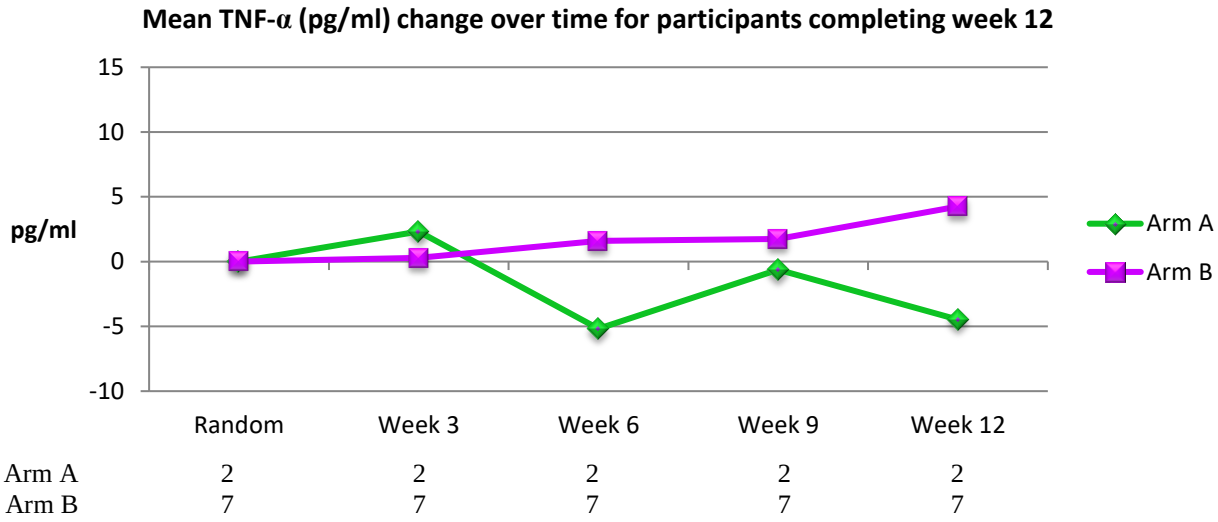


Figure 26 depicts TNF-α data from Arm A and B participants completing week 12. Data above shows one net decreased and one stable level within Arm A participants compared with one net decreased, three stable, and three net increases within Arm B participants. The mean change at week 12 was -4.5pg/ml (-7.4pg/ml, -1.6pg/ml) within Arm A compared with +4.3pg/ml (range -10.5 to +17.5pg/ml, n=7) within Arm B, as depicted in Figure 27. This indicates the reduction and stability of TNF-α levels within some participants at week 12.

Figure 28 ACCeRT change over time in IL-6 levels for individual participants completing week 20

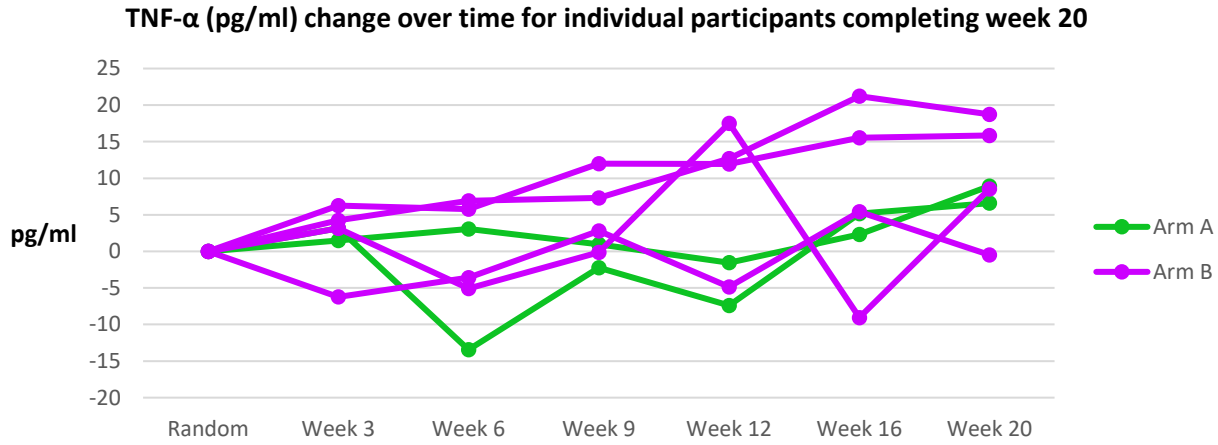
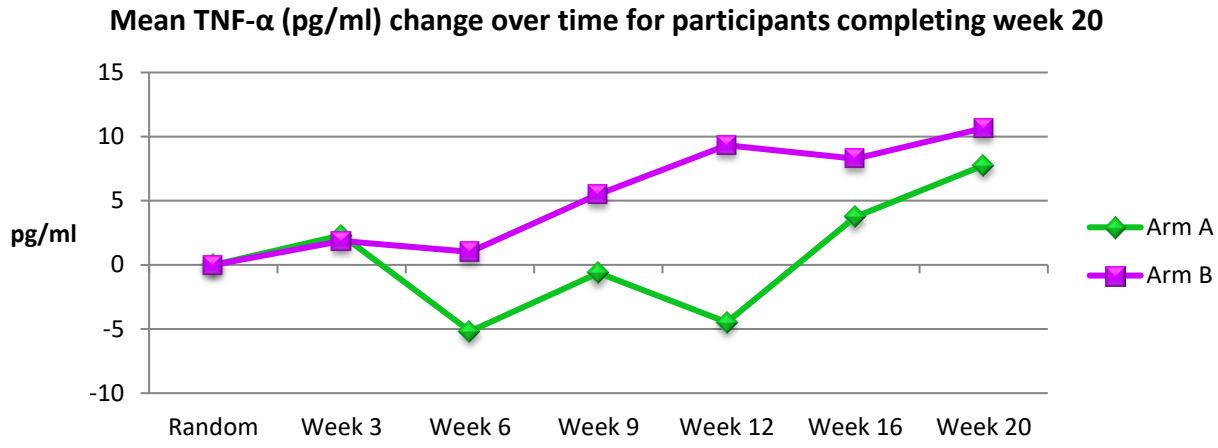


Figure 29 ACCeRT mean change over time in IL-6 levels for participants completing week 20



Arm A	2	2	2	2	2	2	2
Arm B	4	4	4	4	4	4	4

Figure 28 depicts TNF-α data from Arm A and B participants completing week 20. Data shows two net increased levels within Arm A participants compared with one stable, and three net increases within Arm B participants. The mean change at week 20 was +7.8pg/ml (+6.6pg/ml, +8.9pg/ml) within Arm A compared with +10.7pg/ml (range -0.5 to +18.7pg/ml, n=4) within Arm B, as depicted in Figure 29. This indicates the stability of TNF-α level within one Arm B participant at week 20.

This suggests that on average TNF-α level had increased within both groups at week 20. There were similar trends between Arm B participants completing week 12 and week 20.

Results showed the proposed pathophysiology of cancer cachexia i.e. that while proinflammatory cytokine IL-6 levels are reduced and/or stable, an increase in FFM and total weight is achievable. This is incorrect in above study population. Within some participants, increases in BIA FFM were seen while IL-6 levels were increasing. On average, levels of both IL-6 and TNF-α increased within all the participants within the ACCeRT study. Due to low numbers of participants, it is difficult to determine if this process had been reduced with the study treatment compared to levels in un-treated refractory cachexia patients.

7.3.8 Hand-grip strength analysis

All participants underwent hand-grip strength (HGS) testing at each study visit. Data was collected firstly with the Jamar dynamometer for participant 001 (guest) and participant 002. This was then changed due to a fault, to a TTM Smedley's dynamometer at baseline visit for participant 003, all visits onwards. One of Arm B participants had difficulties with a historical neck, bilateral hips and lower spine injury from a childhood road traffic accident, and declined HGS at weeks 6 and 16 study visits. All other participants found it acceptable. The dynamometers were stored carefully in the designated custom-made case to prevent damage.

Results for HGS ≥-1.1kg change defined as net loss, between -1 to +1kg change defined as stable, and ≥+1.1kg change defined as net gain, estimated by study team.

Figure 30 ACCeRT change over time in hand-grip strength for individual participants completing week 12

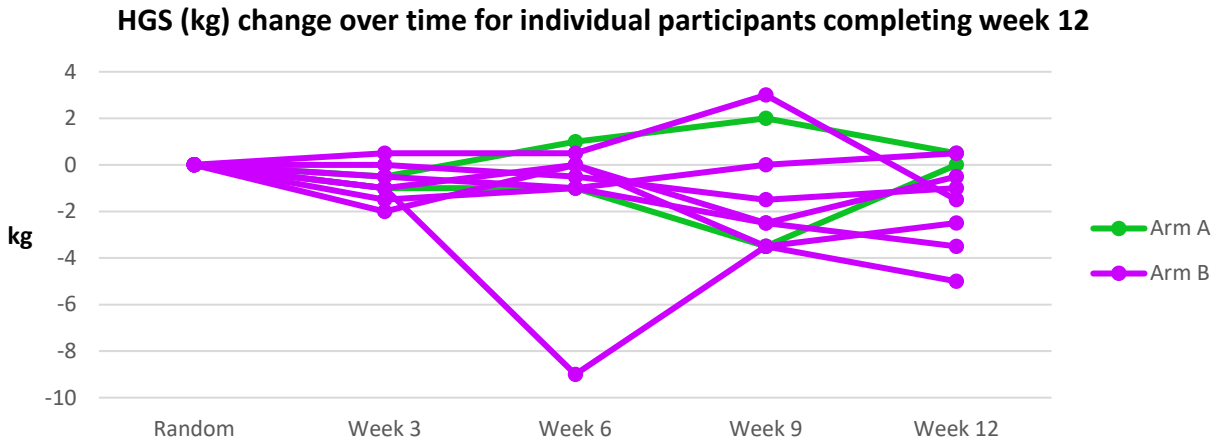
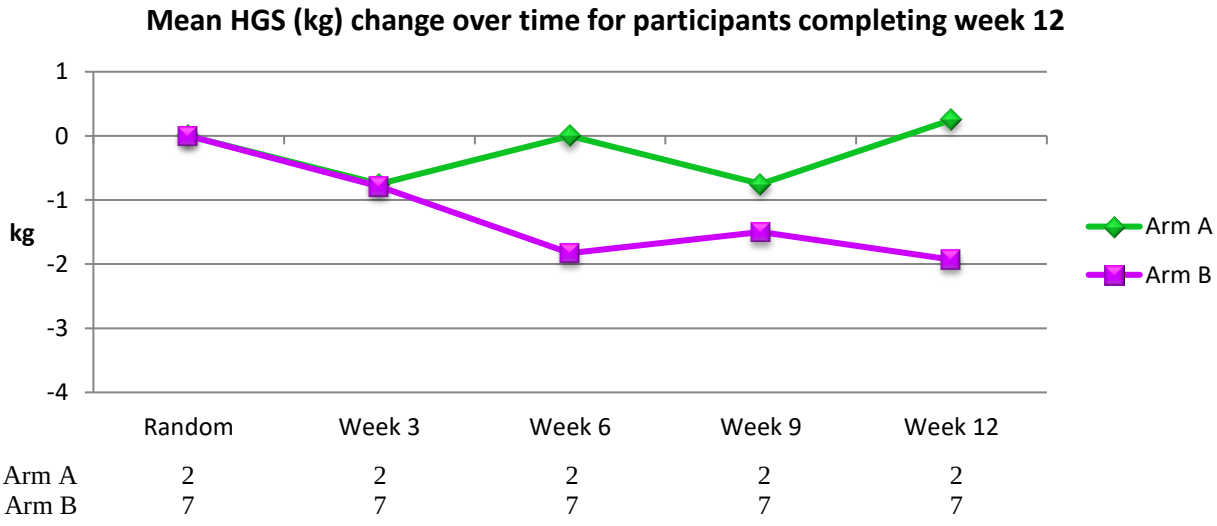


Figure 31 ACCeRT mean change over time in hand-grip strength for participants completing week 12



Arm A	27	27	27	27	27
Arm B	27	27	27	27	27

Figure 30 depicts HGS data from Arm A and B participants completing week 12. Data shows two stable values within Arm A participants compared with three stable and four net losses

within Arm B participants. The mean change at week 12 was +0.3kg (+0.5kg, +0kg) within Arm A compared with -1.9kg (range -3.5 to +0.5kg, n=7) within Arm B, as depicted in Figure 31. This indicates the stability of HGS within some participants at week 12.

Figure 32 ACCeRT change over time in hand-grip strength for individual participants completing week 20

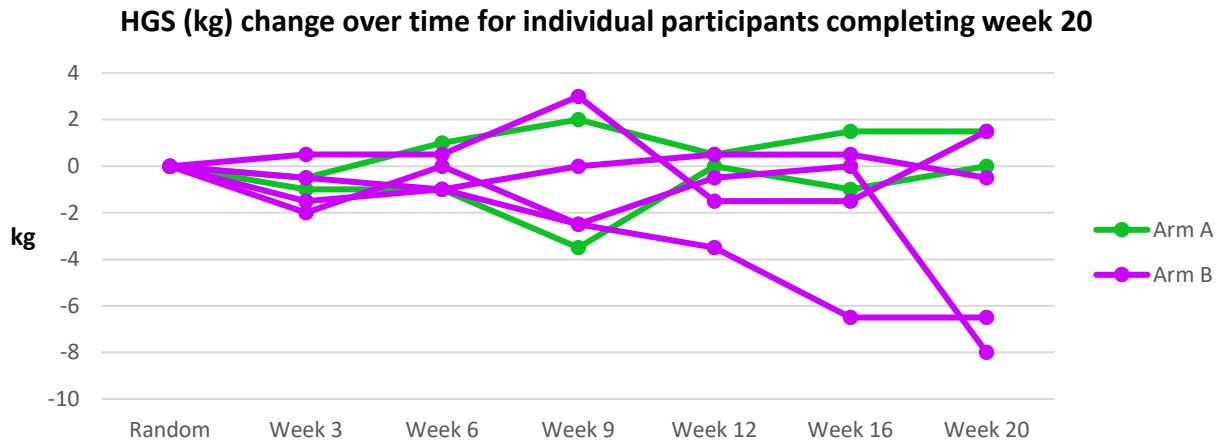
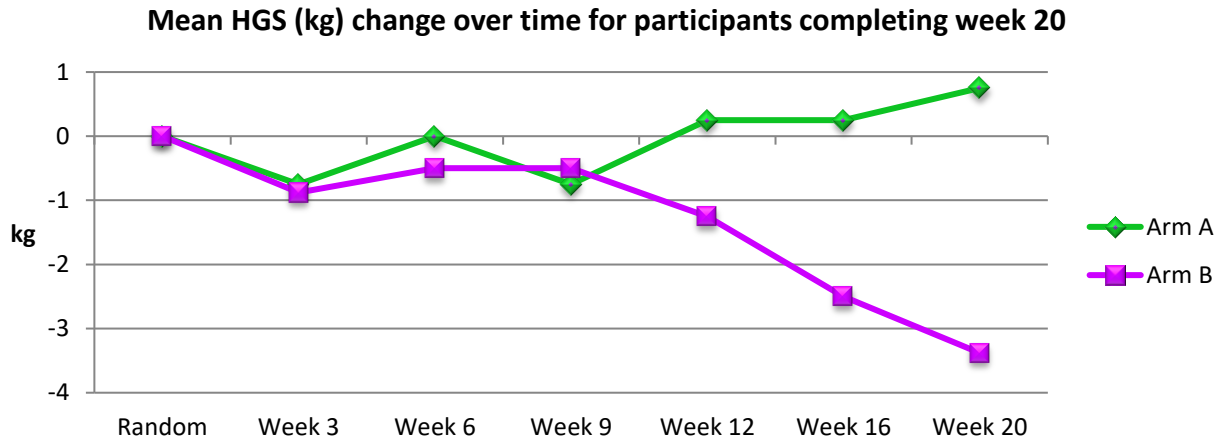


Figure 33 ACCeRT mean change over time for participants completing week 20



Arm A	2	2	2	2	2	2	2
Arm B	4	4	4	4	4	4	4

Figure 32 depicts HGS data from Arm A and B participants completing week 20. Data shows one stable value and one net gain within Arm A participants compared with one net gain, one stable and two net losses within Arm B participants. The mean change at week 20 was +0.8kg (+1.5kg, +0kg) within Arm A compared with -3.4kg (range -8 to +1.5kg, n=4) within Arm B, as depicted in Figure 33. This indicates the reversal and stability of HGS within some participants at week 20, and that the combination of PRT and study medication had minimal effect on HGS over time. There were no differences between Arm B participants completing week 12 and week 20.

The baseline mean was 11.9kg (range 6.5 to 19.5kg, n=7) for females compared with 25.6kg (range 9 to 39kg, n=13) for males, indicating that there was a gender difference in terms of HGS, and future studies should stratify for gender if HGS is the primary endpoint. When compared with age and gender normative data gained from the population study by Massey-Westropp et al. in 2011, it can be seen that for each age group and gender all the participants within the ACCeRT study had lower grip strength values, indicating lower than average muscle strength (Massy-Westropp, Gill, Taylor, Bohannon, & Hill, 2011).

7.3.9 Isometric leg strength MVC analysis (Load cell data only)

Leg strength was assessed by two methods throughout the ACCeRT study. As discussed earlier, originally the PE018 Back Dynamometer (Access Health) was utilised to assess leg strength but this model analysed the strength from both legs. This was then changed to the isometric customised leg extension rig due to both participants' and study team preference, but it had a number of limitations.

Table 39 ACCeRT isometric leg strength MVC analysis (Load Cell only)

	Results in leg strength Newton (N) highest of three attempts (MVC)	
		Newton
Arm A	NA**	
	NA**	
	Baseline only	70.01
	Baseline only	96.24
	Baseline only	283.80
	Baseline	242.33
	Baseline	265.90
	Arm A mean	**191.66**
Arm B	NA*	
	NA**	
	Baseline	465.54
	Baseline only	188.17
	NA**	
	Baseline	165.39
	Baseline only	103.13
	Baseline only	141.01
	Baseline	311.36
	Baseline	443.29
	Baseline	220.34
	Baseline	374.25
	Baseline	114.63
	Arm B mean	**252.71**

*NA PE018 data only
**NA no assessment performed

Table 40 ACCeRT mean (range) in isometric leg strength MVC at baseline by gender

Results in isometric leg strength (N) highest of three attempts (MVC) at baseline by gender		
	Mean	**Range**
Female	135.8	70.0 to 220.3
Male	296.8	96.2 to 465.5

Table 41 ACCeRT mean (range) change over time in isometric leg strength MVC for participants completing week 20

Mean change from baseline to week 20 in isometric leg strength (N) (range) highest of three attempts (MVC)						
	Arm A	**Newton**	**% Difference**	**Arm B**	**Newton**	**% Difference**
Week 20	n=2	+45.6 (+17.2, +73.9)	+17.5%	n=3*	-52.4 (-127.4 to +28.9)	-5.1%

*Please note four participants within Arm B, missing data for one participant

Table 42 Drift analysis of load cell

Mean change of three reading in drift of load cell					
	Jan 2013	**Oct 2015**			
	Calibrated	**kg**	**lbs.**	**difference**	**% difference**
Test 1	25.15 lbs	13.71*	30.23	+5.08	20.19%
Test 2	25.15 lbs	11.55*	25.46	+0.31	1.23%
Test 3	25.15 lbs	11.55*	25.46	+0.31	1.23%
Mean	**Time period 33 months**			**+1.9lbs.**	**7.55%**

*Results gained in kg via load cell and converted to lbs. (x 2.2049) for drift calibration.

Please note that all the study assessments were carried out within The University of Auckland, Clinical Research Centre, which has a shared location and limited equipment storage space. Exercise physiologists from a different university were employed to carry out the leg strength assessment and provide the supervision for the PRT sessions.

Firstly, the exercise physiologists encountered problems gaining results from the load cell on a number of occasions and had to resort to using screwdrivers to tighten connections, reconnecting to the computer and 'manipulating' the wires to gain a signal. Sometimes these actions did not work at the assessment time-point and had to be deferred to a later time-point or the following session. This was later put down to a damaged wire possible due to repeated bending during storage. This was then corrected around February 2014.

Secondly, after the above ‘fix’, all future results were presented in the negative value. The negative results were put down to the polarity, which was accidentally switched when new wiring was put in, and apparently this had no effect on the accuracy of the results.

Thirdly, the equipment did not undergo any calibration during the study. Usually software is used to ‘zero’ the load cell at point of testing. Unfortunately, this aspect was never discussed with the study team until near the end of the study. The exercise physiologists employed for the study did not have access to a technician and access to the Labview software that had the capability to ‘zero’ the load cell prior to each test.

Fourthly, the testing equipment was considered poorly robust due to the above problems. This was again put down to storage issues as all other load cells that the exercise

physiologist used were left in place at a different location and were usually very robust as a consequence.

Fifthly, the acknowledgement that the mechanics of the load cell itself can drift over time as these devices are electronic in nature and the output force in this case is proportional to the voltage, any environmental factors that alter the voltage will therefore alter the recorded force. The only solution to correct for this drift is with software that can 'zero' the load cell. A standard 'weight' was used to determine the drift over the study period. Results presented earlier showed a drift of 7.55% over 33 months. Unfortunately, when the equipment was returned to be fixed it was not known if the load cell was recalibrated at this point. The above drift could potentially be over 20 months instead of 33 months. All the above are factors should be considered in future studies in cancer cachexia, especially if utilising outside expertise and equipment.

Therefore, the results of the isometric leg strength testing were taken with some trepidation, and not further discussed within the thesis. This was further supported by lack of tends within the results and random aberrant results seen in the later participants who were assessed three and four weekly e.g. an Arm A participant had a change from baseline of -11.48% at week 3, +44.71% at week 6, -12.36% at week 9, with the overall range of results from -12.36% to +44.71%. Again, a similar trend was seen within an Arm B participant, with a change from baseline of -40.61% at week 3, +8.05% at week 6, -13.44% at week 9, with the overall range of -40.61% to +8.05%.

The baseline mean was 135.8N (range 70.0 to 220.3N, n=6) for females compared with 296.8N (range 96.2 to 465.5N, n=9) for males, indicating that there was a gender difference in terms of muscle strength, and future studies should stratify for gender if muscle strength is the primary endpoint.

The reliability of the set up and load cell utilised within the ACCeRT study was previously tested on eight subjects four times then re-tested for additional four times 60 minutes later, with a reliability coefficient of 0.95 and coefficient of variation of 3.8% in the first test and 4.1% in the re-test (Presland, Dowson, & Cairns, 2005). Unfortunately, there is no data available for weekly measurement and the difference within an untrained population, to quantify a clinical meaningful difference.

It can be concluded from the ACCeRT study that all participants were happy to undergo this testing. Employing a strong multi-disciplined team to give advice regarding the 'gold-standard' of muscle strength testing is pivotal at the designing and implementation stage.

7.3.10 Arm B Progressive resistance training participant reports

Participants allocated to Arm B attended two individualised progressive resistance-training sessions per week for the study period of 20 weeks.

Table 43 Table of planned progression from baseline to week 20

	Phase I Weeks 1 to 4	Phase II Weeks 5 to 8	Phase III Weeks 9 to 12	Phase IV Weeks 13 to 16	Phase V Weeks 17 to 20
	PRT 1 to 8	PRT 9 to 16	PRT 17 to 24	PRT 25 to 32	PRT 33 to 40
PLANNED	'very light' to 'light' BORG 8-11	'somewhat hard' BORG 12-13		'hard' BORG 14-15	

Table 44 LOWER and UPPER body BORG RPE for Arm B participants completing to week 12

	LOWER			UPPER	
	Baseline	**Week 12**		**Baseline**	**Week 12**
	11	11		11	11
	11	13		11	13
	11	11		11	11
	11	15		11	15
	11	13		11	13
	9	11		9	11
	11	13		11	13
Mean	**10.7**	**12.4**	**Mean**	**10.7**	**12.4**

Table 45 LOWER and UPPER body BORG RPE for Arm B participants completing to week 20

	LOWER			UPPER	
	Baseline	**Week 20**		**Baseline**	**Week 20**
	11	13		11	13
	11	15		11	15
	9	11		9	11
	11	15		11	15
Mean	**10.5**	**13.5**	**Mean**	**10.5**	**13.5**

High adherence rates and high scores on the primary endpoint acceptable questionnaire showed that the participants found engaging in the PRT sessions acceptable. There were no exercise-related adverse events. At each session, participants were assessed and the exercise programme adapted.

It was decided to format the reporting of the PRT sessions in terms of the planned training programme, and if the participants at each phase of the programme either

under-achieved, achieved or over-achieved. This would allow the assessment of the planned programme in terms of achievability in this population, along with gaining data on potentially increasing the programme in terms of sessions.

Results of the individual participants' reports (appendix) showed that all achieved the planned regimen and BORG RPE 11 'light' at the end of phase I-weeks one to four, except two participants. As discussed earlier, one participant only attended three out of six PRT sessions (50%) due to ill health within this first phase, and was withdrawn from the study. Another participant continued throughout the 20 week study, and had the lowest attendance at 80%. As discussed earlier, this participant was the youngest in age to be enrolled onto the study and was the main caregiver for young children, and found it difficult at times to attend for family reasons. Coupled with the historical neck, bilateral hips and lower spine injury from a childhood road traffic accident, her programme was modified to include a slower progression through the intensity levels across the programme phases, and under-achieved at each phase.

