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Exercise and Nutritional Rehabilitation in Patients with Incurable Cancer

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Doctor of Medicine
The University of Edinburgh
2022
Abstract

Background:
Cancer treatments are evolving, so that in many cases cancer is becoming a chronic disease. Rehabilitation is a cornerstone in the management of many chronic diseases, however, it is not yet a routine component of cancer care, in spite of this being advocated (Tiberini R, 2015, Alfano et al., 2016). There is limited evidence for the core components of a rehabilitation programme for patients with incurable cancer. The progressive decline in function and nutritional status in these patients would support an approach that targets these factors. The multi-modal therapeutic approach proposed to treat cancer cachexia, which incorporates exercise and nutrition (Fearon, 2008, Solheim, 2018), has the potential to be adapted as a rehabilitation programme for patients with any type of incurable cancer. However, the feasibility of such a programme remains to be tested.

Aims:
The aims of this thesis were: firstly, to examine the evidence for combined exercise and nutritional interventions in patients with incurable cancer. A phase II, randomised controlled feasibility trial of an exercise and nutritional rehabilitation programme (ENeRgy) versus standard care was designed and undertaken for patients with incurable cancer. Assessing the primary (feasibility) and secondary (exploratory) endpoints of this trial constitute the second and third aims of this thesis.

Methods:
A systematic review was undertaken to assess existing evidence for combined exercise and nutritional interventions for patients with incurable cancer. The internationally recognised Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria were applied to rank evidence relating to patient-important outcomes, detailed in chapter two.
The ENeRgy trial was undertaken as detailed in chapter three. Eligible participants came from two Edinburgh Hospice community palliative care teams or the Edinburgh tertiary Oncology centre. Participants were ≥18 years of age; Karnofsky Performance Status (KPS) ≥ 60; had a diagnosis of incurable cancer (defined as metastatic or locally advanced cancer not amenable to curative treatment); and were not undergoing anti-cancer therapy. Participants were randomised in a 1:1 ratio to receive an eight-week exercise and nutritional rehabilitation programme (intervention arm) or standard care (control arm). The primary endpoints examined feasibility of the trial and compliance with interventions, while secondary endpoints examined recruitment, retention, participant and carer quality of life (QoL) including sleep parameters. Physical activity measures included mean daily step count measured by physical activity monitor (PAM), two minute walk test (TMWT), timed up and go test (TUG), Life Space Assessment (LSA) and KPS. Nutritional status was measured using weight, the abridged Patient Generated Subjective Global Assessment (aPG-SGA) questionnaire and a ten point verbal scale assessment of nutritional intake (AveS). Overall survival was also measured. All endpoints were assessed at trial baseline (week 0), midpoint (week 5) and endpoint (week 9).

Results:
Systematic Review: There are a limited number of published clinical trials examining combined exercise and nutritional rehabilitation in patients with incurable cancer. However, the existing evidence suggests there are multiple beneficial effects: the highest quality body of evidence pertained to improvements in physical function and depression: graded as moderate (B). Improvements in QoL and fatigue were graded as low (C), and the least quality of evidence (very low, D) related to improvements in overall function and nutrition/ weight.

ENeRgy Trial: Forty-five people (28 males) were recruited over 15 months with an attrition rate of 36% (n=16) with a higher rate of attrition in the control
arm (41% vs. 30%). Attrition was mainly due to deterioration in health and no participants withdrew due to the intervention being overly burdensome. Twenty-one participants had a GI or thoracic malignancy and the median [inter-quartile range, IQR] age was 78 years [69-84]. Trial procedures were well tolerated and at least 76% of participants in the treatment arm complied with >80% of the trial interventions. There were no significant differences in participant QoL, with the exception of emotional functioning which remained significantly higher in the intervention arm [P=0.006]. A non-significant improvement in carer QoL was seen in the intervention arm compared to the control arm. There was a non-significant increase in weight in the intervention arm compared to a loss in the control arm (P=0.184). There were no significant differences in step count (P=0.55), TUG (P=0.78), TMWT (P=0.48) and LSA (P=1.0), a-PG-SGA scores (P=0.249), AveS (P=0.398), KPS scores or survival between trial arms.

Conclusions:
Results of the systematic review suggest that there are multiple benefits to be gained for patients with incurable cancer from combined exercise and nutritional rehabilitation programmes, most notably in terms of physical function and mood. This ostensibly could result in improvements in QoL, but adequately powered trials are lacking.

Results from the ENeRgy trial demonstrate that delivering an exercise and nutritional rehabilitation programme in a hospice outpatient setting is feasible in terms of patient recruitment and compliance with interventions, despite attrition. Furthermore there are potential benefits, including improvements in emotional functioning, carer quality of life and weight, which require a larger phase three trial to fully elucidate. Funding for the follow-on phase three trial ‘ENeRgise’ is currently being sought and the results of this trial could lead to fundamental changes in the way we approach rehabilitation in Palliative Medicine.
Lay summary

Rehabilitative palliative care has been advocated for people with life-limiting disease but there is little evidence to support that this is possible and/or would improve QoL for people. Research has focused on exercise but has neglected nutritional intake. Improving a person’s physical activity and nutritional intake are important in the context of cancer: If these are less than adequate, they are related to poor survival overall. Before any research can be done to assess if improving patients exercise and diet actually improves things it is important to assess if doing a trial to investigate this, is actually possible – termed a feasibility trial.

We reviewed current publications to see what kind of evidence is available to support combined diet and exercise programmes for people with incurable cancer. We also undertook the ENeRgy trial – Exercise and Nutritional Rehabilitation in patients with cancer. The trial was not designed to test if delivering an intervention, which targeted exercise and diet worked; rather it was to assess if asking patients to take part in a trial like this was acceptable and if they could manage it.

Patients under the care of hospice community palliative care teams in Edinburgh (St Columba’s Hospice, including East Lothian and Marie Curie Hospice, including West Lothian), and Oncology Services at the Edinburgh Cancer Centre were invited to take part. They were asked about their overall quality of life, symptoms and had their weight, diet and general activity assessed. Then, they were allocated by chance in a 1:1 ratio to receive the trial intervention (eight-week exercise and nutrition programme) either immediately (intervention arm) or after nine weeks (control arm). Participants repeated the initial assessments again at the middle and at the end of the study.

The trial recruited well with 45 people (target 40) enrolled over 15 months. Sixteen participants (36%) did not complete the trial, mostly due to
deteriorating health. Nobody withdrew because they found the intervention too difficult. Twenty one participants out of 23 (two withdrew before starting) received the exercise and nutritional rehabilitation programme as part of the intervention arm, and of these, compliance with the prescribed nutrition and exercise components was higher than 80% in more than three quarters of those taking part.

Of the other measurements, no significant differences were seen in QoL, with the exception of mood which remained significantly higher in those participants in the intervention arm. There was a trend toward improved carer QoL for partner-carers of participants in the intervention arm. There were no statistically significant differences seen in measures of physical function, survival or nutrition between the arms, although those who did the rehabilitation programme appeared to maintain their weight more than those in the control arm. This lack of statistical significance was not unexpected as the trial was not big enough to prove these differences. It did, however show that this type of trial was feasible for this group of patients, which was the main question we set out to prove.

In summary, existing evidence suggests that there are many potential benefits to rehabilitation programmes in patients with cancer. The evidence at present shows that combined exercise and nutritional rehabilitation programmes have the biggest impact on a person’s physical function and can improve people’s mood.

The ENeRgy trial was feasible and acceptable to participants, but a larger follow-on trial is needed to test whether the differences we observed were by chance alone or are genuine. The findings of a larger trial could potentially improve rehabilitation for people with cancer all over the world in the future.
Declaration

I declare that this thesis has been composed solely by myself and that it has not been submitted, in whole or in part, in any previous application for a degree. Except where stated otherwise by reference or acknowledgement, the work presented is entirely my own. Further details are outlined below.

Parts of this work were published in the following peer reviewed journals:


This thesis was conducted whilst in post as Medical Research Fellow at St Columba’s Hospice, Edinburgh and subsequently during my higher specialist training in Palliative Medicine. All chapters were written by myself and where others were involved, this has been acknowledged.

Chapter two, systematic review search and analysis was conducted by myself after the ENeRgy Trial was underway and as such, the results did not
influence the design of the ENeRgy trial. GRADE analysis was completed by myself with the assistance of Jane Cook (Research Nurse, St Columba’s Hospice) and Dr Barry Laird (University of Edinburgh and St Columba’s Hospice, Edinburgh). The GRADE checklist (Appendix two) was designed by myself to ensure a consistent approach to evidence appraisal. The ENeRgy protocol paper was written by myself with guidance from my supervisors, Dr Barry Laird, Professor Marie Fallon (University of Edinburgh and St Columba’s Hospice, Edinburgh) and Mr Richard Skipworth (Clinical Surgery, Royal Infirmary of Edinburgh and University of Edinburgh), as well as Dr Matthew Maddocks (Cicely Saunders Institute of Palliative Care, King’s College London) and proof read by Jane Cook and other authors.

The ENeRgy Trial was funded prior to my appointment as research fellow, but no protocol was in place. The trial protocol was written by myself, with guidance from my supervisors, principally Dr Barry Laird and Professor Marie Fallon. I designed specific elements of the trial based on research and collaboration with co-researchers including outcome measures and timings, selection of PAM for the trial and PAM data capture, diary design, use of outcomes including LSA. Statistical support for the trial and the design of the paper case report forms (pCRFs) was by Catriona Graham and Sharon Tuck (Epidemiology and Statistics Core, Edinburgh Clinical Research Facility, University of Edinburgh) Jane Cook and Lucy Norris (Trial Manager, Institute of Genetics and Molecular Medicine). Liz Dixon (Trial Manager, Southampton Clinical Trials Unit) provided feedback on the protocol as a whole. Matthew Maddocks, inputted in to the specifics of the physical activity intervention for the protocol. Dr Peter Hall and Katharina Diernberger (Health Economists, School of Medicine and Veterinary Medicine, Edinburgh Cancer Research UK) led the health economic design/analysis components of the trial and trial health economic results contributed to Ms Diernberger’s PhD thesis. Novel health economic questionnaires for the trial were developed by myself jointly with Ms Diernberger. Health economic analysis results, however, are beyond the scope of this thesis.
Acknowledgements

First and foremost I would like to thank all of the participants and their loving families, who gave up their very precious time to spend it with the ENeRgy team and helped make this trial a success. We will remember the stories, the laughs and your legacies will live on through our future work.

This work would not have been possible without the loving support of my family. I am so grateful to you all for your patience and encouragement. I hope that one day, my two daughters Sylvia and Robyn will read this thesis and that they will feel proud of their Dad.

Special thanks to Drs Duncan Brown, Erna Haraldsdottir and all the team at St Columba’s Hospice for making this research possible. I am sure that St Columba’s Hospice will continue to grow as an exemplar of high quality palliative research in the future. Thanks also to the fantastic ENeRgy trial team, for all of your hard work, the fun and for lasting friendships. I know that you all meant so much to our participants and their families as well. I loved every minute of working with you all.

Thanks to my supervisors, in particular to Barry and Marie for helping me steer the ship through some turbulent times. Thanks to Skip, for all your valued input as a supervisor and I look forward to many more collaborations with you all in the future.

This thesis is dedicated to my mum, Jan. Mum died in September 2014 from cancer. Mum, you were my best friend and you are still an inspiration to me and to your granddaughters. We miss you every day and I hope that this thesis makes you proud.
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<tbody>
<tr>
<td>AA</td>
<td>Arachidonic Acid</td>
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<tr>
<td>ACCORD</td>
<td>Academic and Clinical Central Office for Research &amp; Development - Joint office for The University of Edinburgh and Lothian Health Board</td>
</tr>
<tr>
<td>ACSM</td>
<td>American College of Sports Medicine</td>
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<tr>
<td>ACTH</td>
<td>Adrenocorticotropic Hormone</td>
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<tr>
<td>AC-QoL</td>
<td>Adult Carers Quality of Life questionnaire</td>
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<tr>
<td>ADL</td>
<td>Activity of Daily Living</td>
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<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>AEE</td>
<td>Activity related Energy Expenditure</td>
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<tr>
<td>AGRP</td>
<td>Agouti-Related Protein</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>aPG-SGA</td>
<td>Abridged Patient Generated Subjective Global Assessment</td>
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<tr>
<td>APPR</td>
<td>Acute Phase Protein Response</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
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<tr>
<td>AveS</td>
<td>Ten point verbal scale assessment of nutritional intake</td>
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<td>BFI</td>
<td>Brief Fatigue Inventory</td>
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<tr>
<td>BIA</td>
<td>Bioelectrical impedance analysis</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CCF</td>
<td>Congestive Cardiac Failure</td>
</tr>
<tr>
<td>CI</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>CNRP</td>
<td>McGill Cancer Nutrition Rehabilitation Programme</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<td>CONSORT</td>
<td>Consolidated Standards of Reporting Trials</td>
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<tr>
<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>COX</td>
<td>Cyclooxygenase (enzyme)- key enzyme in the pro-inflammatory pathway</td>
</tr>
<tr>
<td>CPCT</td>
<td>Community Palliative Care Team</td>
</tr>
<tr>
<td>CPN</td>
<td>Community Psychiatry Nurse</td>
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<tr>
<td>CQOLC</td>
<td>The Caregiver Quality of Life Index-Cancer scale</td>
</tr>
<tr>
<td>CRF</td>
<td>Chronic Renal Failure</td>
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<td>CRH</td>
<td>Corticotropin Releasing Hormone</td>
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<td>CRP</td>
<td>C-Reactive Protein</td>
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<tr>
<td>CSC</td>
<td>Cancer Stem Cell</td>
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<tr>
<td>CT</td>
<td>Coping Thermometer</td>
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<tr>
<td>DHA</td>
<td>Docosahexaenoic Acid</td>
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<tr>
<td>DT</td>
<td>Distress Thermometer</td>
</tr>
<tr>
<td>ECOG-PS</td>
<td>Eastern Cooperative Oncology Group Performance Status</td>
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<tr>
<td>ENeRgise</td>
<td>Proposed phase three multicentre randomised controlled trial of an exercise and nutritional rehabilitation programme for patients with life limiting cancer</td>
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<tr>
<td>ENeRgy</td>
<td>Exercise and Nutritional Rehabilitation in patients with cancer</td>
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<td>ENeRgy-Q</td>
<td>Qualitative sister trial of ENeRgy trial examining patient experiences</td>
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<td>EORTC QLQ C30</td>
<td>European Organization for Research and Treatment of Cancer Quality of Life Questionnaire</td>
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<td>Questionnaire developed to assess the quality of life of palliative cancer care patients</td>
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<tr>
<td>EPA</td>
<td>Eicosapentaenoic acid</td>
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<tr>
<td>EPAS</td>
<td>Edinburgh Supportive and Palliative Care group</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>EQ-5D</td>
<td>Standardised instrument for use as a measure of health outcome (Comprising 2 pages: the EQ-5D descriptive system and the EQ VAS).</td>
</tr>
<tr>
<td>ERAS</td>
<td>Enhanced Recovery After Surgery programme</td>
</tr>
<tr>
<td>ESAS</td>
<td>Edmonton Symptom Assessment Scale</td>
</tr>
<tr>
<td>ESMO</td>
<td>European Society for Medical Oncology</td>
</tr>
<tr>
<td>ESPEN</td>
<td>European Society for Clinical Nutrition and Metabolism (formerly the European Society for Parenteral and Enteral Nutrition)</td>
</tr>
<tr>
<td>FDG</td>
<td>$^{18}$F-fluorodeoxyglucose</td>
</tr>
<tr>
<td>GI</td>
<td>Gastro-Intestinal</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GP</td>
<td>General Practice/Practitioner</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>HGS</td>
<td>Hand Grip Strength</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental Cost-Effectiveness Ratio</td>
</tr>
<tr>
<td>IL-$\alpha$</td>
<td>Interleukin-1 alpha</td>
</tr>
<tr>
<td>IL-$\beta$</td>
<td>Interleukin-1 beta</td>
</tr>
<tr>
<td>IL-$1\text{R}1$</td>
<td>Interleukin-1 Receptor 1</td>
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<tr>
<td>IL-6</td>
<td>Interleukin-6</td>
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<tr>
<td>IPU</td>
<td>Inpatient Unit</td>
</tr>
<tr>
<td>IQR</td>
<td>Inter-Quartile Range</td>
</tr>
<tr>
<td>KPS</td>
<td>Karnofsky Performance Status</td>
</tr>
<tr>
<td>LBM</td>
<td>Lean Body Mass (body mass including bones, water, collagen and muscle minus fat mass)</td>
</tr>
<tr>
<td>LMIC</td>
<td>Low and middle income countries</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>LSA</td>
<td>Life Space Assessment</td>
</tr>
<tr>
<td>MCID</td>
<td>Minimum Clinically Important Difference</td>
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<tr>
<td>MCR-4</td>
<td>Melanocortin-4</td>
</tr>
<tr>
<td>MDFI</td>
<td>Multidimensional Fatigue Inventory</td>
</tr>
<tr>
<td>MDT</td>
<td>Multidisciplinary Team</td>
</tr>
<tr>
<td>MENAC</td>
<td>Multi-modal Exercise, Nutrition and Anti-inflammatory medication for cachexia (trial no. NCT 02330926)</td>
</tr>
<tr>
<td>mGPS</td>
<td>Modified Glasgow Prognostic Score</td>
</tr>
<tr>
<td>MRF</td>
<td>Medical Research Fellow</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute (USA)</td>
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<tr>
<td>NCRI</td>
<td>National Cancer Research Institute (UK)</td>
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<tr>
<td>NEXTAC</td>
<td>Nutrition and Exercise Treatment for Advanced Cancer</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
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<td>NIS</td>
<td>Nutritional Impact Symptoms</td>
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<tr>
<td>NLR</td>
<td>Neutrophil Lymphocyte Ratio</td>
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<tr>
<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drug</td>
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<tr>
<td>NSCLA</td>
<td>Non-Small Cell Lung Cancer</td>
</tr>
<tr>
<td>Ω-3</td>
<td>Omega-3 (fatty acid)</td>
</tr>
<tr>
<td>ONS</td>
<td>Oral Nutritional Supplement</td>
</tr>
<tr>
<td>PA</td>
<td>Physical Activity</td>
</tr>
<tr>
<td>PAM</td>
<td>Physical Activity Monitor – wireless-enabled wearable device that measure data such as number of steps, quality of sleep and other metrics.</td>
</tr>
<tr>
<td>pCRF</td>
<td>Paper Case Report Form</td>
</tr>
<tr>
<td>POMC</td>
<td>Pro-opiomelanocortin</td>
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<tr>
<td>PRP</td>
<td>Ottawa Palliative Rehabilitation Programme</td>
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<tr>
<td>Acronym</td>
<td>Full Form</td>
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<tr>
<td>pCRF</td>
<td>Paper Case Report Forms</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PIS</td>
<td>Participant Information Sheet</td>
</tr>
<tr>
<td>PLR</td>
<td>Platelet Lymphocyte Ratio</td>
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<tr>
<td>PPI</td>
<td>Patient and Public Involvement</td>
</tr>
<tr>
<td>PR</td>
<td>Pulmonary Rehabilitation</td>
</tr>
<tr>
<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</td>
</tr>
<tr>
<td>PRO</td>
<td>Patient Reported Outcome</td>
</tr>
<tr>
<td>PT</td>
<td>Physiotherapist</td>
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<td>QA</td>
<td>Quality Assurance</td>
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<tr>
<td>QoL</td>
<td>Quality of Life</td>
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<tr>
<td>QALY</td>
<td>Quality Adjusted Life Year</td>
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<tr>
<td>RA</td>
<td>Rheumatoid Arthritis</td>
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<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
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<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
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<tr>
<td>REE</td>
<td>Resting Energy Expenditure</td>
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<tr>
<td>RN</td>
<td>Research Nurse</td>
</tr>
<tr>
<td>SACT</td>
<td>Systemic Anti-Cancer Therapy</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SC</td>
<td>Symptom Cluster</td>
</tr>
<tr>
<td>SCNS-LF59</td>
<td>Supportive Care Needs Survey Long Form</td>
</tr>
<tr>
<td>SIR</td>
<td>Systemic Inflammatory Response</td>
</tr>
<tr>
<td>SNS</td>
<td>Sympathetic Nervous System</td>
</tr>
<tr>
<td>SO</td>
<td>Sarcopenic Obesity</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SPPB</td>
<td>Short Physical Performance Battery</td>
</tr>
<tr>
<td>SR</td>
<td>Systematic Review (of the literature)</td>
</tr>
<tr>
<td>TEE</td>
<td>Total Energy Expenditure</td>
</tr>
<tr>
<td>Acronym</td>
<td>Full Form</td>
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<tr>
<td>TEF</td>
<td>Thermic Effect of Food</td>
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<tr>
<td>TMG</td>
<td>Trial Management Group</td>
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<tr>
<td>TMWT</td>
<td>Two Minute Walk Test</td>
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<tr>
<td>TNF-α</td>
<td>Tumour Necrosis Factor- alpha</td>
</tr>
<tr>
<td>TUG</td>
<td>Timed Up and Go test</td>
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<tr>
<td>UK</td>
<td>United Kingdom</td>
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<td>USA</td>
<td>United States of America</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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<tr>
<td>WCRF</td>
<td>World Cancer Research Fund</td>
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Chapter 1. Introduction

Overview
“You matter because you are you, and you matter to the end of your life. We will do all we can not only to help you die peacefully, but also to live until you die.” These words, spoken by Dame Cicely Saunders, represented a key part of her vision for modern palliative care (Saunders, 2006). This adage is just as applicable today as when it was first uttered. Palliative Medicine continues to evolve as a specialty, and is now a key component of the management of cancer and chronic disease (Smith et al., 2012, WHO, 2019, Gomez-Batiste et al., 2017). However with time, as in life, nothing remains without change (Hall, 2014). As the remit of Palliative Medicine widens and more patients come under the umbrella of our care, approaches employed in an ever-growing population within an ever-limited system must adapt, while not compromising our underlying ethos of care. Enabling people to live fully until they die is what we strive for, and the roadmap laid out to us by Dame Cicely leads us neatly on to the topic underpinning this thesis: exercise and nutritional rehabilitation in patients with incurable cancer.