Results for phase II showed three participants under-achieved, two participants achieved, and five participants all over-achieved. Results for phase III showed three participants under-achieved, three achieved, and one over-achieved. Results for phase IV showed two participants under-achieved and three over-achieved. Results for phase V showed two participants under-achieved, and two participants achieved.

The results show a number of events. Firstly, that 83% (n=10/12) participants with various entry levels of fitness and weight loss managed to achieve the planned programme within phase I. Secondly, that all participants under-achieved before exiting the study for progression, while one participant had achieved within phase II before exiting to commence targeted therapy. Thirdly, that the above low volume, low intensity training progressing to a moderate volume, moderate-high intensity training programme was both acceptable and safe within a NSCLC cachectic population.

7.3.11 Participant reported outcome analysis

All participants completed the FAACT questionnaire at each study visit, except for one Arm A participant who was not able to speak or read English. There was an issue with one Arm B participant at the randomisation/baseline visit who did not complete page two of the questionnaire and this was not detected until a later date; therefore, a FAACT total score could not be calculated. However, it was possible to calculate the separate anorexia/cachexia score (ACS) and physical well-being (PWB) score.

For the purpose of the thesis, only the FAACT-ACS (total score 48) and FAACT-PWB (total score 28) will be discussed.

7.3.11.1 FAACT-ACS

From the sensitivity to change in Performance Status Rating table for the FAACT (see appendix), it can been seen for the additional concerns anorexia/cachexia subscale (ACS) with a baseline score of 21.4, a mean change in score of 5 (SD 10.6) would indicate a worsened PSR, while a mean change score of 9.2 (SD 8.8) would indicate no change and 12.2 (10.4) would indicate improved PSR.

Results for FAACT-ACS ≤+5 change defined as worsened Performance Status Rating (PSR), between +5.1 to +12.1 change defined as stable PSR, and ≥+12.2 change defined as improved PSR, as per published guidelines. High scores correspond with high levels of patient reported outcome.

Figure 34 ACCeRT change over time in FAACT-ACS for individual participants completing week 12

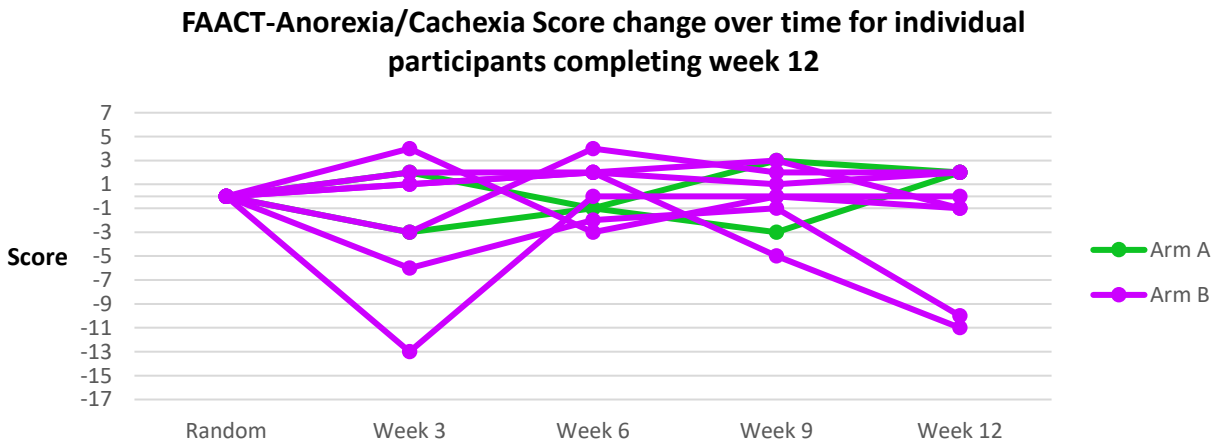


Figure 35 ACCeRT mean change over time in FAACT-ACS for participants completing week 12

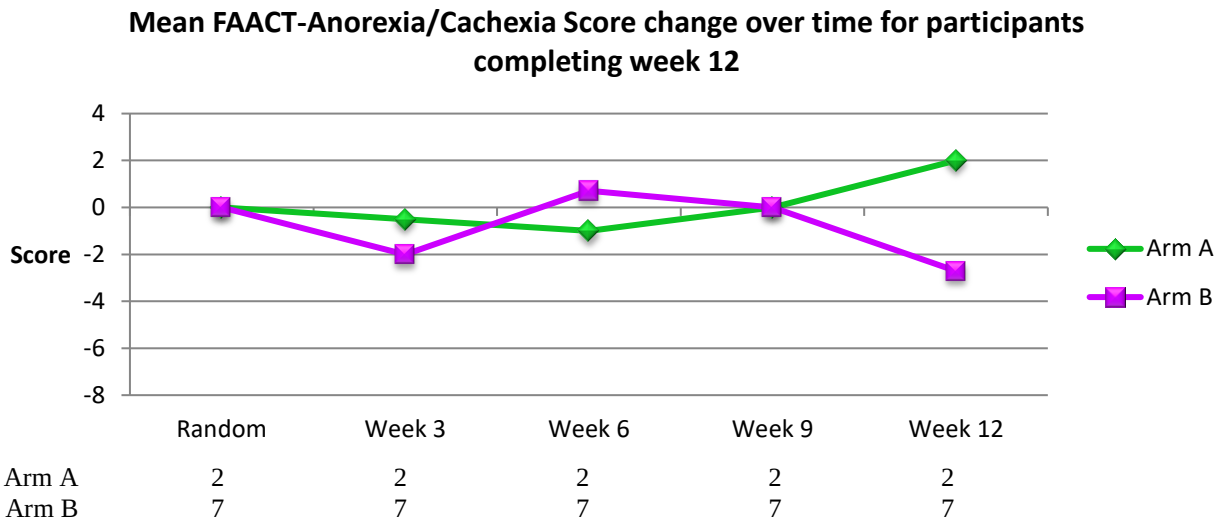


Figure 34 depicts FAACT-ACS data from Arm A and B participants completing week 12. Data shows two worsened PSR scores within Arm A participants compared with seven worsened within Arm B participants. The mean change at week 12 was +2 (+2, +2) within Arm A compared with -2.7 (range -11 to +2, n=7) within Arm B, as depicted in Figure 35.

Figure 36 ACCeRT change over time in FAACT-ACS for individual participants completing week 20

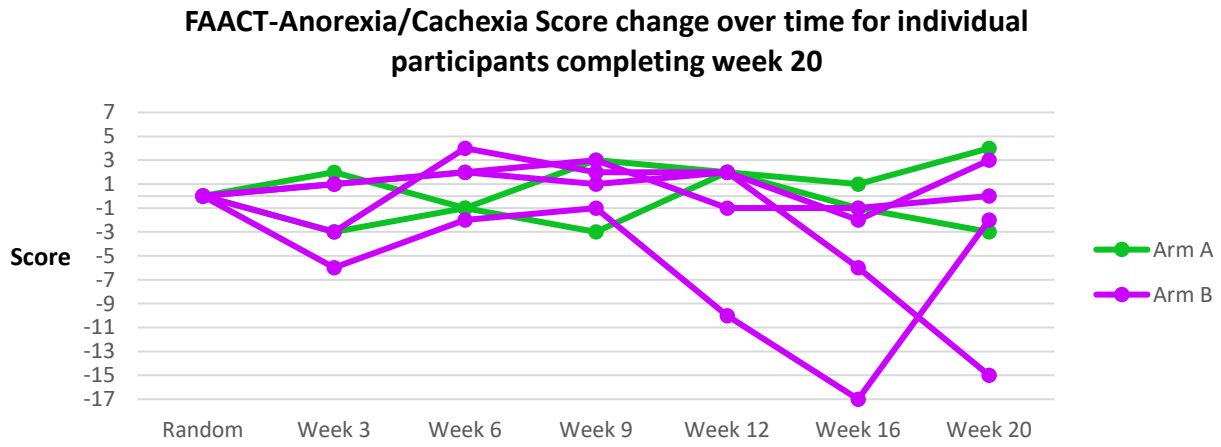


Figure 37 ACCeRT mean change over time in FAACT-ACS for participants completing week 20

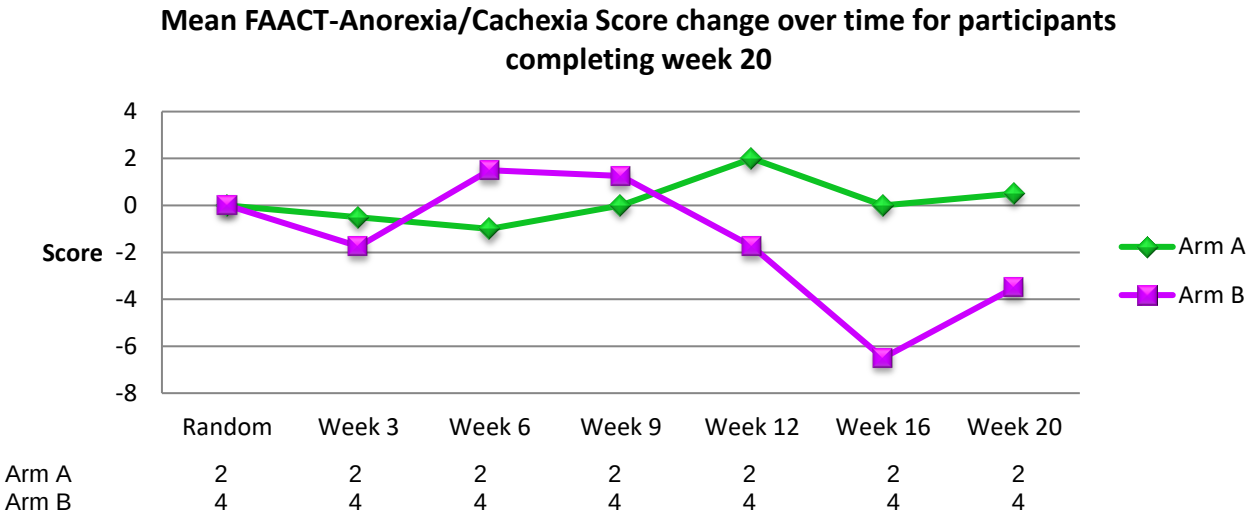


Figure 36 depicts FAACT-ACS data from Arm A and B participants completing week 20. Data shows two worsened PSR scores within Arm A participants compared with four worsened within Arm B participants. The mean change at week 20 was +0.5 (+4, -3) within Arm A compared with -3.5 (range -15 to +3, n=4) within Arm B, as depicted in Figure 37. There were no differences between Arm B participants completing week 12 and week 20.

7.3.11.2 FAACT-PWB

From the sensitivity to change in Performance Status Rating table for the FAACT (see appendix), it can been seen that for the physical well-being (PWB) with a baseline score of 17.6, a mean change in score of -2.1 (SD 6.9) would indicate a worsened PSR, while a mean change score of 1.7 (SD 4.8) would indicate no change and 3.5 (6.6) would indicate improved PSR.

Results for FAACT-PWB ≤-2.1 change defined as worsened PSR, between -2 to +3.4 change defined as stable PSR, and ≥+3.5 change defined as improved PSR, as per published guidelines.

Figure 38 ACCeRT change over time in FAACT-PWB individual participants completing week 12

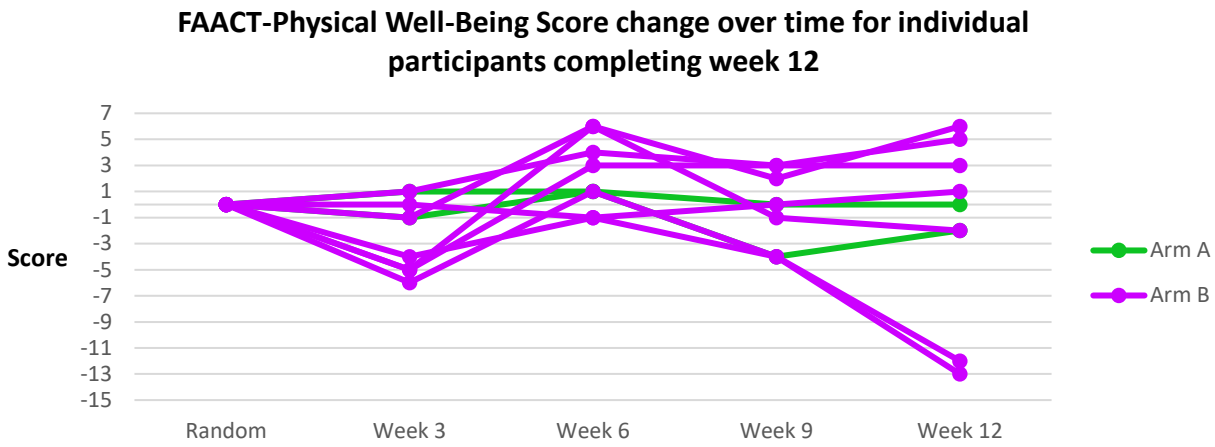


Figure 39 ACCeRT mean change over time in FAACT-PWB for participants completing week 12

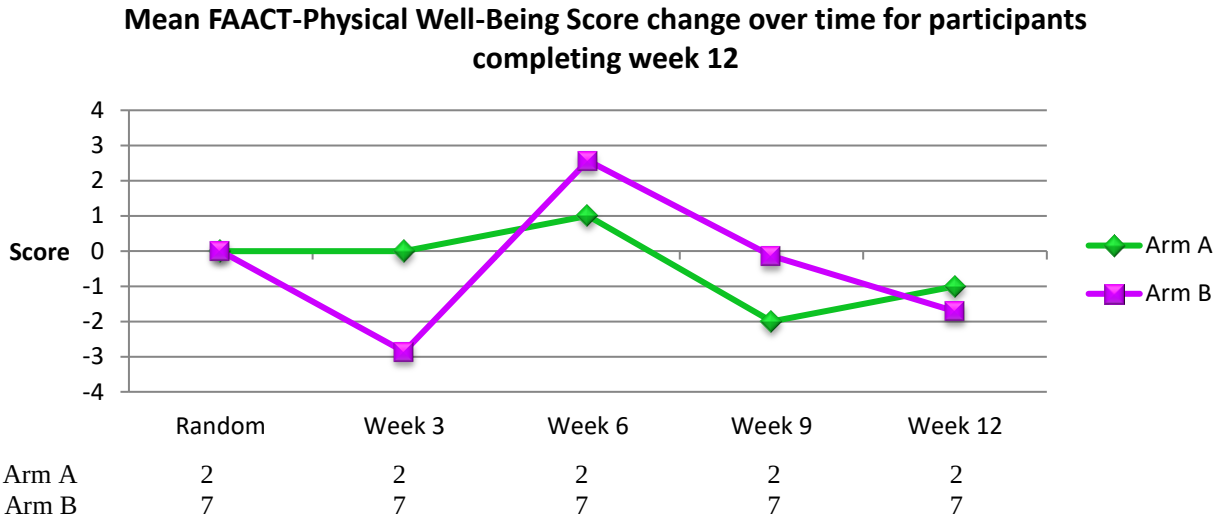


Figure 38 depicts FAACT-PWB data from Arm A and B participants completing week 12. Data shows two stable PSR scores within Arm A participants compared with two improved, three stable and two worsened within Arm B participants. The mean change at week 12 was -1 (+0, -2) within Arm A compared with -1.7 (range -13 to +6, n=7) within Arm B, as depicted in Figure 39. This would indicate a benefit in PRT and study medication within some participants within Arm B only.

Figure 40 ACCeRT change over time in FAACT-PWB individual participants completing week 20

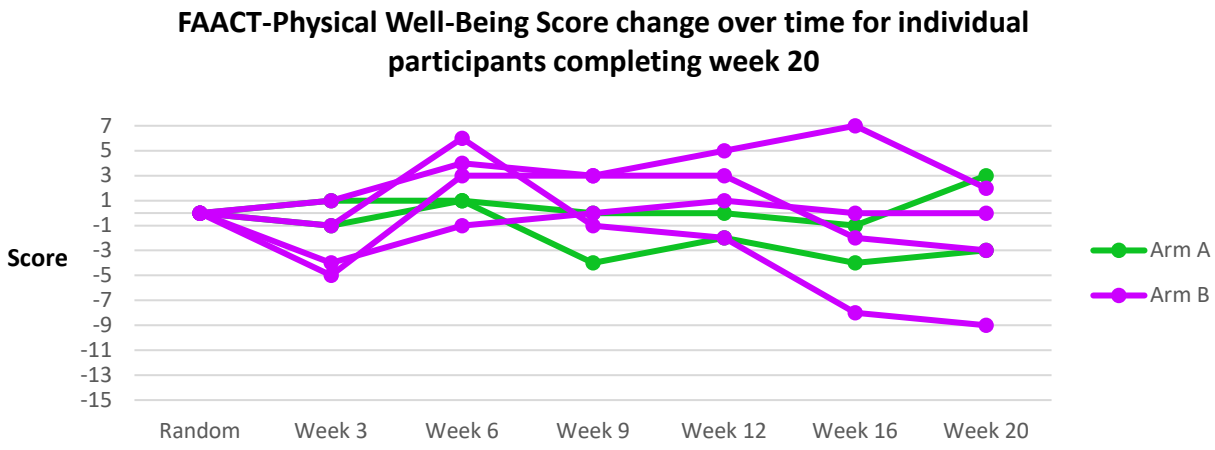
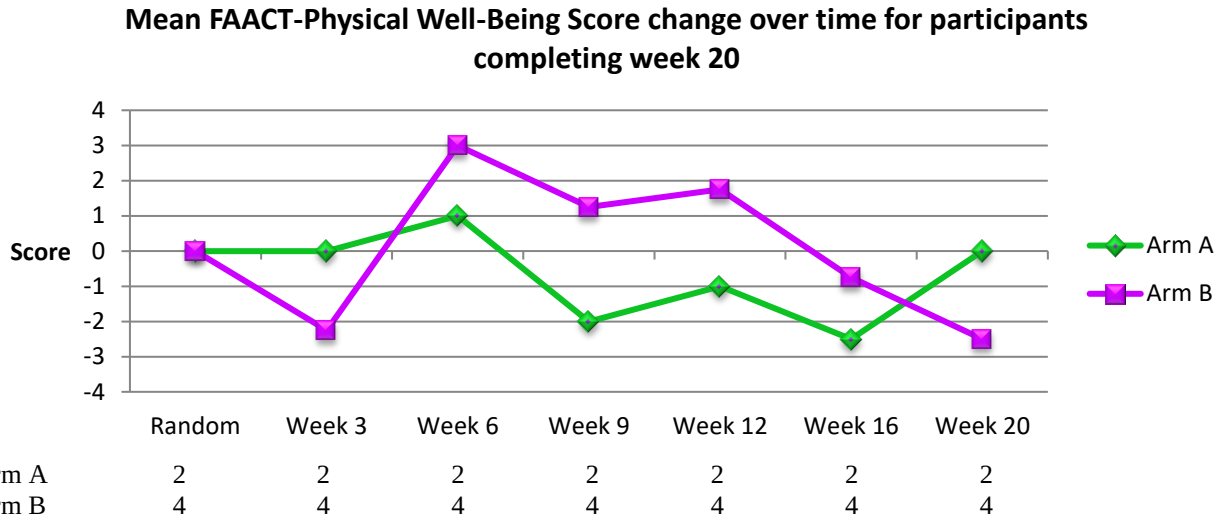


Figure 41 ACCeRT mean change over time in FAACT-PWB for participants completing week 20



Arm A	2	2	2	2	2	2	2
Arm B	4	4	4	4	4	4	4

Figure 40 depicts FAACT-PWB data from Arm A and B participants completing week 20. Data shows one stable and one worsened PSR scores within Arm A participants compared with two stable and two worsened within Arm B participants. The mean change at week 20 was +0 (+3, -3) within Arm A compared with -2.5 (range -9 to +2, n=4) within Arm B, as depicted in Figure 41 Interestingly, Arm B participants completing week 20 had higher scores when compared with Arm B participants completing week 12.

7.3.11.3 MFSI-SF

All participants completed the MFSI-SF questionnaire at each study visit, except for one Arm A participant who was not able to speak or read English. For the purpose of this thesis, only the MFSI-SF-Total score will be discussed, range of -24 to 96.

Results for MFSI-SF-Total score ≥+5.1 change defined as worsened, between +5 to -5 change defined as stable, and ≥-5.1 change defined as improved, estimated by study team. Please note that higher scores indicate increased fatigue and low scores correspond with high levels of fatigue.

Figure 42 ACCeRT change over time in MFSI-SF-Total score for individual participants completing week 12

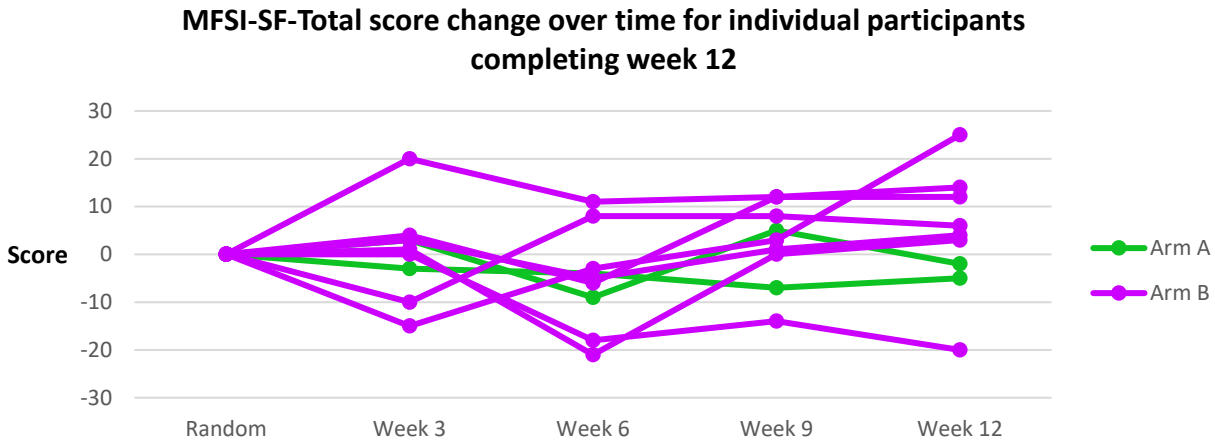


Figure 43 ACCeRT mean change over time in MFSI-SF-Total score for participants completing week 12

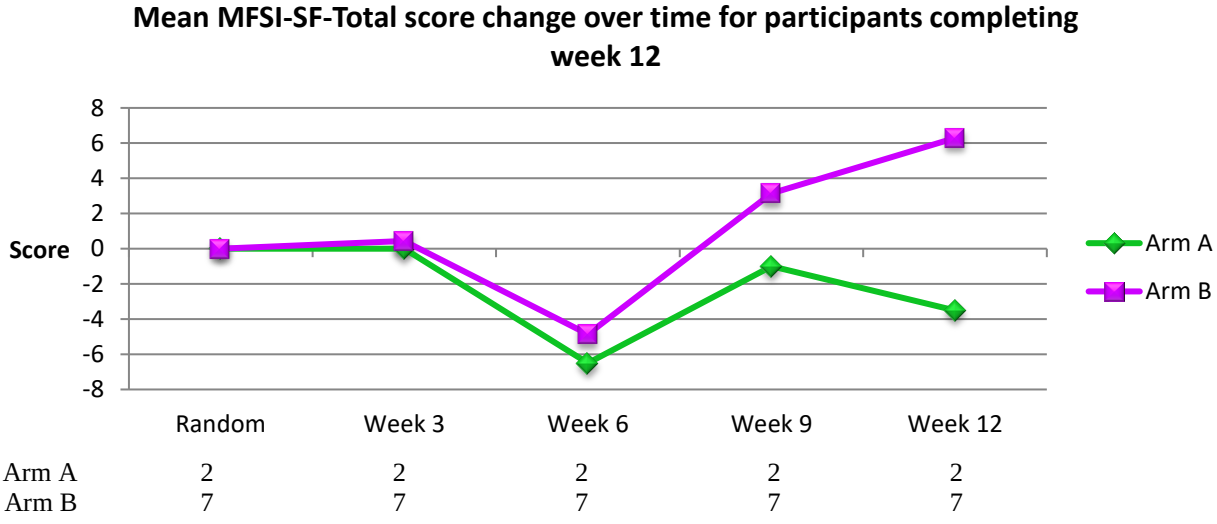


Figure 42 depicts MFSI-SF-Total score data from Arm A and B participants completing week 12. Data shows two stable scores within Arm A participants, compared with one improved, two stable and four worsened within Arm B participants. The mean change at week 12 was

-3.5 (-5, -2) within Arm A compared with +6.3 (range -20 to +25, n=7) within Arm B, as depicted in Figure 43.

Figure 44 ACCeRT change over time in MFSI-SF-Total score for individual participants completing week 20

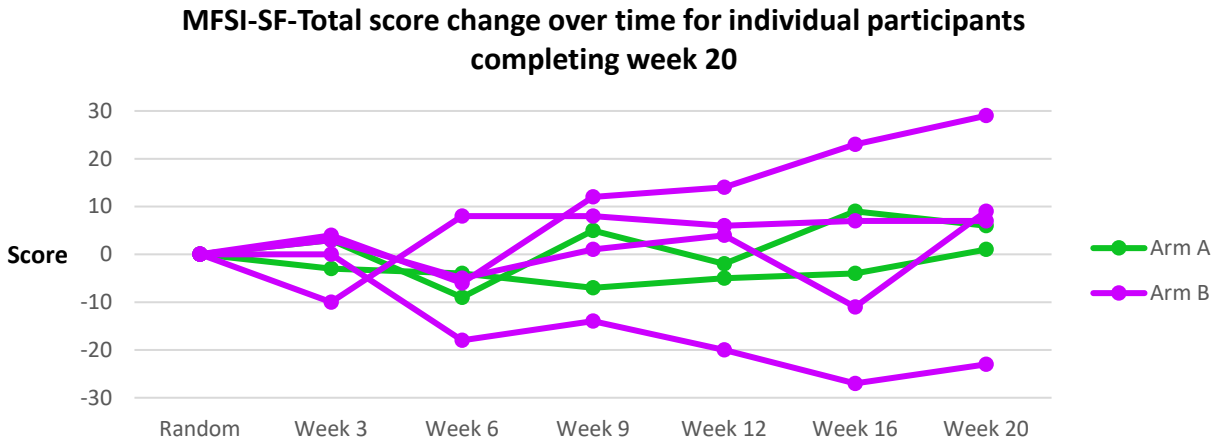
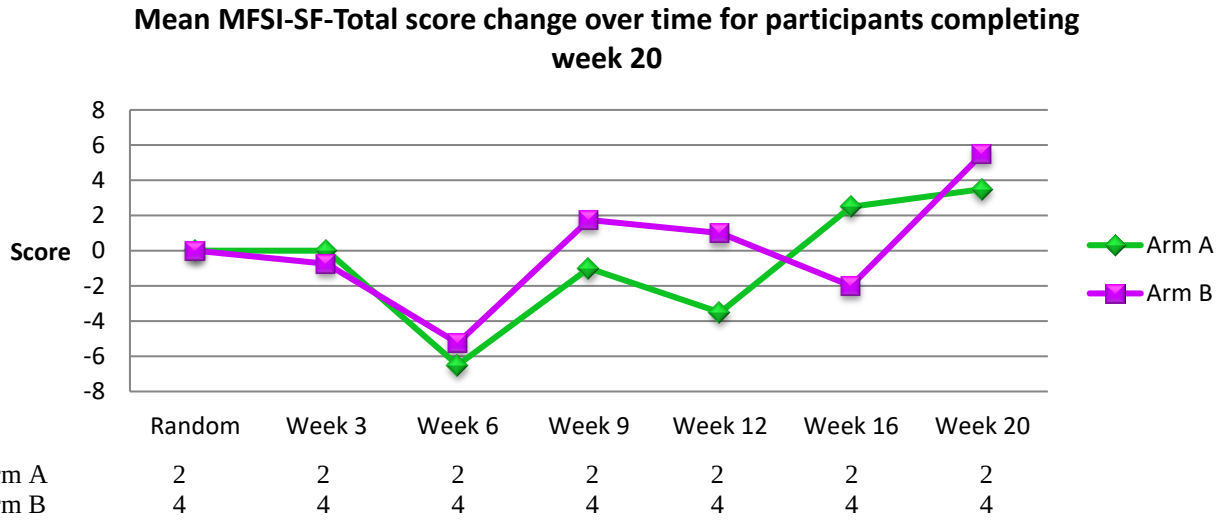


Figure 45 ACCeRT mean change over time in MFSI-SF-Total score for participants completing week 20



Arm A	2	2	2	2	2	2	2
Arm B	4	4	4	4	4	4	4

Figure 44 depicts MFSI-SF-Total score data from Arm A and B participants completing week 20. Data shows one stable and one worsened scores within Arm A participants, compared with one improved and three worsened within Arm B participants. The mean change at week 20 was +3.5 (+1, +6) within Arm A compared with +5.5 (range -23 to +29, n=4) within Arm B, as depicted in Figure 45. For Arm B participants completing week 20 generally showed less fatigue when compared with Arm B participants completing week 12.

7.3.11.4 WHOQOL-BREF

7.3.11.4.1 WHOQOL-BREF overall QOL

All participants completed the English version of the WHOQOL-BREF questionnaire at each study visit, except for one Arm A participant who completed the Mandarin version. For the purpose of this thesis, both overall QOL score (total score of 10) and subscale physical score (range of 7 to 35) will be discussed.

Results for WHOQOL-BREF overall QOL score and physical score ≥-5.1 change defined as worsened, between -5 to +5 change defined as stable, and ≥+5.1 change defined as improved, estimated by study team. High scores correspond with high levels of patient reported outcome.

Figure 46 ACCeRT change over time in WHOQOL-BREF overall QOL score for individual participants completing week 12

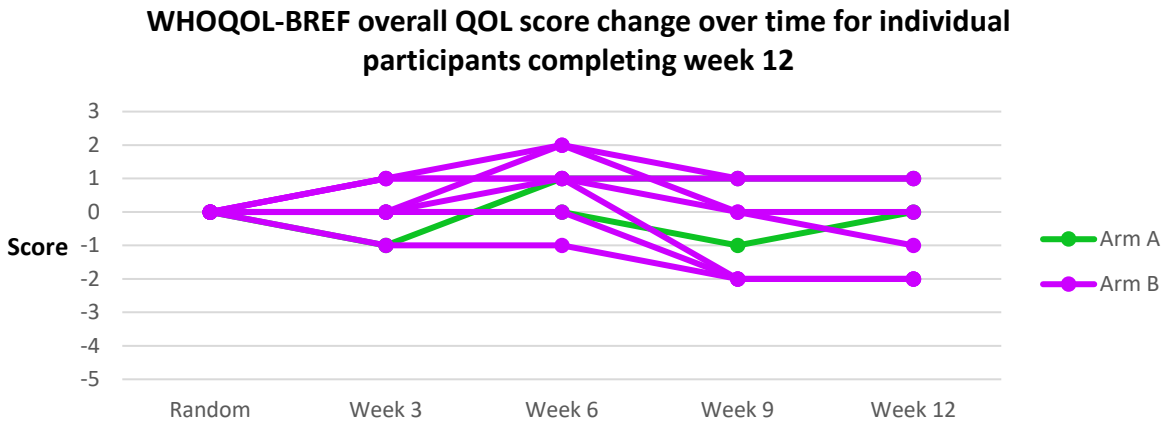


Figure 47 ACCeRT mean change over time in WHOQOL-BREF overall QOL score for participants completing week 12

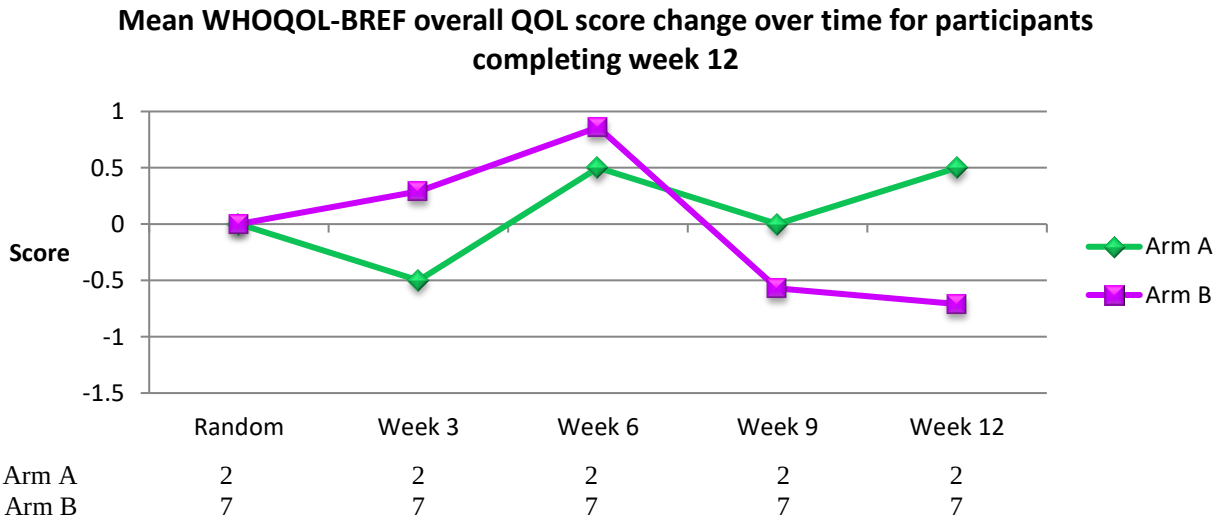


Figure 46 depicts WHOQOL-BREF overall QOL data from Arm A and B participants completing week 12. Data shows two stable scores within Arm A participants, compared with

seven stable within Arm B participants. The mean change at week 12 was +0.5 (+0, +1) within Arm A compared with -0.7 (range -2 to +1, n=7) within Arm B, as depicted in Figure 47.

Figure 48 ACCeRT change over time in WHOQOL-BREF overall QOL score in individual participants completing week 20

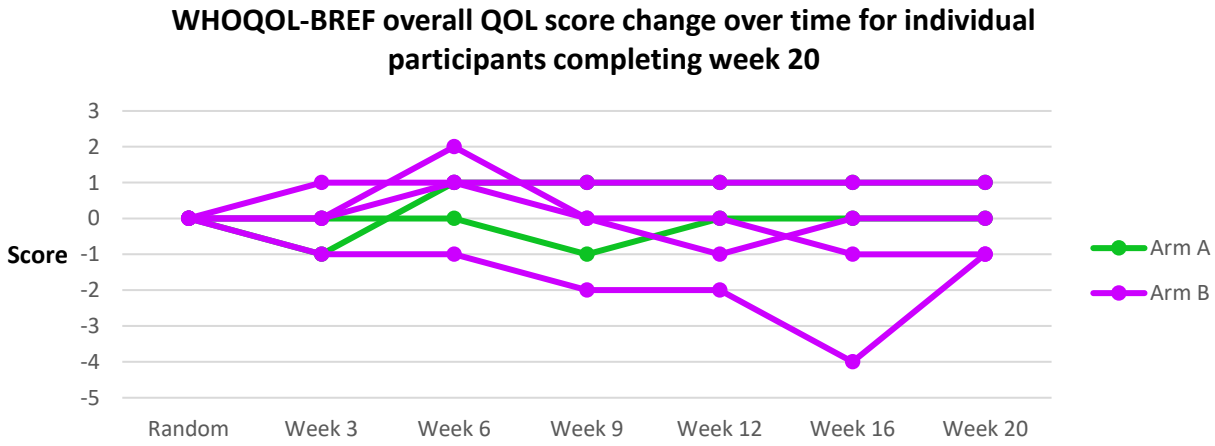
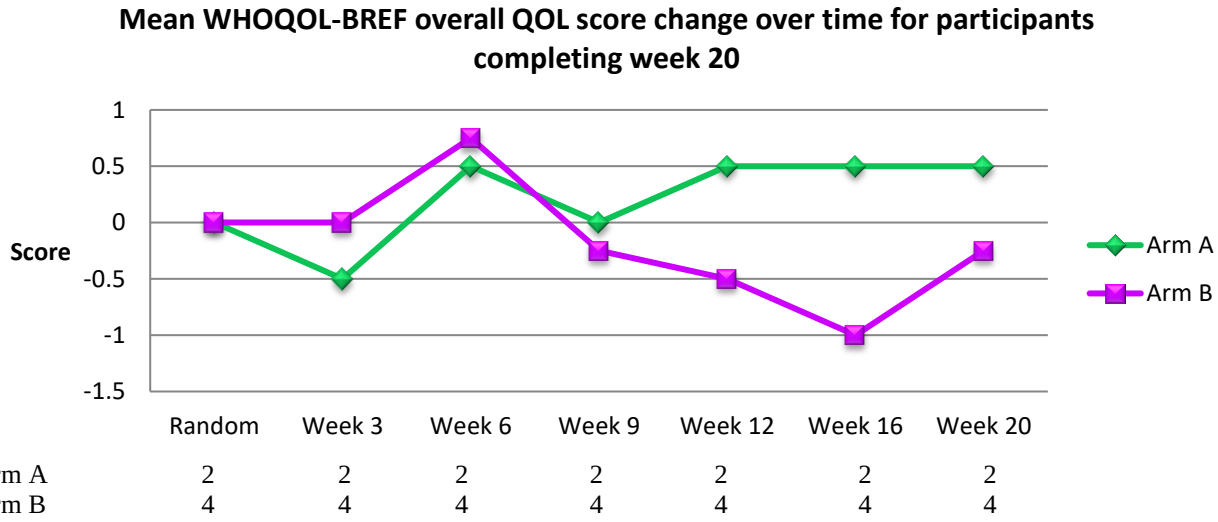


Figure 49 ACCeRT mean change over time in WHOQOL-BREF overall QOL score for participants completing week 20



Arm A	2	2	2	2	2	2	2
Arm B	4	4	4	4	4	4	4

Figure 48 depicts WHOQOL-BREF overall QOL score data from Arm A and B participants completing week 20. Data shows two stable scores within Arm A participants, compared with four stable within Arm B participants. The mean change at week 20 was +0.5 (+0, +1) within Arm A compared with -0.3 (range -1 to +1, n=4) within Arm B, as depicted in Figure 49.

Both sets of results from Arm A and Arm B would indicate stable scores over time. This could be due to the possibility that overall quality of life for these participants was generally stable throughout the study period, possibly attributed to the study regimen, or that the instrument was not sensitive enough to detect small differences. There were no differences between Arm B participants completing week 12 or 20.

7.3.11.4.2 WHOQOL-BREF physical

Figure 50 ACCeRT change over time in WHOQOL-BREF physical score for individual participants completing week 12

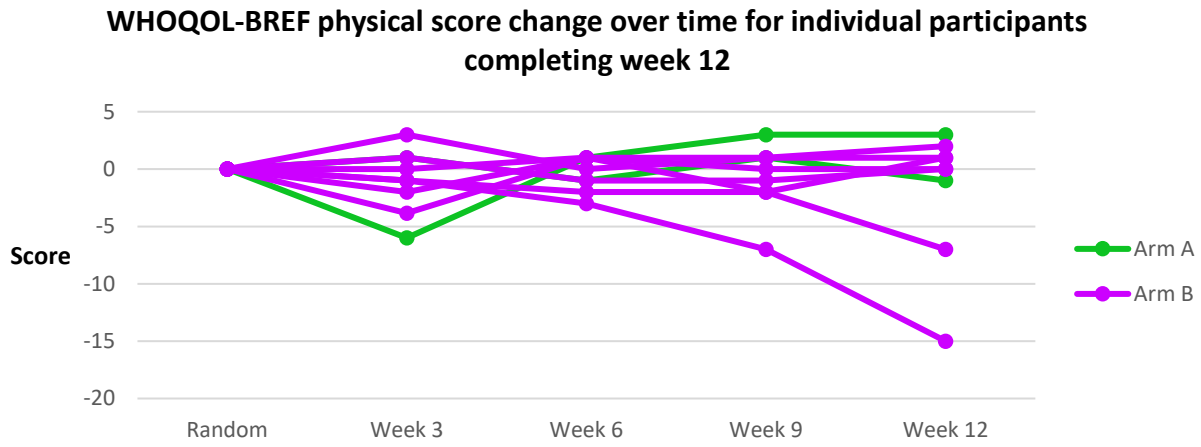


Figure 51 ACCeRT mean change over time in WHOQOL-BREF physical score for participants completing week 12

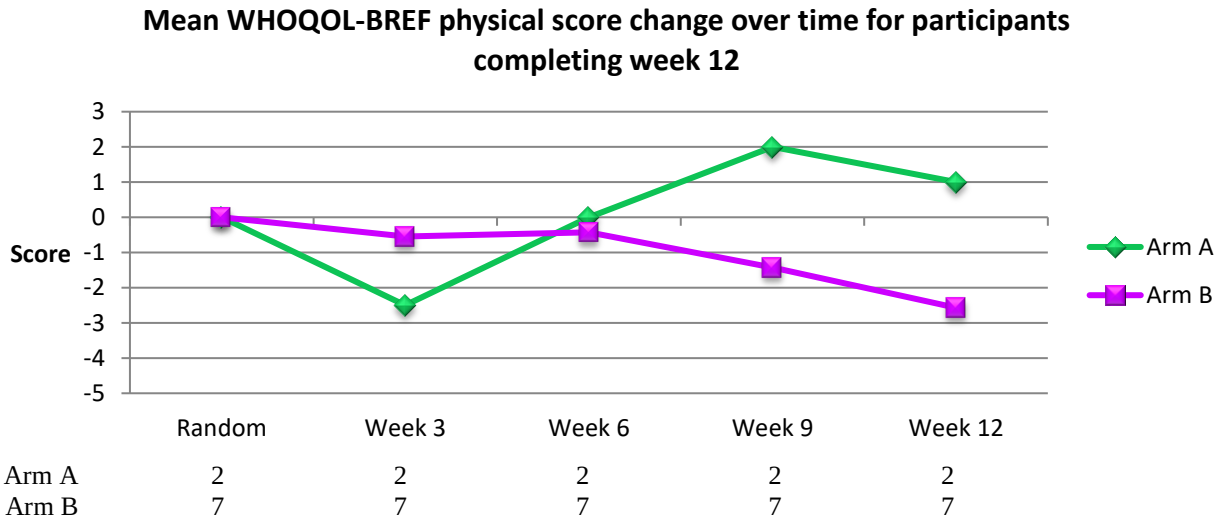


Figure 50 depicts WHOQOL-BREF physical score data from Arm A and B participants completing week 12. Data shows two stable scores within Arm A participants, compared with five stable and two worsened within Arm B participants. The mean change at week 12 was +1 (-1, +3) within Arm A compared with -2.6 (range -15 to +2, n=7) within Arm B, as depicted in Figure 51.

Figure 52 ACCeRT change over time in WHOQOL-BREF physical score for individual participants completing week 20

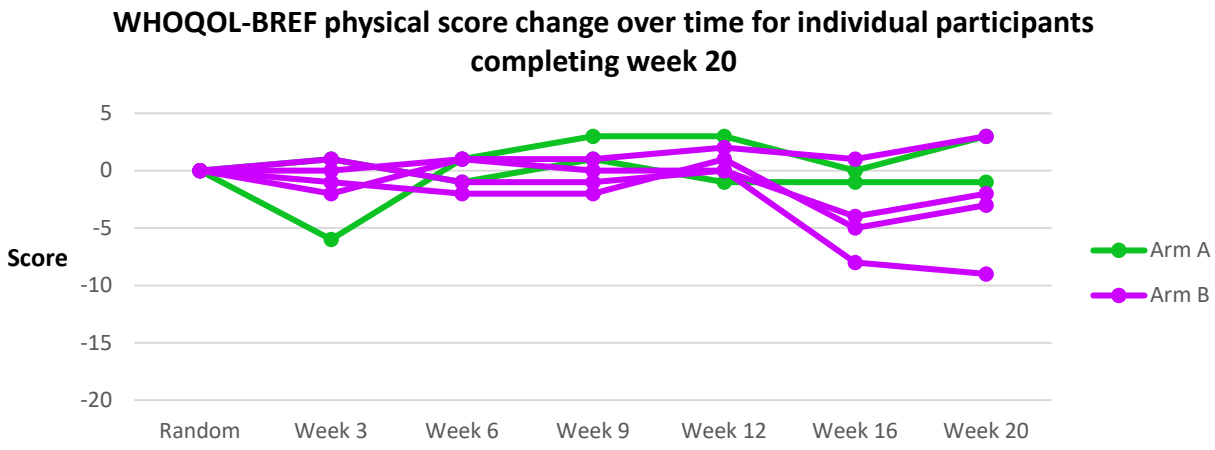
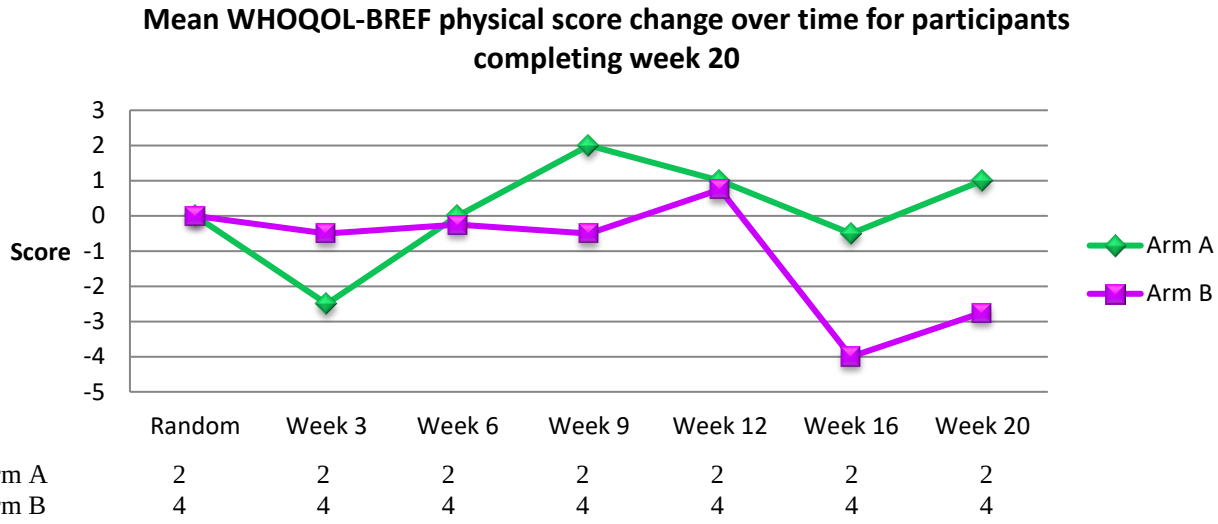


Figure 53 ACCeRT mean change over time in WHOQOL-BREF physical score for participants completing week 20



Arm A	2	2	2	2	2	2	2
Arm B	4	4	4	4	4	4	4

Figure 52 depicts WHOQOL-BREF physical score data from Arm A and B participants completing week 20. Data shows two stable scores within Arm A participants, compared with three stable and one worsened within Arm B participants. The mean change at week 20 was +1 (-1, +3) within Arm A compared with -2.8 (range -3 to +3, n=4) within Arm B, as depicted in Figure 53. Both sets of results from Arm A and Arm B would indicate stable scores over time. Interestingly, Arm B participants completing week 20 had higher scores when compared with Arm B participants completing week 12.

7.3.12 Prognostic/performance status analysis

Please note the change in albumin level testing occurred on the 25th August 2014. This had the following effect on participant data: participants 002 through to 018 all study visit levels measured by the same previous method. Participant 019 measured by previous method for visits baseline through to week 12. New method for weeks 16 and 20. Participants 020 to 022 all levels measured by the new method.

Results for albumin (g/L), ≥-5.1g/L change defined as net loss, between -5 to +5g/L change defined as stable, and ≥+5.1g/L change defined as net gain, estimated by study team.

Results for CRP (mg/L), ≥-10.1mg/L change defined as decreased, between -10 to +10mg/L change defined as stable, and ≥+10.1mg/L change defined as increased, estimated by study team.