Patients with cancer are living longer than ever before (Olsen et al., 2008). Indeed, with the development of new and improved treatments, in many cases cancer is evolving into a chronic disease (Feldstain et al., 2017, Haylock, 2010, Salakari et al., 2015). While this is clearly a positive development, the consequences of patients living longer with cancer are wide and varied. With longer survival comes increased likelihood of morbidity, increased healthcare costs and associated socio-economic implications (Numico et al., 2015, Mariotto et al., 2011). There is the need to take a pro-active approach to this evolving situation and to optimise the overall condition of patients living with cancer, including those with incurable disease (Silver et al., 2013). Rehabilitation, of which exercise and nutritional optimisation are key components, may be one such way of maximising the
function and overall QoL of this patient population. Rehabilitation aims to help people reach their fullest potential, consistent with any physiological or anatomical impairment, environmental limitations, desires and plans (Javier and Montagnini, 2011).

This thesis examines the role of combined exercise and nutritional support as the central components of a rehabilitation paradigm for patients with incurable cancer, principally through two pieces of work [Figure 1]: Firstly, a systematic review examined the evidence for combined (exercise and nutritional) rehabilitation for patients with incurable cancer (Hall et al., 2019). Secondly, a phase II, randomised controlled feasibility trial was designed and undertaken to assess the feasibility of an exercise and nutritional rehabilitation programme (ENeRgy) versus standard care in patients with cancer (Hall et al., 2018). The trial was delivered in the outpatient setting at St Columba’s Hospice, Edinburgh between August 2017 and August 2019 (Hall et al., 2021). The findings of these two pieces of work inform this thesis.
Exercise and nutritional rehabilitation in patients with incurable cancer

Systematic review of the literature

Feasibility of an Exercise & Nutritional Rehabilitation programme for outpatients: (ENeRgy) trial

Figure 1: Thesis overview

Introduction
1.1. Cancer

Cancer is defined as a disease in which abnormal cells divide in an uncontrolled way, and may eventually spread to other tissues (CRUK, 2019). Cancer can result from abnormal proliferation of any of the body’s cell types, and as such there are over 200 types of cancer which vary considerably in their behaviour and response to treatment (Cooper, 2000, CRUK, 2015). The origins of the word cancer date back to Hippocrates (460-370 BC) who used the words *carcinos* and *carcinoma* to describe non-ulcerated and ulcerated tumours, respectively. In Greek, the words refer to a crab, presumably due to the shape of the finger-like spreading projections seen from the tumour (ACS, 2019).

Cancers may arise de-novo (due to spontaneous genetic mutations) or due to inherited genetic abnormalities such as defects in BRCA1 and 2 genes, which encode tumour suppressor genes (Roy et al., 2011). Exposure to risk factors, or a combination of genetic ‘predispositions’ triggered by an environmental stimulus, including epigenetic interactions (Bai et al., 2018) may herald the development of cancer. Environmental risk factors include carcinogens which may be physical (e.g. ultraviolet light or ionizing radiation), chemical (e.g. asbestos, tobacco smoke) or biological (e.g. infections from certain viruses, bacteria or parasites) (WHO, 2018a).

At a cellular level, development of malignant cancer cells from previously healthy cells is a multi-step process which evolves over time. Malignancy occurs as a result of an unregulated, continual proliferation of abnormal cells, which do not respond to signals that control normal cellular behaviour. The progression of genetic changes that occur, confer growth advantage to the malignant cell and this leads to the progressive conversion from normal cells to cancerous cells (Hanahan and Weinberg, 2000). Hanahan et al in their seminal paper in 2000, postulated that there are six hallmarks shared by cancer cells, including: self-sufficiency in growth signalling; insensitivity to
anti-growth signals; evasion of apoptosis; sustained angiogenesis; limitless replicative potential, and tissue invasion and metastasis. At the time this paper was published, the authors postulated that tumourigenesis occurred due to interactions involving not only the cancer cell but also the stromal cells surrounding the tumour— the “micro-environment”. Research over the following decade confirmed this hypothesis, and consolidated the concept that in order to understand the biology of tumours, it is imperative to look not only at the traits of the cancer cells, but also the contributions of the micro-environment. This includes the recruitment and subversion of supporting cells, including inflammatory cells which can promote tumour progression counterintuitively (Hanahan and Weinberg, 2011). This thesis will also discuss the role of the host, or ‘macro-environment’, in tumour genesis.

1.1.1. Prevalence and cancer survival

Cancer is the third leading cause of death worldwide, after ischaemic heart disease and cerebrovascular disease. Eighteen million new cases of cancer were diagnosed in 2018, causing an estimated 9.6 million deaths: one in six of all deaths globally (WHO, 2018a). Cancers of the lung, colo-rectum and female breast are the most commonly diagnosed cancers worldwide, and are responsible for the top two and fifth highest levels of mortality, respectively. Europe and the Americas account for around one quarter of global cancer cases and 14-20% of cancer mortality worldwide, though form only 9-13% of the global population (WHO, 2018b). Cancer is therefore highly prevalent in the developed world. High income countries such as those in Europe and North America have been reported by the World Health Organisation (WHO) as having the highest incidence rates for all cancer sites; however, low and middle income countries (LMIC) are now also reporting increasing rates of incidence and mortality. This reflects a global increase in cancer prevalence (WHO, 2018a), but may also represent improved reporting rates from LMIC countries.
The global increase in cancer incidence is due to multiple factors, including population growth and ageing, and the changing prevalence of risk factors linked with social and economic development (WHO, 2018a). In the UK, overall cancer age-standardised rates from 2015 to 2035 are predicted to rise by 0.07% annually (comprised of an annual decrease in men of 0.03% and an annual increase in women of 0.11%) (Smittenaar et al., 2016). Not only will cancer prevalence increase, prevalence of individual cancers will shift: Smittenaar et al reported that between 2015 and 2035, cancers of the thyroid, liver, oral cavity and kidney will accelerate in incidence, and that breast and prostate cancers will become the most prevalent for women and men, respectively.

Palliative services provide care for patients with both cancer and non-malignant disease, however the majority (up to 94%) of patients under palliative care services in Europe have a cancer diagnosis. Palliative care provision is, for the majority (60%) provided in the community and less than one quarter of patients receive care within a hospice. In 2007 there were a majority of female patients (56%) with a mean age of 66. Most (27%) were fully ambulatory or able to walk independently (28%) and the majority of patients had an expected prognosis of over 6 months (Kaasa et al., 2007). In hospice units in England between 2008 and 2012 the mean age of death of patients was 70.4, having increased from 69.5 in the period 1993-1997. There was an increase in the proportion of deaths in those aged >85 years from 8.2% (1993-1997) to 12.2% (2008-2012). Of those who died within specialist palliative care units in England with a cancer diagnosis between 1993 and 2012, the highest number of deaths were from cancers of the breast and ovary (16% of deaths in 1993 and 26.6% in 2012) followed by cancers of the gastrointestinal (GI) tract, kidney/ bladder, lung then prostate. The lowest deaths by cancer type were the haematological malignancies (6.5% in 1993 and 11% in 2012) (Sleeman et al., 2016, Tobin et al., 2021).
Although cancer incidence is increasing globally, mortality rates from cancer are declining. This is due to improved awareness of risk factors, more widespread screening, earlier detection and improved treatments (Torre et al., 2016, Smittenaar et al., 2016). Improvements in cancer mortality are present in spite of the potential for ‘lead time bias’ whereby increased intensity of screening and earlier diagnosis can skew figures to artificially extend survival times (Duffy et al., 2008).

As a result of the increasing incidence of cancer and improved survival rates, there is a rise in the number of ‘cancer survivors’, a term defined by the National Cancer Institute as ‘a person from the time of cancer diagnosis, through the balance of his or her life’ (NIH, 2014). This definition includes family members, friends, and caregivers. In Europe, the five-year survival rate for all cancers has reached ≥ 47% for men and 56% for women, and this figure will continue to rise (Mewes et al., 2012). In the United Kingdom (UK), one in two people will now be diagnosed with cancer in their lifetime, yet 50% will survive more than ten years; indeed, cancer survival has doubled from 24% to 50% in the last 40 years (CRUK, 2015).
1.1.2. The evolution of cancer as a chronic condition

Due to the aforementioned factors, including earlier detection, improvements in anti-cancer treatments and population-based modification of exposure to carcinogenic risk factors, patients are living longer with incurable cancer (Olsen et al., 2008). Traditionally, the predicted patterns or ‘trajectories’ of illness for a patient with cancer were different from that of chronic disease or frailty [Figure 2- upper graph] (Murray et al., 2005). However, cancer is now frequently likened to a chronic condition: patients are living longer, with periods of morbidity interspersed along that journey (Feldstain et al., 2017, Haylock, 2010, Salakari et al., 2015). In this instance, the trajectory for these patients is shifting toward that of chronic disease: [Figure 2- lower graph], with longer overall survival, and periods of reduced health associated with treatment, interventions, or complications from the cancer (Howell, 2012). This figure also shows the potential impact that rehabilitation could have on the cancer trajectory.

There is a need for prolonged and coordinated care for the ever-changing needs of people living with cancer, and this has associated implications for healthcare systems. People are more likely than ever before to be living longer with cancer, with greater uncertainty and at times falling into gaps in the healthcare system, for example the time after active oncological treatment, when patients are too well to be referred to palliative care services. This can be a very unsettling and uncertain time for patients, who can be fearful and uncertain of what they should or should not do in terms of exercise and dietary intake.
Figure 2: Traditional illness trajectories, trajectory shift and the potential impact of rehabilitation
As well as the increasing survival of people with cancer, in the UK, the population is ageing. Not only will the number of cancer survivors continue to increase by approximately one million per decade from 2010 to 2040, but there will be a particular increase in the older age groups (Maddams et al., 2012). By 2040, Maddams et al estimate that almost a quarter of people aged >65 will be cancer survivors.

Cancer survivors have varied needs which require ongoing and long-term management. These needs can be grouped in to physical, psychological, social and spiritual (Silver et al., 2015). These ongoing needs should form part of their ongoing management throughout the disease (Hodgkinson et al., 2007, Mellon et al., 2006, McGrath, 2004). In 2015, Silver et al, described how cancer survivors endure multiple conditions relating to previous treatments or direct effects of the disease itself resulting in chronic, disabling and medically complex issues. They state that palliative care and cancer rehabilitation are critical components of care for the delivery of high-quality oncological services. Indeed, in 2017, the American Society of Clinical Oncology (ASCO) updated their 2012 provisional clinical opinion, confirming that: “Inpatients and outpatients with advanced cancer should receive dedicated palliative care services, early in the disease course, concurrent with active treatment” (Ferrell et al., 2017, Kaasa et al., 2018).

These developments have wide-ranging implications for health service provision and for people living with a diagnosis of cancer. Patients will be increasingly complex to manage due to their co-morbidities, including concurrent diseases of ageing and multiple chronic conditions. They will encounter an increased duration of disease and treatment-related morbidity, both during and after anti-cancer treatment. Furthermore, there are implications for wider-society: with increased longevity and increased morbidity comes greater socio-economic burden (Numico et al., 2015, Mariotto et al., 2011). Socio-economic burden due to the changing nature of cancer is described in greater detail in chapter 1.1.3.
In the UK, as a result of the changing demographics as well as improved survival, the Department of Health encourages pro-active management of people with long-term conditions, including promotion of wellbeing, self-management, and a focus on prevention and early intervention with individualised care planning (UK, 2009). This drive was deemed necessary in order to meet the predicted challenges of increased healthcare burden associated with chronic disease.

In 2013, Hospice UK (the national charity for hospice care) recognised that a change was also required to the provision of hospice and palliative care, driven by changing demographics, and a predicted surge in demand for palliative, supportive and end-of-life care. Hospice UK published a report in 2015 challenging palliative care providers to adapt the way they deliver their care: they advocated that “an approach incorporating rehabilitation is ‘an essential component’ of palliative care” (Tiberini R, 2015). However, robust evidence underpinning the essential components of a rehabilitation programme for patients with incurable cancer is lacking. The concept of rehabilitative palliative care is discussed in more detail in chapter 1.3.
1.1.3. Socio-economic burden of cancer

The increase in survival of people with cancer has significant implications due to the rise in associated healthcare costs and financial constraints. In 2010, the total cost of the four main cancers (colorectal, lung, breast and prostate) to the National Health Service (NHS) in the UK was £1.5 billion, constituting three percent of the total cost of hospital care in England (£47.3 billion) (Laudicella et al., 2016). This cost is set to rise further in the coming years.

Primary cost drivers for patients with advanced cancer are hospitalisation, General Practice (GP) and domiciliary visits (Guest et al., 2006). Over the course of a person’s lifetime, the majority of health and social care costs occur as the person approaches the last year of life, often due to emergency inpatient admissions (Lynn, 2003, Mariotto et al., 2011). Reduced functional capacity and disability are positively associated with longer hospital stays and increased need for subsequent social care, which exacerbates this socio-economic issue in terms of cost and service provision (Kelley et al., 2012, Portegijs et al., 2012). There are, therefore, direct socio-economic benefits to be gained from maintaining, optimising or improving the functional capacity of patients living with incurable disease, including cancer. Keeping patients more physically able or functionally independent for longer could reduce care-associated costs, reduce numbers of hospital admissions and/or reduce lengths of hospital inpatient stays. In keeping with this, major guidelines, including ASCO, advocate that cancer care should incorporate palliative care and rehabilitation at an early stage (Smith et al., 2012, Silver et al., 2015, Tiberini R, 2015).

Before moving on to the rationale for the interventions used in the ENeRgy trial, this thesis will now focus on cancer metabolism, the host-tumour relationship and how this leads to a pro-inflammatory state frequently
accompanied by cancer cachexia, which has multiple deleterious effects on people living with incurable cancer.

1.1.4. Cancer metabolism

Cancer biology and the metabolism of cancer cells has been a focus of intense research for many years. Almost a century ago, Otto Warburg observed that cancer cells ‘re-wired’ their metabolism to promote the cell’s growth, survival, proliferation and long-term maintenance even in adverse conditions (Liberti and Locasale, 2016). Even in the presence of oxygen, Warburg noted that cancer cells reprogrammed their glucose metabolism, and thus their energy production to anaerobic glycolysis (the ‘Warburg Effect’) (Liberti and Locasale, 2016, Hanahan and Weinberg, 2011). Other discoveries, including the genetic alterations observed within cancer cells, led to the evolution of the so called ‘classical oncology’ approach and the development of cytotoxic systemic anti-cancer therapies (SACT), aimed at destroying or quietening the cancer cells (Arends, 2010).

1.1.5. The ‘host-tumour relationship’

As well as the necessary cellular changes leading to cancer/tumour development, it has also been acknowledged that the ‘host’ or ‘environment’ is critically important as well. The interactions between the two, are known as the ‘host-tumour’ relationship. This includes both the tumour micro-environment (i.e. immediate environment around the tumour - the ‘stroma’), and the tumour macro-environment. The macro-environment takes into account the body’s metabolic processes and includes activation of the body’s systemic inflammatory response (SIR). Both the micro- and macro-environments affect tumour growth, and as such, both have the potential to be modified in order to reduce or restrict it. For example, it is known that metabolic risk-factors such as the metabolic syndrome may favour tumour growth and recurrence (Arends, 2010, Hsu et al., 2007), and that diabetes
and high fasting glucose levels are associated with increases in cancer mortality (Barone et al., 2008, Jee et al., 2005). Whole body metabolism is strongly influenced by muscular activity, and recurrence and death rates for patients with stage I-III breast and colon cancer can be reduced by increasing physical activity levels (Holmes et al., 2005, Meyerhardt et al., 2006b, Meyerhardt et al., 2006a). There is a hypothesis based on observed prognostic data to suggest that moderating the body’s SIR using anti-inflammatory agents, may have positive impacts on the symptoms of advanced cancer such as anorexia, weight loss, reduced physical function, fatigue, pain and depression (Roxburgh and McMillan, 2014). This shift in approach, has led to the adage “treat the tumour and treat the host” (Roxburgh and McMillan, 2014). This concept, along with evolving principles of cancer cachexia management, underpin the design of the EneRgy trial intervention: a combination of exercise, nutritional optimisation and (anti-inflammatory) oral nutritional supplements (ONS). Further detail on the rationale for these interventions is provided in chapter 1.3.4.

1.1.6. Cancer and the systemic inflammatory response

The observation that cancer is increased in frequency at sites of chronic inflammation is well documented (Dvorak, 1986, Schafer and Werner, 2008). Hanahan and Weinberg described in 2011 that (contrary to previous assumptions) cancers are not made up of a single malignant cell clone, rather they involve multiple histopathologically diverse cell types. These include cancer stem cells, endothelial cells and pericytes (forming tumour associated vasculature) and cancer-associated fibroblasts. They also noted, importantly, that cancer tissues were frequently heavily infiltrated by immune inflammatory cells.

The large numbers of inflammatory cells seen histologically within tumour tissues were previously assumed to be due to activation of the host’s immune response i.e. to target the tumour. However, evidence began to emerge
throughout the 1990’s that the infiltration of tumours by inflammatory cells can counterintuitively promote tumour progression (Hanahan and Weinberg, 2011). Multiple different immune cells, including macrophage subtypes, mast cells, neutrophils, T and B lymphocytes are now recognised as tumour promoting, via release of signalling molecules, including growth factors, chemokines and cytokines with tumour-promoting actions. Hanahan and Weinberg summarised the actions of these tumour infiltrating immune cells as follows: inducing and sustaining tumour angiogenesis; stimulation of cancer cell proliferation; facilitation of tissue invasion; and supporting metastatic dissemination and seeding of cancer cells to distant sites. They hypothesised that the presence of both tumour-antagonising and tumour-progressing cells within tumours are linked with the dual role of the immune system. On one hand, its role is to detect and target infectious or harmful agents (tumour antagonising immune cells). On the other hand, its role is to help promotion of wound healing (including promotion of angiogenesis, secretion of epithelial growth factors and matrix remodelling by sub-classes of macrophages and neutrophils). It is the latter sub-class of the immune system, whose cells are preferentially recruited and subverted in the neoplastic process to tumour agonising cells, which support cancer progression.

As well as the effects of immune cells within the tumour microenvironment promoting tumour growth, the presence of the tumour also stimulates the body’s SIR (Gabay and Kushner, 1999, Skipworth et al., 2007, Arends, 2010). Over time, the sustained SIR has a multitude of detrimental effects. There is now consistent evidence that the effects of the sustained SIR are instrumental in the development of cancer-associated weight loss, loss of lean tissue, elevated resting energy expenditure (REE) and functional decline (McMillan, 2009). The SIR is one of the central drivers of cancer-associated cachexia, which is described in more detail in chapter 1.2. Figure 3 depicts the actions of the SIR and how this leads to adverse symptoms in the person with cancer.
Figure 3: Relationship between tumour micro-environment and host systemic inflammatory response
Adapted from Roxburgh and McMillan 2014
1.1.7. The systemic inflammatory response and cancer-related symptoms

For a long time, there has been concern that symptoms associated with cancer could be linked with the SIR; in particular, those of progressive loss of weight and lean tissue (Roxburgh and McMillan, 2014). Indeed, in recent years, progressive inflammation has been shown to be positively correlated with cancer pain (Laird et al., 2011a), reduced survival (Laird et al., 2013), reduced patient-reported QoL (Laird et al., 2016) as well as symptom clusters (SCs) associated with advanced disease (Roxburgh and McMillan, 2014). Animal models have shown that pro-inflammatory cytokines induce sickness behaviour which replicates many of the symptoms seen in patients with cancer (Illi et al., 2012). Symptoms of advancing disease rarely occur in isolation, and SCs in patients with progressive cancer include: appetite loss, weight loss and reduced physical function (Solheim et al., 2014) as well as fatigue, pain and depression (Laird et al., 2011b). Symptom clusters in patients with cancer may represent the body's neurological response to stimulation of the innate immune response (Dantzer, 2004), and are more pronounced in aggressive and advanced cancers associated with greater activation of the SIR such as cancers of the lung and GI tract (Roxburgh and McMillan, 2014).

The presence of cancer activates the host’s SIR which triggers the acute-phase protein response (APPR). The APPR is a systemic response of the host to a number of physiological disturbances including infection, trauma, surgery, burns, tissue infarction and cancer. It is activated not only in acute, but also chronic conditions, including cancer. (Gabay and Kushner, 1999). The APPR leads to changes in concentrations of plasma proteins (‘acute phase proteins’), as well as behavioural, biochemical and nutritional changes (including fever, anorexia, somnolence, leucocytosis, muscle loss and negative nitrogen balance). ‘Positive acute-phase proteins’ are those whose concentration increase ≥ 25% (including C-reactive protein (CRP), fibrinogen and ferritin), and ‘negative acute-phase proteins’ are those whose
concentration decrease by >25% (including serum albumin) (Gabay and Kushner, 1999).

Pro-inflammatory cytokines (inter-cellular signalling polypeptides) are produced locally by the tumour, which in turn stimulate the body's own pro-inflammatory cells to release further cytokine cascades, activating the APPR. As many as half of all patients with epithelial malignancies may exhibit an APPR (depicted by elevated CRP) at the time of diagnosis (Falconer et al., 1995). Pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNFα) stimulate CRP production in the liver (Laird et al., 2011a). IL-6 is upregulated by interleukin 1α (IL-1α) and it is postulated that IL-1α is a key modulator of many pro-inflammatory cascades mediating cancer cachexia (McDonald et al., 2018). This is described in more detail in chapter 1.2.2.