7.3.12.1.1 Albumin

Figure 54 ACCeRT change over time in albumin level for individual participants completing week 12

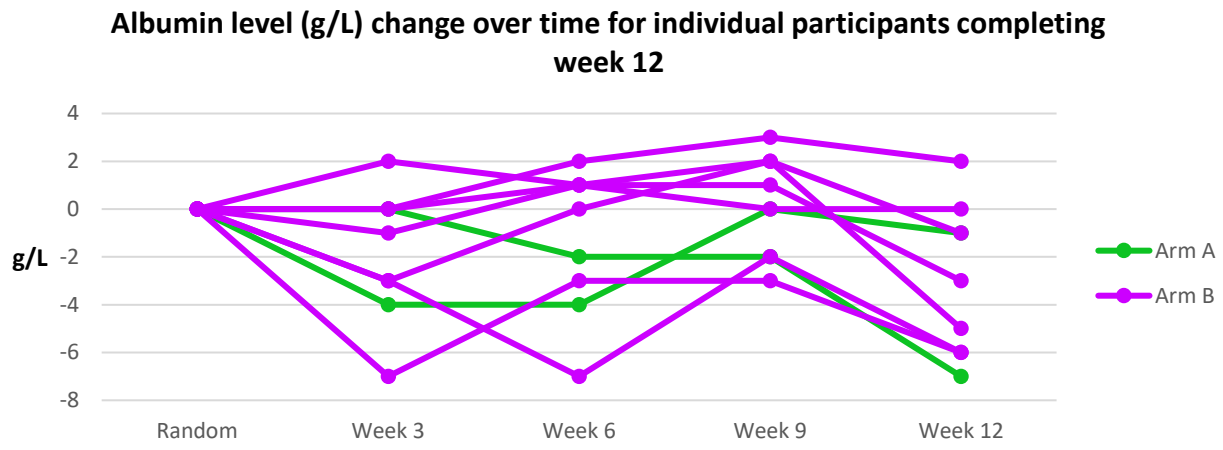
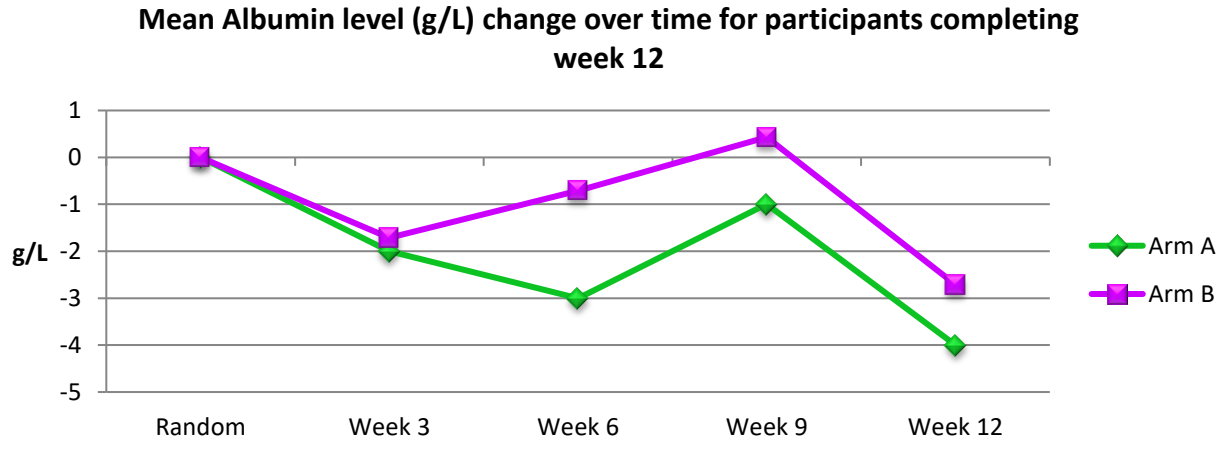


Figure 55 ACCeRT mean change over time in albumin level for participants completing week 12



Arm A	2	2	2	2	2
Arm B	7	7	7	7	7

Figure 54 depicts albumin data from Arm A and B participants completing week 12. Data shows one stable level and one net loss within Arm A participants, compared with five stable and two net losses within Arm B participants. The mean change at week 12 was -4g/L (-1g/L, -7g/L) within Arm A compared with -2.7g/L (range -6 to +2g/L, n=7) within Arm B as depicted in Figure 55.

Figure 56 ACCeRT change over time in albumin level for individual participants completing week 20

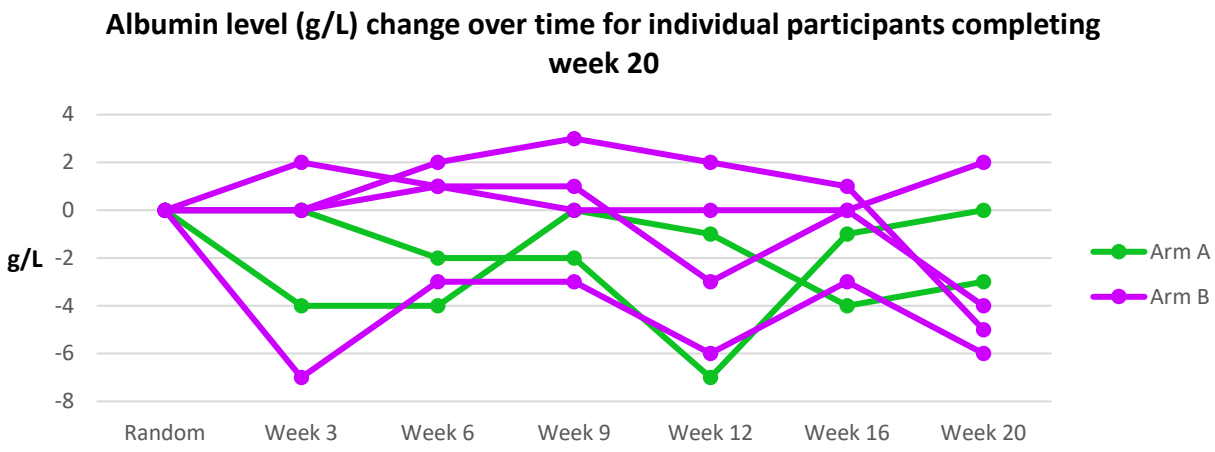
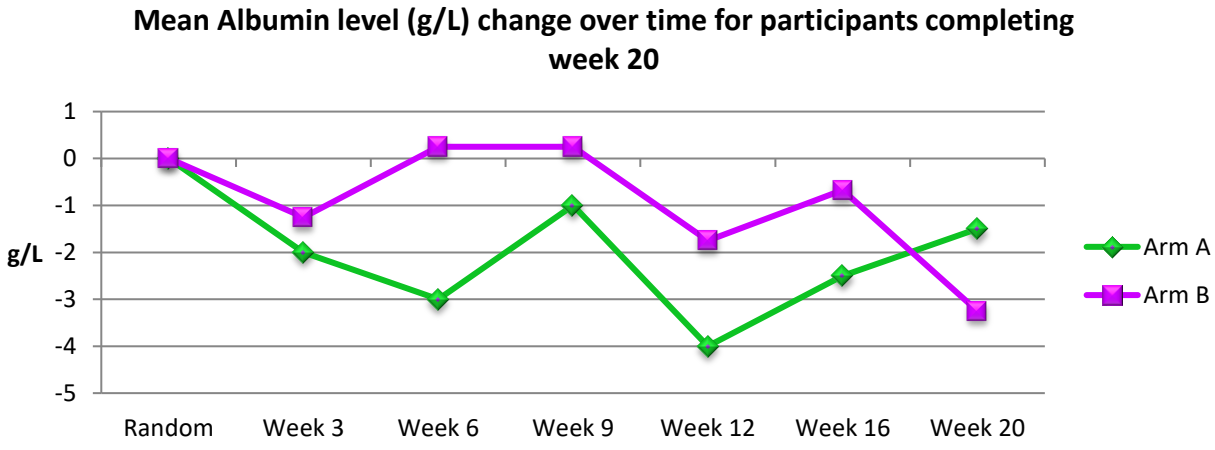


Figure 57 ACCeRT mean change over time in albumin level for participants completing week 20



Arm A	2	2	2	2	2	2	2
Arm B	4	4	4	4	4	4	4

Figure 56 depicts albumin data from Arm A and B participants completing week 20. Data shows two stable levels within Arm A participants, compared with three stable and one net loss within Arm B participants. The mean change at week 20 was -1.5g/L (-3g/L, +0g/L) within Arm A compared with -3.3g/L (range -6 to +2g/L, n=4) within Arm B, as depicted in Figure 57.

The above results show from week 6 to 16, on average, a slower decline in nutritional status within Arm B compared with Arm A. Arm B participants completing to week 20 had

improved albumin levels when compared with Arm B participants completing to week 12. Overall, the mean albumin levels changed from 39 to 37.5g/L at week 20 within Arm A and 36.8 to 33.5g/L at week 20 within Arm B. These changes were small over a period of 20 weeks in a refractory cachexia population.

7.3.12.1.2 CRP

Figure 58 ACCeRT change over time in CRP level for individual participants completing week 12

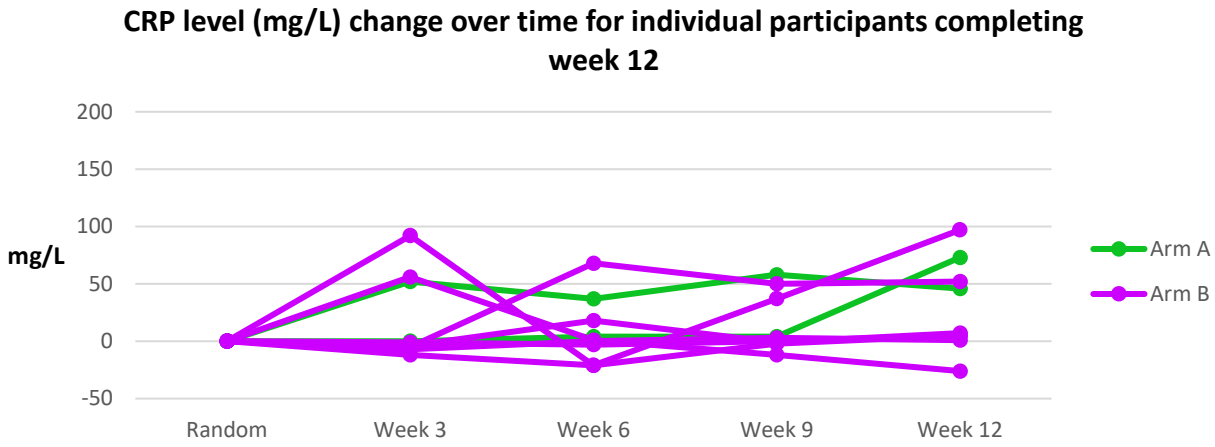


Figure 59 ACCeRT mean change over time in CRP level for participants completing week 12

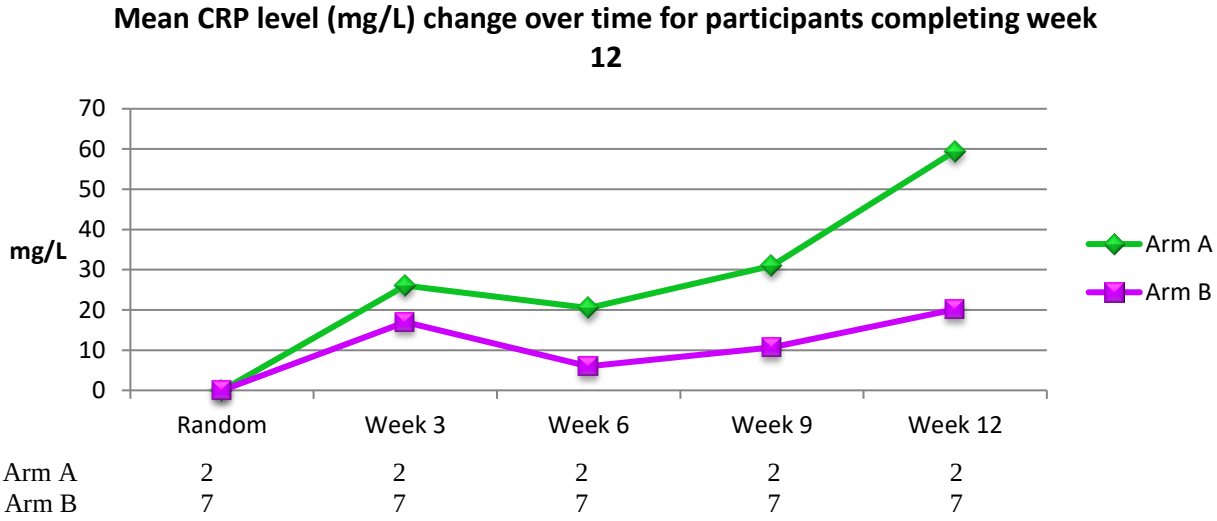


Figure 58 depicts CRP data from Arm A and B participants completing week 12. Data shows two net increased levels within Arm A participants, compared with one net decrease, four stable and two net increases within Arm B participants. The mean change at week 12 was +59.5mg/L (+46mg/L, +73mg/L) within Arm A compared with +20.1mg/L (range -26 to +97mg/L, n=7) within Arm B, as depicted in Figure 59.

Figure 60 ACCeRT change over time in CRP level for individual participants completing week 20

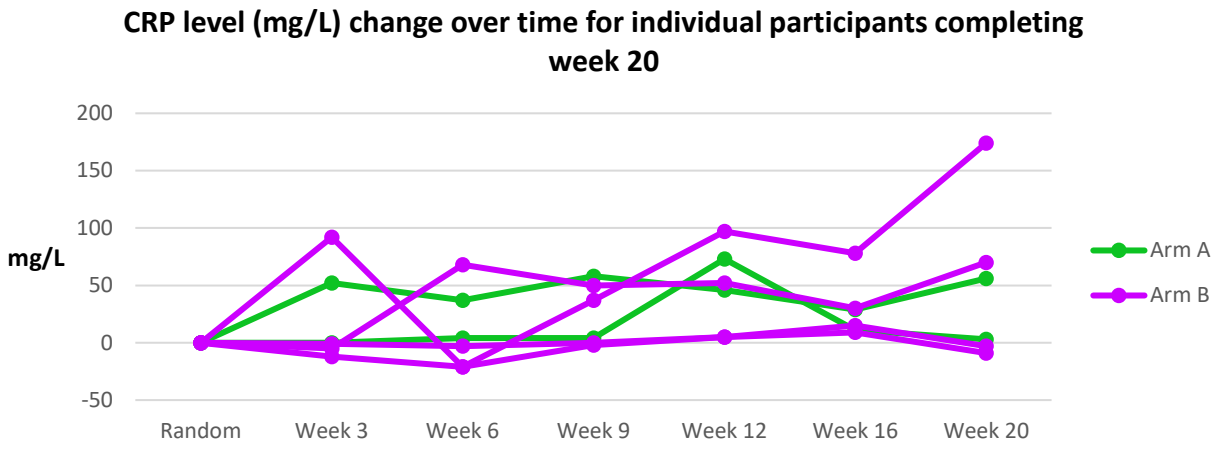
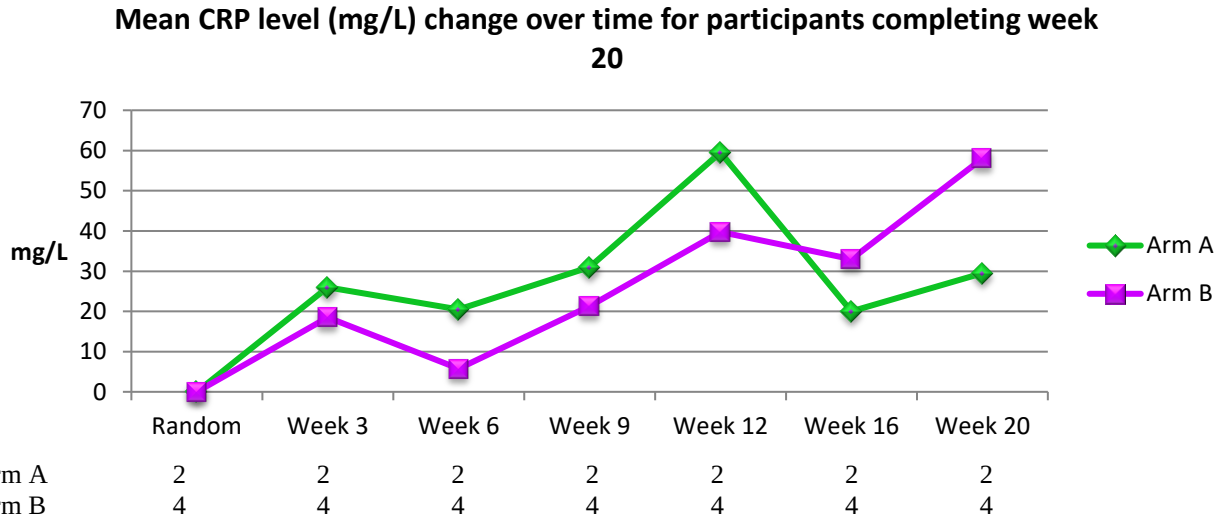


Figure 61 ACCeRT mean change over time in CRP level for participants completing week 20



Arm A	2	2	2	2	2	2	2
Arm B	4	4	4	4	4	4	4

Figure 60 depicts CRP data from Arm A and B participants completing week 20. Data shows one stable and one net increased level within Arm A participants, compared with two stable and two net increases within Arm B participants. The mean change at week 20 was +29.5mg/L (+56mg/L, +3mg/L) within Arm A compared with +58mg/L (range -9mg/L to +174mg/L, n=4) within Arm B, as depicted in Figure 61.

The trend shown within Arm B indicates that the levels of inflammation was reduced until week 9, and then levels start to increase from weeks 12 to 20. CRP levels on average were lower within Arm B compared with Arm A at weeks 3 to 12. This could be attributed to the PRT sessions and study medication allocated to Arm B. There were no differences between Arm B participants completing week 12 or week 20.

High CRP ≥75 mg/L vs Low CRP <75 mg/L have been shown to be prognostic of survival in ICU patients (Gülcher, Bruins, Kingma, & Boerma, 2016). As per table 34, CRP levels ranged at baseline from 30 to 279mg/L for participants not completing, compared with a

range of 5 to 62mg/L for participants completing to both 12 and 20 weeks. Only three participants (all Arm B) had levels of ≥75 mg/L, (106mg/L, 171mg/L and 279 mg/L). All responded initially to study medication. Albumin levels ranged at baseline from 32 to 41g/L for participants not completing, compared with a range of 25 to 44g/L for participants completing to both 12 and 20 weeks. Acknowledging that this is a small group of data, there was a slight trend in higher CRP levels within participants not completing to week 12, compared similar ranges within baseline albumin and GPS levels. Overall, the combination of EPA and celecoxib were not adequate in reducing or maintaining reduced CRP levels in many of the participants.

7.3.12.1.3 GPS

All participants were assessed for GPS (calculated from albumin and CRP levels) at each study visit. Overall, the mean GPS changed from 1.3 to 1 at week 20 within Arm A, and 1.3 to 1.3 at week 20 within Arm B (appendix). These results indicated minimal change over a 20 week period within a refractory cachexia population, suggesting a positive effect on inflammation and nutrition within both study treatment regimens.

7.3.12.1.4 KS and ECOG-PS

All participants were assessed for KS and ECOG-PS at each study visit. Overall, the change over the study period was minimal in terms of KS and ECOG-PS within both groups. All of the participants within Arm B attended the PRT sessions, with a history of waking up, showering, having breakfast, and attending the sessions with less than 50% of waking hours resting. This clinical picture has been allocated an ECOG-PS of 2 and ranges from 60 to 70 on the Karnofsky Score. These scores do not reflect the overall performance status of these patients. Therefore, these scores are not reflective of an end-stage/refractory cachexia population. For the purpose of this thesis, both of these will not be discussed further.

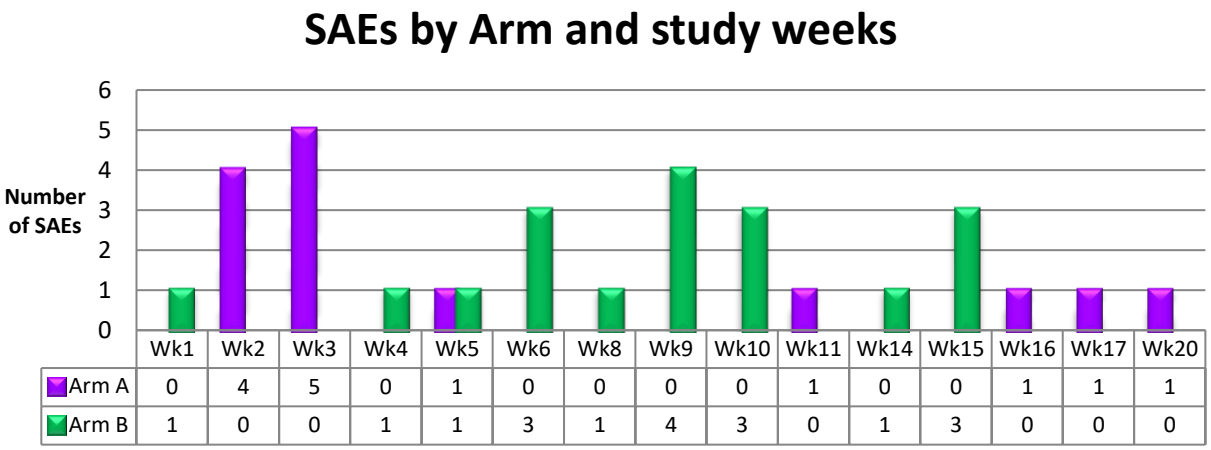
7.3.13 Serious Adverse Events and overall survival analysis

All participants at study visits were investigated for adverse and serious adverse events. For the purpose of the thesis, only the serious adverse events will be discussed. The general population recruited to the ACCeRT study were end-stage in their NSCLC disease trajectory and it was expected that there would be a high number of events.

Table 46 SAEs by CTCAE version 3 grading/description

	Arm A				Arm B			
	GD 2	**GD 3**	**GD 4**		**GD 1**	**GD 2**	**GD 3**	**GD 4**
CARDIAC								
hypotension							1	
GASTROINTESTINAL								
dehydration		1						
diarrhoea		1						
obstruction						1		
INFECTION		1				1	3	
METABOLIC								
hyperbilirubinaemia								1
hypercalcaemia							1	
hyponatraemia							1	
MUSCULOSKELETAL								
other		3						
NEUROLOGY								
cranial CNVII							1	
confusion	1		1		1			
motor							1	
PAIN								
bone							3	
tumour	1							1
PULMONARY/UPPER RESPIRATORY								
dyspnoea		2						
pleural effusion	2	1						
RENAL								
incontinence-urinary						1		
VASCULAR								
thrombosis							1	

Figure 62 Graph of ACCeRT SAEs by Arm and study weeks



Serious adverse events for participants **four weeks** post Last or week 20/End of Trial visit.

Table 47 SAEs by CTCAE version 3 grading/description four weeks post week 20/End of Trial visit

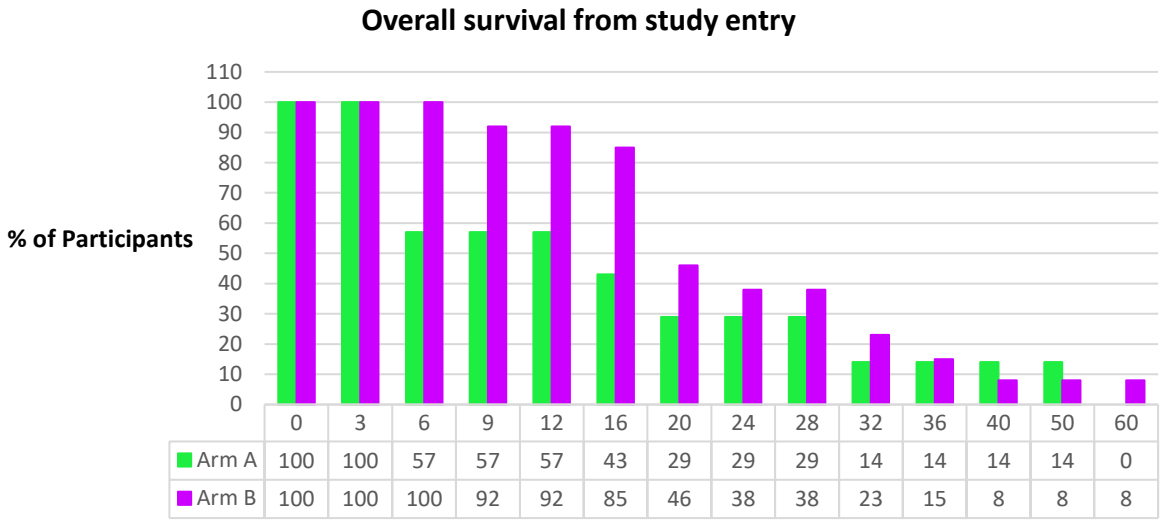
	Arm A			Arm B		
	GD 2	**GD 3**	**GD 4**	**GD 2**	**GD 3**	**GD 4**
MUSCULOSKELETAL						
other		1				
PAIN						
bone		1				
PULMONARY/UPPER RESPIRATORY						
dyspnoea				1		

There were 32 adverse events in all participants. Fourteen events within five participants (71%) in Arm A, with 10 of serious grade 3 to 4. Eighteen events within eight participants (62%) in Arm B, with 14 of serious grade 3 to 4. There were no exercise-related events, and no treatment-related deaths. There was one possible case of study medication-induced atrial fibrillation within one Arm A participant at week 12. The participant was asymptomatic and did not require hospital admission and it was decided to continue with the study medication under regular surveillance, as it was possible that this symptom was related to his underlying condition of progressing NSCLC. Atrial fibrillation (AF) is often seen in the older population, with a rate of 7.2% in ≥65 years of age, increasing to 10.3% at ≥75 years of age (Sankaranarayanan, Kirkwood, Dibb, & Garratt, 2013). Chronic pulmonary disease has been shown to be a factor (Farmakis, Parissis, & Filippatos, 2014). Post-operatively, thoracic surgery is the most frequent form of cancer-related AF, and there has been the suggestion that the inflammatory complication of cancer is represented by AF (Farmakis et al., 2014). All the

above factors were seen within this participant, with age at study entry of 71 years, history of exploratory thoracic surgery, along with increased levels of IL-6 and CRP at week 12, following a hospital admission due to dyspnoea at week 11. As per Table 63 (appendix), 35% (n=7/20) of participants were already receiving a cardiac medication at baseline.

7.3.14 Overall survival from study entry

Figure 63 Overall survival from ACCeRT study entry



	0	3	6	9	12	16	20	24	28	32	36	40	50	60
Arm A	100	100	57	57	57	43	29	29	29	14	14	14	14	0
Arm B	100	100	100	92	92	85	46	38	38	23	15	8	8	8

Interestingly, there was a trend for survival being higher within participants allocated to Arm B as depicted in Figure 63. Overall survival related to either the maintenance or increase in LBM in patients experiencing cancer has recently become an outcome measure in a number of clinical nutrition studies (Baracos, Pichard, & Attaix, 2012). No further discussion is made due to the fact that a high level of ongoing disease progression were expected within this population of end-stage disease.

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8 Discussion

8.1 CONSORT

Consent rate into the study was lower when compared with other cancer cachexia studies, ranging from 86% for both ROMANA 1 and 2 (Temel et al., 2016) and 100% in other studies (Madeddu et al., 2012; Mantovani, Macciò, Madeddu, Serpe, Massa, et al., 2010). This could be for a number of reasons. Firstly, other organisations have a record of accomplishment of recruiting to cachexia studies. It took a period of time to engage the medical team to be involved and refer patients onto a cachexia study. Secondly, other cachexia studies are recruiting participants during their chemotherapy and/or radiotherapy treatment period. Participants in these studies are already attending the hospital for visits for their treatment. The ACCeRT study relied on participants attending visits at the end-stage of their disease trajectory, with the possibility of attending a total of between 8 and 20 visits if randomised to Arm A or 42 visits if randomised to Arm B. Thirdly, study participation also relied on family members bringing them to study visits if the participant could not drive safely. Auckland District Health Board covers a large geographical area. The study expanded to three locations after the amendment version 3.0 in November 2012. This reduced travelling times for participants randomised to Arm B, making the study more amenable.

The international consensus definition comprises of pre-cachexia, cachexia and refractory cachexia. Refractory cachexia is seen in patients experiencing >5% weight loss, pre-terminal with very advanced progressive cancer, unresponsive to anticancer therapy, with a life expectancy of less than three months (Fearon et al., 2011). Interestingly a study compared both of these cachexia definitions on 167 participants over one year. As per Fearon et al., definition, 70% developed cachexia with overall survival of 0.97 years, compared with 40% and overall survival of 0.55 years by the definition by Evans et al., (Vanhoutte et al., 2016). Utilising the definition by Evans et al., showed a more significant difference in overall survival between cachectic and non-cachectic participants. The extra factors within the Evans et al., definition of anaemia, chronic inflammation etc. improves its overall prognostic value (Vanhoutte et al., 2016).

The completion rate in this study was higher when compared to other cancer cachexia studies. A study by Jatoi et al., 2002 had the completion rate of 45% at 4 weeks (Jatoi et al., 2002), along with a 37% completion rate at 8 weeks in the study by Berk et al., (Berk et al., 2008), which are both lower than the ACCeRT week 3 rate of 80% and week 9 rate of 60%. Conversely, a higher completion rate was seen in the ROMANA 1 and ROMANA 2 study, with the average of 73% at 12 weeks (Temel et al., 2016), along with 67% completing the 16 week study investigating enobosarm (Dobs et al., 2013), compared with 45% at week 12 and

30% at week 16 in the ACCeRT study. What is interesting about these rates is the fact that all of the above studies were in cachexia patients and not late cachexia/refractory cachexia population as per ACCeRT participants.

As previously noted, the guest participant recruited to the study completed the twenty week study period, therefore it was deemed achievable for other participants. This was followed by participants completing twelve weeks (002), nine weeks but then withdrew to start target therapy (003), three weeks but then withdrew due to language problems/unable to attend (004), not completing three weeks (005), completed twenty weeks (006), completed nine weeks (008), not completing three weeks (009), completed twelve weeks (010), completed twelve weeks (011), completed three weeks (012), withdrew to nursing home (013), not completing three weeks (014), completing three weeks (015), completed nine weeks (016), completed twenty weeks (017, 018, 019), completed six weeks (020), and completed twenty weeks (021, 022). With the attrition from Arm A, a change was made to actively encourage Arm A participants to attend weekly visits instead of weekly telephone calls between study visits. While losing the participant to language problems, a decision was made to recruit only English speaking participants. Due to limited funding, and feasibility study, participants not completing the study were not replaced.

The ACCeRT study was designed as a feasibility study investigating the acceptability, trends in efficacy and the safety of a multi-targeted approach of supportive care in the above population and was not powered to determine differences between groups. Therefore, the results and discussion are restricted to trends within both groups.

8.2 Primary endpoint – acceptability

For the purpose of the thesis, the discussion on the acceptability questionnaire will be combined with the compliance of each study treatment, as they are inter-related.

8.2.1 Eicosapentaenoic Acid

The results conclude that, on average, EPA was acceptable in this population at this daily dose. It has been stated that tolerance of this supplement is often moderate due to gastrointestinal symptoms and aversion to the palatability (Pottel et al., 2014). Previous studies have discussed the tolerability of EPA e.g. five out of the 30 participants who received single agent EPA (18 large capsules/per day), for a period of 14 days stopped the medication due to nausea (n=2), vomiting (n=1) and fish belching (n=2). Eight participants randomised to the 'fish oil' arm rated the amount as 'slightly difficult' (Bruera et al., 2003). Other studies have utilised EPA-enriched supplements. In a study investigating a multi-targeted regimen, 66% of participants consumed the full study dose of 'ProSure' per day of EPA-enriched nutritional supplement. Unfortunately, the publication does not discuss the palatability or acceptability of this supplement (Mantovani et al., 2006). A later study utilised either 'ProSure', 'Resource®' or 'Forticare®', equalling 2.2g/day of EPA. Again, the publication did not state the palatability or acceptability of the supplements (Mantovani, Macciò, Madeddu, Serpe, Massa, et al., 2010).

Other sources include the plant-based echium oil, which is an alternative to fish oil for vegetarians. In 2014, Pottel et al. published results from a double-blind, randomised controlled study investigating echium oil versus n-3 PUFA deficient sunflower oil (control) in patients with head and neck cancer undergoing curative concurrent chemo/radiotherapy for a period of 7 weeks (Pottel et al., 2014). Compliance was high with 80.6% within the control sunflower oil group compared with 86.7% within the echium oil group. Tolerability was also good with 71.4% within the control group and 72.1% within the echium oil group. The latest conversion rates would indicate that 2.4g of EPA would equal 60ml of echium oil. The above study used 7.5mls b.d.s., approximately half the recommended daily dose (Pottel et al., 2014).

These results are comparable to ACCeRT results in terms of EPA compliance and acceptability/tolerability.

8.2.2 Celecoxib

The results conclude that, on average, celecoxib was acceptable in this population at this daily dose. Patient compliance was high in the participants without issues. This is interesting as previously there has been concern around the use of celecoxib and the increased risk of myocardial infarction, stroke and cardiovascular thrombotic events. For safety, all participants within the ACCeRT study received omeprazole 20mg o.d. and received a 12-lead ECG at baseline, week 12 and week 20. Celecoxib has been utilised in various cancer cachexia studies including 200mg b.d.s. as per study involving lung cancer participants concurrent with medroxyprogesterone and dietary intervention over 6 weeks (Cerchietti et al., 2004). Results showed that celecoxib was well tolerated with no worsening of gastrointestinal symptoms. A 21 day study investigated the use of celecoxib 200mg b.d.s. in head and neck and gastrointestinal cancer patients pre initiation of their chemotherapy therapy. Compliance was 74% in the celecoxib arm with no reported adverse events. This is comparable to ACCeRT results in terms of celecoxib compliance (Lai et al., 2008). Celecoxib at a dose of 200mg o.d. concurrent with high polyphenol content, pharmaconutritional support, EPA, antioxidant treatment and medroxyprogesterone acetate was investigated over 16 weeks in advanced cancer patients. Compliance data for celecoxib was not presented (Mantovani et al., 2006). This group then increased the dose to 300mg o.d. as monotherapy for 16 weeks in advanced cancer patients. Results stated that compliance was good (Mantovani, Macciò, Madeddu, Serpe, Antoni, et al., 2010). This group then used this same dosing for a multi-targeted regimen in advanced gynaecological cancer patients. Results again stated that overall compliance was good (Macciò et al., 2012).

8.2.3 Progressive Resistance Training

This element of the study treatment scored the highest on the acceptability and this was shown in the high compliance and attendance/participation rates. The exercise sessions were designed on a 1:1 basis with an exercise physiologist, but it was noted that participants were happy to either wait around after their session or arrive a little early to converse with other participants on the study, all indicating the high rate of acceptability of PRT in this study population.

Currently, ACCeRT is the first clinical study utilising an exercise component within a cancer cachexia study. The attendance was high when compared with other exercise-based clinical studies.

In 2012, Quist et al. published results from a non-randomised study in lung cancer patients undergoing chemotherapy and concurrent home (walking and relaxation) and supervised hospital-based training, twice weekly for a period of 6 weeks. Attendance rate for the supervised sessions was 73.3% and 8.8% to the home-based programme, which is lower

when compared to 93.9% attendance for 12 sessions/6 weeks on the ACCeRT study (n=11) (Quist et al., 2012).

In 2012, Hwang et al. published results from a randomised controlled study of lung cancer patients receiving targeted therapy and three times weekly out-patient exercise sessions utilising a cycling ergometer and treadmill for a period of 8 weeks. Mean attendance rate was 71.2% (range 4.2 to 100%) with 12.5% of the population having 100% attendance (n=3) (Hwang, Yu, Shih, Yang, & Wu, 2012). This is lower when compared to 50% having 100% attendance at 8 weeks (n=10) within the ACCeRT study.

In 2014, Courneya et al. published results from the START study in breast cancer patients undergoing exercise three times a week concurrently with adjuvant chemotherapy. Attendance of 72% within the aerobic exercise training arm and 68.2% within the resistance exercise training arm over 18 weeks (Courneya et al., 2014). This is lower when compared to 95.1% attendance for 36 sessions/18 weeks within the ACCeRT study (n=4).

This is interesting as in all of the above studies participants were attending the hospital for visits around their treatment of either radiotherapy, chemotherapy or targeted therapy, while participants on ACCeRT study were attending purely for the exercise sessions.

8.2.4 Essential Amino Acids

The results conclude that on average, EAA were acceptable in this population at this dose. Other studies have looked at the ingestion of amino acids in this population. The study by May et al., utilising β-Hydroxyl β-Methyl Butyrate (HMB)/Arg/Gln did not report compliance rates (May et al., 2002). The RTOG 0122 study randomised advanced cancer patients to HMB, arginine and glutamine mixture versus an isonitrogenous isocaloric control mixture taken twice a day for eight weeks. Compliance was low with only 40% of patients on the HMB/Arg/Gln arm completing the treatment and 34% in the placebo arm, with patient preference being the main factor of non-compliance in 35% and 42% of patients respectively (Berk et al., 2008). This is lower when compared with the ACCeRT results in terms of EAA compliance. Advanced cancer patients received one sachet b.d.s. of AMINOTROFIC mixed with 200ml of water for a period of eight weeks, concurrently with anti-cancer treatment. Compliance stated that all 25 participants completed the planned treatment without dose reductions (Madeddu et al., 2010). This is higher when compared with the ACCeRT results in terms of EAA compliance.

Overall, acceptability and compliance was high in terms of EPA, celecoxib, PRT sessions and EAA, with rates comparable to other cancer cachexia and exercise studies.

8.3 Secondary outcomes

8.3.1 Body composition by Bioelectrical Impedance

The same BIA analyser was used throughout the ACCeRT study; therefore, the net gain or loss in kg and percentage loss was considered as a true effect for that particular participant, acknowledging that BIA data is now not considered the gold standard of measuring body composition. Taking into account the limitations of utilising BIA for body composition, results did show a trend in the increase of FFM over time within Arm B group with some participants gaining up to +3kg (+4.75%) and +2.4kg (+6.11%) both at week 3, and gain of +7.4kg (13.91%) and +5.6kg (+14.25%) at week 6, and +7.5kg (+19.08%) at week 9 and +0.6kg (+1.53%) at week 16. One Arm A participant gained +6.8kg (+11.26%) at week 12. These data indicated that a net gain of FFM was achievable within refractory cachexia patients and that participants peaked at different time points in terms of FFM from week 3 through to week 16.

The ACCeRT body composition results corresponds somewhat with the disease trajectory time course and data presented by Prado et al., who suggested from analysis of CT scans over time from advanced cancer patients that there were periods within the disease trajectory that maintenance, and even an increase in weight and muscle was possible in cancer cachexia patients. Also, that a combination of inactivity, inflammation and poor nutritional status may prevent the reversal of this weight and muscle loss. It was suggested that this reversal of cachexia by an intervention was unlikely in the last 90 days of life (Prado et al., 2013). The ACCeRT study data suggests that this is in fact not true and a reversal and net gain was possible within this period. Indicating that research should continue in the refractory cachexia population.

There has been a number of studies reporting significant differences in LBM and body weight during and post recruitment to the ACCeRT study, as per Table 2. A significant increase was seen in mean LBM by DEXA in participants randomised to enobosarm 3mg of +1.3kg (p=0.046), and enobosarm 1mg of +1.5kg (p=0.0012), over 113 days (16 weeks). Participants allocated to placebo only had a mean increase of +0.1kg (p=0.88) (Dobs et al., 2013).

Results also showed a significant difference with the median change for LBM by DEXA of -0.47kg within the placebo group and +0.99kg (+0.61 to +1.36kg) within the anamorelin group for ROMANA 1 study (p<0.0001), and a significant difference with the median change for LBM of -0.98kg within the placebo group and +0.65kg (+0.3 to +0.91kg) within the anamorelin group for the ROMANA 2 study (p<0.0001) (Temel et al., 2016). LSM was utilised for the secondary outcomes of body weight data, even though geographical area was used within the stratification and a randomisation algorithm was used to ensure relative

balance for data integrity. Results showed a significant difference with the mean change of +0.14kg within the placebo group versus +2.2kg within the anamorelin group for ROMANA 1 study (p<0.0001), along with a mean change of -0.57kg within the placebo group versus +0.95kg within the anamorelin group for the ROMANA 2 study (Temel et al., 2016).

Results from the ACT-ONE study showed a significant difference in slope of weight change of -0.21kg/4 weeks within the placebo group versus +0.54kg/4 weeks within the high dose group (mITT, p<0.0001). A significant percentage weight change of -0.4%/4 weeks within the placebo group versus +1.04%/4 weeks within the high-dose group (mITT, p<0.0001) and a significant difference of median LBM of +1.76kg within high-dose and +0.57kg within placebo (mITT, p=0.012). (Stewart Coats et al., 2016).

As seen above there has been a change in analysing and presenting LBM and weight data within cancer cachexia studies. As per ROMANA 1 and 2 studies, the change in LBM was defined as the average of change from baseline to week 6, and the change from baseline to week 12. This was considered by the study team to be a more conservative approach than just utilising week 12 data (Temel et al., 2016). More recently, data has been assessed as per change in kg/4 weeks as per the above ACT-ONE study (Stewart Coats et al., 2016).

It must be noted that utilising the average of change as per both ROMANA studies could result in artificially increasing the results. For example, change from baseline to week 6 of +2kg, but then the change from baseline to week 12 of +0kg; then the average would be +1kg at week 12, instead of the true effect of +0kg. This would always be true for any decreasing weight and LBM seen over the 12 week period, e.g. change from baseline to week 6 of +1kg, and change from baseline to week 12 of -1kg would result in +0kg instead of the true effect of -1kg.

It must also be noted that choosing the wrong modality could result in an imprecise and insensitive analysis and may hide positive and negative results, as seen in the following two studies that utilised BIA, DEXA and L3-CT data. In 2010, Mantovani et al. utilised these three models for body composition analysis within the phase III, randomised, five-arm study of different combination treatments. When reviewing the different modalities, it was shown that there was a non-significant change in mean LBM via BIA analysis (p=0.609). However, it showed a significant change by DEXA analysis (p=0.0148), and a significant change in estimated LBM by L3-CT for 25 of the 322 participants (p=0.001), all allocated to Arm 5 of the study (Mantovani, Macciò, Madeddu, Serpe, Massa, et al., 2010). In 2012, Madeddu et al. again utilised three models for body composition analysis for all 60 participants within the phase III randomised combination treatments. Results showed a non-significant change in LBM via BIA within both groups. Interestingly, a significant difference was seen within both

groups in LBM by both DEXA and L3-CT (Madeddu et al., 2012). The ACCeRT study only utilised BIA data, therefore we do not know if there would have been a difference in results if gained by either DEXA or L3-CT.

Body composition analysis can be confounded by ascites, dehydration and lymphoedema depending on each cancer cohort. BIA utilises resistance and reactance to estimate total body water, dependent on equations. It has high reproducibility and is less expensive than CT, DEXA, and MRI analysis. Advanced cancer patients can be dehydrated, which may underestimate FFM. BIA could be utilised either as a single modality or in combination with another analyser. (Di Sebastiano & Mourtzakis, 2012; Mourtzakis et al., 2008). DEXA utilises the principle of photon x-ray attenuation by different human tissues. Using a three-compartment model of bone mineral content/mass, FM and LBM, appendicular skeletal muscle mass can be determined. Advantages include low cost and low radiation exposure, with disadvantages including the low precision when compared to either MRI or CT and the lack of distinction between visceral and subcutaneous adipose tissue (Yip et al., 2015). Currently CT and MRI are considered the gold standard in measurement of body composition (Yip et al., 2015). L3-CT single-slice taken at the 3rd lumbar vertebrae is strongly related to whole-body FFM and appendicular skeletal muscle mass as determined by DEXA. Advantages include reproducible results and high accuracy, with disadvantages including the relative cost of acquisition of scans and analysis, radiation exposure, and limited relevance to functional muscle groups (Scott et al., 2017; Yip et al., 2015). Interestingly only the study by Madeddu et al, utilised L3-CT data (Madeddu et al., 2012). MRI is able to quantify the three adipose tissue depots, visceral, intramuscular and subcutaneous. Analysis is expensive with maintenance of the equipment, technicians needed to operate and acquire the scans, and carrying out the analysis (Di Sebastiano & Mourtzakis, 2012). Gaining funding for early feasibility and phase I studies is difficult, and BIA was a reasonable choice in this setting for prospective measures.

There is still confusion around the optimum modality as per the twenty-five currently open and recruiting cancer cachexia studies. Eight studies are measuring weight (modality not stated), with seven utilising BIA; two BIA plus DEXA, and one BIA plus L3-CT, along with two studies utilising DEXA, and two L3-CT. As seen above there has been a range of modalities investigating and analysing body composition within cancer cachexia clinical studies. Body composition is currently an important outcome in cancer cachexia studies, and there is a need to generate an international consensus on the modality and format of analysis e.g. either average of time points or change in kg/4 weeks for future studies.

8.3.2 MRI Total quadriceps muscle volume

Greig et al. published the only other study investigating cancer cachexia utilising MRI scan data. This phase I/II, single-centre, non-randomised, uncontrolled, open-label study investigated the combination of formoterol 40µg b.d.s. and megestrol acetate 320mg mane and 160mg nocte, for a study period of eight weeks (Greig et al., 2014). This study used a 1.5T MRI scanner and had set a pre-defined definition of response, as per Table 10 (Greig et al., 2014).

When comparing data from the study by Greig et al. in 2014, only seven participants completed the eight week study. MRI data from both the left and right limbs, with range of change of -13.6% to +8.45% (mean +4%) for the right limb and range of -11.5% to +13.45% (mean +6%) for the left limb (Greig et al., 2014). These results are higher when compared to the above ACCeRT results, but the data was acquired on a 1.5T MRI scanner and participants were allowed to continue with concomitant chemotherapy during the study, which could have affected the results.

As stated by Gray et al. in 2011, scans of muscle from participants experiencing both cachexia and sarcopenia show non-contractile tissue within the muscle. The MRI analysis did show this to be present within the ACCeRT study population. Greig et al. used k-means clustering to reduce this error (Gray et al., 2011; Greig et al., 2014).

The use of MRI total quadriceps muscle volume and cross-sectional areas have been used in other exercise intervention studies. A study investigating the exercise intervention in untrained women participating in endurance and strength training, gained imaging by a 1.5T MRI scanner at baseline and twelve weeks (Hudelmaier et al., 2010). Participants were randomised to a supervised strength training (ST) group versus endurance training (ET) group versus a control group. ST and ET involved three sessions per week for 60 minutes. Over the twelve weeks a significant increase was seen within all muscles for participants allocated to the ST group of +14.47%, compared with only a significant increase in the sartorius and extensor muscles within the ET group with an increase in the total volume of +10.39%. There were no relevant changes seen within the control group with a net loss of -2.8%. This study indicates the benefits of strength training over endurance training, along with the sensitivity of MRI scans to determine exercise-induced changes within the muscle (Hudelmaier et al., 2010). Currently there are twenty-five open clinical studies investigating cancer cachexia, with only one study (BAT-Cachexia study NCT02500004) utilising PET/MRI for body composition analysis (Clinicaltrials.gov, 2015).

It has been recently discussed the importance and rationale behind the choice of outcomes/endpoints and that these should be compatible with the study intervention and/or action of drug (Le-Rademacher, Crawford, Evans, & Jatoi, 2017). The ACCeRT study was

investigating the acceptability of a multi-targeted approach encompassing a PRT element in this population and to quantify if this intervention had an effect on muscle volume and strength. By utilising 3T MRI analysis, this potential outcome was correctly assessed. Utilising three MRI scan points within the ACCeRT study was discussed within the design stage, with scans at baseline, and weeks 12 and 20. Due to limited funding, this was reduced down to baseline and Last or week 20/End of Trial visit. This has resulted in the loss of potential data on whether the early effect of net gain of the FFM seen by BIA data was a true effect verified by MRI data. Coupled with the effect of attrition, especially within Arm A, no reasonable statement can be made.

It must be noted that it is difficult to burden the participant with attending for repeated CT or MRI scanning appointments, especially in the refractory cachexia population. Routine CT scanning can be used in pre-cachexia and cachexia populations as usually the participants are still undergoing either concurrent chemo and/or radiotherapy treatment with the cachectic treatment and are receiving routine surveillance scanning (Di Sebastiano & Mourtzakis, 2012).

8.3.3 Serum proinflammatory cytokines

In 2010, Mantovani et al. published results from a non-randomised, open label study that investigated COX-2 inhibitor celecoxib at a dose of 300mg/day for a study period of sixteen weeks (Mantovani, Macciò, Madeddu, Serpe, Antoni, et al., 2010). Results showed a non-significant reduction in IL-6 levels (p=0.499), with a significant reduction in TNF-α levels (p=0.007). This study also showed that this significant reduction of TNF-α and reducing levels of IL-6 induced a significant increase in LBM by both BIA and DEXA (p<0.0001). This study supports the proposed pathway and the benefit of down-regulating the production and release of TNF-α and increase in muscle, and that this pathway can be manipulated by utilising anti-inflammatories (Mantovani, Macciò, Madeddu, Serpe, Antoni, et al., 2010).

Recent results showed a non-significant increase in IL-6 levels at end of study for both enobosarm 1mg and 3mg dosing, and placebo groups. Results also showed a significant increase in LBM for both the enobosarm 1mg and 3mg dosing. This indicates that manipulating another pathway can result in the increase of LBM in the presence of increasing proinflammatory cytokines (Dobs et al., 2013). Similar results showed a non-significant increase in IL-6 levels, TNF-α levels and IL-1β levels, within the Japanese anamorelin study. Again, a significant difference in LBM for the anamorelin 100mg dosing group was seen, indicating that manipulating another pathway could result in the increase of LBM while proinflammatory cytokines were increasing. Interestingly, this study showed detectable levels in IL-1β (Takayama et al., 2016).

There are limitations of utilising the above proinflammatory cytokines including the fact that there are now other potential cancer cachexia biomarkers that could have been investigated within the ACCeRT study. Myostatin is a member of the TGFß (Transforming growth factor beta) superfamily, and is a negative regulator of skeletal muscle growth. High levels have been found in cancer patients, along with lower levels found in cachectic cancer patients (Elkina et al., 2011; Loumaye et al., 2015). Myostatin has also been linked with insulin resistance (Hittel et al., 2010). Research has shown a correlation between levels of plasma myostatin and muscle index, muscle density, and muscle strength (Loumaye et al., 2015). Activin A is a member of the TGFß superfamily, with high levels involved with skeletal muscle atrophy. Increased levels have been shown in some cancer patients, especially those who have bone metastases (Loumaye et al., 2015). A recent clinical study ACTICA, (NCT01604642) has shown circulating plasma levels of Activin A are associated with the anorexia/cachexia syndrome in recently diagnosed lung and colorectal patients. Activin A levels negatively correlate with skeletal muscle strength and decreased muscle function. In a murine model, treatment with an antagonist to Activin A showed improved muscle performance and mass (Busquets et al., 2012). IGF-1 is a positive regulator of increased muscle mass, and competes with the above myostatin/Activin A-SMAD pathway as the dominant factor (Elkina, von Haehling, Anker, & Springer, 2011). High levels of IGF-1 results in muscle hypertrophy, while low levels results in decreased protein synthesis and simultaneously, this results in increased proteolysis. Conversely, a high level of myostatin/Activin A has been shown to inhibit the IGF-1/PI3K/AKT/mTOR pathway (Cohen, Nathan, & Goldberg, 2015). The adipocytokine/adipokine leptin has been shown to be involved with inflammation and regulation of appetite (Ntikoudi, Kiagia, Boura, & Syrigos, 2014). Leptin has also been shown to correlate with body fat, i.e. total fat mass and fat cell volume. Higher leptin levels have been shown in early disease and in patients with less weight loss, while low levels of leptin correlate with low fat mass in cancer patients. Overall, a number of studies in lung cancer patients have shown lower leptin levels when compared to healthy/control patients and even lower levels when lung cancer non-cachectic patients were compared to lung cancer cachectic patients (Ntikoudi et al., 2014). Leptin levels of <31ng/ml have been correlated with poor survival (Mondello et al., 2014). Zinc-α2-glycoprotein (ZAG/ZA2G) is an adipokine, and ZAG acts directly on the adipocytes resulting in the release of glycerol and free fatty acids (Topkan et al., 2007). Increased levels have been shown to be released from adipose tissue in cachectic cancer patients and plasma levels can be up to seven times above normal (Cabassi & Tedeschi, 2013; Rydén et al., 2012). Exercise has been shown to modulate muscle metabolism, with documented effects including improved insulin

sensitivity and decreased systemic inflammation, while conversely, up-regulation of myostatin and proinflammatory cytokines have been shown with muscle disuse (Biolo, Cederholm, & Muscaritoli, 2014; Grande et al., 2014). All of the above biomarkers, if analysed, would have helped to identify the true effect of the PRT and EAA on the muscle anabolic pathway, and body composition in terms of fat mass.