Measurement and monitoring of serum acute-phase proteins can help to assess the degree of the inflammatory response within a person with cancer, and this has the potential to aid prognostication and guide management for these patients. Combination methods of measuring inflammation have been validated extensively, including the modified Glasgow Prognostic Score (mGPS), which takes into account CRP and albumin. The mGPS is able to predict poor survival in patients with cancer, independent of tumour site (McMillan, 2013). Other serum combinations, including the neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR), have also been shown to have prognostic value in patients with cancer. The mGPS has recently been shown (when used in combination with Eastern Cooperative Oncology Group performance status [ECOG-PS]) to have superior prognostic value than other validated prognostic indicators alone. The mGPS/ECOG-PS combination is superior at identifying patients with increased risk of symptom burden, short prognosis (death within three months) and those who may benefit from early referral to palliative care services (Simmons et al., 2019).
This objective classification is likely to become more widely incorporated into routine oncological practice in the future.

1.1.8. Neuro-hormonal changes in patients with cancer

As well as stimulation of the SIR, there are other host-tumour interactions which contribute to cancer-associated symptoms of functional decline, including activation of the body’s neuro-endocrine systems. These include the increased production of corticotropin-releasing hormone (CRH), corticotropin and cortisol (the body’s ‘stress hormone’). Cortisol has catabolic effects on skeletal muscle. Weight-losing cancer patients often exhibit inadequate neuro-hormonal anabolic activity and/or excess expression of catabolic factors. For example, weight-losing patients with cancer frequently exhibit insulin resistance, elevated cortisol: insulin ratios (Costelli et al., 2006), growth hormone resistance, hypogonadism (Strasser et al., 2006) and increased myostatin expression (McFarlane et al., 2006). Furthermore, there is also frequently dysregulation of the autonomic nervous system (up to 81% in one study (Strasser et al., 2006)) including an increase in sympathetic nervous system (SNS) outputs. This has been postulated to contribute to tumour angiogenesis via adrenergic stimuli (Skipworth et al., 2007).

In patients with advanced cancer, there is consistent, high quality evidence that the resultant metabolic changes, driven by activation of the SIR are associated with increased weight loss, elevated energy expenditure, loss of lean tissue and functional decline (McMillan, 2009). Activation of the SIR and the neuro-endocrine response, as well as dysregulation of the autonomic nervous system are also fundamental components in the development of the multifactorial syndrome of cancer cachexia. Figure 4 depicts the relationship between inflammation of the host environment, the downstream effects (in terms of cancer cell proliferation), amplification of the SIR and the development of cancer cachexia.
Figure 4: Inflammation, cancer proliferation and cachexia
1.2. Cancer cachexia

Cachexia is a multi-factorial phenomenon seen in cancer as well as many chronic disease states, and has been acknowledged throughout medical history. The origins of the word come from the Greek kakos ‘bad'; hexis ‘stable arrangement’ often translated as ‘condition’ (Bennani-Baiti and Walsh, 2009). Hippocrates (c. 460–377 BC) linked hydropsy to cachexia: “The flesh is consumed and becomes water… the abdomen fills with water, the feet and legs swell, the shoulders, clavicles, chest and thighs melt away… This illness is fatal” (Doehner and Anker, 2002).

Cachexia is distinguished from starvation (which can be readily reversed by nutrients) by a predominant loss of muscle, as well as fat (Fearon and Preston, 1990). Cachexia is frequently associated with chronic diseases such as chronic obstructive pulmonary disease (COPD), congestive cardiac failure (CCF), and chronic renal failure (CRF), acquired immune deficiency syndrome (AIDS) and rheumatoid arthritis (RA); however, compared with other diseases, the loss of muscle mass has been shown to occur most rapidly in patients with cancer-associated cachexia (Giordano et al., 2003).

Perhaps the most widely accepted definition of cancer cachexia is a ‘multifactorial syndrome, defined by ongoing loss of skeletal muscle mass (with or without loss of fat mass) that can be partially but not fully reversed by conventional nutritional support, causing progressive functional impairment. Its pathophysiology is characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism’ (Fearon et al., 2011). More recently there has been debate as to whether the definition should be extended to include vital organs; e.g., loss of cardiac muscle, which can be seen concurrently in animal models of cancer cachexia (Kazemi-Bajestani et al., 2014).

Furthermore, there is still not an adequate consensus as to the specific criteria to define the stages of cancer cachexia, and multiple different
definitions are used in the literature. At present, the majority of definitions of cachexia focus on weight loss alone, including the consensus statement which cites involuntary weight loss of >5% from historical weight over six months; a body mass index (BMI) <20kg/m² with any degree of weight loss >2%; or a skeletal muscle index consistent with sarcopenia (the loss of skeletal mass and function) with any degree of weight loss >2% (Fearon et al., 2011).

Staging of cancer cachexia is the subject of much debate, and as yet, a single unified set of diagnostic criteria does not exist. However, weight loss, with other associated factors (anorexia, reduced food intake, loss of muscle, reduced strength, fatigue and biochemical markers) are generally included (Baracos et al., 2018). A weight loss of >5% is considered to be the threshold for poor clinical outcomes and three stages of cachexia are the subject of varied definitions within the literature over the last 20 years. Although cancer cachexia is a continuum, there are three recognised stages of clinical relevance [Figure 5]:

Introduction
Figure 5: Stages of cancer cachexia
Adapted from Fearon et al. 2011 (international consensus definition)
A criticism of the definition of cachexia is that it does not take into account other hallmarks of disease including inflammation, changes in body composition, increased protein degradation, increased treatment toxicity, fatigue and reduced QoL (von Haehling and Anker, 2010). There is an argument that progress in the investigation and treatment of cancer cachexia may be facilitated by incorporating objective measures of systemic inflammation into the definition and using the mGPS to stratify patients (Douglas and McMillan, 2014). There is also ongoing academic debate as to how best to incorporate objective markers of the SIR into the definition of cancer cachexia. However, it appears that the two are inextricably linked, and systemic inflammation is a significant driver in the multi-modal pathophysiology of cancer-associated cachexia.

1.2.1. Cancer cachexia: prevalence and impact

Cachexia is highly prevalent in solid tumours, in particular those of the lung and GI tract, which together account for over 50% of cancer deaths worldwide (Baracos et al., 2018). Cachexia affects over half of all patients with advanced cancer (von Haehling et al., 2016), yet may affect different individuals with similar disease in different ways. This may be due to genetic variations in susceptibility (Johns et al., 2017), sex (men are more susceptible than women), comorbidities and treatment-related catabolic effects (Baracos et al., 2018). Obesity can make the diagnosis of cachexia more challenging, and severe sarcopenia can be present in obese individuals without detection (Baracos et al., 2018). In patients with cancer cachexia, the majority of weight loss may be due to loss of fat; however, it is thought that the loss of muscle accounts for most of the morbidity and mortality (McMillan, 2009).

The impact of cancer cachexia on patients and outcomes is considerable. Cancer cachexia adversely affects function, QoL and is an independent predictor of poorer chemotherapy treatment response, side-effect profiles
and shorter survival (Prado et al., 2008, Yang et al., 2011, Fearon, 2008, Dewys et al., 1980, Stephens et al., 2008, Kazemi-Bajestani et al., 2016). Cachexia also has a significant psychological impact on people living with cancer and their families. It is cited as one of the two most frequent and devastating problems in advanced cancer along with pain (McClement, 2005). Alterations in a person’s self-image can have a significant effect psychologically: people with cachexia may feel ‘unable to recognise the person in the mirror’ or liken themselves to the appearance of concentration camp victims in World War II (Reid et al., 2009). These changes can lead to reduced social engagement, with cachectic patients more likely to choose to isolate themselves. Such behaviour can be exacerbated by conflicts with family over food, and lead to further isolation and associated distress (McClement et al., 2004). A summary of the overall impact cancer cachexia is depicted in Figure 6.
Figure 6: Impact of cachexia for patients with incurable cancer
**1.2.2. Pathophysiology of cancer cachexia**

The pathophysiology of cancer cachexia has been described as multi-modal, as well as interlinked with the effects of a prolonged SIR found in people with cancer.

There are multiple cytokines implicated in the SIR; and recent research has highlighted interleukin-1 (IL-1) as a critical modulator of both local and systemic immunity, which may contribute to cancer cachexia. As such there is research underway to ascertain whether targeted treatments (such as IL-1α inhibitors) have a role in the treatment of cancer cachexia (McDonald et al., 2018).

IL-1 genes (IL-1A and IL-1B) encode cytokines IL-1α and IL-1β respectively. Binding of these cytokines to IL-1R1 receptors causes upregulation of pro-inflammatory cytokines such as IL-6 and TNF-α. IL-1α can modulate the pro-inflammatory microenvironment which drives carcinogenesis in rodent and human models (Mantovani et al., 2018). IL-1α acts directly on the appetite centres of the central nervous system (CNS) by increasing the levels of plasma tryptophan, which has the downstream effect of increasing serotonin production in the hypothalamus. This mediates symptoms including loss of appetite and early satiety (Laviano et al., 1996). Dysfunction of the hypothalamus is also postulated as directly causing weight loss and atrophy of skeletal muscle. Other systemic responses mediated by IL-1α include gluconeogenesis, fever, fatigue and hypotension. Alteration of the hypothalamic microenvironment leads to alteration in the function of populations of neurones regulating proteolysis of lean tissue and lipolysis of adipose tissue (pro-opiomelanocortin [POMC] and agouti-related protein [AGRP]). Other neurones including melanocortin-4 (MCR-4), which regulate appetite and energy expenditure, are also influenced resulting in reduced hunger and an increase in energy expenditure. IL-1α also stimulates the release of CRH which stimulates some of the neuro-endocrine features of
cancer cachexia, including release of adrenocorticotropic hormone (ACTH) and cortisol. An overview of the actions of IL-1α in mediating cancer cachexia can be seen in Figure 7.
Figure 7: Interleukin-1α in cancer cachexia pathophysiology
With permission from (McDonald et al., 2018)
As well as the neurochemical changes mediated by IL-1α, chemosensory changes (changes in taste and smell) combine to reduce appetite, and upper GI tract dysmotility contribute to early satiety and nausea. These additional factors contribute to reducing daily food intake in patients with cachexia (Fearon et al., 2011).

The reduced caloric consumption is perpetuated by the shift in the body’s metabolic rate, which results in a higher resting energy expenditure (REE) (Hall and Baracos, 2008). Body weight remains stable when there is a balance of energy (caloric) intake, and total energy expenditure (TEE). Body weight is lost when there is a shift in balance between caloric intake and TEE, of which REE is one part, along with activity-related energy expenditure (AEE) and the thermic effect of food (TEF). In cancer cachexia, there is a shift to a higher REE, which represents ‘energy metabolism’, in part due to increasing demands from the tumour metabolism, but also due to activation of the SIR and shifts in metabolic cycling. Shifts in metabolic cycling include: increased whole body glycolysis; increased gluconeogenesis from the lactic acid cycle (the “Warburg effect”) (Hall and Baracos, 2008), as well as postulated increases in ‘fat browning’ or futile cycling (Kir and Spiegelman, 2016). Loss of body weight loss occurs due to imbalance on both sides of the scale [Figure 8].
Figure 8: Energy intake and expenditure imbalance in cancer cachexia
Adapted from (Baracos et al., 2018)
Arrays of cytokines released by the tumour itself, also activate the SIR. This promotes release of pro-catabolic factors which further modulate the activity of hypothalamus (Braun et al., 2011). Hypothalamic dysfunction modulates neuro-endocrine outputs (as described via IL-1α) and also alters autonomic outputs (increased SNS activation).

Behavioural outputs mediated by the CNS include sickness behaviours such as anorexia and fatigue. The combination of these factors activates proteolysis and lipolysis in skeletal muscle, adipose tissue and cardiac muscle. In addition, due to cancer-related symptoms (such as pain) and behavioural sequelae of the SIR (importantly, fatigue), people living with cancer often are less physically active, leading to deconditioning of skeletal muscle. These neural, humoral and behavioural outputs combine to create the multi-modal pathophysiology of cancer cachexia [Figure 9].
**Interorgan relationships in cancer-associated cachexia.** On the basis of clinical and experimental findings, tumour-derived catabolic factors have been shown to act on target tissues to elicit excess catabolism. Numerous pro-inflammatory cytokines are generated through tumour cross talk with associated stromal cells and the immune system, which act directly on target tissues as well as through alteration of central nervous system (CNS) controls of energy intake and expenditure. Mobilization of adipose tissue results from reduced food intake as well as specific tumour-derived lipolytic molecules (such as adrenomedullin), tumour factors that induce uncoupling and futile cycling in this tissue (such as parathyroid hormone-related protein) and/or induce lipolysis by activating the sympathetic neural output to adipocytes. Skeletal and cardiac muscle mobilization is induced by multiple pro-inflammatory cytokines, eicosanoids and transforming growth factor-β (TGF-β) family effectors (such as activin A and myostatin). Inflammation in the CNS alters the balance of orexigenic neuropeptide Y and anorexigenic melanocortins, resulting in reduced food intake. CNS inflammation evokes a catabolic programme in muscle, rapidly inducing atrophy. This effect is dependent on the production of glucocorticoids by the adrenal gland. The dashed arrow represents a new finding, the importance of which in patients is currently unclear.

GDF15, growth/differentiation factor 15; HSP, heat shock protein; LIF, leukaemia inhibitory factor; miR, microRNA; PGE2, prostaglandin E2; TNF, tumour necrosis factor; TNFRSF12A, TNF receptor superfamily member 12A; TRAF6, TNF-receptor-associated factor 6; TWEAK, TNF-related weak inducer of apoptosis (also known as TNFRSF12).

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**Figure 9: Multi-modal pathophysiology of cancer cachexia**
Reproduced with permission from (Baracos et al., 2018)
1.2.3. Approach to the management of cancer cachexia

Over the last 30 years, a huge amount of research has gone in to understanding not only the pathophysiology of cancer cachexia, but also how best this debilitating consequence of cancer may be managed.

It is clear that for such a multi-faceted problem, a multi-modal treatment is required (Fearon, 2008, Solheim, 2018); however, as yet, there is no effective or accepted treatment for this condition (Vaughan et al., 2013). Trials of cachexia treatment previously have been hampered by the lack of consensus in the classification of the stages of cachexia, and the use of unimodal interventions with limited success (Temel et al., 2016, Dobs et al., 2013). Also, trials have been impacted by inclusion of individuals with mixed stages of cachexia, including refractory cachexia which is thought to be unresponsive to treatment (Fearon et al., 2011).

In 2011, Professor Kenneth Fearon, with the backing of the international Delphi consensus group, advocated the development of multi-modal therapies for cancer cachexia, combining exercise, nutrition and anti-inflammatory medication (Fearon et al., 2011, Solheim, 2018). A phase two feasibility trial of a structured home-based exercise programme, Omega-3 enriched ONS, dietary advice, and celecoxib for patients with lung and pancreatic cancer embarking on chemotherapy showed that this treatment was feasible and safe (Solheim et al., 2017b). A phase three international clinical trial is underway, entitled the MENAC Trial: ‘A Randomised, Open-label Trial of a Multimodal Intervention (Exercise, Nutrition and Anti-inflammatory Medication) Plus Standard Care Versus Standard Care Alone to Prevent/Attenuate Cachexia in Advanced Cancer Patients Undergoing Chemotherapy’ (NCT 02330926). This trial examines changes in body weight, muscle mass and function for patients undertaking a six week multimodal exercise, nutritional and anti-inflammatory intervention versus standard care alone.
Due to the high prevalence of cachexia in patients with incurable cancer (>50%), and the significant impact it has on function and QoL, there is a strong argument that any rehabilitation intervention for this group should consider key components of cachexia including exercise, nutritional support and anti-inflammatories (Solheim, 2018).

1.2.4. Functional decline in cancer

Almost inevitably, patients with cancer have a reduction in physical fitness and tolerance to activities over the course of their illness. The reasons for this are multifactorial. Patients with cancer often have significant impairments in cardio-respiratory fitness, i.e. reduced capacity to transport atmospheric oxygen to skeletal muscles for energy production (Jones et al., 2008). These can be due to patient characteristics (e.g. age and comorbidities), as well as direct effects of anti-cancer therapies including anaemia or conditions such as radiation-induced pneumonitis. Anti-cancer therapies indirectly perpetuate the problem due to deconditioning from physical inactivity (Scott et al., 2018, O'Neill et al., 2018, Jones et al., 2009). Loss of function may also be due to a person’s reduced tolerance to exercise-related symptoms such as fatigue and breathlessness (Jones and Killian, 2000). There are changes in skeletal muscle and its ability to use oxygen once it is delivered, known as ‘muscular fitness’.

Anti-cancer therapies can have direct adverse effects on muscle and fat-free mass (Awad et al., 2012), via mechanisms which include direct inhibition of protein synthesis, limitation of the stimulating effect of amino acids, and anti-angiogenic properties (Antoun et al., 2010). Cancer-associated cachexia accelerates the decline in physical function (LeBlanc et al., 2015) and the definition of cachexia itself emphasises the key element of muscle loss in the development of frailty and disability; indeed, reduced muscle mass is a cardinal feature of cachexia (Fearon et al., 2011). Sarcopenia is frequently found at diagnosis or when starting treatment (Awad et al., 2012) and
reduced muscle mass leads to impaired oxidative capacity. The quality of muscle (force per unit/mass) is also frequently affected –particularly seen in males or those who have lost substantial amounts of weight (Stephens et al., 2012, Weber et al., 2009).

Exercise stimulates skeletal muscle anabolism, leading to increased muscle mass and strength (Kumar et al., 2009); however, supra-normal protein intake is required to achieve the same post-prandial anabolic effects in cachectic patients (Fearon, 2008). Introducing exercise without nutritional support in patients who may have cancer-associated cachexia has the potential to exacerbate the negative energy balance and should thus be considered synchronously. It was felt, therefore, to be imperative that the intervention delivered in the ENeRgy trial was multi-modal and include both nutritional support and physical exercise.

1.2.5. Physical exercise in cancer

Physical exercise is defined as an activity that is planned, structured, repetitive and purposeful, with the aim to improve or maintain one or more components of physical fitness, i.e. endurance, muscular strength and body composition (Caspersen et al., 1985). There is sufficient evidence to support the promotion of physical activity and exercise for adult cancer patients (Segal et al., 2017, Stout et al., 2017). Exercise interventions are feasible in patients with incurable cancer and have been shown to have multiple beneficial effects on physical wellbeing, functional mobility, fatigue, depression and overall QoL (Litterini et al., 2013, Salakari et al., 2015, Oldervoll et al., 2011). There is a growing awareness of the benefits of exercise for cancer survivors; such that aerobic and resistance training is now recommended (Schmitz et al., 2010, Arends et al., 2017b).

Even in advanced cancer, exercise has the potential to prevent or reverse functional decline, control symptoms, and help maintain independence
(Eyigor and Akdeniz, 2014). A recent Cochrane review of exercise for cancer cachexia found that at present there are insufficient data to support the use of exercise alone or as part of a multi-modal intervention, due to the available evidence being very low certainty (Grande et al., 2021). However it was noted that the potential findings of the MENAC trial, outlined in chapter 1.2.3, may have a substantial impact on the overall interpretation of results presented in the review. The results of the ENeRgy trial will further add to the evidence base in this field also.

1.2.5.1. Exercise regimens

It is advocated that exercise regimens should be a continuous and integral part of care for all cancer survivors (Buffart et al., 2014). Recommendations of intensity and duration are variable; for example, the American College of Sports Medicine (ACSM) previously recommended that patients with cancer should partake in 150 minutes of moderate exercise (e.g. walking) or 75 minutes of vigorous exercise (e.g. jogging) per week. However, this is more of a long-term goal and is not appropriate as an initial prescription for patients who have been sedentary or are undergoing anti-cancer treatment. More applicable to an incurable cancer population are those recommendations which encourage daily physical activity to promote a move from sedentary to a more active lifestyle (Campbell et al., 2012, Doyle et al., 2006). The most recent ACSM roundtable recommendations for exercise in cancer survivors includes moderate intensity aerobic training at least three times per week to an equivalent of ninety minutes, and resistance training at least two times per week. However the need to individually tailor the prescriptions is highlighted (Campbell et al., 2019, Jones et al., 2010).

In terms of uptake, approximately two thirds of patients with cancer offered a physical activity programme or activity regimen will accept and around half of those will complete it (Maddocks et al., 2009). A review examining patients with advanced cancer identified 24 trials with most reporting significant
between- and/or within-group improvements in physical function, QoL, fatigue, body composition, psychosocial function, and sleep quality (Heywood et al., 2018).

1.2.5.2. Exercise type

Most trials for patients with cancer have seen patients advised to complete moderate-intensity aerobic training on at least three separate occasions per week. Moderate-to-vigorous exercise is the best level of intensity to improve physical function (Stout et al., 2017). The addition of resistance type exercise, defined as: ‘periodic exercise whereby external weights provide progressive overload to skeletal muscles in order to make them stronger and often result in hypertrophy’ (Phillips and Winett, 2010) to target muscle strength and mass is particularly applicable to patients with cachexia. This is due to the pathophysiology of cachexia whereby muscle dysfunction contributes directly to functional impairment (Arends et al., 2017b). A systematic review has concluded that both aerobic and resistance exercise can improve upper and lower body muscle strength more than usual care for cancer patients undergoing treatment (Stene et al., 2013). Exercise in patients with cachexia may attenuate some of the hormonal abnormalities while providing a strong anabolic signal to counterbalance the accelerated catabolism leading to reduced muscle mass and function (Maddocks et al., 2013, Pring et al., 2018).

A previous systematic review examined the effects of exercise interventions for patients with advanced cancer. Twenty six studies were identified, with varied designs (14 randomised controlled trials across 12 countries for patients with advanced or metastatic cancer (Dittus et al., 2017). The results showed that aerobic capacity was frequently improved after an exercise intervention: 73.7% (14 of 19 studies) showed a significant improvement, while 26.3% (5 of 19 studies) showed no change in ‘peak V02’ (maximum rate of oxygen consumption measured with expired gas analysis) and six
minute walk test (6MWT). Similarly, of studies examining strength, significant improvements were seen in 11 of 12 (91.7%) studies. All studies examining physical function measures showed some improvement, though the outcome measures varied widely, including sit-to-stand, TUG, functional reach, gait speed, balance, 400 metre walk test speed and six metre walk speed. Fatigue was measured in 19 studies using various self-report surveys. RCT trials did not clearly identify improved fatigue with exercise interventions compared to controls. However, within-subject assessment of fatigue as measured in pre/post interventions predominantly reported significant improvements in fatigue. Changes in participant QoL were frequently assessed, most often using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). Overall, there was marked heterogeneity of QoL surveys which made comparison difficult and just over half (52.6%) of all studies identified improvements in QoL with physical exercise. The remainder found no difference. Notably, however, numbers of participants in the positive studies were greater. The authors concluded that overall, albeit with wide variations in study design and endpoint measurements, exercise is beneficial for many of the primary outcomes measured in patients with advanced cancer (Dittus et al., 2017).

1.2.5.3. Challenges, barriers and facilitators

It is known that supervised training permits a higher training intensity and subsequent improvement in physical function than unsupervised interventions. For home interventions, with light supervision, effects on function are greater when a higher weekly energy expenditure is prescribed (Sweegers et al., 2018). A person’s pre-conceived ideas about the benefits, value and enjoyment of exercise can influence their motivation to participate. For example, those persons who do not see themselves as ‘exercisers’ may be less motivated to participate in a formal exercise programme, and as such, use of simple programmes with walking as the primary modality can be
useful. (Cheville et al., 2012, Granger et al., 2017, Granger et al., 2018) This type of activity may be perceived more as ‘being active’ and therefore less intimidating to the non-exerciser, which can improve compliance (Wong et al., 2018).

How physical activity and exercise is proposed to patients is an important influencer. Advice from any health care professional reduces barriers (Granger et al., 2017), but some patients perceive that doctors are most influential in terms of compliance (Williams et al., 2013). Some patients are attracted to potential benefit around fitness whilst some may be more willing to participate if programmes are promoted to help them to carry on with usual routines and roles of normal life, or to improve their mental well-being (Granger et al., 2017, Bayly et al., 2018). Professionals should explore patients’ interests and preferences to facilitate optimal uptake of physical activity interventions. Families and friends are also important in the delivery of exercise regimens. Patients report it can be difficult to overcome family advice to rest (Granger et al., 2018). Time is a barrier for some people especially when receiving anti-cancer treatments. For some, physical activity or exercise needs to fit into daily routines or alongside scheduled hospital visits, whereas for others, lack of support is a barrier and group activities are more appropriate (Granger et al., 2017, Bayly et al., 2018).

A further challenge is the difficulty of overcoming recall and response bias when participant physical activity is reliant upon self-reported diaries (Zanni, 2007) or questionnaires (Gresham et al., 2018). Wearable physical activity monitors (PAMs) can overcome this barrier by measuring real-time objective physical activity and sleep data, and they are increasingly being used and validated in clinical trials. Due to the increase in consumer demand, commercially available PAMs are, in many cases, as accurate as research grade monitors, which can be more cumbersome and expensive (Imboden et al., 2018).
Cancer symptoms such as breathlessness or fatigue, can act as barriers especially if they increase in intensity during or after physical activity (Ormel et al., 2018). Patients may lack confidence regarding how to exercise safely and have fears relating to over-exertion, potential harm or disease progression (Cheville et al., 2012, Granger et al., 2017, Granger et al., 2018). For this reason, the ENeRgy trial design included regular weekly reviews by a physiotherapist.

1.2.6. Dietary interventions

Optimising nutritional intake is of key importance in the management of cachexia [Fearon 2011]; however, dietary interventions alone are not effective in reversing it (Gullett et al., 2011, Fearon, 2008). This is due to the metabolic alterations, including elevated TEE, excess catabolism and inflammation, which together prevent muscle anabolism and have been coined the ‘anabolic blockade’ (Fearon, 2008).

Guidelines issued in 2017 by the European Society for Clinical Nutrition and Metabolism (ESPEN) have advocated increased attention to nutritional support in all patients with cancer (Arends et al., 2017a). Their recommendations specify that regular screening should occur from the onset of cancer diagnosis, including those with advanced disease, and that patients with identified nutritional disturbance should undergo regular dietary assessment. A recent systematic review examining the evidence for nutrition support via oral nutritional interventions (including nutrition counselling with or without the use of oral nutritional interventions) in patients with incurable cancer demonstrated that there is limited evidence for the most effective nutritional intervention for patients with incurable cancer (Blackwood et al., 2019). The review demonstrated that the overall quality of evidence supporting the need for increased attention to nutrition support in patients with incurable cancer is moderate, in support of the ESPEN
recommendations. However, despite statistically significant results being reported, the clinical effects of these interventions were small.

While due attention is therefore paid to the nutritional status of patients with incurable cancer, it can be argued that any intervention to combat cancer-related cachexia should be multi-modal, and as well as improving nutritional intake, should also target reduced physical function and inflammation (Fearon, 2008, Solheim et al., 2017b, Solheim, 2018). This underpins the rationale for the use of omega-3 enriched ONS in the ENeRgy trial, which are discussed in more detail in the following section.

1.2.7. Anti-inflammatories

Patients with cancer often are systemically inflamed and this is one of the key pathophysiological drivers in cancer cachexia. As such, attenuating the pro-inflammatory response is argued as a necessary component of any therapy for cachexia (Solheim, 2018). The main choices of anti-inflammatory agent for patients with cancer are omega-3 (Ω-3) fatty acid supplementation or Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

1.2.7.1. Omega-3 fatty acids:

Omega-3 (Ω-3) fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid, (DHA) are polyunsaturated fatty acids commonly found in natural fish oils. Both EPA and DHA are competitive substrates with arachidonic acid (AA) for the cyclooxygenase (COX) pathway, and greater intake of Ω-3 fatty acids results in a lesser production of pro-inflammatory lipid modulators. This has a net anti-inflammatory effect (Calder, 2015).

The use of Ω-3 supplementation has been studied extensively in patients with cachexia. Early studies in the late 1990s and 2000s were promising in terms of benefits of Ω-3, such as improvements in lean body mass (LBM),
appetite and QoL (Barber et al., 1999, Wigmore et al., 2000, Moses et al., 2004); however, some reviews of the evidence for the use of EPA supplementation in cancer cachexia have been mixed (Ries et al., 2012, Murphy et al., 2011b). There have been reports of positive benefits in terms of weight and muscle mass maintenance (Murphy et al., 2011a, Weed et al., 2011), and also on multiple outcomes, including preservation of body composition, improved QoL, physical function and global health status for patients undergoing chemo- or radiotherapy (de Aguiar Pastore Silva et al., 2015).

Doses of Ω-3 that have shown benefits are EPA > 2g per day and DHA > 1g per day, and these can be administered either by capsules or as a component of an ONS. The benefit of delivering Ω-3 in ONS is that the supplements also provide a concurrent supply of calories, high-quality proteins and micro-nutrients (Solheim, 2018). Compliance with prescriptions of Ω-3 rich ONS have been reported as problematic in the past due to unpalatability (Laird, 2018); however, for patients with incurable cancer they offer a safer alternative to NSAIDs. The anti-inflammatory effect of Ω-3 fatty acid, as well as the improved safety profile, underpins the rationale for their use in the ENeRgy trial intervention [see chapter 3.4.2].

**1.2.7.2. Non-Steroidal Anti Inflammatory Drugs:**

Other trials, including MENAC, have chosen an NSAID such as ibuprofen to provide the anti-inflammatory component of their multi-modal intervention. This drug is cheap and widely available; however, there are potential interactions and side effects which limit its use in a frailer population of patients with more comorbidities such as those with incurable cancer. NSAIDs act by blocking the enzyme COX. COX converts AA to prostaglandins, resulting in inflammation and pain (via the COX-2 pathway). NSAIDS have been reported in certain cachexia clinical trials to improve body weight (compared to controls), performance status and inflammatory
parameters (Maccio et al., 2012, McMillan et al., 1997, Wigmore et al., 1995, Rainsford, 2009). Routine use of NSAIDS for cancer cachexia is not yet indicated, however, due to the current evidence limitations and their side effect profiles, most notably concurrent inhibition of COX-1 enzymes which results in reduced production of mucosa-protective prostaglandins and an increased risk of GI haemorrhage.

This chapter has introduced the rationale for the interventions utilised in the ENeRgy trial. The following sections of this chapter will now examine the use of rehabilitation in palliative care and how the above interventions can be combined as a rehabilitation paradigm for patients with incurable cancer.

1.3. Rehabilitation

1.3.1. Definitions and application to palliative care

Rehabilitation is a term which has multiple connotations. The definition according to the Cambridge dictionary is “the process of returning to a healthy or good way of life, or helping someone do this after they have been in prison, been very ill, etc.” (Dictionary, 2019). This widely accepted concept (i.e. returning someone to a ‘healthy’ state) may make, to some, the concept of rehabilitation in incurable disease seem paradoxical (Tiberini R, 2015). However, the goal of rehabilitation is to help individuals “reach the fullest physical, psychological, social, vocational and educational potential consistent with his or her physiological or anatomical impairment, environmental limitations, desires and plans” (Javier and Montagnini, 2011).

The approach is closely aligned with the approach and philosophy of palliative care, and rehabilitation and palliative care share many common features. Both use interdisciplinary models to identify goals of care; both aim to improve function through person and family-centred models of treatment; both use holistic approaches incorporating medical, physical, social and
psychological elements; and both employ a symptom-oriented approach (Santiago-Palma and Payne, 2001). Indeed, in Dame Cicely Saunders’ original vision for modern palliative care, she stated “The work of all the professional team is to enable the dying person to live until he dies, at his own maximal potential performing to the limit of his physical and mental capacity with control and independence whenever possible” (Saunders, 2006).

1.3.2. Rehabilitation in non-malignant disease

Rehabilitation is a cornerstone in the management of non-malignant chronic disease; including cardiac, neurological and respiratory conditions. Such is the strength of evidence for pulmonary rehabilitation (PR), that a Cochrane review has stated it is now inappropriate to conduct further randomised controlled trials comparing it with standard care (Lacasse et al., 2015). PR is described here as an example of a successful multi-modal rehabilitation programme.

In COPD, there is persistent airflow limitation due to chronic inflammation within the airways and lung in response to noxious particles or gases. People with this condition have symptoms of breathlessness (dyspnoea) and impaired exercise capacity which impacts on their health-related QoL (Vestbo et al., 2013). In people living with COPD, a major consequence of dyspnoea is physical inactivity. Inactivity is detrimental to their health and is associated with an increased risk of hospital admissions and mortality (Pitta et al., 2006, Garcia-Aymerich et al., 2006). Physical inactivity leads to deconditioning and loss of muscle mass, which can lead to deteriorating dyspnoea, anxiety and refractory breathlessness (Maddocks et al., 2014).

In COPD, as well as disuse muscle atrophy there is a depletion of fat-free mass (i.e. lean mass) even in the absence of weight loss (Schols et al., 1993), and pathophysiological features that are similar to cancer cachexia. A
substantial proportion of patients with moderate to severe COPD exhibit an elevated resting metabolic rate and an increased total energy expenditure (Baarends et al., 1997). Additionally, in this subset of patients there is evidence of elevated acute phase proteins and soluble TNF receptors in peripheral blood indicative of systemic inflammation (Schols et al., 1996). In patients losing weight in COPD there is a significant inverse relationship between weight and TNFα (de Godoy et al., 1996). It is therefore felt that tissue depletion in COPD is partly related to catabolism driven by systemic inflammation in a similar way to cancer cachexia, and for this reason nutritional support alone is not sufficient to reverse weight loss completely in COPD. Low body weight is an independent predictor of poor prognosis in patients with COPD, and appropriate oral nutritional therapy as part of the management of these patients is postulated to negate this risk (Schols et al., 1998).

PR is defined as “a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours” (Spruit et al., 2013). PR has a broad, high quality evidence base to support its use, and is an embedded component of COPD management. PR is associated with improvements in breathlessness, fatigue, improved physical function, emotional function, feelings of control, and reduced frequency of hospital admissions, regardless of disease severity (McCarthy et al., 2015). Supervised exercise is a cornerstone of PR, and attention to nutrition is also essential [Figure 10] (Hill et al., 2013). A recent RCT has shown that patients with COPD who undertake a targeted nutritional intervention (including ONS enriched with leucine, vitamin D, and Ω-3 fatty acids) in combination with exercise training showed improvements in nutritional status, inspiratory muscle strength and physical activity levels (van de Bool et al., 2017).
Figure 10: Components of pulmonary rehabilitation
Adapted from (Hill et al., 2013)
1.3.3. Cancer rehabilitation

Rehabilitation is embraced widely in Western medicine for the management of acute and chronic illness, but is not yet routinely incorporated in cancer care. Yet rehabilitation is now advocated for patients with cancer, including those receiving treatment with palliative intent (Chasen et al., 2014, Tiberini R, 2015, Maddocks, 2017).

Rehabilitation for patients with cancer is not a new concept; indeed, some of the earliest evidence for the worth and efficacy of cancer rehabilitation came from the American Oncologist J. Herbert Dietz (Dietz, 1969). Dietz outlined important distinctions between rehabilitation goals, ranging from restorative to palliative [Table 1].
<table>
<thead>
<tr>
<th>Rehabilitation Goal</th>
<th>Context</th>
<th>Aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Restorative</strong></td>
<td>Patient has good potential to re-gain function</td>
<td>To return patients to a previous level of function</td>
</tr>
<tr>
<td>2. <strong>Preventative</strong></td>
<td>Patients at risk of deconditioning and weakness due to reduced activity</td>
<td>To prevent avoidable deterioration in patient’s function due to disease/treatment</td>
</tr>
<tr>
<td>3. <strong>Supportive</strong></td>
<td>Maximising function in the context of established impairment/disability</td>
<td>To maximise patient’s functional independence and involvement in activities</td>
</tr>
<tr>
<td>4. <strong>Palliative</strong></td>
<td>Adaptation and habituation with irreversible loss of function and new functional reality</td>
<td>Supporting patients to adapt to irreversible changes or loss of function</td>
</tr>
</tbody>
</table>

Adapted from (Tiberini R, 2015, Dietz, 1981)
Modern palliative care is evolving and moving towards earlier integration of symptom control alongside active treatment, at any point from diagnosis to death in response to need. This is reiterated in the WHO definition of palliative care and the 2018 Lancet Oncology commission on integration of Palliative Care with Oncology (WHO, 2019, Kaasa et al., 2018). As such, patients falling under the umbrella of palliative care are more likely to have ‘preventative’ or ‘supportive’ goals with scope for considerable functional improvement.

The concept of ‘prehabilitation’, which occurs between diagnosis and treatment, is a different form of rehabilitation but is noteworthy. Prehabilitation is an area of interest in cancer treatment, due its potential to improve cancer-related outcomes and thereby reduce cancer associated healthcare costs (Silver and Baima, 2013). Prehabilitation is applicable to any treatment modality including surgery, chemotherapy and radiotherapy; however, the vast majority of evidence for prehabilitation is for those undergoing surgery (Bloom, 2017, Hughes et al., 2019). A meta-analysis of 15 RCTs has shown a significant reduction in overall and pulmonary morbidity in prehabilitation groups prior to major abdominal surgery and the authors suggest that prehabilitation could be used routinely, however, as yet, there is no precise protocol established (Hughes et al., 2019).

A review of the current evidence for prehabilitation by a National Cancer charity in the UK, (MacMillan Cancer Support) highlighted that prehabilitation interventions should include core access to physical activity, dietary and psychological support (Bloom, 2017) and echoes the need for a multi-modal intervention including physical exercise and optimisation of nutrition even at the earlier stages of rehabilitation.

Examples of established cancer prehabilitation programmes include: physical activity programmes such as pelvic floor exercises prior to surgery for patients with prostate cancer to reduce post-operative incontinence, and
swallowing exercises prior to head and neck surgery (CSP, 2016, Govender et al., 2017). Nutritional prehabilitation interventions can broadly be split into ‘eat well’ nutrition counselling (80%) and ‘nutritional interventions’ (including ONS, artificial nutrition, and drug therapy in combination with physical activity) (20%) as per the ESPEN guidelines (Arends et al., 2017a). Psychological interventions range from low level (non-specialist) support to specialist support by mental health professionals such as psychologists or psychiatrists (Tsimopoulou et al., 2015). Combining the above components into multi-modal prehabilitation interventions is also feasible and beneficial. For example, a combination of educational materials, physiotherapy instruction, and a self-management group-based seminar for patients and their partners prior to radical prostatectomy for management of localised prostate cancer was shown to be acceptable and beneficial (Paterson et al., 2019).

Opportunities for rehabilitation in cancer care can be viewed as a spectrum from optimising the condition of patients close to diagnosis and prior to anti-cancer treatment (prehabilitation), to palliative rehabilitation for patients with incurable disease (post-treatment) where optimising QoL is paramount. The interventions described in this thesis are focussed on the latter group of patients, however, the rehabilitation model presented here has the potential also to be applied to patients at much earlier stages of disease.

For patients with advanced progressive disease, rehabilitation aims to ‘improve and/or maintain function where the effects of the illness or its treatment threaten to cause decline, or to ease the transition towards dependency when functional deterioration is inevitable. Promotion of patients’ own interests, social engagement and optimising functional independence are fundamental’ (Maddocks, 2017). In this context, it has been suggested that the term ‘habilitation’ may be more appropriate to dispel any expectations of returning to previous levels of physical function (which the
Introduction

‘re-’ might imply to the lay person), and this term is recognised among physiotherapists (Tiberini R, 2015, Therapy, 2019).

For patients with incurable cancer, the chief goals of a rehabilitation intervention should be to: reduce symptom impact (such as pain and anxiety); maintain or improve functional status; maintain or improve independence and improve QoL (Javier and Montagnini, 2011).

Maintenance of function, independence and ‘normality’ are highly valued, and rate in many cases among the most important priorities for patients with incurable cancer alongside preparing for death (Carter et al., 2004, la Cour et al., 2009, Johnston, 2010). Rehabilitation, even in the context of incurable disease has the potential not only to maintain a person’s level of function/QoL but to improve it. Even when a person is living with an irreversible impairment or disability and requires assistance with activities of daily living, a palliative rehabilitative approach can help to deliver that person’s care in such a way as to support them proactively to maintain their autonomy where possible and preserve their sense of dignity and self-worth (Cotterell, 2008).

Patients, their families and clinicians now realise that optimising QoL is a fundamental component of good cancer care and that maintaining physical function and nutrition are as important as good symptom control (Smith et al., 2012). Although clear guidance exists on symptom control, programmes which optimise physical and nutritional function have been the exception rather than the norm. Whilst there is evidence of the benefits of rehabilitation in non-malignant conditions, extrapolating these models to incurable cancer care needs careful evaluation. There is a strong rationale that exercise and nutrition should be key constituents of any rehabilitation intervention for patients with cancer; however, the details of any such programme remain to be elucidated (Chasen et al., 2014). The research presented in this thesis aims to take the first steps towards creating an evidence base for such an intervention for patients with incurable cancer.
1.3.4. Application of cachexia management to cancer rehabilitation

The pro-active and multi-modal approach advocated for cancer cachexia including exercise, nutritional support and anti-inflammatories (Solheim et al., 2017b, Fearon, 2008) has the potential to be adopted usefully as a rehabilitation approach for the general population of patients with incurable cancer, where cancer cachexia may be present in between 50-80% (Argiles et al., 2014). Previous studies have demonstrated the detrimental effects of deteriorating physical function on survival (Laird et al., 2013). It follows, therefore, that optimising physical function may have survival benefits. At the very least it may enable patients to remain independent for longer periods.

An exercise, nutrition and anti-inflammatory based intervention is feasible for patients with lung and pancreatic cancer undergoing chemotherapy (Solheim et al., 2017b), and there is RCT evidence demonstrating good adherence to an exercise and nutritional intervention in palliative lung and GI cancer patients, with beneficial effects on symptoms of nausea and vomiting, and on daily protein intake (Uster et al., 2017). More recently, a small, prospective cohort study of a multimodal exercise, nutrition, and palliative care intervention in patients with advanced lung cancer has confirmed the safety, feasibility and tolerability of such a programme (Ester et al., 2021). No adverse events (AEs) were reported relating to the intervention and a qualitative arm of the trial reported high participant satisfaction.

The hypothesis that a multi-modal rehabilitation programme, incorporating exercise, nutritional support including Ω-3 rich ONS, would be beneficial for a general population of outpatients with incurable cancer, remains to be tested. It underpins the design of the ENeRgy trial interventions, and forms the basis for this thesis, and future work in this area. The justification and potential benefits of ENeRgy trial are summarised in Figure 11.
Figure 11: Potential impact of ENeRgy trial interventions
1.4. Aims of thesis

Introduction:
It has been discussed that, in patients with incurable cancer, the cancer state is often inflammatory and frequently may be associated with variable stages of cancer cachexia. However, the potential role of exercise and nutrition as a specific intervention requires evaluation.

1.4.1. Hypotheses:

1. Combined exercise and nutritional rehabilitation programmes are feasible and result in significant improvements in functional and nutritional status, mood and quality of life for patients with incurable cancer.
   - This hypothesis was tested by performing a systematic review of the literature.

2. An eight-week, multi-modal rehabilitation programme, incorporating weekly reviews and a home based exercise and nutritional programme, is feasible in terms of patient compliance and data capture for a general population of outpatients living with incurable cancer.
   - This hypothesis was tested by undertaking the phase two randomised controlled trial of an exercise and nutritional rehabilitation programme (ENeRgy) for hospice outpatients living with advanced cancer.

3. An eight-week, multi-modal rehabilitation programme, incorporating exercise, nutritional support with Ω-3 rich ONS, results in trends toward improvement in physical function, nutritional status and patient/carer QoL for a general population of outpatients living with incurable cancer.
   - This hypothesis was also tested by undertaking the ENeRgy trial.
1.4.2. Aims

**Aim 1:** To examine current evidence for combined exercise and nutritional interventions in patients with incurable cancer by way of a systematic review of the literature. The systematic review is presented in chapter two.