8.3.4 Hand-grip strength

There are a number of ways of presenting HGS data: either separately with data gained from both arms, and using just the dominant arm with results presented, either as one attempt, best/highest of three, mean of two, mean of three, first of two attempts, or the best of six attempts from three right and three left. There have also been differences around participants seated or standing, and the use of verbal encouragement. The American Society of Hand Therapists published guidelines in 1992 recommending the use of the Jamar dynamometer with the handles set at the second position and the participant's elbow flexed at 90°; however, some published studies have not used these guidelines (Bohannon, Peolsson, Massy-Westropp, Desrosiers, & Bear-Lehman, 2006).

The highest reliability in terms of test-retest was seen when the mean of the three attempts were used (Mathiowetz et al., 1985). In general, higher scores are seen with results gained from the right hand when compared to the left within each participant, and show little difference between left hand-dominant and right hand-dominant participants. Generally female scores are lower when compared with male scores, and there is a curvilinear relationship between grip strength and age, with the maximum score peaking around age 25 to 50 years and then decreasing with age (Mathiowetz et al., 1985). The ACCeRT study utilised the maximum value of three attempts, this was due to outlying values, which would have affected the mean result.

There has been a number of studies reporting a non-significant difference in HGS. In 2010, Mantovani et al. published results from a phase III, randomised five arm study (Mantovani, Macciò, Madeddu, Serpe, Massa, et al., 2010). Results showed within all arms a non-significant difference between baseline and end of study for the HGS data. Interestingly, all participants within this study commenced with a higher baseline values ranging from 23.3 ± 9.4kg to 27.2 ± 13.9kg compared to 19kg (Arm A) and 21.9kg (Arm B) seen within the ACCeRT study, re-enforcing that ACCeRT participants were at a later stage within their disease trajectory.

Results from a phase III study within gynaecological cancer patients showed a non--significant difference between baseline and end of study for the HGS. Again, baseline levels

were higher than those seen within the ACCeRT study with values of 24.2 ± 7.2kg (Arm 1) and 25.4 ± 8.1kg (Arm 2) (Macciò et al., 2012).

Other studies have also shown a non-significant difference in HGS data, including the phase III study in advanced cancer patients (Madeddu et al., 2012), the enobosarm study (Dobs et al., 2013), the anamorelin studies carried out in Japan, and the phase III ROMANA 1 and 2 studies (Takayama et al., 2016; Temel et al., 2016).

The following study is the only one to demonstrate a significant difference between groups in HGS values. Result showed a significant difference both within the low and high-dose espindolol groups, with absolute change in LSM from low-dose to placebo of +4.16kg (p=0.0006) and high-dose to placebo of +2.36kg (p=0.0134). No further details of the HGS protocol was stated (Stewart Coats et al., 2016).

Interestingly all of these studies had the mean value of HGS at baseline of approximately 20.6 to 28.2kg, which was at a higher value than the baseline from the ACCeRT study, and all permitted concomitant anti-cancer treatment. With the recent results from the large phase III ROMANA studies, the use of HGS within future cancer cachexia trials is currently being debated.

8.3.5 Isometric leg strength

The previously discussed technical issues and reliability of the isometric leg strength results within the ACCeRT study is presented with some sadness, as other studies have successfully investigated muscle mass and strength in cancer patients undergoing physical exercise (Stene et al., 2013).

In 2003, Coleman et al. published results from a randomised controlled study in patients with multiple myeloma who were receiving anti-cancer treatment. 1RM (one-repetition maximum) strength was measured from four tests measured on the Keiser pneumatic equipment, including the chest press, double leg press, arm pull, leg curl and leg extension (Coleman et al., 2003).

In 2007, Battaglini et al. published results from a randomised controlled study in patients undergoing treatment for breast cancer, and an individualised exercise intervention. Strength assessments were measured on the Quantum (Salford, Texas) and LifeFitness (Schiller Park, Illinois). Predicated 1RM from submaximal endurance protocol, sum of the results from the seated leg curl, lateral pull-down and seated chest press (Battaglini et al., 2007).

In 2009, Baumann et al. published results from a randomised controlled study in patients undergoing haematopoietic stem cell transplantation and an exercise intervention.

Isometric strength testing was performed utilising the 'Digimax' by Mecha Tronic GmbH, (Hamburg, Germany), which measured the extensor thigh muscles (Baumann et al., 2009).

In 2009, Adamsen et al. published results from a randomised controlled study in patients undergoing chemotherapy that investigated the effect of a multimodal high intensity exercise intervention. Muscle strength was assessed by utilising the 1RM performed on the Technogym (Gambettola, Italy) (Adamsen et al., 2009).

In 2009, Segal et al. published results from a randomised controlled study in patients with prostate cancer receiving radiation therapy. Estimated 1RM was measured by the maximum weight that could be lifted eight times on the horizontal bench and leg press (Segal et al., 2009).

In 2009, Schwartz et al. published results from a randomised controlled study in female patients following cancer treatment. Strength was assessed by 1RM for legs (leg press), shoulders (overhead press) and chest (seated rowing) (Schwartz & Winters-Stone, 2009).

In 2011, Wiskemann et al. published results from a randomised controlled study in patients before, during and post allogeneic stem cell transplantation, and a partly self–administered home-based exercise programme. A hand-held dynamometer (C.I.T Technics) was used to measure maximal isometric voluntary strength of the elbow extensors and flexors, shoulder abductors, knee extensors and flexors, hip flexors and abductors. The mean was taken from three repeated measurements (Wiskemann et al., 2011).

All the above studies have used a number of different methods to determine muscle strength, within very different populations. Recently, a systematic review investigated strength assessment within NSCLC (Granger, McDonald, Parry, Oliveira, & Denehy, 2013). Thirteen different outcome measures were identified and investigated within 31 studies in NSCLC participants, in terms of physical activity, functional capacity and muscle strength. In terms of muscle strength, only three studies used measured strength as an outcome measure.

In 2002, Knols et al. utilised a Mecmesin FB50K pull-gauge hand-held dynamometer for dominant upper and lower limb measurements. The device showed good inter-rater reliability ICC=0.9 (elbow), and ICC=0.96 (knee), but with a large standard error of measurement between examiners SEM=10.6, 18.8 respectively, and the smallest detectable difference SDD=29.4, 54.8 respectively (Knols, Stappaerts, & Fransen, 2002). In 2005, Brown et al. utilised the sit-to-stand test (Brown, McMillan, & Milroy, 2005). In 2008, Trutschnigg et al. utilised a hand-held dynamometer (Jamar) to measure hand-grip strength with a mean value of two to three measurements. The device showed moderate intra-rater reliability with the per cent coefficient of variation of 6.3 (Trutschnigg et al., 2008). None of the above tests were validated against the gold-standard of iso-kinetic dynamometry (Granger et al., 2013).

Recently, the reliability of a new mobile instrument for measuring isometric quadriceps muscle strength (Q Force) showed excellent relative test-retest reliability, but limited absolute test-retest reliability. Results from the limits of agreement varied between 15.7N (22.5%) and 23.6N (36%) in magnitude. This indicated that the ability of the device to detect changes over time was limited and that a true change in results had to be at least 22.5% (Douma et al., 2016).

Overall, measurements utilised to evaluate effectiveness in NSCLC patients and responsiveness to/over time need to be reliable. Standardisation of measurements would allow study results to be compared across clinical trials. Unfortunately, that requires expensive equipment, experienced technicians and advanced monitoring. Hand-held and hand-grip dynamometers did not show strong reliability; therefore, a recommendation for a particular device was not made. Further reliability and validity tests are still required within the NSCLC population. Minimal important difference and responsiveness has not been established for any of the thirteen tests utilised within the review (Granger et al., 2013).

8.3.6 Participant reported outcome

8.3.6.1 FAACT

There have been a number of published studies that have also utilised the FAACT questionnaire within cancer cachexia studies. Results showed within the FAACT-ACS subscale a non-significant mean increase of +2.31 within the placebo group (p=0.16), while a significant increase of +6.95 was seen within the enobosarm 1mg dosing group (p=0.001), and an increase of +3.12 within the enobosarm 3mg dosing group (p=0.051) (Dobs et al., 2013). This highlights that as per PSR data, the increase of +2.31 would indicate worsening of symptoms within the placebo group. Even though there was a significant change at end of study within the 3mg dosing group, the increase of +3.12 again suggests worsening of symptoms. Within the 1mg dosing group, a significant difference was detected and with the increase of +6.95, this would suggest an improvement in symptoms.

Results showed significant changes in FAACT-ACS subscale at week 3 (p=0.018), week 6 (p<0.0007), week 9 (p=0.0004), and week 12 (p<0.0012) within the ROMANA 1 study between anamorelin and placebo in favour of the anamorelin group. In addition, a significant difference was seen within the ROMANA 2 study, at week 3 (p=0.007), week 6 (p=0.0013), week 9 (p=0.0033) and week 12 (p=0.015) (Temel et al., 2016).

Both of the above published studies have compared scores between groups and have not looked at whether this resulted in a meaningful PSR change as discussed earlier. It could be stated that the FAACT questionnaire is not sensitive enough to detect the levels of worsening change as would be expected within a refractory cachexia population.

Recently, a systematic review was carried out investigating HRQOL instruments for patients experiencing cancer cachexia (Wheelwright et al., 2013). This review identified 67 studies that utilised a HRQOL. Most of these studies used a generic instrument, including the most often used European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) (49%), while only 21% used the cachexia specific questionnaire FAACT. Other instruments reviewed in alphabetically order included: COOP-WONCA, Edmonton Symptom Assessment Scale EORTC QLQ-H&N35, EORTC QLQ-LC13, EuroQL-5D, Functional Assessment of Chronic Illness Therapy- Fatigue, FACT-G, FLIC, GHQ, Hospital Anxiety and Depression Scale, HQLI, LASA scales McGill QOL, modified Tchekmedyian scale, Padilla index, QL, RSCL, SF-36, single item uniscale for assessment of global quality of life, Spitzer QOL, and the Uppsala questionnaire. This review acknowledged the content validity of the FAACT questionnaire, but commented on poor reliability, structural validity and internal consistency when using the COSMIN checklist, along with the measurement error, and not addressing the social impact of cachexia. The use of the FAACT questionnaire is limited to the English language. It was concluded that, overall, the FAACT questionnaire does cover many symptoms attributed to cancer cachexia, but is lacking in the area of relationship and psychosocial issues (Wheelwright et al., 2013).

In 2015, LeBlanc et al. published results from a validation of the FAACT in participants with advanced NSCLC experiencing cancer anorexia-cachexia syndrome (CACS) (LeBlanc et al., 2015). This study demonstrated internal validity of Cronbach alpha of 0.9 for the FAACT Total score and 0.79 for the FAACT-ACS. When the study compared advanced NSCLC participants experiencing CACS, results showed a mean FAACT-ACS score of 33.1 (SD 7.7) with non-CACS mean FAACT-ACS score of 37.2 (SD 6.5) (p=0.011), and with an effect size of 0.58. The study also compared FAACT-ACS in the above NSCLC participant group, split into those with weight loss who had a mean score of 31.4 (SD 7.9) compared with non-weight losing participants who had a mean score of 38.3 (5.4) (p=0.0001). The study also compared the above score in relation to mean FAACT Total score in participants experiencing CACS of 111.0 (SD 17.4)) compared with non-CACS FAACT Total score of 113.7 (SD 20.9) (SD 6.5) (p=0.399), and with an effect size of 0.14. The study compared mean FAACT Total score in weight losing participants, with a score of 106.4 (SD 19.5) compared with non-weight loss score of 115.8 (19.3) (p=0.04). Please note that 41.8% of the participants were receiving chemotherapy during the study (LeBlanc et al., 2015).

These results reflect those seen within the ACCeRT study. All participants were experiencing weight loss as per study eligibility criteria and were experiencing cachexia with a

baseline mean FAACT-ACS score of 29.1 and FAACT-Total score of 105.8, thereby re-enforcing the end-stage refractory cachexia population of this study.

Recently, a study investigated the cut-off point for anorexia utilising the FAACT-ACS in participants commencing chemotherapy (Blauwhoff-Buskermolen et al., 2016). Results showed a score of ≤37 with a 80% sensitivity and 81% specificity for the assessment of anorexia (Blauwhoff-Buskermolen et al., 2016). Interesting, 78.9% (n=15/19) of participants within the ACCeRT study had FAACT-ACS scores of ≤37 at all study time points.

Interestingly, the EORTC QLQ-CAX24 questionnaire has recently been developed to be utilised in clinical trials (Wheelwright et al., 2017), along with the validated Chinese version of the FAACT questionnaire (Zhou et al., 2016). With these recent developments, the use of FAACT within future cancer cachexia trials needs to be debated.

8.3.6.2 MFSI-SF

There have been a number of published studies that have also utilised the MFSI-SF questionnaire within cancer cachexia studies. Results showed a non-significant difference within Arms 1, 3 and 4. A significant difference was seen within Arm 2 baseline 17.3 ± 18.7 to 27.4 ± 18.6 at end of study, indicating a significant increase in fatigue (p=0.051). Arm 5 showed a significant decrease, indicating improved fatigue with a baseline of 26.9 ± 16.8 to 20 ± 23.1 at end of study (p=0.047) (Mantovani, Macciò, Madeddu, Serpe, Massa, et al., 2010).

Results from an open-label, phase III randomised controlled study comparing combination treatment of celecoxib, L-carnitine and antioxidants (alpha lipoic acid and carboxycysteine) and megestrol acetate (Arm 1) versus megestrol (Arm 2) alone for 16 weeks, in patients with gynaecological cancers (Macciò et al., 2012). Results showed a significant difference with decreasing scores indicating an improvement in fatigue within Arm 1, (p=0.045). Arm 2 showed a non-significant increase indicating worsening fatigue, (p=0.483). There was also a significant difference between groups at end of study (p=0.049) (Macciò et al., 2012).

Interestingly, baseline scores from the ACCeRT study were lower than all the above studies, except for Arm 2 within the five arm phase III, randomised, open-label study by Mantovani et al, in 2010. The overall increase in ACCeRT scores indicated a worsening of fatigue and is reflective of the refractory cachexia population.

The MFSI-SF has been show to demonstrate moderate test retest reliability over time and Cronbach's alpha coefficient from 0.83 to 0.93. Reported high correlation with other instruments shows concurrent validity, moderate to high convergent validity, divergent validity, and sensitivity to change over time. However, at this point a minimal clinically

important difference is yet to be reported (Donovan et al., 2015), and the use of MFSI-SF within future cancer cachexia trials needs to be debated.

8.3.6.3 WHOQOL-BREF

Results from WHOQOL-BREF within both Arm A and Arm B could either indicate that their physical score was generally stable throughout the study period possibly attributed to the study regimen, or that the instrument was not sensitive enough to detect small differences. A similar trend in physical well-being (PWB) was seen within the FAACT instrument. These data would indicate that both of these instruments showed little difference within scores over time regarding the physical well-being within ACCeRT participants. Again, possibly attributed to the study regimen, or that both instruments were not sensitive enough to detect small differences.

8.3.7 Prognostic/performance status

When comparing results from other cancer cachexia studies, most present change in overall GPS and do not present separate data on albumin and CRP levels.

In 2010, Mantovani et al. published results from a phase II open-label, non-randomised prospective study that investigated celecoxib at a dose of 300mg/day for 4 months in advanced cancer patients (Mantovani, Macciò, Madeddu, Serpe, Antoni, et al., 2010). Participants at baseline had a GPS of 1.3 ± 0.77, which reduced significantly to 0.8 ± 0.7 (p=0.0004). However, it must be taken into consideration that 83.3% of the study population received concomitant chemotherapy, which could have affected the overall inflammation process and GPS data (Mantovani, Macciò, Madeddu, Serpe, Antoni, et al., 2010).

In 2010, Madeddu et al. published results from an open-label, non-randomised study that investigated the use of 4g of amino acids (AMINOTROFIC) b.d.s. in cancer cachexia patients for a period of eight weeks (Madeddu et al., 2010). Albumin levels of 2.99 ± 0.67 g/L increased significantly to 3.6 ± 0.3g/L (p=0.0003). Albumin levels were gained by a different technique i.e. nephelometric and were at lower levels than generally seen. CRP levels of 24.7 ± 18.1 decreased to 17 ± 11.4 (p=0.066). Units were not stated. Again, >90% of participants received concomitant chemotherapy while on study (Madeddu et al., 2010).

In 2013, Wen et al. published results from a single-centre, randomised controlled, open label study that investigated the combination of megestrol acetate 160mg b.d.s. plus thalidomide 50mg b.d.s. (trial group) versus megestrol acetate 160mg b.d.s. (control group) (Wen et al., 2013). Participants had baseline GPS of 1.5 ± 0.7, which significantly reduced to 1.2 ± 0.8 after eight weeks (p=0.05) within the trial group, while a non-significant difference was seen within the control group with a baseline of 1.4 ± 0.8 to 1.3 ± 0.77 at end of study

(p=0.71). Again, 59.6% (control group) and 65.2% (trial group) received concomitant chemotherapy (Wen et al., 2013).

In 2015, Garcia et al. published results from two phase II, randomised, placebo controlled, double-blind studies that investigated anamorelin 50mg (Garcia et al., 2015). CRP levels were analysed via a different technique of chemiluminescence immunoassay and published with different units (nmol/L). Again, a high proportion of participants received concomitant chemotherapy with 80% within the anamorelin group and 79% within the placebo group. There was a non-significant difference seen between groups. (Garcia et al., 2015).

All the above studies had a high proportion of participants who received concomitant chemotherapy, which has the potential to affect albumin and CRP levels and, therefore, the resultant GPS.

9 Limitations

The ACCeRT study has a number of limitations. These include the attrition rate within both Arms, but especially within Arm A which was greater than in Arm B, and resulted in only 57% (n=4/7) completing week 3 and then 28.5% (n=2/7) completing from week 6 to 20. This decreased the data gained within this study arm. The study participants all had lost ≥5% weight loss and all but one had evidence of their NSCLC disease further progressing indicating refractory cachexia. Therefore, these results are restricted to patients experiencing NSCLC and refractory cachexia, and generalisability to other tumour groups and pre-cachexia and cachexia population cannot be made. It must be acknowledged that the lack of a placebo arm and open-label design, and missing values increases the risk of bias. The ACCeRT study utilised BIA only for body composition changes instead of DEXA scan data, and more recently L3-CT data. BIA method can underestimate the FFM compared with CT or DEXA analyses in surgical and oncologic patients because of fluid shifts. However, since the participants did not show any signs of oedema, ascites, or dehydration underestimation is likely to be a minor issue. The expense of the 3T MRI acquisition scans and the staff to perform the analysis is not always possible at all research/clinical centres. The analysis of 'classic cachexia' proinflammatory cytokines instead of analysing the newer biomarkers e.g. myostatin, Activin A, IGF-1, leptin and ZAG, which would have determined if a true 'anabolic' and a reduction of the 'catabolic' effect was seen. There were limitations in utilising HGS as a measure of upper body strength by hand-held dynamometer. Limitations to the ACCeRT HGS protocol include firstly, the brand of dynamometer with the Jamar® model being the most widely used device, with good inter and intra-rater reliability and established test-retest. Secondly, the use of the maximum value instead of the mean of three attempts. This decision was made due to the nature of the participants and the random outlying results that were gained during the measurements. This included seven participants at different study points. This outcome could have been improved by utilising other strength analysis equipment with both increased specificity and sensitivity. Limitations were also seen in the measurement of isometric leg strength testing. As discussed earlier, the ACCeRT study encountered a number of problems, and the choice of how to measure this in future studies is currently being debated. The study was also not powered to investigate a difference between groups, and not designed to investigate if either PRT sessions or EAA alone or in combination had an overall effect in this population. Limitations in terms of patient-reported outcomes include the need to utilise an instrument that has validated translations available, and with a defined, minimal clinically important difference or meaningful performance status rating change.

Overall, the study team acknowledge that missing data was a potential source of bias. This is very important in confirmatory clinical studies, as it can lead to uncertainty of the likely treatment effect, and needs to be addressed and minimised. This can be achieved by favouring study designs that minimise this problem, e.g. the longer the follow up the greater the likelihood of missing values. Choosing the nature of the outcome variable, with the occurrence of missing values is expected to be lower when the outcome variable is e.g. mortality. Missing values are more frequent in those diseases where the adherence of patients to the study protocol is usually low. Experience from exploratory trials e.g. ACCeRT and from other trials in related indications should inform expectations for missing data when planning future trials. When patients drop out of a trial, full reporting of all reasons for their discontinuation should be given where possible. This has been carried out within the ACCeRT study thesis. A detailed description of the pre-planned methods used for handling missing data will be included and reported in future ACCeRT studies.

10 Changes to future ACCeRT studies

The study team still believes that there is a place to address refractory cachexia within future studies. The ACCeRT study enrolled participants with documented 5% weight loss at the end-stage of their cancer journey and maybe for future refractory cachexia studies this could be at a lower threshold for the preceding months before study entry e.g. ≥2% over the preceding two-three months, or as per recently published protocols for the POWER studies investigating enobosarm who have decided not to have a minimum or maximum weight loss limit for study entry (Crawford et al., 2016).

Attrition rates are now known in this population, these will be factored into recruitment figures. Future studies could include a deferred allocation design of including a two-week run-in period, along with shorter primary endpoint at six and twelve weeks, with the study continuing onto for 24 weeks, similar in design of the ROMANA 1, 2, and ROMANA 3 studies (Temel et al., 2016). This is supported by the ACCeRT data completion/attrition rates which indicated that if a participant's performance status was adequate to remain on the study at the week 12 visit, they then went on to complete the 20 week study. This highlights the benefit of continuing cachexia studies past 12 weeks, as this would demonstrate if the intervention being tested showed a longer-term benefit. The study design could possibly contain a placebo arm and where possible allocation blinded; this could be in the form of a placebo versus celecoxib, an isocaloric, isonitrogenous oral supplement versus EPA, and simple gentle stretching exercises that do not stimulate anabolic pathways versus PRT. A defined protocol to be stated on the handling of missing values i.e. "truncation due to death", possibly as per recently proposed protocol (Wang, Scharfstein, Colantuoni, Girard, & Yan, 2017).

The study design should include DEXA scans at relevant time points, and/or the use of L3-CT data if possible. Future studies could include more frequent MRI scanning, and combine the L3-MRI, i.e. abdomen and thigh cross-sectional analysis within the same scan to reduce costs and patient burden.

There has been recent interest in n-3 Polyunsaturated Fatty Acids (PUFA) from the Antarctic krill (*Euphausia superba*) zooplankton. This resource has recently shown similar oral bioavailability of both EPA and Docosahexaenoic Acid (DHA) in different formulations e.g. fish-oil ethyl ester, fish-oil triglyceride and krill oil formulations (Yurko-Mauro et al., 2015). Krill oil has shown safety within a randomised study of healthy volunteers (Ulven et al., 2011). Future refractory cancer cachexia studies could randomise either to liquid EPA oil or to krill oil, or if participants found EPA oil unpalatable, they could switch to another formulation with equivalent amounts of EPA and DHA in the form of echium oil. Future

studies could also randomise participants to different composition of liquid and capsulated EAA.

Factors and outcomes still need to be standardised within future cancer cachexia studies, as this would allow comparisons to be made between different study interventions. These include the optimum entry criteria especially in the level of weight loss, the primary and secondary outcomes, along with the modality and format of analysis of body composition, and upper body and lower body strength and/or power.

11 Conclusion

All the enrolled ACCeRT study participants except one within Arm B had evidence of their NSCLC disease progressing further, indicating refractory cachexia either while on the study or shortly afterwards.

The primary endpoint of acceptability of the multi-targeted approach of supportive care within cachectic NSCLC participants completing to week 20 was high. One hundred per cent of participants scored either 4 = 'tend to agree' or 5 = 'strongly agree' for EPA and celecoxib within both groups, and 100% for PRT sessions and EAA within Arm B only. Compliance was also high with 99.6% (Arm A) and 86.8% (Arm B) for EPA and 60.7% (Arm A) and 100% (Arm B) for celecoxib. With 94.4% for PRT sessions and 76.5% for EAA within Arm B only.

The ACCeRT study showed some trends in efficacy in terms of improvement or stability in a number of cachexia markers. Please note it was difficult to discuss trends within Arm A, due to the limited data from only two participants.