**Aim 2:** To ascertain whether an eight-week rehabilitation programme incorporating exercise and nutritional support with Ω-3 rich ONS (ENeRgy) for outpatients with incurable cancer is feasible, including the following primary endpoints: compliance with treatments (ONS and exercises prescribed); compliance with trial procedures including completion rates of questionnaires and tests; compliance with PAM; missing data and reasons for missing data. The design and methodology of the ENeRgy trial is presented in chapter three and the results of the primary (feasibility) endpoints are presented in chapter four.

**Aim 3:** To explore the efficacy of the intervention on key secondary endpoints including: feasibility of recruitment and retention/attrition rates; impact on physical function, nutritional status, patient and carer QoL; contamination in the control group and impact on survival. The results of the secondary (exploratory) endpoints are presented in chapter five.
Chapter 2. Systematic review

A systematic review of combined exercise and nutritional rehabilitation in outpatients with incurable cancer

2.1. Introduction

The following chapter details the methodology, results and discussion of a systematic review (SR) undertaken to examine the current evidence for combined exercise and nutritional rehabilitation in patients with incurable cancer. This SR was undertaken after the protocol for the ENeRgy trial was finalised, therefore the results did not inform the design of the trial. The following chapter was published in the journal Supportive Care in Cancer in April 2019 (Hall et al., 2019)- [Appendix 1].

Patients with cancer are living longer than ever before, indeed in many cases cancer is now considered a chronic disease (Feldstain et al., 2017, Salakari et al., 2015). While this is clearly a positive development, the consequences of patients living longer with cancer are wide and varied. With longer survival comes an increase in morbidity, increases in healthcare costs with associated socio-economic implications (Mariotto et al., 2011). There is a need to take a pro-active approach to this evolving situation and to optimise the overall condition of patients living with cancer, including those with incurable disease (Silver et al., 2013). Rehabilitation may be one such way of optimising the function and overall quality of life (QoL) of this patient population.

Rehabilitation is a concept widely embraced by Western medicine for management of acute and chronic illness, and has recently been advocated for patients with incurable cancer: including those receiving treatment with palliative intent (Chasen et al., 2014, Tiberini R, 2015, Maddocks, 2017).
Although ‘rehabilitation’ for patients with incurable cancer may seem paradoxical, there is a plausible argument that patients whose overall condition is compromised have the most to gain from appropriately tailored intervention (Maddocks, 2017). In patients with advanced disease, rehabilitation aims to improve and/or maintain function where the effects of the illness or its treatment threaten to cause decline, or to ease the transition towards dependency when functional deterioration is inevitable. Promotion of patients’ own interests, social engagement and optimising functional independence are fundamental (Maddocks, 2017). It is acknowledged widely that rehabilitation in patients with incurable cancer should be multi-modal and tailored (Maddocks, 2017, Silver et al., 2015, Chasen et al., 2014) yet there is a lack of evidence as to the most efficacious components of a rehabilitation programme for this patient population (Salakari et al., 2015).

The emerging principles of optimising physical and nutritional function in patients with cancer cachexia would seem appropriate to be applied to a broader rehabilitation concept in all patients with cancer. Cachexia is defined as ‘an ongoing loss of skeletal muscle mass (with or without fat mass) that cannot be fully reversed by conventional nutritional support and leads to protein breakdown, and resultant loss of muscle mass and functional decline’ (Fearon et al., 2011). It is common in solid tumours, which account for over 50% of cancer deaths worldwide and affects over half of all patients with advanced cancer (Baracos et al., 2018). Cachexia adversely affects function, QoL and is an independent predictor of poorer treatment response, side-effect profiles and shorter survival (Fearon, 2008, Dewys et al., 1980, Stephens et al., 2008). The high prevalence of cachexia in patients with incurable cancer alone, means that any rehabilitation intervention for this group should consider key components of cachexia.

Cachexia is characterised by involuntary weight loss and a negative energy balance created by reduced oral intake, alterations in body metabolism and inflammation (Baracos et al., 2018). Dietary interventions alone are not
effective in reversing cancer-related cachexia, (Gullett et al., 2011, Fearon, 2008) due to metabolic alterations including elevated energy expenditure, excess catabolism and inflammation (Baracos et al., 2018), which together prevent muscle anabolism (the ‘anabolic blockade’) (Fearon, 2008). Exercise stimulates skeletal muscle anabolism, leading to increased muscle mass and strength, however supra-normal protein intake is required to achieve the same post-prandial anabolic effects in cachectic patients (Fearon, 2008). Introducing exercise without nutritional support in this group of patients may exacerbate the negative energy balance. Work to date has demonstrated that cancer cachexia is best targeted through a pro-active, multimodal intervention that aims to improve lean mass (muscle), physical function and overall QoL (Solheim et al., 2017a, Fearon, 2008). This pro-active and multimodal approach advocated for cancer cachexia has the potential to be adopted usefully as a rehabilitation approach for patients with incurable cancer.

Exercise is feasible in patients with incurable cancer and has multiple beneficial effects on physical well-being, fatigue, and depression, all impacting on overall QoL (Litterini et al., 2013, Salakari et al., 2015). Based on work to date, there is a strong rationale that exercise and nutrition in combination should be key constituents of any rehabilitation programme for patients with cancer; however the details of any such programme remain to be elucidated (Chasen et al., 2014).

The aim of this systematic review was to examine the current evidence for combined exercise and nutritional rehabilitation interventions in patients with incurable cancer. Specifically to address the following questions: Are combined exercise and nutritional interventions feasible for patients with incurable cancer? How common are adverse events? What are the predictors of programme completion? Do these programmes significantly improve the physical, nutritional, emotional and psychological status of...
patients or their quality of life? Which outcomes are most frequently used to measure these differences?

2.2. Methods

Ethical approval was not required for this SR. The following databases were searched electronically: MEDLINE, EMBASE and the Cochrane Library. The following search terms were used: “Cancer”, “Exercise”, “Nutrition”, “Palliative”, “Rehabilitation”, “Prehabilitation”. Combinations and results of these searches are detailed within Appendix 1. Search terms were within ‘title’ and results limited to human subjects and English language journals from year 1990 to May 2018.

2.2.1. Inclusion criteria

Studies met the following inclusion criteria: Patients with incurable cancer (defined as metastatic cancer [histological, cytological or radiological evidence] or locally advanced cancer being treated with palliative intent); rehabilitation programmes including both exercise and nutritional components; all methodologies; studies in humans and in the English language.

2.2.2. Exclusion criteria

Studies were excluded if they met any of the following criteria: studies of cancer survivors or carers of cancer patients; unimodal rehabilitation interventions; reviews; protocols; case reports; retrospective case note reviews; conference abstracts; rehabilitation or prehabilitation programmes for cancers managed with curative intent.
2.2.3. Appraisal process

Titles were reviewed by myself (CH), and then relevant abstracts were screened by CH and Dr Barry Laird (BL). Abstracts deemed relevant or requiring clarification were reviewed at full text by CH and BL. Full texts were reviewed by CH and BL, then thematic analysis applied to the remaining included papers by CH and Jane Cook (JC).

Estimates of effect extracted from studies included change scores (pre-post measurements), effect sizes and P values. Values were synthesised according to patient-important outcomes (see below) as well as outcomes of methodological interest for future study design: feasibility, dropout rates, predictors of completion, and cost effectiveness.

To appraise eligible research papers robustly, the internationally acknowledged GRADE system was used (Schünemann, 2013, Atkins et al., 2004). GRADE analyses were undertaken by CH and JC. Due to the complexity and to improve inter-rater reliability, a checklist was developed by CH [Appendix 2] based on the GRADE handbook and a validated checklist for meta-analyses (Meader et al., 2014, Schünemann, 2013). This was applied to individual studies, then to the body of evidence for patient-important outcomes, which were decided *a priori* between authors and ranked in order of importance. Where GRADE discrepancies existed, these were discussed among the authors and a consensus reached. A consort diagram was performed as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009) [Figure 12].
Figure 12: Consort diagram: literature search process
2.3. Results

The following numbers of articles were retrieved from each database: 781 (MEDLINE), 1625 (EMBASE), and 18 (Cochrane Database of Systematic Reviews).

A summary of included studies is detailed in Table 2. Eight studies were eligible enrolling a total of 685 participants. Studies included two RCTs (Uster et al., 2017, Jones et al., 2013), three prospective studies (Chasen and Bhargava, 2010, Glare et al., 2011, Gagnon et al., 2013), two secondary analyses of quasi-experimental data (Feldstain et al., 2016, Feldstain et al., 2017) and one exploratory study (Chasen et al., 2013).

All interventions were outpatient-based rehabilitation programmes: seven in hospitals and one hospice-based. Three studies examined the eight to twelve-week McGill Cancer Nutrition Rehabilitation Programme (CNRP) (Chasen and Bhargava, 2010, Gagnon et al., 2013, Glare et al., 2011), and three studies examined the eight-week Ottawa Palliative Rehabilitation Programme (PRP) (Feldstain et al., 2016, Feldstain et al., 2017). Two studies examined novel rehabilitation programmes in the UK (Jones et al., 2013) and Switzerland (Uster et al., 2017). All programmes were interdisciplinary and were individually tailored. Seven studies included core components combining dietary modification/supplementation and exercise (Chasen and Bhargava, 2010, Chasen et al., 2013, Feldstain et al., 2017, Feldstain et al., 2016, Gagnon et al., 2013, Glare et al., 2011, Uster et al., 2017). The remaining study included dietary and physiotherapy interventions as an optional (non-core) element dependent on patient goals: it was not possible to ascertain numbers of participants receiving input from both these types of specialists (Jones et al., 2013).
<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Design</th>
<th>Participants</th>
<th>Setting</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Aim(s)</th>
<th>Outcome Measures (Time points)</th>
<th>Main Findings &amp; Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chasen et al. 2010</td>
<td>Observational Study</td>
<td>N=53 Gastro- Oesophageal Cancers Stage 2 (n=7) Stage 3 (n=33) Stage 4 (n=13)</td>
<td>Outpatient Clinic (Montreal, Canada)</td>
<td>Eight-week CNRP</td>
<td>Nil</td>
<td>Evaluate whether an individualised rehabilitation programme affects symptoms and QoL</td>
<td>-ESAS -PG-SGA -BFI -DT -6MWT (Pre &amp; post)</td>
<td>Physical Endurance/ Depression: Significant improvements in appetite, strength, nervousness, pain, depression, constipation, depression, nausea. Non-Significant improvement in mean 6MWT distance. Significant reduction in distress. QoL/ Fatigue: Significant improvements in enjoyment in life, general activity, usual fatigue &amp; fatigue now. Nutritional Status: Significant reduction in median PG-SGA scores. Dropout Rates: High dropout rate- (36%) due to disease progression/ death, (23%) unable to attend regularly enough to be included.</td>
</tr>
<tr>
<td>Chasen et al. 2013</td>
<td>Exploratory Study</td>
<td>N=116 Heterogeneous cancers (completed anti-cancer treatments) Stage 3 (n= 36) Stage 4 (n= 80)</td>
<td>Outpatient Clinic (Ottawa, Canada)</td>
<td>Eight-week PRP</td>
<td>Nil</td>
<td>1. Effect of the PRP on physical, nutritional, social, and psychological functioning. 2. Determine medical factors associated with program completion.</td>
<td>-ESAS -MD Anderson Symptom Index -PG-SGA -MDFI -BBS -Functional Reach Test -TUG -Grip Test -6MWT -ECOG PS -FBC, serum electrolytes, CRP, alb, TSH, glu,LDH (Pre &amp; post)</td>
<td>Physical Endurance/ Overall Function: Significant improvements in ECOG PS, endurance, mobility, nutrition, general fatigue, and physical fatigue. Moderate non-significant improvement in walking, balance and HGS. Nutrition: Significant improvement in overall nutritional risk. Depression/ Fatigue: Small-to-moderate (non-significant) improvements in symptom interference in mood, enjoyment, general activity, and work; decreased activity; balance and function; and several symptoms. Moderate non- significant improvements in: severity of drowsiness, appetite symptoms, interference in relationships and decreased motivation. No worsening of symptoms in any domain. Dropout Rate/ Predictors of Completion: 42% did not complete (23% disease progression, 16% personal/ unknown, 2% died, 1% too well). Patients were more likely to complete the programme if CRP was &lt;10</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Sample Size</td>
<td>Cancer Stages</td>
<td>Location</td>
<td>PRP Duration</td>
<td>PRP Details</td>
<td>Outcome Measures</td>
<td>Key Findings</td>
</tr>
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<tr>
<td>Feldstain et al. 2016</td>
<td>Secondary analysis of quasi-experimental data.</td>
<td>N = 131</td>
<td>Heterogeneous cancers Stage 3 (n=25), Stage 4 (n=55)</td>
<td>Outpatient Clinic (Ottawa Canada)</td>
<td>Eight-week PRP</td>
<td>Nil</td>
<td>To examine the impact of three aspects of the PRP (inflammation, self-efficacy, and exercise), on depression.</td>
<td>-Serum CRP &lt;br&gt; -6MWT &lt;br&gt; -General Self-efficacy scale &lt;br&gt; -HADS Depression subscale (Pre &amp; Post)</td>
</tr>
<tr>
<td>Feldstain et al. 2017</td>
<td>Secondary analysis of quasi-experimental data.</td>
<td>N = 44</td>
<td>Heterogeneous cancers (post anti-cancer treatment) Stage 3 (n=20), Stage 4 (n=24)</td>
<td>Outpatient Clinic (Ottawa Canada)</td>
<td>Eight-week PRP</td>
<td>Nil</td>
<td>To ascertain if reductions in depression are maintained three months post PRP completion.</td>
<td>-HADS (T1 = Pre-PRP, T2 = completion, T3 = 3/12 post-PRP)</td>
</tr>
<tr>
<td>Gagnon et al. 2013</td>
<td>Uncontrolled prospective intervention study</td>
<td>N = 188</td>
<td>Heterogeneous cancers &amp; haematological cancers not eligible for BMT Stage 3-4 (numbers of each stage not specified)</td>
<td>Outpatient Clinic (Montreal, Canada)</td>
<td>Ten to twelve week CNRP</td>
<td>Nil</td>
<td>To report the degree to which a CNR programme improves symptom control, nutrition status, physical function, psychosocial wellbeing, &amp; overall QoL</td>
<td>-Modified ESAS adapted for palliative patients (QOL and symptom scores) &lt;br&gt; -MDFI &lt;br&gt; -DT &lt;br&gt; -CT &lt;br&gt; -6MWT &lt;br&gt; -5m walk test &lt;br&gt; -6 month recall weight loss &lt;br&gt;-Presence of Fatigue/Weakness/Insomnia: Significant reduction in weakness. Small reductions (effect size 0.4) in: sleepiness, insomnia, pain, anorexia. Strong improvements in MDFI activity and physical fatigue (effect size 0.8-1.1). Small improvements in motivation &amp; mental fatigue (effect size 0.4). Depression/ QoL: Significant reduction in depression &amp; nervousness. Moderate reduction in distress, coping ability &amp; overall QoL. Physical Endurance/ Strength: Mean 6MWT improved by 41m (effect size 0.7) &amp; maximal gait speed by 0.15m/s (effect size 0.6). Patients attended mean 82% scheduled physio sessions. Nutritional Status: 77% maintained weight (within 2 kg), or gained &gt; 2kg</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>N</td>
<td>Cancer</td>
<td>Stage</td>
<td>Intervention</td>
<td>Outcome Measures</td>
<td>Dropout Rate/ Predictors of Completion:</td>
<td></td>
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<tr>
<td>Glare et al. 2011</td>
<td>Prospective Study</td>
<td>54</td>
<td>Heterogeneous cancers (majority lung, colorectal and upper GI) undergoing variable treatments</td>
<td>Cancer stages not available</td>
<td>Outpatient Clinic (Sydney, Australia)</td>
<td>Eight-week CNRP</td>
<td>Significant reduction in taste/smell alterations. (Pre &amp; Post)</td>
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<td></td>
<td>Programme non-completion (30%) associated with poor ECOG PS, CRP &gt;20mg/L, poor nutrition status &amp; worse anorexia. Non completers: 7% ‘drop-out’ 15% disease progression, 9% died.</td>
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<td></td>
<td>Dropout Rate/ Predictors of Completion:</td>
<td>Feasibility: 72% recruitment target achieved, &gt;90% patients reported CNRP as important to them. Nutritional Status: Baseline nutrition subnormal in 80%: (critical need for dietary intervention in typical patient). Baseline albumin abnormally low in 26%, baseline CRP elevated (&gt;10mg/L) in 72%. Patients still in the programme at 2 months had lost less weight, were better nourished, fitter &amp; less likely to have elevated CRP than those who had dropped out. Physical Endurance/ Strength: Median 6MWT &amp; RHGS improved by 1/3rd as well as reductions in ESAS symptom scores.</td>
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<td></td>
<td>Depression: Significantly lower unmet needs for psychological support for patients receiving the intervention.</td>
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<td></td>
<td>Cost Effectiveness: Significant reduction in healthcare resource use and a corresponding improvement in QoL. Intervention associated with greater total costs &amp; greater QoL (mean difference 0.05 QALYs) resulting in an ICER of £19,391 per QALY gained: cost effective in 55.4% &amp; 73.3% of simulations at cost thresholds £20,000/ £30,000 respectively.</td>
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<td></td>
<td></td>
<td></td>
<td>QoL: Effects on sexuality support needs, continuity of care</td>
<td></td>
</tr>
<tr>
<td><strong>Uster et al. 2017</strong></td>
<td><strong>Parallel group Randomised Control Trial</strong></td>
<td><strong>N = 58</strong></td>
<td><strong>GI or lung cancers metastatic (n=57) or locally advanced (n=1)</strong></td>
<td><strong>Trial cut short due to slow accrual</strong></td>
<td><strong>Cancer centre (Winterthur, Switzerland)</strong></td>
<td><strong>Three month nutrition and physical exercise programme</strong></td>
<td><strong>Standard Cancer Centre Medical Therapy</strong></td>
<td><strong>To test the effects of the programme in terms of 1. Global health status/QoL Scale 2. Dietary intake</strong></td>
</tr>
</tbody>
</table>
**Table 2 glossary of terms:**

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBS</td>
<td>Berg Balance Scale</td>
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<tr>
<td>BIA</td>
<td>Bioelectrical Impedance Analysis</td>
</tr>
<tr>
<td>BFI</td>
<td>Brief Fatigue Inventory</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BMT</td>
<td>Bone Marrow Transplant</td>
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<tr>
<td>CRP</td>
<td>C-Reactive Protein</td>
</tr>
<tr>
<td>CT</td>
<td>Coping thermometer</td>
</tr>
<tr>
<td>DT</td>
<td>Distress Thermometer</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>Eastern Cooperative Oncology Group Performance Status</td>
</tr>
<tr>
<td>EORTC QLQ-C30</td>
<td>Self-reported questionnaire designed to assess quality of life of cancer patients</td>
</tr>
<tr>
<td>EQ-5D/ EQ-VAS</td>
<td>EuroQol-5 Dimensions/ Comprising 0-100 Visual Analogue Scale of perceived health state</td>
</tr>
<tr>
<td>ESAS</td>
<td>Edmonton Symptom Assessment Scale</td>
</tr>
<tr>
<td>FBC</td>
<td>Full Blood Count</td>
</tr>
<tr>
<td>FFM</td>
<td>Fat Free Mass</td>
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<tr>
<td>GPS</td>
<td>Glasgow Prognostic Score</td>
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<tr>
<td>H&amp;N-35</td>
<td>Head and Neck Specific EORTC self-reported questionnaire with sections relating to Head and Neck cancer symptoms/ issues</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental Cost Effectiveness Ratio</td>
</tr>
<tr>
<td>K10</td>
<td>Kessler Psychological distress scale</td>
</tr>
<tr>
<td>KPS</td>
<td>Karnofsky Performance Status</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate Dehydrogenase</td>
</tr>
<tr>
<td>MDFI</td>
<td>Multidimensional Fatigue Inventory</td>
</tr>
<tr>
<td>PG-SGA</td>
<td>Patient-Generated Subjective Global Assessment</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality Adjusted Life Year</td>
</tr>
<tr>
<td>RHGS</td>
<td>Right Hand Grip Strength</td>
</tr>
<tr>
<td>SCNS-LF59</td>
<td>Supportive care needs survey long form</td>
</tr>
<tr>
<td>SOB</td>
<td>Shortness of Breath</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid Stimulating Hormone</td>
</tr>
<tr>
<td>TUG</td>
<td>Timed up and go test</td>
</tr>
<tr>
<td>6MWT</td>
<td>Six Minute Walk Test</td>
</tr>
</tbody>
</table>
Table 2 GRADE column footnotes:

Note: Studies (a-f) all started as GRADE ‘C’ (‘low’) evidence quality due to study type, g and h started as ‘A’ (high) evidence quality due to study type

a: GRADE score reduced (-1) due to high dropout rate (58% dropout rate), variable intervention, small sample size, small numbers included in analysis. Although effect consistent with rapid effect, GRADE score not increased due to these limitations

b: GRADE score reduced (-1) due to high dropout rate (42%), incomplete analysis of enrolled patients, variable intervention. GRADE score increased (+1) due to magnitude of effect and rapidity across subjects with larger sample

c: GRADE score reduced (-1) due to dropout rate (39%), missing data (unquantified), variable interventions in relation to the primary outcome, surrogate outcome measure (HADS) with limited diagnostic sensitivity for clinical vs. subclinical depression. GRADE score not increased due to these limitations.

d: GRADE score reduced (-1) due to large loss to follow up and small numbers of participants, sample bias and variable interventions given. GRADE score increased (+1) due to rapidity & consistency of effect as well due to attempts to analyse demographic of non-responders (confounding)

e: GRADE score reduced (-1) due to use of non-validated tools, variable interventions, unexplained absence of data for outcomes. GRADE score increased (+1) due to large magnitude and consistency of effect which was rapid.

f: GRADE score reduced (-1) due to high dropout rate, variable intervention, lack of adequate control for confounding (67% on chemotherapy), small sample size and missing data. GRADE score not increased due to these limitations.

g: GRADE score reduced (-1) due to low numbers (17% predicted recruitment), variability of interventions, wide confidence intervals (due to small sample size). GRADE score not increased due to these limitations.

h: GRADE score reduced (-1) for selection bias and failure to adequately control for confounding & small sample size. GRADE score not increased due to these limitations.
2.3.1. Feasibility and adverse events

Three studies (n=300 patients in total) commented on feasibility of the rehabilitation programmes or constituents of their interventions. Patients attended a mean of 67% of bi-weekly exercise training classes over three months, and all patients managed at least half of the ONS after each training session in one RCT (Uster et al., 2017). Similarly for a 10-12 week CNRP, patients attended 82% of prescribed exercise sessions (Gagnon et al., 2013). No adverse effects were reported, but this was only mentioned in one study (Uster et al., 2017). In the same trial, three-month dropout rates due to death or withdrawal were lower in the intervention group compared to the control group: 4% vs. 24%, indicating feasibility. Over 90% of patients reported the CNRP as important to them; however, introducing this programme in a busy cancer centre was labour-intensive, requiring a nurse, administrative and financial support to be viable (Glare et al., 2011).

2.3.2. Dropout rates and predictors of programme completion

Completion rates from CNRP/PRP programmes ranged from 42-70% (Chasen and Bhargava, 2010, Gagnon et al., 2013). Dropout rates due to disease progression/death accounted for between 49% and 61% (Chasen et al., 2013, Feldstain et al., 2016). Other reasons included geographical inaccessibility (Chasen and Bhargava, 2010) or unknown/personal reasons (37%) (Chasen et al., 2013). Schedules of medical appointments made it hard to adhere to the CNRP, and at times the amount of information to take in could be overwhelming (Glare et al., 2011). Predictors of programme completion included lower baseline CRP levels (Chasen and Bhargava, 2010, Gagnon et al., 2013), lower ECOG performance status and better nutritional status (Gagnon et al., 2013). Glare et al (Glare et al., 2011) cited a baseline six minute walk test (6MWT) >420m, (i.e. better endurance) as a predictor of programme completion. Although programme completers
demonstrated improvements in multiple domains, high dropout rates (>50%) meant that earlier identification of the population who will best respond is needed.

2.3.3. Physical endurance, strength and overall function

Studies used multiple outcome measures; however, the 6MWT was frequently cited as a marker of endurance and mean distances improved in six studies (n=342). Two studies reported performance status (ECOG/KPS) as primary endpoints (n=81).

Feldstain and Chasen reported significant increases in mean 6MWT distance \[t(79)= -3.91, P=<0.001\] (Feldstain et al., 2016) and \[d=0.80\ i.e.\ moderate-to-large\ effect\ size, P<0.001\] (Chasen et al., 2013) after the PRP. Studies utilising the CNRP quoted improvements in mean 6MWT distances between 41m [95% CI: 29m-52m: effect size 0.7, P not reported (Gagnon et al., 2013)] and 58m (Chasen and Bhargava, 2010) [non-significant, median 6MWT increase: P=0.01]. Glare and Uster reported non-significant increases in 6MWT [n=25, median 441m (186-675) to 570m, range not reported, (Glare et al., 2011), data presented graphically (Uster et al., 2017)], and other physical parameters, though both studies were underpowered. Chasen in 2013 reported an improvement in ECOG PS (P<0.001, \(t= 6.43, d= 0.90\)) from mean 1.8 (+0.7) to 1.29 (+0.46) for patients completing the PRP, and Glare in 2011 reported non-significant improvements in median KPS score (n=25) from 70% (score \(\geq 50%:100\%\)) to 80% (score \(\geq 50%:100\%\)) in programme completers.

2.3.4. Nutritional status

Two studies measured weight as an outcome (Gagnon et al., 2013, Uster et al., 2017), two used the Patient Generated Subjective Global Assessment
Systematic Review

PG-SGA (Chasen and Bhargava, 2010, Chasen et al., 2013), and one a combination of both (Glare et al., 2011). Comparison between studies is hampered by lack of detail on nutritional interventions, heterogeneity of subjects and varied outcome measures. Nutritional counselling, dietary advice, and ONS are mentioned by most. Details of dietary interventions varied: 72% saw the physician, physiotherapist and dietitian, with 25% seeing the physician and dietitian only in one study (Glare et al., 2011); 60-70% saw the dietitian in another (Feldstain et al., 2017); and in another, 94.7% received dietary counselling, with 80.2% receiving ONS (Gagnon et al., 2013). One RCT ensured patients received ≥1.2g protein/Kg/day, and encouraged protein dense ONS (18-20g in 125-200mL) after exercise. Significant improvements in protein intake (P=0.01), but no significant differences in energy intake or nutritional status were seen between arms; indeed, weight increased in both (Uster et al., 2017). Patients undergoing nutritional interventions within multidisciplinary programmes maintained (77% within 2kg) (Gagnon et al., 2013) or increased their weight (Uster et al., 2017), although longitudinal data are lacking. Increases in protein intake were not maintained three months post-intervention, dropping below baseline in both groups, more so in the control group (Uster et al., 2017).

PG-SGA score improvements (median baseline 12.0 (2-24), to 9.0 (1-18) at completion P=0.05) were reported following the CNRP (Chasen and Bhargava, 2010), and also post-PRP (baseline mean (+SD): 8.15 (±5.29) to 5.98 (±4.14), t=3.49, P=0.001, d= 0.46) (Chasen et al., 2013). There was a higher mean PG-SGA score (89% ≥9 versus 70% ≥9) in drop-outs of CNRP compared with those who returned for their two month CNRP follow up (Glare et al., 2011).

2.3.5. Fatigue, weakness and insomnia

Four studies described changes in fatigue (n=211 patients in total) using the Brief Fatigue Inventory (BFI) (Chasen and Bhargava, 2010), the
Multidimensional Fatigue Inventory (MDFI) (Chasen et al., 2013, Gagnon et al., 2013) and the EORTC QLQ-C30 symptom scales (Uster et al., 2017).

Chasen (Chasen and Bhargava, 2010) described improvements in BFI usual fatigue [5.0 (1–10)–3.0 (1–9); P=0.03] and fatigue now [5.0 (0–10)–3.0 (0–10); P=0.05]. Furthermore, in 2013 using the MDFI, Chasen also reported reductions in general and physical fatigue d=0.61 and 0.55, both P<0.001 (Chasen et al., 2013). Gagnon reported strong improvements in MDFI activity and physical fatigue (mean 4.6 [95% CI 3.6-5.6] to 3.7 [95% CI 2.6-4.7] respectively, both P<0.001, effect size: 0.8-1.1); moderate reductions in general fatigue (mean change 2.8 [95% CI 1.8-3.8] P<0.0001, effect size 0.7); and small but significant improvements in motivation and mental fatigue (mean change 1.6 [95% CI 0.8-2.5] P=0.0004 and 1.7 [95% CI 0.8-2.6] P=0.0005: effect size both 0.4). Reductions were seen in weakness (mean change 1.5 [95% CI 1.1-1.8] P<0.0001, effect size 0.7), as well as reductions in sleepiness and insomnia (mean change 1.1 [95% CI 0.6-1.6] P<0.0001 and mean change 1.0 [95% CI 0.5-1.4] P=0.0001 effect size both 0.4) (Gagnon et al., 2013).

2.3.6. Effects on depression and quality of life

Six studies included endpoints examining depression (n=371 patients in total) using the Edmonton Symptom Assessment Scale (ESAS) (Chasen and Bhargava, 2010, Chasen et al., 2013, Gagnon et al., 2013), the Hospital Anxiety and Depression Scale (HADs) (Feldstain et al., 2017, Feldstain et al., 2016) and the psychological subscale of the Supportive Care Needs Survey Long Form (SCNS-LF59) (Jones et al., 2013). Studies frequently mentioned QoL but only three studies reported a QoL outcome using questions from the ESAS (Gagnon et al., 2013), EORTC QLQ-C30 (Uster et al., 2017) and EQ-5D/ EQ-VAS questionnaires (Jones et al., 2013).
Chasen in 2010 reported improvements in nervousness and depression (4.5 (0–10)–1.5 (0–5); P=0.02 and (3.0 (0–9)–2.0 (0–7); P=0.04 respectively), and depression scores for those completing the PRP (P=0.005, d=0.37) (Chasen et al., 2013). Similarly, Gagnon in 2013 reported reductions in (ESAS) depression scores (mean change 1.4 (95% CI 1.1-1.8) P<0.0001, effect size 0.7) as well as reduced (DT) distress (mean change 1.4 [95% CI 0.9-1.9] P<0.0001, effect size 0.5), improved (CT) coping (mean change 1.8 [95% CI 1.2-2.4] P<0.0001, effect size 0.7), and (ESAS) QoL (mean change 1.0 [95% CI 0.6-1.3] P<0.0001 effect size 0.5) after the CNRP. One RCT demonstrated reduced unmet psychological support needs on the psychological subscale of the SCNS (adjusted difference -16.8 points [95% CI -28.34 to -5.3] P=0.006), and improvements in (EQ-5D) self-reported health state (12.8, (95% CI 3.2-22.4) P=0.01) compared with controls (Jones et al., 2013). Conversely, the other RCT (Uster et al., 2017) showed no difference in global QoL. There was a non-significant trend towards improvement; however, this trial was curtailed due to poor recruitment and lacked power. Feldstain in 2016 described increased self-efficacy [27.86 (SD=6.16) to 31.23 units (SD=5.77), P<0.001], and reduced depression scores [7.14 (SD=3.91) to 5.95 units (SD=3.51), P=0.002] after the PRP. Changes in ‘self-efficacy’ (the perception that one can influence life events/quality of functioning) accounted for the greatest change (11%) in depression scores. In a subsequent study (Feldstain et al., 2017), depression score improvements were maintained three months post-PRP (mean difference T1-T3= 2.21, SE 0.78, P=0.007).

### 2.3.7. Cost effectiveness

One RCT (n= 41) examined the cost effectiveness of a three-month, complex hospice-based rehabilitation programme plus usual care versus usual care alone (Jones et al., 2013). The intervention was associated with greater total costs (mean difference £955, 95% CI £82-£1,975) and greater QoL (mean difference 0.05 QALYs, 95% CI 0.000-0.112) resulting in an Incremental Cost
Effectiveness Ratio (ICER) of £19,391 per Quality-Adjusted Life Year (QALY) gained. The cost per QALY was only calculated over the three-month (intervention) period and was close to the £20,000 threshold often used for incorporation of an intervention in to the UK National Health Service. The authors postulated that if the benefits of the programme were maintained for one year, the ICER would decrease to approximately £4,400 making the projection cost effective in 92.7% of simulations at a threshold of £20,000 per QALY.

Studies and patient-important outcomes were evaluated using the GRADE approach. The quality of evidence for each patient-important outcome, is summarised and presented in Table 3.
Table 3: Summary of findings, modified due to study types

**Patients or population:** Patients with incurable cancer

**Settings:** Outpatient

**Intervention:** Multi-modal rehabilitation programmes comprising exercise & nutrition

**Comparison:** (Where available- standard care)

<table>
<thead>
<tr>
<th>Patient-Important Outcomes</th>
<th>Studies</th>
<th>N= Total Participants* (Breakdown per outcome measure)</th>
<th>Quality of the body of evidence (GRADE)- See definitions p74</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Life</td>
<td>3 (Gagnon et al., 2013, Jones et al., 2013, Uster et al., 2017)</td>
<td>N = 214 129 (ESAS) 41 (EQ-VAS) 44 (EORTC C30)</td>
<td>LOW (C)</td>
<td>Two moderate quality studies with conflicting results, one low quality study showing improvement, studies have limitations and inconsistencies in outcome variables.</td>
</tr>
<tr>
<td>Overall Function</td>
<td>2 (Chasen et al., 2013, Glare et al., 2011)</td>
<td>N = 81 56 (ECOG PS) 25 (KPS)</td>
<td>VERY LOW (D)</td>
<td>Two studies with low and very low quality examined changes in functional status scores, one finding significant and one non-significant improvements. Sparse data with limitations.</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (Chasen and Bhargava, 2010, Chasen et al., 2013, Gagnon et al., 2013, Uster et al., 2017)</td>
<td>N = 203 22 (BFI) 137 (MDFI) 44 (EORTC QLQ-C30)</td>
<td>LOW (C)</td>
<td>Two low, one very low quality studies with limitations showing significant improvements in fatigue in spite of sparse data, and one high quality (underpowered) study showing non-significant improvements in intervention group compared to control</td>
</tr>
<tr>
<td>Physical Endurance/Strength</td>
<td>6 (Chasen and Bhargava, 2010, Chasen et al., 2013, Feldstain et al., 2016, Gagnon et al., 2013, Glare et al., 2011, Uster et al., 2017)</td>
<td>N = 342 6MWT (342) HGS (64 within two of the above studies)</td>
<td>MODERATE (B)</td>
<td>Six studies with quality overall 'low' quality, with limitations: variable consistency in significance levels but overall magnitude of effect seen was improvement in spite of low statistical power of studies: GRADE of evidence increased (+2)</td>
</tr>
<tr>
<td>Depression</td>
<td>6 (Chasen and Bhargava, 2010, Chasen et al., 2013, Feldstain et al., 2016, Feldstain et al., 2017, Gagnon et al., 2013, Jones et al., 2013)</td>
<td>N = 371 211 (ESAS) 124 (HADS) 36 (SCNS-LF59)</td>
<td>MODERATE (B)</td>
<td>Overall low quality studies with limitations but GRADE of evidence increased (+2) due to studies all showing consistent significant improvements in depression/psychological subscales.</td>
</tr>
<tr>
<td>Nutrition / Weight</td>
<td>5 (Chasen and Bhargava, 2010, Chasen et al., 2013, Gagnon et al., 2013, Uster et al., 2017, Glare et al., 2011)</td>
<td>N = 285 107 (PG-SGA) 178 (Weight)</td>
<td>VERY LOW (D)</td>
<td>Five studies of overall low quality with serious limitations and indirectness (variable interventions). Two low/very low quality studies showed improved PG-SGA scores but the highest quality RCT showed only significant increases in protein intake. Evidence not strong enough to be upgraded.</td>
</tr>
</tbody>
</table>
* Total participants includes numbers actually analysed within studies for each outcome as opposed to table 2 showing ‘N’ as numbers enrolled in to each trial.

**Definitions of GRADE quality of the body of evidence:**

**High:** We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

**Very Low:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
2.4. Discussion

There are few data available for multi-modal rehabilitation programmes incorporating exercise and nutritional interventions for patients with incurable cancer. However of those outcomes important to patients, many showed improvements following the interventions described. Factors associated with programme completion are higher baseline nutritional or functional status and lower levels of inflammation. Of the studies analysed, methodological quality was frequently limited by study design and statistical power. Heterogeneity of study design (including interventions and outcome measures) meant meta-analysis was not appropriate.

In patients with incurable cancer, the highest quality of evidence pertains to improvements in depression and physical endurance following multi-modal rehabilitation programmes including exercise and nutritional support. Depression is one of the commonest mental health problems in patients with advanced cancer (Al-Shahri et al., 2012). Six studies showed improvements in depression scores, using outcomes including the HADs. This scale however, does not differentiate clinical depression from sub-threshold symptomatology, which is a limitation to its use in this patient population (Feldstain et al., 2016).

A high level of evidence exists for exercise in rehabilitation trials (Gerber et al., 2017, Salakari et al., 2015), and this review suggests that the combination of exercise and nutritional support also improves physical endurance in patients with incurable cancer. Evidence for change in overall function remains very low due to serious limitations in the evidence. Plausibly, however, improvements in physical endurance may impact on overall function via reductions in dependency.

Evidence for improved fatigue remains low; a finding is in keeping with the lack of interventions for fatigue in advanced incurable disease. Rehabilitation
studies in patients with cancer are at risk of selection bias as patients recruited may be more motivated, acknowledged by Uster (Uster et al., 2017). Three studies measured QoL, but overall evidence for improvement remained low. Cancer negatively affects QoL by many modalities; hence the necessity of a multi-modal approach in this patient group.

Results for nutritional parameters were variable and it was difficult to make comparisons, resulting in a very low rating of evidence. Weight is a key feature of cachexia and (as an outcome) is meaningful to both patients and clinicians (Solheim, 2018), but does not take in to account body composition. PG-SGA scores reflect changes in weight but also symptoms so may not reflect alterations in nutritional status alone. In addition, patients with incurable cancer are more likely to be at a ‘refractory’ stage of cachexia that is poorly responsive to treatment; thereby this level of evidence is unsurprising (Fearon et al., 2011). A further confounding factor is that of contamination, whereby the control group mimics the intervention. Both groups gained weight and improved hand grip strength (HGS) within Uster’s RCT, which may have contributed to lack of statistical significance (Uster et al., 2017).

Cancer rehabilitation trials are frequently limited by design and sample size, and high attrition rates are common (Hui et al., 2013). Recruitment issues were encountered in both RCTs; one cut short due to poor recruitment (Uster et al., 2017), the other recruiting just 17% of expected patients. In this RCT, 189 eligible patients were not approached and interviews with recruiting clinicians revealed reasons including: discomfort with the trial design; lack of confidence discussing prognosis; and anxieties about delivering the intervention at a hospice (Jones et al., 2013). Other barriers to recruitment include difficulties identifying participants (complex inclusion criteria) and high refusal rates (competing priorities, fear of randomisation to non-preferred arm, lack of acceptable control). Healthcare professional gatekeeping is when healthcare professionals prevent researchers from approaching eligible
patients or carers. This may be due to their fears of overburdening patients, lack of belief in research, or believing their patients are too unwell, stressed or distressed. They may also have a lack of faith in the intervention, or lack confidence discussing studies or prognosis. This type of gatekeeping can be one of the most difficult barriers to overcome when recruiting (Dunleavy et al., 2018) and almost certainly had an impact in the trial by Jones and colleagues. It has been noted however, that patients find symptom control trials beneficial irrespective of whether they obtain improvements in their symptoms (Middlemiss et al., 2015).

The findings presented here are worthy of comparison with other diseases. As outlined in chapter 1.3.2, the importance of exercise and nutritional intervention is acknowledged in established models of rehabilitation for non-malignant disease, including PR. Multi-modal interventions including exercise and nutritional supplementation have beneficial effects on body weight, exercise tolerance, physical activity, depression and survival in patients with COPD (van de Bool et al., 2017, Spruit et al., 2013). These observations provide further grounds for optimism that exercise and nutrition-based rehabilitation programmes in patients with incurable cancer are viable.

There is also a growing body of evidence for the use of new technologies in oncology trials such as physical activity monitors, which provide an objective measurement of patient activity in their usual environment (Maddocks and Granger, 2018).

There is now strong international consensus that cachexia is a multi-modal problem which requires multi-modal treatment (Fearon, 2008, Baracos et al., 2018). One of the challenges in cancer cachexia, however, is that the optimal endpoints are not clear and this appears similar in cancer rehabilitation studies where consensus on endpoints is not evident (Laird, 2018). Potential outcomes are numerous, though it is important that measures are validated and clinically meaningful (Gerber et al., 2017). GRADE discourages the use
of ‘surrogate outcomes’, which can result in downgrading of evidence for indirectness (Schünemann, 2013). The aforementioned difficulties in comparing trials, due to the clinical and methodological heterogeneity of interventions and outcomes, may be one reason for the slow growth of evidence in this field. There are inherent difficulties, however, performing clinical trials in a field where personalised care makes standardising interventions challenging (Gerber et al., 2017).

For patients with incurable cancer, concerns about nutrition, loss of function and increased dependency are commonplace. Loss of independence can compromise a person’s sense of dignity and fears of functional decline can surpass fears of impending death (Baile et al., 2011). As the population changes, with improvements in anti-cancer treatment and greater numbers of patients being treated under the umbrella of palliative care, there is the need to enable patients to live their lives as fully as possible, while minimising social-care costs. Such an approach, incorporating rehabilitation, places living before dying and is at the heart of palliative care (Tiberini R, 2015).

2.4.1. Limitations

The search strategy may have precluded relevant articles due to stringency of the search criteria. One such factor was exclusion of studies with ‘cancer survivors’. The definition of this term is very broad, from initial diagnosis to death, and may also include family, friends or caregivers (National_Cancer_Institute, 2006). Another limitation of this study was the heterogeneity of cancer types included in certain studies: for example cancers from grade two to four which may have greatly different prognoses (Chasen and Bhargava, 2010) and other studies not detailing cancer stage (Glare et al., 2011). Furthermore not all studies detailed the proportion of patients with cancer cachexia or nutritional baseline status.
Application of the GRADE criteria can be advantageous due to transparency of judgements about quality; however, limitations of the system (including its use for assessment of individual studies) are acknowledged (Guyatt et al., 2011b). A further challenge with GRADE is the complexity which can result in poor-to moderate inter-rater agreement (Hartling et al., 2012). Our GRADE checklist was designed to improve this, and though effective, it is not a validated tool. The lack of randomised control trials (two studies) meant that meta-analysis was not possible. However, use of the robustly validated GRADE system of analysis (Meader et al., 2014, Schünemann, 2013, Atkins et al., 2004) ensured that conclusions drawn were as accurate as possible.
Chapter 3. The ENeRgy trial: Methods

3.1. Introduction
The following chapter details the methodology of the ENeRgy trial. This chapter was published in Pilot and Feasibility Studies in 2018 (Hall et al., 2018) [Appendix 3].

3.2. Design
A randomised, unblinded feasibility trial of an exercise and nutritional rehabilitation programme (ENeRgy) versus standard care, in patients with incurable cancer was undertaken. Full ethical approval was obtained (17/WS/0226 [Appendix 4]) and the trial was conducted according to principles of Good Clinical Practice and the Declaration of Helsinki. The trial was conducted at a single centre (St Columba’s Hospice) serving a geographically-defined region in the UK (NHS Lothian - Edinburgh) with a population of approximately one million. Trial-related assessments took place within the hospice outpatient area.