For participants completing week 12, trends in efficacy in individual data and mean change values were seen within the following outcomes. The body composition BIA data showed some participants experienced net gain in FFM and total weight within both Arms. The mean change in FFM was +1.3kg within Arm A and +0.7kg within Arm B. The proinflammatory cytokine data showed one participant experienced decreased levels of IL-6 within Arm B only, and some participants experiencing decreased TNF-α level within both Arms. The mean change in IL-6 levels was +15.8pg/ml within Arm A and +8.7pg/ml within Arm B. TNF-α levels of -4.5pg/ml within Arm A and +4.3pg/ml within Arm B. The HGS data showed that some participants experienced stability within both Arms, with the mean change of +0.3kg within Arm A and -1.9kg within Arm B. The FAACT-PWB data showed some participants improved within Arm B only, with the mean change of -1 within Arm A and -1.7 within Arm B. The MFSI-SF Total score data showed one participant experienced improved fatigue in Arm B only, with the mean change of -3.5 within Arm A and +6.3 within Arm B. The WHOQOL-BREF overall score data showed stability within both Arms, with the mean change of +0.5 within Arm A and -0.7 within Arm B. The WHOQOL-BREF physical score data showed that some participants experienced stability within both Arms, with the mean change of +1 within Arm A and -2.6 within Arm B. The albumin level data showed some participants experienced stability within both Arms. A slower decline in nutritional status was seen within Arm B, with the mean change of -4g/L within Arm A and -2.7g/L within Arm B. The CRP level data showed one participant experienced decreased levels in Arm B only, with the mean change of +59.5mg/L within Arm A and +20.2mg/L within Arm B.

For participants completing week 20, trends in efficacy in individual data and mean change values were seen within the following outcomes. The body composition BIA data showed one participant experienced a net gain of FFM within Arm B only, with the mean change of -1.5kg within Arm A and -1.7kg within Arm B. The proinflammatory cytokine data showed one participant experienced decreased levels of IL-6 within Arm A only, along with one participant who experienced stability of TNF-α level within Arm B only. The mean change of IL-6 levels of +3pg/ml within Arm A and +21pg/ml within Arm B, and mean change of TNF-α levels of +7.8pg/ml within Arm A and +10.7pg/ml within Arm B. The HGS data showed that some participants experienced net gain within both Arms, with the mean change of +0.8kg within Arm A and -3.4kg within Arm B. The FAACT-PWB data showed some participants experienced stability within both Arms, with the mean change of +0 within Arm A and -2.5 within Arm B. The MFSI-SF Total score data showed that one participant experienced improved fatigue within Arm B only, with the mean change of +3.5 within Arm A and +5.5 within Arm B. The WHOQOL-BREF overall score showed all participants experienced stability within both Arms, with the mean change of +0.5 within Arm A and -0.3 within Arm B. The WHOQOL-BREF physical score showed that some participants experienced stability within both Arms, with the mean change of +1 within Arm A and -2.8 within Arm B. The albumin level data showed that some participants experienced stability in levels within both Arms, with the mean change of -1.5g/L within Arm A and -3.3g/L within Arm B. The CRP level data showed that some participants experienced stability in levels within both Arms, with the mean change of +29.5mg/L within Arm A and +58mg/L within Arm B. Greater improvements in the above outcomes were seen within Arm B over both 12 and 20 weeks.

The MRI data showed that some participants experienced a net gain in total quadriceps muscle volume within both Arms. While the PRT reports showed that all participants with various entry levels of fitness and weight loss managed to achieve the planned programme within phase I, except for the one participant who had a history of neck, bilateral hips and spine injury from a childhood road traffic accident who underwent a modified exercise programme, and one participant with 50% attendance due to ill-health. Within phase II, three participants under-achieved, two achieved and five over-achieved the planned programme (n=10). During phase III, three participants under-achieved, three achieved and one over-achieved the planned programme (n=7). During phase IV, two participants under-achieved with three over-achieving (n=5). During the final phase V, two participants under-achieved and two achieved the planned programme (n=4). Data indicate that there was a trend in

participant's achieving/over-achieving during the programme and participants under-achieving in the phase of leaving the study.

The isometric leg strength results were taken with some trepidation as stated before. This was due to a number of technical issues, and supported by the lack of trends within the results and random aberrant results seen within participants enrolled at a later stage who underwent a more intensive testing schedule. Formal assessment of isometric leg strength testing is required in this population before being used as outcome measure in future cachectic studies.

There were no exercise-related adverse events, with one possible medication-related AE of asymptomatic AF at weeks 12 to 20 within one Arm A participant.

It can be concluded that the combination of EPA, celecoxib, EAA high in leucine and the low volume, low intensity training progressing to a moderate volume, moderate-high intensity training programme, was both acceptable and safe within a NSCLC cachectic population. The above trends in efficacy in a number of cachexia markers, and the minimal toxicity, support further evaluation of this study regimen within a larger phase II study.

This study is adding to the scientific literature in the following areas:

Firstly, it is the first published study investigating a multi-modal supportive approach within a cancer refractory cachexia population.

Secondly, the study population did not receive any concomitant chemotherapy treatments throughout the 20 week study.

Thirdly, this is the first study to utilise two sessions of progressive resistance training per week, followed by an amino acid supplement high in leucine.

Fourthly, this study utilised 3T MRI scanner data for total quadriceps muscle volume change analysis.

Finally, all these data can serve as a baseline for future refractory cachexia studies.

12 Appendices

12.1 Health and Disability Ethics Committee approval

12.1.1 Version 2, dated 1st August 2011

Health and Disability Ethics Committees

Health and Disability Ethics Committees
Freyberg Building
20 Alfken Street
PO Box 5013
Wellington
0800 4 ETHICS
hdecs@moh.govt.nz

2 September 2011
Amended 15 August 2016

Prof Rod MacLeod
School of Population Health
University of Auckland
Private Bag 92 019, Auckland 1142

Dear Prof MacLeod -

Ethics ref:	**NTY/11/06/064 (please quote in all correspondence)**
Study title:	**ACCeRT Study. Auckland's Cancer Cachexia evaluating Resistance Training Study.** **A randomised feasibility study of EPA and Cox-2 inhibitor (Celebrex) versus EPA, Cox-2 inhibitor (Celebrex), Resistance Training followed by ingestion of essential amino acids high in leucine in NSCLC cachectic patients.**
Investigators:	**Prof Rod MacLeod, Dr Justin Keogh, Mrs Joanna Stewart, Ms Elaine Rogers.**

This study was given ethical approval by the Northern Y Regional Ethics Committee on 2 September 2011.

Approved Documents

- Protocol version 2 dated 1st August 2011
- Information sheet and Consent form version 2 dated 1st August 2011

This approval is valid until 1 September 2013, provided that Annual Progress Reports are submitted (see below).

Access to ACC
For the purposes of section 32 of the Accident Compensation Act 2001, the Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out. Participants injured as a result of treatment received in this trial will therefore be eligible to be considered for compensation in respect of those injuries under the ACC scheme.

Amendments and Protocol Deviations
All significant amendments to this proposal must receive prior approval from the Committee. Significant amendments include (but are not limited to) changes to:

- the researcher responsible for the conduct of the study at a study site
- the addition of an extra study site

12.1.3 Australian New Zealand Clinical Trials Registry (ANZCTR)

//www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=343304&isReview=true

VIEW TRIAL AT REGISTRATION

VIEW HISTORY

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Trial registered on ANZCTR

Trial ID	ACTRN12611000870954
Ethics application status	Approved
Date submitted	5/08/2011
Date registered	16/08/2011
Type of registration	Prospectively registered

Titles & IDs

Public title	Anti-inflammatory and nutritional support, with simple exercises in lung cancer patients with weight loss.
Scientific title	ACCeRT: Auckland's Cancer Cachexia evaluating Resistance Training study. EPA, Cox-2 inhibitor versus EPA, Cox-2 inhibitor, PRT plus essential amino acids intervention to assess acceptability in Non-Small-Cell Lung Cancer cachectic patients
Secondary ID [1]	Nil
Universal Trial Number (UTN)	1111 - 1123 - 4962
Trial acronym	ACCeRT
Linked study record	

12.2 FAACT

FAACT (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

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

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

FAACT (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I feel sad	0	1	2	3	4
GP2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GP3	I am losing hope in the fight against my illness	0	1	2	3	4
GP4	I feel nervous	0	1	2	3	4
GP5	I worry about dying	0	1	2	3	4
GP6	I worry that my condition will get worse	0	1	2	3	4

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

FAACT (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
CN	I have a good appetite	0	1	2	3	4
ACT1	The amount I eat is sufficient to meet my needs	0	1	2	3	4
ACT2	I am worried about my weight	0	1	2	3	4
ACT3	Most food tastes unpleasant to me	0	1	2	3	4
ACT4	I am concerned about how thin I look	0	1	2	3	4
ACT5	My interest in food drops as soon as I try to eat	0	1	2	3	4
ACT7	I have difficulty eating rich or "heavy" foods	0	1	2	3	4
ACT8	My family or friends are pressuring me to eat	0	1	2	3	4
CC	I have been vomiting	0	1	2	3	4
ACT10	When I eat, I seem to get full quickly	0	1	2	3	4
ACT11	I have pain in my stomach area	0	1	2	3	4
ACT13	My general health is improving	0	1	2	3	4

12.2.1 FAACT sensitivity to change in performance status rating

FAACT (vers. 3) Sensitivity to change in Performance Status Rating (PSR)

Scale	Baseline (*n*=213)		Group	*n*	Change score Mean	Change score SD	*p*-value	Effect size 1*	Effect size 2**
	Mean	SD							
Physical Well-being (7-item) (PWB)	17.6	5.9	Worsened PSR	60	-2.1	6.9	<0.001	-0.36	-0.30
			No change	80	1.7	4.8		0.29	0.35
			Improved PSR	19	3.5	6.6		0.59	0.53
Social/Family Well-being (7-item) (SWB)	20.9	5.9	Worsened PSR	60	0.8	4.1	0.370	0.14	0.20
			No change	80	1.0	3.5		0.17	0.29
			Improved PSR	19	2.3	4.2		0.39	0.55
Emotional Well-being (6-item) (EWB)	14.4	4.1	Worsened PSR	60	0.1	3.5	0.190	0.02	0.03
			No change	80	0.9	3.1		0.22	0.29
			Improved PSR	19	1.5	3.1		0.37	0.48
Functional Well-being (7-item) (FWB)	14.7	5.7	Worsened PSR	60	-2.4	5.7	<0.001	-0.42	-0.42
			No change	80	0.3	4.6		0.05	0.07
			Improved PSR	19	3.6	3.9		0.63	0.92
FACT-G Total score (27-item)	75.1	16.4	Worsened PSR	60	-4.2	14.7	<0.001	-0.26	-0.29
			No change	80	3.3	11.1		0.20	0.30
			Improved PSR	19	11.5	13.5		0.70	0.85
Additional Concerns (12-item) (A/CS-12)	21.4	8.0	Worsened PSR	60	5.0	10.6	0.007	0.63	0.47
			No change	80	9.2	8.8		1.15	1.05
			Improved PSR	19	12.2	10.4		1.53	1.17
FAACT Total score (39-item)	98.1	22.1	Worsened PSR	60	1.3	22.9	<0.001	0.06	0.06
			No change	80	12.2	17.0		0.55	0.72
			Improved PSR	19	24.3	22.5		1.10	1.08
Trial Outcome Index (26-item) (TOI = PWB+FWB+A/CS-12)	53.7	15.8	Worsened PSR	60	0.7	19.0	<0.001	0.04	0.04
			No change	80	11.2	14.1		0.71	0.79
			Improved PSR	19	19.3	17.0		1.22	1.14

* Effect size 1 = standardized mean difference = change from baseline / SD at baseline

** Effect size 2 = standardized response mean = change from baseline / SD of the change score

Source: Ribaudo, J., Cella, D., Hahn, E.A., Lloyd, S.R., Tchekmedyian, N.S., Von Roenn, J., & Leslie, W.T. (2001). Re-validation and shortening of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire. Quality of Life Research, 9, 1137-1146.

12.3 MFSI-SF

MFSI

Below is a list of statements that describe how people sometimes feel. Please read each item carefully, then circle the one number next to each item which best describes **how true each statement has been for you in the past 7 days.**

		Not at all	A little	Moderately	Quite a bit	Extremely
1.	My glands are swollen	0	1	2	3	4
2.	I am not interested in sex	0	1	2	3	4
3.	I am bewildered	0	1	2	3	4
4.	I have pain in my chest	0	1	2	3	4
5.	I feel frustrated	0	1	2	3	4
6.	I am clumsy	0	1	2	3	4
7.	I have trouble remembering things	0	1	2	3	4
8.	I limit my social activity	0	1	2	3	4
9.	My neck is tender	0	1	2	3	4
10.	I have trouble talking with others	0	1	2	3	4
11.	I feel irritable	0	1	2	3	4
12.	My shoulders are stiff	0	1	2	3	4
13.	I have trouble finishing things	0	1	2	3	4
14.	My muscles ache	0	1	2	3	4
15.	I have trouble doing simple tasks	0	1	2	3	4
16.	My head feels heavy	0	1	2	3	4
17.	I have trouble sitting up	0	1	2	3	4
18.	My legs feel weak	0	1	2	3	4
19.	I sleep during the day	0	1	2	3	4
20.	I am short of breath	0	1	2	3	4
21.	I feel cheerful	0	1	2	3	4
22.	I feel lively	0	1	2	3	4
23.	I feel angry	0	1	2	3	4
24.	I feel washed out	0	1	2	3	4
25.	I feel feverish	0	1	2	3	4

12.4 WHOQOL-BREF

The questionnaire –

Please read the question, assess your feelings **OVER THE LAST TWO WEEKS** and **circle the number** on the scale for each question that gives the best answer for you.

PART A- Generic Questions

		Very Poor	Poor	Neither Poor nor Good	Good	Very Good
1	How would you rate your quality of life?	1	2	3	4	5

		Very Dissatis-fied	Dissatisfied	Neither Satisfied nor Dissatisfied	Satisfied	Very Satisfied
2	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the **last two weeks**.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3	To what extent do you feel that physical pain prevents you from doing what you need to do?	1	2	3	4	5
4	How much do you need any medical treatment to function in your daily life?	1	2	3	4	5
5	How much do you enjoy life?	1	2	3	4	5
6	To what extent do you feel your life to be meaningful?	1	2	3	4	5
7	How well are you able to concentrate?	1	2	3	4	5
8	How safe do you feel in your daily life?	1	2	3	4	5
9	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about **how completely** you have experienced **or** were able to do certain things in the **last two weeks.** Circle your best answer number.

		Not at all	A little	A moderate amount	Very much	Extremely
10	Do you have enough energy for everyday life?	1	2	3	4	5

11	Are you able to accept your body appearance?	1	2	3	4	5
12	Have you enough money to meet your needs?	1	2	3	4	5
13	How available to you is the information you need in your day-to-day life?	1	2	3	4	5
14	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5
15	How well are you able to get around physically?	1	2	3	4	5

The following questions ask about **how good or satisfied** you have felt about aspects of your life over the **last two weeks.**

		Very Dissatisfied	Dissatisfied	Neither Satisfied nor Dissatisfied	Satisfied	Very Satisfied
16	How satisfied are you with your sleep?	1	2	3	4	5
17	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18	How satisfied are you with your capacity for work	1	2	3	4	5
19	How satisfied are you with yourself?	1	2	3	4	5
20	How satisfied are you with your personal relationship?	1	2	3	4	5
21	How satisfied are you with your sex life?	1	2	3	4	5
22	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23	How satisfied are you with the conditions of your living place?	1	2	3	4	5
24	How satisfied are you with your access to health services?	1	2	3	4	5
25	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to **how often** you have felt or experienced certain things in the last two weeks.

		Never	Seldom	Quite Often	Very Often	Always
26	How often do you have negative feelings such as blue mood, despair, anxiety or depression?	1	2	3	4	5

PART B - National Questions

The following question asks about **how good or satisfied** you have felt about various aspects of your life over the last two weeks.

		Very Dissatisfied	Dissatisfied	Neither Satisfied nor Dissatisfied	Satisfied	Very Satisfied
27	How satisfied are you that you are able to meet the expectations placed on you?	1	2	3	4	5

The following questions ask about **how completely** you have experienced **or** were able to do certain things in the **last two weeks**.

		Not at all	A little	A moderate amount	Very much	Extremely
28	To what extent do you feel respected by others?	1	2	3	4	5
29	To what extent are you able to manage personal difficulties?	1	2	3	4	5

The following questions ask **how much** you have experienced certain things in the **last two weeks.**

		Not at all	A little	A moderate amount	Very much	Extremely
30	To what extent do you have feelings of belonging?	1	2	3	4	5
31	To what extent do you feel you have control over your life?	1	2	3	4	5

Do you have any comments about this questionnaire?

_____

_____

_____

Please complete the other side of this page.

12.5 Individual participant data graphs

12.5.1 Fat Free Mass

Figure 64 ACCeRT change over time in fat free mass for individual participants completing week 12

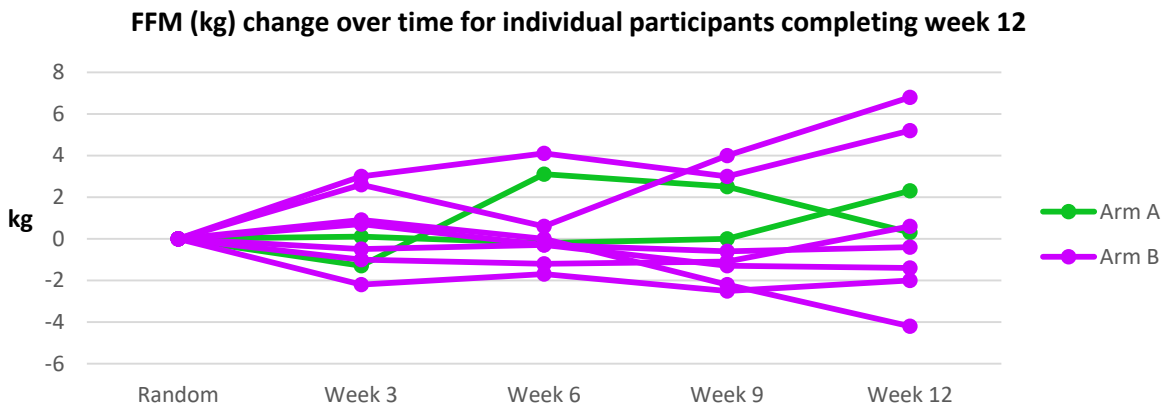
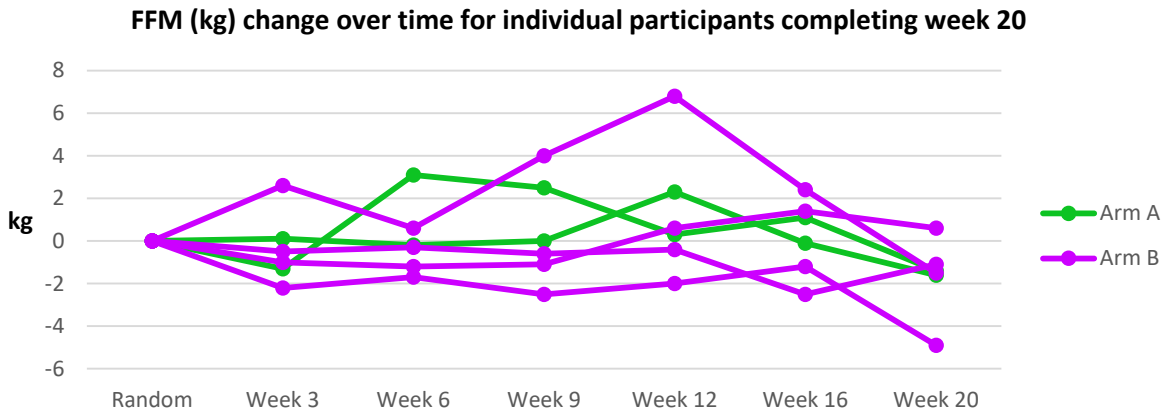


Figure 65 ACCeRT change over time in fat free mass for individual participants completing week 20



12.5.2 Weight

Figure 66 ACCeRT change over time in weight for individual participants completing week 12

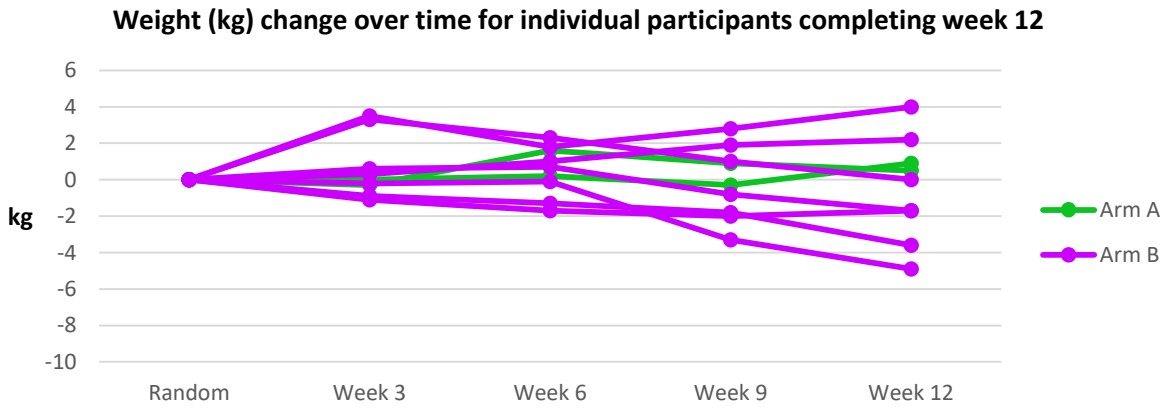
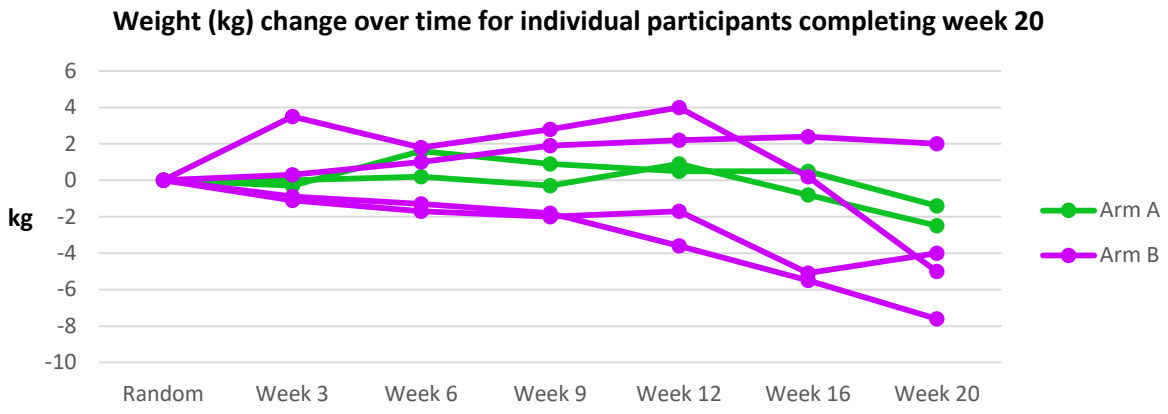


Figure 67 ACCeRT change over time in weight for individual participants completing week 20



12.5.3 Fat Mass

Figure 68 ACCeRT change over time in fat mass for individual participants completing week 12

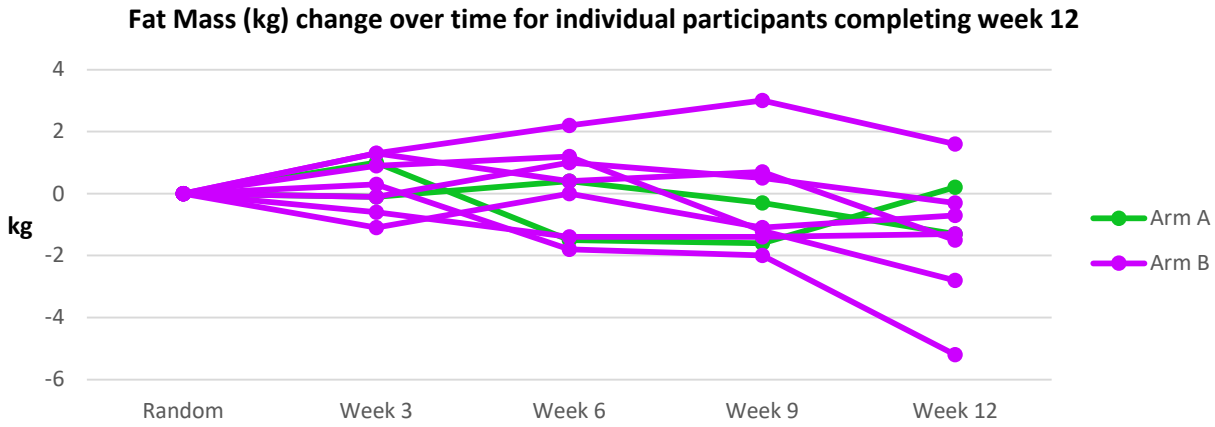
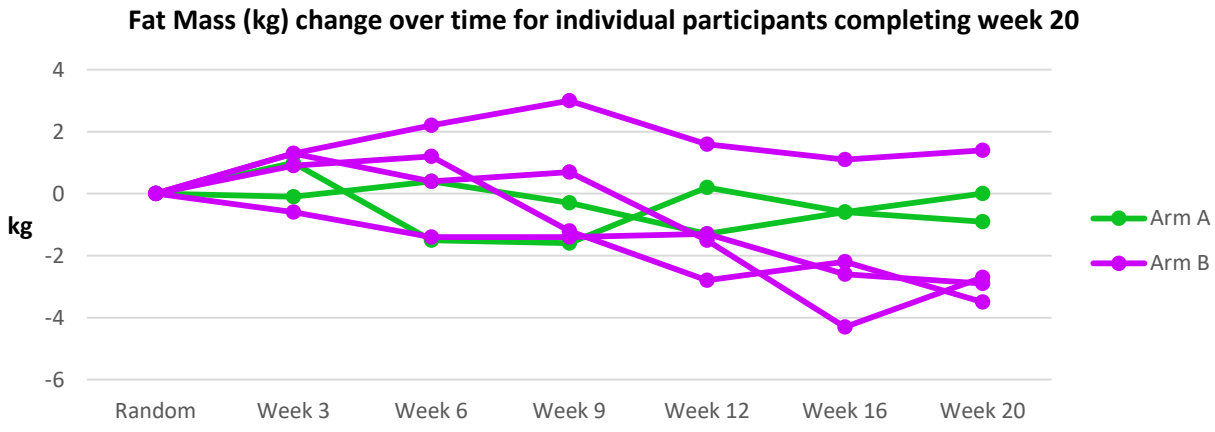


Figure 69 ACCeRT change over time in fat mass for individual participants completing week 20



12.5.4 Progressive resistance training reports

Arm B participant: During phase 1, the participant performed one set of up to eight repetitions of the leg extension, leg curl, chest press and row exercises. Each of these exercises were performed in a seated position. For session 1, the participant began exercising with the use of a yellow theraband, which provided an initial familiarisation of the movement under

“very light” on the BORG RPE scale load conditions. To achieve the initial phase prescribed intensity of “very light”, the yellow tubing was kept, with the amount of pretension being manipulated to suit. During the latter stage of this phase, the prescribed intensity was increased to “light” and as such, the resistance tubing were increased to the thicker red tubes.

During phase 2, the participant continued with the same four exercises that were used in phase 1 with the addition of a bicep curl, and the addition of a second set. In the initial stages of this phase, the participant developed the sensation of weak legs and as such the intensity of the training sessions were maintained at the “light” level. During the latter stages of the phase, the thicker red tube was used to maintain achieving the “light” level of intensity.

During phase 3, the participant continued to exercise; however, sessions were intermittent and as such, the intensity was maintained at the “light” level and were kept to the seated position as described in phase 1. Last study visit - week 12. Last PRT attendance - PRT 21.

Arm B participant: Presented with bone metastases in the right pelvis, hip, femur and tibia, left knee, tibia and proximal tibia, and T5-T9. Subsequently, the PRT programme was modified to exclude the leg extension and leg curl exercises of the affected limbs.

During phase 1, the participant performed one set of up to eight repetitions of the leg extension, leg curl, chest press and row exercises. Each of these exercises were performed in a seated position. For session 1, the participant began exercising using yellow tubing that the participant rated as “very light” on the BORG RPE scale. This provided an initial familiarisation of the movement under very light load conditions. To achieve the initial phase prescribed intensity of “very light” the red tubing was used to provide greater resistance. During the latter stage of this phase, the prescribed intensity was increased to “light” and as such, the resistance tubing were increased to the thicker green tubing.

PRT sessions 8, 9 and 10 planned leave.

During phase 2, the participant continued with the same four exercises that were used in phase 1 with the addition of a bicep curl. The exercise intensity was increased from “light” to “somewhat hard”, and the exercise volume was increased by adding a second set. To achieve the desired intensity the green tubing was used while a dumbbell was used with the bicep curl.

The participant received RT to T5-T9 spine for disease progression during PRT 15 and 16. Last study visit - week 9. Last PRT attendance – PRT 19.

Arm B participant: During phase 1, the participant performed one set of up to eight repetitions of the leg extension, leg curl, chest press and row exercises. Each of these exercises were performed in a seated position. For session 1, the participant began exercising using yellow tubing that they rated as "very light" on the BORG RPE scale. This provided an initial familiarisation of the movement under very light load conditions. The participant continued with the yellow tube until session 3 of phase 1 as they adapted to the resistance provided and so the red band was then utilised to achieve the desired intensity of "very light. During the latter stage of this phase, the prescribed intensity was increased to "light" and as such, the resistance tubes were increased to the thicker green tubing.

During phase 2, the participant continued with the four exercises stated above but with the addition of a bicep curl. Furthermore, prescribed intensity was progressed from "light" to "somewhat hard" and a second set was added. To achieve the desired BORG RPE the thicker purple tube was used, which was increased in the later part of the phase to the black tube. Over the weekend prior to the final week of the phase, the participant experienced a chest infection (PRT 14 and 15) and as such, the immediate post training session had the exercise intensity reduced.

During phase 3, a partial squat was introduced and the upper body exercises were performed in a standing position. The purpose of adopting a standing position was to increase the functional relevance and postural challenge of the exercises. The desired intensity was maintained as "somewhat hard" and so the black band was maintained. Towards the end of the phase, the band was increased to the thicker grey band in order to achieve the desired intensity.

During phase 4, the participant maintained the same group of exercises as in the previous phase; however, the intensity was increased to "hard". This was achieved by manipulating the length and amount of pre-tension of the grey tubing. The squat exercise was still performed using body weight only.

During phase 5, the participant experienced hypotension, lower-respiratory-tract infection and fatigue. As such, exercise intensity was reduced to a BORG RPE of "somewhat hard". This was achieved by using black tubing, which has a lesser thickness than the tubing used previously. The participant completed the 20 weeks of training. Last study visit - week 20. Last PRT attendance – PRT 40.

Arm B participant: During phase 1, the participant performed one set of up to eight repetitions of the leg extension, leg curl, chest press and row exercises. Each of these exercises were performed in a seated position. For session 1, the participant began exercising using

yellow tubing that they rated as “very light” on the BORG RPE scale. This provided an initial familiarisation of the movement under very light load conditions. The participant continued with the yellow band until session 4 of phase 1 as they adapted to the resistance provided and so the red band was utilised to achieve the desired “very light” intensity level. During the latter stage of this phase, the prescribed intensity was increased to “light” which was achieved by manipulating the length and amount of pre-tension on the tubing.

During phase 2, the participant continued with the same four exercises that were used in phase 1 and the exercise volume was increased by adding a second set. However, during the transition from phase 1 to phase 2 the participant missed two exercise sessions due to low haemoglobin levels (PRT 8 and 9) and subsequently, exercise intensity was initially reduced to very light for the first session back and then increased to “light”. This was achieved by using the thicker green tubing. From session 4 of phase 2 onwards, due to disease-related pain (PRT 12) on the affected side of the chest, the seated chest press and row exercises were only performed on the non-affected side.

During phase 3, the participant performed two sessions, which continued with exercises being performed in the seated position and exercise intensity being maintained at a “light” level. Last study visit week - 9, Last PRT attendance - PRT 19.

Arm B participant: Presented with multiple thoracic and lumbar bone metastasis and a previous history of treated/resolved spinal compression. Consequently, all exercises were performed in a controlled, seated position and squat type movements were omitted.

During phase 1, the participant performed one set of up to eight repetitions of the leg extension, leg curl, chest press and row exercises. Each of these exercises were performed in a seated position. For session 1, the participant began exercising using red tubing that the participant rated as “very light” on the BORG RPE scale. This provided an initial familiarisation of the movement under very light load conditions. To achieve the initial phase prescribed intensity of “very light” the tubing was maintained with the yellow band. During the latter stage of this phase, the prescribed intensity was increased to “light” and as such, the resistance tube was increased to the thicker red tube.

During phase 2, the participant continued with the same four exercises that were used in phase 1 with the addition of a bicep curl. The exercise intensity was increased from “light” to “somewhat hard”, and the exercise volume was increased by adding a second set. To achieve the desired change in intensity the participant exercised with red tubing in the initial half of the phase, and then increased to the thicker green tubing in the second half. The participant experienced a chest infection during PRT 12.

The participant performed the initial session of phase 3; however, experienced pain, vascular–thrombosis and infection from PRT 17 onward. Last study visit - week 12. Last PRT attendance - PRT 21.

Arm B participant: During phase 1, the participant performed one set of up to eight repetitions of the leg extension, leg curl, chest press and row exercises. Each of these exercises were performed in a seated position. For session 1, the participant began exercising using the red tubing that the participant rated as “very light” on the BORG RPE scale. This provided an initial familiarisation of the movement under very light load conditions. To achieve the initial phase prescribed of “very light” intensity, tubing was increased to green for the upper body exercises and blue for the lower body exercises. During the latter stage of this phase, the prescribed intensity was increased to “light” and as such, the resistance tubing were increased in thickness to the red tubing for all exercises.

During the initial stage of phase 2, the participant experienced intermittent diarrhoea (PRT 09) and thus was maintained at the “light” level of intensity until resolved. The exercise intensity was increased from “light” to “somewhat hard” and the exercise volume was increased by adding a second set. To achieve this intensity, the participant moved from red to green tubing.

During phase 3, a partial squat was introduced and the upper body exercises were performed in a standing position. The purpose of adopting a standing position was to increase the functional relevance and postural challenge of the exercises. The exercise intensity was increased from “somewhat hard” to “hard”.

During phase 4, the participant showed signs of disease progression/jaundice (PRT 24 and 25). The participant still experienced intermittent diarrhoea. To minimise the likelihood of exercise-induced fatigue, the squat was removed and the exercise intensity was reduced to “somewhat hard”. Last study visit - week 12. Last PRT attendance – PRT 29.

Arm B participant: During the initial weeks of phase 1, attendance was intermittent due to fatigue - attended five out of eight planned sessions. PRT was limited to one set of six repetitions of the leg extension, leg curl, chest press and row exercises, and exercise intensity was limited to “very light”. Last study visit - week 3. Last PRT attendance – PRT 10

Arm B participant: During phase 1, the participant performed one set of up to eight repetitions of the leg extension, leg curl, chest press and row exercises. Each of these were performed in a seated position. For session 1, participant 016 began exercising using yellow tubing, which provided an initial familiarisation of the movement under “very light” BORG

RPE scale intensity conditions. The participant continued with the yellow band until session 3 of phase 1, at which point the red tubing was introduced to maintain the same relative intensity. During the latter stage of this phase, the prescribed intensity was increased to "light".

During phase 2, the participant continued with the same four exercises that were used in phase 1 with the addition of a bicep curl. The exercise intensity was increased from "light" to "somewhat hard" and the exercise volume was increased by adding a second set. To achieve the desired BORG RPE the participant was moved to the thicker green tubing and then at the later sessions to the purple tubing for the push and pull movements. With respect to the bicep curl, the participant was able to match the desired BORG RPE through use of the red tubing and eventually increased to the green tubing. Last study visit - week 9. Last PRT attendance - PRT 20.

Arm B participant: During phase 1, the participant performed one set of up to eight repetitions of the leg extension, leg curl, chest press and row exercises. Each of these exercises were performed in a seated position. For session 1, the participant began exercising using the yellow tubing that the participant rated as "very light" on the BORG RPE scale. This provided an initial familiarisation of the movement under very light load conditions. The participant continued with the yellow band until session 3 of phase 1, at which point the red tubing was introduced to maintain the same relative intensity. During the latter stage of this phase, the prescribed intensity was increased to "light".

During phase 2, the participant continued with the same four exercises that were used in phase 1 with the addition of a bicep curl. The exercise intensity was increased from "light" to "somewhat hard" and the exercise volume was increased by adding a second set. To achieve the desired BORG RPE the participant was moved onto the thicker green tubing and then at the later sessions to the purple tubing for the push and pull movements. For the bicep curl, the participant was able to match the desired BORG RPE through use of the red tubing.

During phase 3, a partial squat was introduced and the upper body exercises were performed in a standing position. The purpose of adopting a standing position was to increase the functional relevance and postural challenge of the exercises. To maintain the intensity level of "somewhat hard" the participant increased from the green to the black tubing for the lower body exercises and purple tubing for the upper body exercises. The bicep curl was performed using the red tubing.

During phase 4, the participant performed the same set of exercises as the previous phase; however, the intensity was increased to "hard". The black and purple tubing provided

sufficient resistance for the lower and upper body respectively to generate the appropriate intensity. Squats were performed using body weight alone and the red tubing was maintained for the bicep curl.

During phase 5, the participant continued with the aforementioned intensity and exercises. Participant 017 completed 20 weeks of training. Last study visit - week 20. Last PRT attendance – PRT 40.

Arm B participant: Presented with a historical neck, bilateral hip and lower spine injury from a childhood road traffic accident, which resulted in chronic regional pain. Subsequently, the exercise programme was modified to include a slower progression through intensity levels across the programme phases.

During phase 1, the participant performed one set of up to eight repetitions of the leg extension, leg curl, chest press and row exercises. Each of these exercises were performed in a seated position. For session 1, the participant began exercising using the red tubing that the participant rated as “very light” on the BORG RPE scale. This provided an initial familiarisation of the movement under very light load conditions. All exercises through the phase were performed using the yellow tubing.

During phase 2, the participant continued with the same exercises as the previous phase; however, the intensity was increased from “very light” intensity to a “light“. This was achieved by moving up to the red tubing across the phase. The bicep curl exercise that was typically added during this phase was excluded. This conservative approach was taken to avoid the potential of exacerbating the chronic pain and discomfort experienced by the participant.

During phase 3, the participant maintained the same set of exercises and intensity level. Typically, during this phase a squat movement would be performed; however, the participant found this uncomfortable to perform due to their chronic pain. As such, the squat exercise was omitted from the programme.

During phase 4, no changes were made to the exercises other than an increase in intensity to “somewhat hard”. To achieve this intensity, the participant was moved up to the green tubing.

During phase 5, no changes were made to the exercises. However, toward the end of this phase the participant experienced a period of chronic pain resulting in moderate discomfort. In response, the exercise intensity was reduced to a “light” level. The participant completed 20 weeks of training. Last study visit - week 20. Last PRT attendance – PRT 40.

Arm B participant: During phase 1, the participant performed one set of up to eight repetitions of the leg extension, leg curl, chest press and row exercises. Each of these exercises were performed in a seated position. For session 1, the participant began exercising using the yellow tubing that the participant rated as “very light” on the BORG RPE scale. This provided an initial familiarisation of the movement under very light load conditions. Towards the end of the phase, the participant increased to a “light” level of intensity and as such was moved onto using the red tubing to achieve the desired intensity.

Participated in four out of eight sessions due to radiotherapy for right sided chest and pelvis metastases. Following this, the participant experienced radiotherapy-induced oesophagitis, which resulted in the participant being unable to fully engage in the training sessions.

During phase 2, the participant attended but was unable to participate in PRT 05 to PRT 19. Last study visit - week 6. Last PRT attendance – PRT 19.

Arm B participant: Presented with a historic left shoulder rotator cuff injury and as such, appropriate modifications to exercises were made.

During phase 1, the participant performed one set of up to eight repetitions of the leg extension, leg curl, chest press and row exercises. Each of these were performed in a seated position. Due to the previous shoulder injury, push movements of the affected limb were performed at a lighter resistance level and an additional, isometric rotation exercises were performed. For session 1, the participant began exercising using yellow tubing that the participant rated as “very light” on the BORG RPE scale. This provided an initial familiarisation of the movement under very light load conditions. The participant continued with the yellow band until session 5 of phase 1, at which point the red tubing was introduced to maintain the same relative intensity. During the latter stage of this phase, the prescribed intensity was increased to “light”.

During phase 2, the participant continued with the exercises stated above but without the addition of a bicep curl. Alternatively, isometric internal and external rotation exercises were performed. The exercise intensity was increased from “light” to “somewhat hard”, and the exercise volume was increased by adding a second set. The red tubing was used for the lower and upper body exercises to maintain the desired level of intensity.

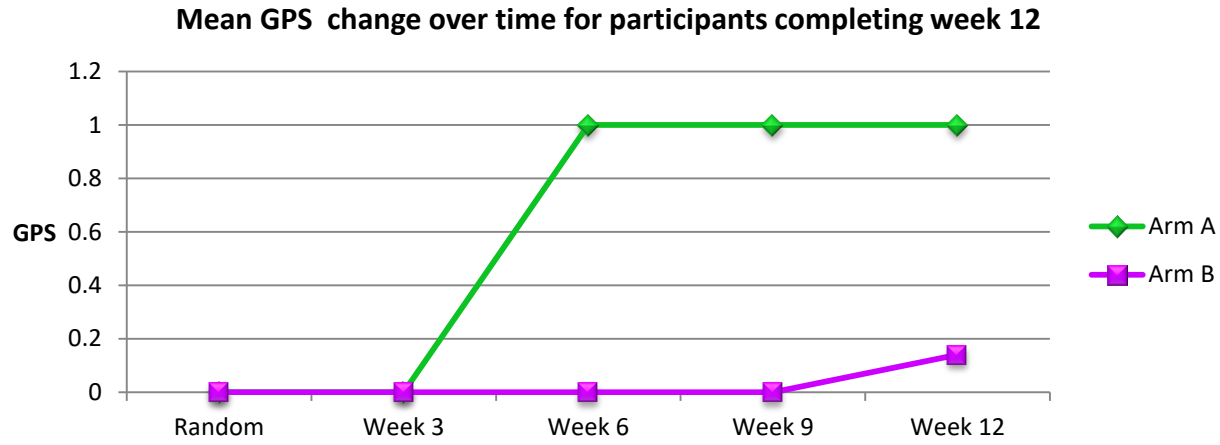
During phase 3, the upper body exercises were performed in a standing position. The purpose of standing was to increase the postural challenge of the exercises. To maintain the intensity level of “somewhat hard” the participant was moved up to green tubing.

During phase 4, the participant performed the same exercises in the previous phase with the addition of body weight squats. The exercise intensity was increased to “hard”. As such, the participant moved from using the green tubing to the thicker purple to generate the appropriate intensity.

During phase 5, the participant maintained the same exercises and intensity utilised in the previous phase. The participant completed 20 weeks of training. Last study visit - week 20. Last PRT attendance – PRT 40.

12.5.5 Mean GPS change over time

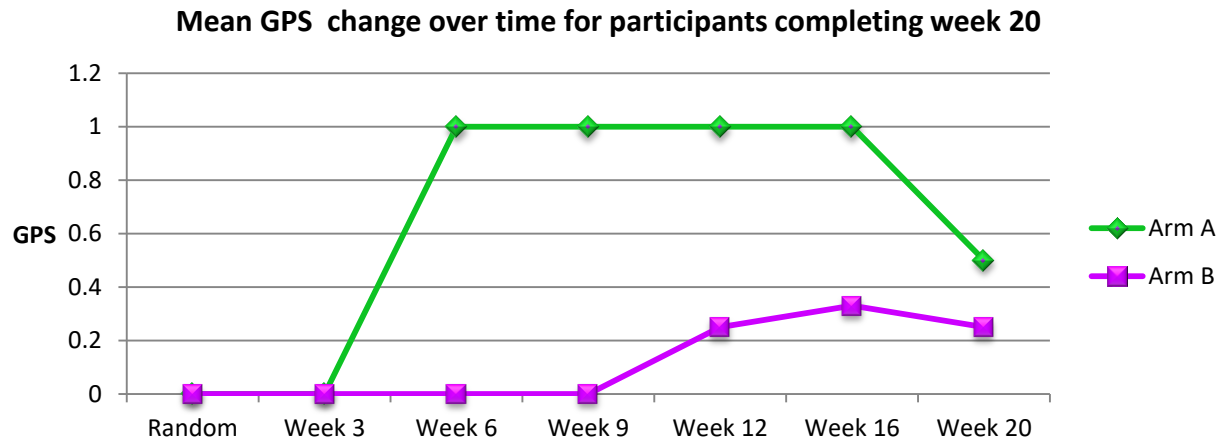
Figure 70 ACCeRT mean change over time in Glasgow Prognostic Score for participants completing week 12



Arm A	2	2	2	2	2
Arm B	7	7	7	7	7

For participants completing to week 12, data shows the mean change in GPS +1 within Arm A, compared with +0.14 within Arm B.

Figure 71 ACCeRT mean change over time in Glasgow Prognostic Score for participants completing week 20



Arm A	2	2	2	2	2	2	2
Arm B	4	4	4	4	4	4	4

For participants completing to week 20, data shows the mean change in GPS +0.5 within Arm A, compared with +0.3 within Arm B.

12.5.6 Arm A individual participant SAE data

Two participants with no SAE

Two participants with two SAEs

Two participants with three SAEs

One participant with four SAEs

Table 48 Arm A participant SAEs

Week 2	Pulmonary/Upper respiratory	Pleural effusion	Grade 2
Week 3	Pulmonary/Upper respiratory	Pleural effusion	Grade 3

Table 49 Arm A participant SAEs

Week 2	Gastrointestinal	Diarrhoea	Grade 3
Week 2	Pain	Tumour	Grade 2
Week 2	Neurology	Confusion	Grade 4

Table 50 Arm A participant SAEs

Week 3	Gastrointestinal	Dehydration	Grade 3
Week 3	Neurology	Confusion	Grade 2
Week 3	Infection		Grade 3
Week 3	Pulmonary/Upper respiratory	Pleural effusion	Grade 2

Table 51 Arm A participant SAEs

Week 16	Musculoskeletal	Other	Grade 3
Week 17	Musculoskeletal	Other	Grade 3
Week 20	Musculoskeletal	Other	Grade 3

Table 52 Arm A participant SAEs

Week 5	Pulmonary/Upper respiratory	Dyspnoea	Grade 3
Week 11	Pulmonary/Upper respiratory	Dyspnoea	Grade 3

12.5.7 Arm B individual participant SAE data

Five participants with no SAE

Three participants with one SAEs

Two participants with two SAEs

One participant with three SAEs

Two participants with four SAEs

Table 53 Arm B participant SAEs

Week 15	Cardiac	Hypotension	Grade 3
Week 15	Infection		Grade 3

Table 54 Arm B participant SAEs

Week 9	Pain	Bone	Grade 3
Week 14	Pain	Tumour	Grade 4

Table 55 Arm B participant SAEs

Week 1	Pain	Bone	Grade 3
Week 9	Infection		Grade 3
Week 9	Vascular	Thrombosis	Grade 3
Week 9	Pain	Bone	Grade 3

Table 56 Arm B participant SAE

Week 15	Metabolic	Hyperbilirubinaemia	Grade 4

Table 57 Arm B participant SAEs

Week 6	Neurology	Confusion	Grade 1
Week 6	Renal	Incontinence-urinary	Grade 2
Week 6	Infection		Grade 2

Table 58 Arm B participant SAEs

Week 5	Infection		Grade 3
Week 10	Gastrointestinal	Obstruction	Grade 3
Week 10	Metabolic	Hypercalcaemia	Grade 2
Week 10	Metabolic	Hyponatraemia	Grade 3

Table 59 Arm B participant SAE

Week 4	Neurology	Motor	Grade 3

Table 60 Arm B participant SAE

Week 4	Neurology	Cranial CN VII	Grade 3

12.5.8 Arm A individual participant SAE data post study

One participant with two SAEs post week 20/End of Trial visit

Table 61 Arm A participant SAEs post week 20/End of Trial visit

Week 24	Musculoskeletal	Other	Grade 3
Week 24	Pain	Bone	Grade 3

12.5.9 Arm B individual participant SAE data post study

One participant with one SAE post Last study visit (week 12)

Table 62 Arm B participant SAE post Last study visit

Week 16	Pulmonary/Upper respiratory	Dyspnoea	Grade 2

12.5.10 Cardiac medication and ECG changes through the study

Table 63 Participants summary of cardiac medication and ECG changes through the study

	Visit	Visit	Visit	Baseline medication	
Arm A	Baseline			Metoprolol 23.75mg o.d.	
Arm A	Baseline				
Arm A	Baseline			Metoprolol 95mg o.d.	
Arm A	Baseline			Dilatrend Carvedilol 25mg o.d.	
Arm A	Baseline			Amolipidine 2.5mg o.d.	
Arm A	Baseline	Wk 12	Wk 20	Metoprolol 95mg o.d.	No significant changes
Arm A	Baseline				No significant changes
Arm A		Wk 12		Metoprolol	Atrial fibrillation (AF)*
Arm A			Wk 20	Metoprolol & Digoxin	AF* still present
Arm B	Baseline	Wk 12			No significant changes
Arm B	Baseline	Wk 9		Metoprolol 47.5mg o.d.	No significant changes
Arm B	Baseline	Wk 12	Wk 20		No significant changes
Arm B	Baseline				
Arm B	Baseline	Wk 12			No significant changes
Arm B	Baseline	Wk 12			No significant changes
Arm B	Baseline				
Arm B	Baseline	Last			No significant changes
Arm B	Baseline				
Arm B	Baseline	Wk 12	Wk 20		No significant changes
Arm B	Baseline	Wk 12	Wk 20	Cilazapril 50mg o.d.	No significant changes
Arm B	Baseline				
Arm B	Baseline	Wk 12	Wk 20		No significant changes

*asymptomatic and did not require hospital admission. Unsure if related to underlying condition or medication.

13 References

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