The trial schematic is detailed in Figure 13.
Figure 13: Trial schematic
3.3. Participants

Eligible participants met the following criteria: ≥18 years of age; KPS ≥60; diagnosis of incurable cancer (defined as metastatic or locally advanced cancer not amenable to curative treatment); not undergoing anti-cancer therapy (though hormonal treatment or bisphosphonates were permitted) with a prognosis greater than three months (judged by referring clinician). Eligible participants were community dwelling, and required capacity to consent and the ability to complete trial based assessments and follow the trial protocol. Participants were identified and referred to the trial from St Columba’s or Marie Curie Edinburgh hospice community palliative care teams, or from the regional Oncology service.

Patients undergoing anti-cancer therapy (excluding hormone or bisphosphonate treatments), using enteral nutrition, unable to swallow or co-enrolled in drug trials were excluded.

Duration of participant involvement was ten weeks in total. Participants allocated to the control arm were able to participate in the eight-week rehabilitation programme following the conclusion of their study participation if they wished (wait-list control design).

The consent process was opt-in, and written informed consent was obtained by the trial research nurse or doctor. A computer-generated randomisation schedule was produced using a random block size to allocate participants in a 1:1 ratio to either the intervention arm (personalised exercise & nutrition regimen) or control arm (standard care) via sealed envelopes. Group allocation was revealed to the participants only after the baseline assessments were complete. The randomisation was stratified by KPS. The KPS scale allows patients to be classified as to their functional impairment. This can be used to assess the prognosis in individual patients and also assess the efficacy of different treatments. The lower the KPS score, the
worse the survival for most serious illnesses (Schag et al., 1984). Participants were stratified into different groups based on their KPS score due to its influence on prognosis to ensure that participants with differing prognoses were equally distributed between arms (KPS of 60-80% versus KPS 90-100%). Randomisation occurred at baseline (week 0) but was blinded to participants until week one when it was revealed by the research nurse so as not to influence baseline activity levels during baseline assessments.

3.4. Interventions

An eight-week intervention was chosen in order to be long enough to provide benefit for participants but not so long as to be overly burdensome or risk excessive rates of attrition in a potentially frail population of patients. Previous multi-modal RCTs have employed similar interventions ranging from six weeks (Solheim et al., 2017b) to 12 weeks (Uster et al., 2017).

The intervention arm was an exercise and nutritional rehabilitation programme. Participants allocated to this arm had an interview with the trial physiotherapist and dietitian at week one. This enabled the physiotherapist to ascertain physical ability and any contraindications to specific exercises, and the dietitian to ascertain baseline food habits using the 24-hour dietary recall method. Participants were then given instructions on the exercise and nutritional rehabilitation programme. Key components of this programme are depicted in Figure 14.
Figure 14: ENeRgy trial interventions
3.4.1. Exercise

A home-based exercise programme was prescribed, supported by a booklet. The exercise programme was developed by the trial lead Physiotherapist and modified following a previous feasibility trial (Solheim et al., 2017b) to enable all exercises to be undertaken at home without specialised equipment. There is evidence that both aerobic or resistance exercise regimens improve muscle strength as well as exercise regimens combining both types (Stene et al., 2013) but some suggestion that resistance exercise may improve muscle mass more than aerobic exercise (Courneya et al., 2007). This approach has further been validated by the ASCO interdisciplinary roundtable guidelines for cancer survivors, which states that “combined moderate intensity aerobic and resistance exercise performed on at least two to three times per week for at least 12 weeks results in improvements in health-related QoL both during and after treatment” and that “the benefit of combined aerobic plus resistance training programs appears more potent than programs consisting of only aerobic or resistance training” (Campbell et al., 2019, Sweegers et al., 2018).

The home exercise regimen consisted of aerobic and resistance exercise in divided sessions of the participant’s choosing. The aerobic component comprised a total of 60 minutes of physical activity over the course of each week at moderate intensity [i.e. feeling warm and getting slightly out of breath (able to talk)]. This is equivalent to an intensity of 3-4 rating of perceived exertion on a modified Borg Scale (Borg, 1982). Walking was recommended as the main type of physical activity, although cycling or more vocational forms of activity (e.g. heavy housework, gardening) could also be counted as long as they provoked the desired level of exertion. Aerobic exercise was recorded on trial diaries and checked by the trial research nurse or physiotherapist at weekly review clinic visits or by telephone.

The resistance exercise component involved exercises working the major muscle groups in the upper and lower body (e.g. half squats, standing press-
ups, shoulder press), guided by a booklet given to participants at week one. This booklet contained pictorial images of the exercises to be completed [Appendix 5]. Additional resistance was added where appropriate at the discretion of the physiotherapist at weekly review appointments. No specialist equipment was provided and additional resistance was provided utilising ONS bottles (220mL=220g) or 500mL bottles of water (=500g). Resistance exercises were recommended in three separate sessions per week. Participant diaries included reminders each week of the amount of resistance exercises to complete, and enabled participants to record the amounts of resistance and aerobic exercise taken daily and any difficulties with particular exercises [Appendix 5.1].

3.4.2. Nutrition

The main goal of the nutritional intervention was to promote energy balance and to ensure optimal nutritional intake. The nutritional component consisted of individual dietary counselling to enhance overall dietary intake (Solheim and Laird, 2012, Solheim et al., 2017b) as well as a prescription of Ω3 rich ONS with a target of two cartons per day.

Individual dietary counselling continued weekly throughout the trial, guided by the trial dietitian. Dietary advice was tailored and took into account any specific requirements e.g. ethnic background. Fortification advice was tailored to the individual by the dietitian, but included suggestions such as the use of full cream milk, drinking milk-based drinks with calorie rich snacks, avoiding low-fat and low-sugar products and enriching food and drinks with cream, butter, cheese, evaporated milk or sugar to maximise caloric intake. ONS prescriptions were introduced to the intervention arm using a titration regimen used effectively in a previous trial (Solheim et al., 2017b). During week one a total of 11 ONS were prescribed, with the goal of achieving the target dose of two ONS per day by day seven. As participants progressed through the trial, their prescription of ONS was reviewed on a weekly basis.
by the trial dietitian. Each 220mL ProSure® (Abbott Laboratories) carton contained 1g of EPA, 500mg DHA, 14.63grams of high biologic value protein and 280Kcal in total. The caloric distribution of this product is relevant for cancer patients experiencing unintended weight loss, with 61% of energy coming from carbohydrate, 21% from protein, and 18% from fat. Participants not able to tolerate the ONS due to personal preference were offered an alternative, ONS plus capsules containing 2g EPA. Participant information leaflets detailed various ways to take the ONS to improve compliance, and participant diaries recorded numbers of ONS taken daily. Where ONS were thought to be directly causing AEs, or causing symptoms, the prescription of ONS was amended by the trial dietitian and AEs were recorded accordingly.

At weekly review appointments, participant diaries were reviewed by the research nurse for healthcare-related resource use, and AEs relating to the trial interventions were screened for and logged. The trial dietitian reviewed the participants’ dietary intake and compliance with the ONS, and where necessary adjusted ONS prescription. The trial physiotherapist reviewed exercise progress, offered goal-setting, and prompted any changes needed to maintain compliance.

In previous trials, a cut-off to define feasibility has been used relating to adherence to trial interventions, for example >50% of components in >50% of participants (Solheim et al., 2017b). Solheim et al also regarded a ≥10% recruitment rate and an attrition rate of under 26% as feasible, citing previous literature from Stone and Hui (Stone et al., 2013, Hui et al., 2013). In the present trial it was decided that it would not be appropriate to set such limits, as no predefined feasibility limits are established for this type of trial or patient group as there are often high attrition rates. Adding feasibility levels for a bigger phase three trial may be necessary and one of the purposes of the phase two trial is to inform the design of the larger phase three trial.
3.4.3. Control

Having a control group was an important aspect of the design of the ENeRgy trial. This is because the design (randomised controlled) is of a higher quality (even unblinded) at the baseline than cohort trials which form the majority of evidence for similar trials in this field (Hall et al., 2019). In the past palliative care trials have been hampered due to poor recruitment from gatekeeping and fears of patients being randomised to the non-preferred (control) arm (Dunleavy et al., 2018). The ENeRgy trial therefore used a waiting list control design, so that patients randomised to the control arm would not feel disadvantaged and there may be less chance for contamination. Having the control arm allows inter-group comparison rather than just pre-post measurements as would be possible with a cohort study.

Participants randomised to the control arm continued to receive standard care from their GP and community palliative care teams according to individual need. This care could also include referral to other members of the community allied healthcare professional multidisciplinary team if required (e.g. counsellors, occupational therapist or social workers). The control arm participants were phoned at weekly intervals by the research nurse to ascertain levels of healthcare-related utility and AEs. In the control arm, participants were also given diaries to record any (non-trial) nutritional supplements they were taking, as well as the amount and type of exercise undertaken each week. This was to help gauge any degree of contamination in the control group [Appendix 5.2].

3.5. Outcomes and time points

The trial provided the opportunity for the use of novel outcome measures, rarely seen before in this patient population. For example, the use of a commercially available PAM (Fitbit® Flex 2). The use of real time activity measurement in this group of participants is a novel use of an emerging
technology and was used alongside the Life Space Assessment (LSA), a validated measure of a person’s movement within their own environment in the preceding four weeks (Peel et al., 2005). Both of these outcome measures assessed participant’s function within their own environments, rather than one-off volitional measurements such as hand grip strength (HGS). The usefulness of HGS as a surrogate outcome measure for physical function has been cast in to doubt following the findings of multi-centre cachexia trials (Temel et al., 2016).

3.5.1. Primary endpoints

The primary endpoint was to evaluate the feasibility of the trial and delivering the intervention (an exercise and nutritional rehabilitation programme) in a hospice outpatient context. It was assessed by measuring compliance with the rehabilitation programme (numbers of exercises and nutritional supplements versus those advised). Compliance with trial procedures was also measured, including completion of diaries & questionnaires, percentage withdrawal, completion of physical tests and completeness of physical activity monitor data.

3.5.2. Secondary endpoints

Secondary (exploratory) endpoints examined the feasibility of recruitment and retention, evidence of contamination in the control group and changes in physical function and nutritional status. QoL measures for participants (+ partner-carers) and impact on participant healthcare-related resource use in terms of cost between sectors of the NHS, social services, third sector, participant expenses and carer costs were also examined, however health-economic evaluation is beyond the scope of this thesis. All endpoints were assessed at trial baseline (pre-randomisation– week zero), midpoint (week five) and endpoint (week nine). Survival data were gathered for all participants entering the trial. Data collection ended at week ten. Although
the intervention was offered to the control group at week ten, this was outwith the trial and no data were recorded. A summary of trial-related assessments and time points is shown in Table 4.
**Table 4: Trial related assessments and time points for both arms**

<table>
<thead>
<tr>
<th>Measures</th>
<th>Baseline Measures (week 0)</th>
<th>Midpoint (week 5)</th>
<th>Endpoint (week 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Gender, primary tumour site &amp; tumour status; metastatic sites; current hormone/ bisphosphonate or steroid treatment.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Physical Measures:</td>
<td>Height</td>
<td>Weight</td>
<td>Weight</td>
</tr>
<tr>
<td>Quality of Life Measures:</td>
<td>Participant QOL (EORTC QLQ-C15-PAL questionnaire) (Groenvold et al., 2006)</td>
<td>Participant QOL (EORTC QLQ-C15-PAL)</td>
<td>Participant QOL (EORTC QLQ-C15-PAL)</td>
</tr>
<tr>
<td></td>
<td>Partner-Carer QOL* (Caregiver Quality of Life Index- Cancer Questionnaire (CQOLC) (Weitzner et al., 1999)</td>
<td>Partner-Carer QOL* (CQOLC)</td>
<td>Partner-Carer QOL* (CQOLC)</td>
</tr>
<tr>
<td></td>
<td>EQ-5D-5L &amp; EQ-VAS (Foundation, 2017) questionnaires</td>
<td>EQ-5D-5L &amp; EQ-VAS questionnaires</td>
<td>EQ-5D-5L &amp; EQ-VAS questionnaires</td>
</tr>
<tr>
<td>Functional Measures:</td>
<td>Karnofsky Performance Status (KPS) (Mor et al., 1984) Life Space Assessment questionnaire (LSA) (Peel et al., 2005)</td>
<td>KPS Two minute walk test Timed Up and go test</td>
<td>KPS Two minute walk test Timed up and go test</td>
</tr>
<tr>
<td></td>
<td>Two Minute Walk Test (Bohannon et al., 2015) Timed Up and Go Test (Podsiadlo and Richardson, 1991)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Socio-Economic Measures:</td>
<td>Socio-economic background: (employment status, benefits received, carer responsibilities, current use of social services) Healthcare utilisation and expenses questionnaire</td>
<td>Healthcare utilisation and expenses questionnaire</td>
<td>Healthcare utilisation and expenses questionnaire</td>
</tr>
<tr>
<td>Physical Activity Monitor:</td>
<td>PAM worn continuously for 7 days** (data retrieved at week 1) Mean daily step count Hours asleep/ restless/ awake per night</td>
<td>(PAM worn only at baseline and end point)</td>
<td>PAM worn continuously for 7 days** (data retrieved at week 10) Mean daily step count Hours asleep/ restless/ awake per night</td>
</tr>
<tr>
<td>Nutritional Measures:</td>
<td>Abridged Patient-Generated Subjective Global Assessment (aPG-SGA) (Vigano et al., 2014) Ten point verbal analogue scale (AveS) (Thibault et al., 2009)</td>
<td>aPG-SGA AveS</td>
<td>aPG-SGA AveS</td>
</tr>
</tbody>
</table>

**Partner-carer** was a partner with whom the participant was married, cohabiting or non-cohabiting, and the participant also described as their carer.

**PAM data for weekend and part complete days (eg. date of issue and return) were excluded.
3.6. Statistical considerations

The primary endpoint of this study was to assess the feasibility of the trial (an exercise and nutritional rehabilitation programme). As such a formal sample size calculation was not performed. The recruitment plan was to recruit for 13 months and aim to obtain at least 40 participants to enable adequate numbers to assess feasibility. During 2015 a total of 1311 patients were seen by the two trial centres (661 at Marie Curie and 650 at St Columba’s). The assumption was that if a similar number of patients were seen during the study period then the target of 40 patients would represent only 3% of the population at these two centres which would be achievable.

An intention-to-treat analysis was performed. The primary endpoints are presented descriptively in chapter four using appropriate summary statistics (with corresponding confidence intervals or inter-quartile ranges [IQR]). Demographic statistics and secondary (exploratory) endpoints were presented using appropriate summary split by treatment arm. Continuous outcome measures, e.g. change in daily step count/change in weight, were compared between arms using non-parametric tests, as these are applicable to both normally and abnormally distributed data, of which there were a mix. Rates of compliance are reported along with completion rates for all other outcome measures. This feasibility trial was not powered to explore treatment efficacy but these estimates of variability will be used to inform the sample size and choice of primary endpoint for a future phase three trial. No interim analysis was performed while recruitment was on-going or before follow-up was completed.
3.7. Other considerations

3.7.1. Data collection

Paper case report forms (pCRF) were used and data were entered directly into an electronic data base (Microsoft Access). A 10% check was undertaken on all inputted data to ensure validity. Participants were identified by a unique trial identification number, and participant identifiable data was kept locked securely within the hospice. Standard operating procedures (SOPs) issued by the trial sponsor (ACCORD/NHS Lothian) were adhered to [e.g. reporting deviations from the protocol, AEs or Serious Adverse Events (SAEs)].

3.7.2. Trial management, patient and public involvement

Management of the trial was overseen by a Trial Management Group (TMG) which met on a three monthly basis during the trial. The TMG consisted of the following people whose roles are detailed below:

The principal investigators (Dr Laird and Professor Fallon), had overall responsibility for the trial. Their roles included liaising with trial funders (Marie Curie UK and Chief Scientist Office) on trial progress and ensuring that the trial team was appropriately managed. The research fellow (myself) and trial manager (Lucy Norris) from the University of Edinburgh, Edinburgh Palliative and Supportive Care (EPAS) would also provide updates at TMG meetings.

One of my roles as research fellow in collaboration with the EPAS trial manager was to ensure that the trial was conducted in accordance with NHS Lothian Academic and Clinical Centre for Research and Development (ACCORD) governance processes. This ranged from ensuring that the trial protocol was written according to the ACCORD template for non-CTIMP trials to ensuring that AEs and SAEs were recorded in a timely fashion. I liaised with the research and ethics committee (REC) and reported progress back to the TMG. I registered the trial with the international clinical trials portfolio (clinicaltrials.gov NCT03316157) and progress updated as the trial progressed. My role was also to oversee the day-to-day running of the trial.
As well as the Edinburgh Trial Manager the TMG received guidance from another Trial Manager (Liz Dixon) at the Southampton Clinical Trials unit (SCTU). Liz was able to review processes (mainly around the trial set up) and advise regarding logistics of the trial from an objective and impartial point of view. This collaboration was important also as the future phase three ENeRgise trial will include oversight and management from the SCTU.

The TMG included research leads from collaborating hospices in Edinburgh (Anne Finucane) and Glasgow (Emma Carduff) who were able to bring any updates from their own sites and discuss logistics of recruiting trial patients from these sites. Although the trial was not recruiting from Glasgow, it was helpful to have representation from there as the future phase three trial plans to include this site.

The TMG included key St Columba’s Hospice stakeholders- in particular the research lead (Erna Haraldsdottir) and medical director (Duncan Brown). They were able to feedback directly on trial progress to the CEO of the hospice and the hospice board of governors and were able to discuss any trial site issues or concerns.

The lead physiotherapist (Matthew Maddocks) from the Cicely Saunders Institute, London was included in the TMG meetings and the trial team were able to feedback on specifics of the exercise regimen, as well as ask for advice in relation to managing the patients’ exercise goals and delivery of the physical exercise aspects of the trial.

The TMG meetings were often led with updates from the research fellow, research nurse, dietitian and trial research volunteers. The research volunteers were initially involved to help with the smooth running of the trial but over time it became apparent that their views were helpful as an extension to the patient and public involvement (PPI) representatives. Over time the roles of the research volunteers adapted and became more complex.

There was also presence at the TMG from the affiliated health economists from the School of Medicine and Veterinary Medicine, Edinburgh Cancer
Research UK (Katharina Diernberger and Peter Hall) who oversaw the health economic aspects of the trial (out with the scope of this thesis).

The trial statisticians were invited to take part in the TMG meetings (Catriona Graham and Sharon tuck) from the Epidemiology and Statistics Core, Edinburgh Clinical Research Facility, University of Edinburgh. They were heavily involved in the design of the pCRFs for the trial and gave oversight on the trial statistical analysis, which was run by Dr Laird and myself.

Importantly, the trial involved two PPI representatives from an early stage in the development of the trial documents and also throughout the trial. One representative came from Marie Curie’s ‘Expert Voices’ PPI group, and the other was an ex-carer of a cancer survivor, known to the PIs of the trial. The PPI representatives inputted into the design and checking of initial participant-facing trial documents including the Participant information sheet (PIS) and gave us patient and family feedback as to the importance and meaning of the trial from their perspectives and experience.

3.7.3. Research volunteers

To facilitate the smooth running of the trial clinics and to improve participant experience, the hospice advertised two positions for research volunteers. In 2013, Hospice UK advocated a role for volunteers in hospice based research (Payne, 2013). In the UK, there are as many as 125,000 hospice volunteers, and their contribution reduces hospice costs by an estimated £200 million per year (HospiceUK, 2020), however there is limited evidence for their potential role in research. Research volunteers have been previously documented as having logistical roles such as transporting trial medication (Dunleavy et al., 2011) and also administrative roles such as assisting with statistical analysis (Payne, 2013). We decided to utilise the skills of our research volunteers for the ENeRgy trial in a novel way.

A person specification and interview process was led by the trial research nurse, in collaboration with the volunteer managers at the hospice and many
volunteers applied. Two volunteers were appointed to assist for the duration of the project, both with a background in healthcare. The trial volunteer role was initially developed to meet and greet participants involved in the trial, and to facilitate their movement between rooms at the outpatient review clinics, organise taxis and arrange refreshments. Over time it became clear that the research volunteers were more than capable of performing these roles and were keen to take on more responsibilities. They were given training and were latterly also able to assist with some of the more technical elements of the trial including (supervised) measurements, e.g. timing and measurements of physical tests, participant height and weight, and helping to gather certain elements of weekly review data (such as reviewing diaries with participants prior to these being checked formally by the trial researchers).
Chapter 4. Results: ENeRgy trial primary endpoints

4.1. Introduction

As discussed in chapter one, the key aim of the ENeRgy trial was to assess the feasibility of a trial to undertake an eight-week combined exercise and nutritional rehabilitation programme for outpatients with incurable cancer. Chapter four now details the results of the primary endpoints including compliance with the rehabilitation programme (numbers of exercises and nutritional supplements versus those advised). Compliance with trial procedures is also presented, including completion of diaries & questionnaires, percentage withdrawal, completion of physical tests and completeness of PAM data. Results of the primary and secondary endpoints were published in the Journal of Cachexia, Sarcopenia and Muscle in 2021 (Hall et al., 2021) [Appendix 6].

4.2. Population

4.2.1. Demographics

There were a greater number of participants in the KPS 60-80 group than the KPS 90-100 group in both arms of the trial. Participants recruited to intervention and control arms had mean ages of 71yrs and 76yrs respectively and the median age was 75yrs in both groups. Over all the median age was 78yrs for all participants. Males outnumbered females in intervention and control arms (61% and 55%, respectively). Of participants who identified their partner as their carer, all carers in the intervention arm, and all but one in the control, agreed to participate in the trial.

There was a higher proportion of gastrointestinal cancers in the intervention arm than the control arm, and there were more breast and urological/
gynaecological cancers in the control arm. Otherwise, there was a relatively even spread of cancer types between arms considering the small sample size. There was an even mix in both arms of loco-regionally advanced and metastatic disease.

Both arms of the trial included participants who had lost weight (based on own estimated weight from aPG-SGA results) in the six months leading up to the trial. The mean (SD) BMI for the entire study population was 25.7 (6.1); this was lower at 24.2 (5.8) for the intervention arm than the control arm at 27.2 (6.2). At baseline, median weight loss in the previous 6 months was 5% (IQR -12% to 0%). The demographics of the study population are shown in Table 5.
Table 5: Participant demographics

<table>
<thead>
<tr>
<th></th>
<th>Intervention Arm (n=23)</th>
<th>Control Arm (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Age &lt;55/55-65/&gt;65</td>
<td>6/3/14</td>
<td>26/13/61</td>
</tr>
<tr>
<td>Male gender</td>
<td>14</td>
<td>61</td>
</tr>
<tr>
<td>Primary Cancer</td>
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<td></td>
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<tr>
<td>Gastrointestinal*</td>
<td>12</td>
<td>52</td>
</tr>
<tr>
<td>Thoracic</td>
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<td>4</td>
</tr>
<tr>
<td>Breast</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Urological/Gyn**</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Myeloma</td>
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<td>9</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Other: (Endocrine)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Cancer Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loco-regional</td>
<td>8</td>
<td>35</td>
</tr>
<tr>
<td>Metastatic</td>
<td>15</td>
<td>65</td>
</tr>
<tr>
<td>Current Cancer Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormonal</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Bisphosphonate</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Steroids</td>
<td>6</td>
<td>26</td>
</tr>
<tr>
<td>Performance Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-80%</td>
<td>15</td>
<td>65</td>
</tr>
<tr>
<td>90-100%</td>
<td>8</td>
<td>35</td>
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<tr>
<td>Body Mass Index</td>
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<tr>
<td>&lt;18.5</td>
<td>4</td>
<td>17</td>
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<tr>
<td>18.5-25</td>
<td>9</td>
<td>39</td>
</tr>
<tr>
<td>25.1-30</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>&gt;30.1</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Weight change at baseline (&lt;1 month)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gained</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Loss 0-5%</td>
<td>18</td>
<td>78</td>
</tr>
<tr>
<td>Loss &gt;5%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Weight change at baseline (&lt;6 months)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gained</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Loss 0-5%</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td>Loss &gt;5%</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>17</td>
</tr>
</tbody>
</table>

* Gastrointestinal (includes oesophageal/ pancreatic/ liver/ colo-rectal cancers)
** Urological/ gyn (includes bladder/ gynaecological/ prostatic/ renal and testicular cancers)
* Perceived weight change in previous 1 month (from aPG-SGA)
** Perceived weight change in previous 6 months (from aPG-SGA)
4.3. Compliance with trial interventions

Compliance with prescribed trial interventions was very high for the intervention arm over the whole trial. More than three quarters of all participants were able to comply with >80% of prescribed interventions. Median compliance levels for prescribed interventions across the whole trial (ONS, resistance and aerobic exercise) are presented in Table 6.
Table 6: Median compliance: intervention arm components

<table>
<thead>
<tr>
<th>Compliance with individual intervention components</th>
<th>Withdrew following consent</th>
<th>&lt;50%</th>
<th>&gt;50%</th>
<th>&gt;80%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>ONS (n=23)*</td>
<td>2 (5)</td>
<td>1 (9)</td>
<td>4 (19)</td>
<td>16 (76)</td>
</tr>
<tr>
<td>Resistance (n=23)*</td>
<td>2 (5)</td>
<td>1 (5)</td>
<td>3 (14)</td>
<td>17 (81)</td>
</tr>
<tr>
<td>Aerobic (n=23)*</td>
<td>2 (5)</td>
<td>1 (5)</td>
<td>2 (10)</td>
<td>18 (86)</td>
</tr>
<tr>
<td>Compliance with combined intervention components</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;50%</td>
<td>&gt;50%</td>
<td>&gt;80%</td>
<td></td>
</tr>
<tr>
<td>Aerobic Resistance</td>
<td>1 (5)</td>
<td>4 (19)</td>
<td>16 (76)</td>
<td></td>
</tr>
<tr>
<td>Aerobic ONS</td>
<td>1 (5)</td>
<td>6 (29)</td>
<td>14 (67)</td>
<td></td>
</tr>
<tr>
<td>Resistance ONS</td>
<td>1 (5)</td>
<td>7 (33)</td>
<td>13 (62)</td>
<td></td>
</tr>
<tr>
<td>Aerobic Resistance ONS</td>
<td>1 (5)</td>
<td>8 (38)</td>
<td>12 (57)</td>
<td></td>
</tr>
</tbody>
</table>

*Two participants withdrew from the trial post-randomisation
4.3.1. Oral nutritional supplements

Two participants did not start the trial ONS as they withdrew at week one (one due to deteriorating health and the other due to travelling abroad and not returning to the trial). The following calculations (for compliance) are therefore based on the 21 participants who had ONS prescriptions.

ONS prescriptions were introduced to the intervention group using a titration regimen of 11 supplements in week one and 14 from week two.

Nine participants in the intervention group (43%) managed the full prescription of two ONS per day for the entire study without AEs. One participant (5%) took the full prescription of two ONS per day for the duration of the trial but reported an increase in flatulence. This symptom was mild and the participant did not wish to reduce the prescription, but this was nonetheless recorded as an AE related to the ONS.

Three participants (14%) were unable to take the full prescription of ONS due to tolerance issues relating to their underlying condition; as such these were not recorded as AEs. One participant had longstanding early satiety and managed eight of their week one supplements but then withdrew at week two due to deteriorating health. One participant had longstanding nausea and took just one ONS during week one and then none in week two in spite of dietetic advice on how to minimise this symptom. This participant withdrew soon after because they left the country in search of alternative treatments. The third participant became acutely unwell due to their disease and tried to continue with the prescribed ONS dose, but was unable due to an acute change in taste and the ONS became unpalatable (too sweet). This participant died two weeks later from a sudden (cancer-related) event.

One participant did not have ONS prescribed until week seven. This participant declared at week one after enrolment that her Oncologist had
advised her to avoid soy-containing products (which Prosure® is). This was due to potential adverse effects on oestrogen levels (the participant was on oestrogen-blocking hormonal treatment for breast cancer). This participant declined to take the omega three capsules due to their size. She took advice from her oncologist and was eventually started on an alternative (non Ω-3 containing) ONS (Ensure Plus Juce®) at week seven but took these for just one week then declined to take further ONS. Her dietetic input therefore consisted of dietetic advice on fortification for the majority of her time in the trial.

Six participants (26%) had their weekly prescription of ONS reduced at the discretion of the dietitian, due to AEs relating to the product. Four participants had five AEs: all of which resolved with dose reductions. Four AEs were due to flatulence (including one participant with a stoma whose bag was filling rapidly) and one was due to nausea. In all cases, symptoms resolved with a reduction in ONS prescription to one carton per day. In one case, the ONS prescription was reduced to one daily for one week with an improvement in symptoms, however a trial of one and a half ONS per day resulted in a recurrence of symptoms. The dose therefore remained at one per day for the remainder of the trial and the participant completed the intervention.

The remaining two participants had AEs which did not resolve with dose reductions: one described persistent nausea and the other described increased flatulence with increased stool frequency. Both participants withdrew from the trial soon after dose reductions (at week six) due to deteriorating health.

One participant requested to stop the ONS at week three rather than trial a dose reduction. This participant had been experiencing an increased frequency of stool from his stoma and preferred to stop the ONS due to significant anxiety around his stoma bag bursting. This participant stopped taking the ONS at week three and was also referred to the community stoma
nurse. His symptoms improved, as did his anxiety regarding stoma management, and he continued on to complete the trial. Of note, due to his stoma concerns, this participant had significantly reduced oral dietary intake. Using the 24-hour recall method, the trial dietitian was quickly able to establish this and offer dietary fortification advice to optimise his caloric intake. A histogram illustrating ONS outcomes for participants in the intervention arm can be seen in Figure 15.
Figure 15: Intervention arm oral nutritional supplement outcomes
4.3.2. Aerobic exercise

All participants were advised to undertake a minimum of 60 minutes of aerobic exercise per week, in divided sessions of their choosing with a minimum of ten minutes per session. This prescription was the same for all participants in the intervention arm. Compliance with the aerobic exercise component was high: 86% of participants in the treatment arm achieved at least 60 minutes of aerobic exercise per week.

The most commonly cited reason for not achieving 60 minutes of aerobic exercise per week was fatigue, followed by lack of motivation, then pain or other symptoms (often reported as participants feeling ‘too unwell’). Where ‘other’ was cited reasons included: 1) anaemia 2) misunderstanding of instructions, 3) lack of confidence walking and 4) too hot (i.e. climate) to exercise.

Where fewer than 60 minutes of aerobic exercise were recorded, reasons for this are illustrated in Figure 16.
Figure 16: Reasons for not managing prescribed aerobic exercise
4.3.3. Resistance exercise

Participants were given individualised resistance exercise prescriptions each week from a total of eight different exercises detailed in the participant take-home exercise leaflet [Appendix 5]. According to the individual’s ability, up to three sets of eight different resistance exercises (maximum 24) were prescribed weekly. Participants were instructed to record in their trial diaries [Appendix 5.1] how many types of prescribed exercise they were able to manage per workout (not numbers of individual repetitions done) in order to identify any exercises which caused particular difficulties.

Compliance with resistance exercise prescription was high as shown in Table 6 (page 104), with 17 of 21 (81%) participants completing a median of >80% resistance exercises prescribed over the whole trial.

Where the prescription of resistance exercise was not met, reasons are illustrated in Figure 17. The most commonly cited reason was fatigue, followed by pain and lack of motivation. In many cases, multiple reasons were cited by participants for not completing prescribed exercises. Fatigue and a lack of motivation were commonly cited together as reasons for not being able to manage prescribed aerobic or resistance exercises in the intervention arm.

Two participants reported they were unable to manage a particular exercise: one reported the ‘step ups’ were too challenging and the other participant reported being unable to complete the ‘half squats’ (or any of the leg exercises) due to generalised leg weakness. There were no particular exercises which were consistently reported as being too difficult to undertake by participants.
Figure 17: Reasons for not managing prescribed resistance exercise
4.4. Compliance with trial procedures

4.4.1. Questionnaires

Participants were informed in advance of weeks they were due for physical tests and questionnaires and that they would be needed for a longer time at the clinic. There were no cases of participants declining to complete questionnaires on the day that they were due for assessments.

Twenty-one carers completed a total of 46 CQOLC questionnaires. The question most commonly left unanswered was question four, “I am satisfied with my sex life” (33% unanswered) followed by questions seven and 34: “I am concerned about our insurance coverage”; and “I am satisfied with the support I get from my family”, respectively. Both of these questions were unanswered in 7% of questionnaires.

4.4.2. Physical testing

Participants were asked to complete a timed up and go (TUG) and a two minute walk test (TMWT) at weeks zero, five and nine as part of the intervention and control arms.

Of 107 TUG tests, 105 were completed (98%). Two were not attempted, one due to fatigue (this was also the case for the TMWT for this participant) and the other because the participant was a hospice inpatient at the time of the assessment and only able to complete the questionnaire sections.

For the TMWT, of 108 tests recorded, 95 tests were completed (88%) i.e. participants walked for two minutes. Two participants did not start the test: one participant was a hospice inpatient, the other (as above) was too fatigued. Eleven started the test but did not complete it for reasons illustrated in Figure 18.
Figure 18: Reasons two minute walk test was not completed

*Other comprised one participant who felt dizzy as she was not wearing glasses
4.4.3. Completeness of physical activity monitor data

PAM measurements were complete (i.e. full steps and sleep data at baseline and endpoint assessments) in 21 of 29 participants (72%) who completed the trial and for 100% of 16 baseline measurements for participants who subsequently withdrew. Overall, of the 45 participants enrolled, there was 82% complete PAM data.

Seventy-three individual PAM data files were collected from all participants (45 baseline measurements and 28 endpoint). At the time of returning a PAM, issues with the monitor were documented. There were 24 recorded issues categorised as either participant- or device-related. Of note, participant problems (such as reinserting the sensor upside down after charging) did not necessarily impact on the data retrieved from the PAM.

Fifteen issues relating to the participant were registered and nine issues relating to the device were registered, see Figures 19 & 20.
*In cases where participants forgot to charge the monitor: one participant’s PAM had recorded no data (steps or sleep), but in the other two participants there were full data for seven days.

The manufacturer indicated that battery life = five days, hence our request to participants to charge it at the weekend. Where PAMs were lost during the assessment week they were both eventually returned at a later date and data recovered (albeit incomplete).
Where PAM data were incomplete for sleep but step data were present, reasons included: one participant who had problems removing the bracelet due to lymphoedema (two days of sleep data missing), three participants who wore the bracelet for more than the specified week or wore it for one week but returned it at a later date. In this instance, steps were stored in the memory but all sleep data were erased. There were two instances where all sleep data were lost but the reason was unclear. Of note, this was the same participant at baseline and endpoint with different monitors, so it was more likely to be participant-related (e.g. removing the bracelet at night time).

**Where PAM data were incomplete with missing steps and sleep data, reasons included: one participant who lost the PAM after two days and one participant who reinserted the sensor incorrectly.
***In the instance where no data (sleep or steps) were recorded the participant admitted they had forgotten to charge the PAM.

****Other was one participant who mobilised with a four wheeled walker and had consistently low step counts for both weeks of monitoring, inconsistent with the levels of activity she was reporting.
Chapter 5. Results: ENeRgy trial secondary endpoints

5.1. Introduction

As well as the primary (feasibility) outcomes described in chapter four, secondary (exploratory) outcomes of the ENeRgy trial are reported in chapter five. These include the feasibility of recruitment and retention, evidence of contamination in the control arm and changes in physical function and nutritional status. QoL measures for participants, partner-carers and survival are also discussed. All endpoints were assessed at baseline (week 0) midpoint (week 5) and at trial endpoint (week 9). Tests of change compared baseline and endpoint measurements. This chapter also contains details of any AEs and SAEs and impact on survival.

5.2. Feasibility of recruitment and retention

5.2.1. Screening and referral sources

Over the course of the recruitment period, 121 potential participants were entered into the screening log. Participants were identified by various means. As well as recruiting teams referring participants (all Lothian based Community Palliative Care Teams (CPCT) and the tertiary Oncology centre), all new hospice referrals were also screened for eligibility to avoid potential participants being missed. Numbers of participants identified by different methods, as well as numbers entering the trial from each source are detailed in Table 7 and illustrated in Figure 21.
Table 7: Referral sources, numbers and participants entering the trial

<table>
<thead>
<tr>
<th>Referral Source</th>
<th>Number of referrals identified (n)</th>
<th>Number entering the trial per referral source (n)</th>
<th>Percentage recruitment per source (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening of all hospice new referrals</td>
<td>52</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>St Columba’s Hospice In Patient Unit (IPU)</td>
<td>5</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>St Columba’s Hospice Day Therapies</td>
<td>6</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>St Columba’s Hospice CPCT</td>
<td>27</td>
<td>15</td>
<td>56</td>
</tr>
<tr>
<td>East Lothian CPCT</td>
<td>9</td>
<td>4</td>
<td>44</td>
</tr>
<tr>
<td>Marie Curie Hospice CPCT</td>
<td>3</td>
<td>2</td>
<td>67</td>
</tr>
<tr>
<td>West Lothian CPCT</td>
<td>4</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>Pain Clinic (Western General Hospital)</td>
<td>8</td>
<td>7</td>
<td>88</td>
</tr>
<tr>
<td>Oncology (Western General Hospital)</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Referred after completion of other trial (Western General Hospital)</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
</tbody>
</table>
Figure 21: Referrals and recruitment to the ENeRgy trial
Of 121 potential participants, the trial was discussed with 92 (76%). There were 29 potential participants with whom the trial was not discussed. Reasons for this included:

- Three due to investigator decisions: one was attending a regular exercise class (potential for contamination in the control arm); one person’s community psychiatric nurse (CPN) felt they needed social support; and one person had Asperger’s and their CPN advised that they would not manage the intervention regimen.

- Twenty were ineligible on closer examination of their records due to: KPS<60 (6), prognosis <3 months (6), unable to complete assessments (4), unable to comply (8), unwilling to attend for trial assessments (1), undergoing anti-cancer therapy (6) and co-enrolment in drug trials (1). (Note, some participants were ineligible for multiple reasons).

- Six were not approached for ‘other’ reasons: two died, three were not contactable, and one person opted to attend the hospice day therapies centre in preference to starting the trial.

The population of patients who were not suitable for the trial does reflect the usual population of palliative cancer patients, which ranges from those at the early stages close to diagnosis, to those who are referred at a late stage in their disease trajectory: and those not suitable largely fell in to this category. Although it is now advocated that patients are referred to palliative care from early in their disease trajectory, even at diagnosis (Ferrell et al., 2017), the majority of patients are still referred at a later stage when prognosis is often short and at a stage when they are functionally very frail. This is partly due to clinician’s broader understanding of the role of palliative care- some still perceive that our role is management of the ‘end of life’. It is also due to the fact that there are not enough palliative care specialists to be involved with all
patients with a terminal diagnosis. For services with limited numbers of specialists, there is a degree of ‘gatekeeping’ in to their service ie. only seeing those patients ‘complex enough’ to need specialist palliative care input, which can lead to clinicians referring patients only at a very late stage when their (often very capable) generalist palliative care skills are exhausted.

Of the 92 people approached about the trial:

- Forty-five (49%) were recruited, 9 (10%) were ineligible, 32 (35%) declined, 1 (1%) was not recruited due to an investigator decision and 5 (5%) for other reasons.

Reasons for declining to enter the ENeRgy trial were most often due to the time commitment, which is understandable for a population of patients who may have a limited prognosis and increasing symptom burden (such as fatigue, pain, low mood). Indeed the second and third most common reasons cited for not enrolling were fatigue/ other/ no reason given, travel distance and feeling too unwell.

Reasons for participants declining to take part are shown in Figure 22.
Figure 22: Reasons people declined to participate
5.2.2. Recruitment

The trial opened to recruitment on 30th January 2018 with the initial target of recruiting 40 participants in 13 months by the end of February 2019. A goal of 40 participants was set to enable feasibility endpoints to be ascertained. At TMG meeting number seven on 15th January 2019, following analysis of recruitment rates versus targets, it was decided that an extension to recruitment was appropriate to 24th April 2019 (15 months in total). At that time there had been a drop in recruitment over the Christmas period (32 recruited at that stage). Prior to Christmas, the trial had been recruiting to target. A no-cost extension was agreed by the TMG group, with the hope that recruitment rates would improve in the New Year and the target participant number would be achieved.

As anticipated, recruitment to the study improved in January 2019 and the total number of participants recruited to the study by the end of recruitment (24th April 2019) was 45 of 121 screened (recruitment rate of 37%). Cumulative recruitment versus target is shown in Figure 23.

It is acknowledged that recruitment at the trial site exceeded recruitment at the other sites and reasons for this are discussed in chapter 6.5.2 along with implications for a larger multi-centre trial.
Figure 23: Cumulative versus target recruitment
5.2.3. Attrition

Twenty-nine participants completed the trial. The overall attrition rate from the trial was 36% (16 of 45 participants enrolled). There was a higher rate of attrition in the control arm (41%) than the intervention arm (30%).

Reasons for attrition are outlined in Figure 24, the majority (12 cases, 75%) were due to deteriorating health.

Figure 25 details the trial profile from screening to enrolment to trial completion.
Figure 24: Reasons for withdrawal from the ENeRgy trial

*‘Other’ reasons included one participant who travelled abroad to seek alternative treatments, and one participant who left the country on holiday and did not return.
Figure 25: Consort diagram: the ENeRgy trial
5.3. Contamination

Evidence of contamination was ascertained by collecting records of any (non-trial) supplements disclosed by participants in their trial diaries. Five participants in the treatment arm (22%) and five participants in the control arm (23%) were taking ONS at the point of enrolment into the trial. Four participants in the treatment arm switched to the trial ONS for the duration of the trial and one continued to take a supplement (Complan®) alongside the trial ONS.

In the control arm there was one participant who started taking ONS (external to the trial) one week after enrolment, and another who changed their ONS prescription from one to two types one week after enrolment. Details of the types of ONS can be seen in Table 8.

Amounts of aerobic exercise reported weekly by the treatment and the control arms showed that there was a higher mean (and median) number of minutes aerobic exercise per week in the control arm. The difference was not significant; however, this does suggest that those in the control arm were undertaking a lot of aerobic exercise [Table 9]. Comparative step data between the two arms are described in chapter 5.4.
### Table 8: Additional oral nutritional supplements taken by participants

<table>
<thead>
<tr>
<th>Intervention Arm</th>
<th>N</th>
<th>Dose</th>
<th>Control Arm</th>
<th>N</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure Plus Juce®</td>
<td>1</td>
<td>Unknown</td>
<td>Ensure Plus Juce®</td>
<td>1</td>
<td>1 per day</td>
</tr>
<tr>
<td>Fortijuce®</td>
<td>1</td>
<td>1 per day</td>
<td>Ensure®</td>
<td>1</td>
<td>1 per day</td>
</tr>
<tr>
<td>Fortisip®</td>
<td>1</td>
<td>1 per day</td>
<td>Fortisip®</td>
<td>1</td>
<td>100mL/ day</td>
</tr>
<tr>
<td>Type Unknown</td>
<td>1</td>
<td>Unknown</td>
<td>Ensure Compact®</td>
<td>1</td>
<td>2 per day</td>
</tr>
<tr>
<td>Complan®*</td>
<td>1</td>
<td>Unknown</td>
<td>Ensure Plus Fibre®</td>
<td>1</td>
<td>2 per day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Complan® plus Ensure®</td>
<td>1</td>
<td>3 per day</td>
</tr>
</tbody>
</table>

Clear cells indicate ONS taken by participants at the outset of the trial.
Brown denotes a participant who was unable to tolerate the trial ONS due to soy content and was prescribed this mid-trial by their oncologist.
Green denotes a patient who started taking ONS one week after enrolment.
Blue denotes a patient in the control arm who increased their ONS prescription from Complan® alone, to Complan® plus Ensure® one week after enrolment.

*Denotes a participant who continued to take Complan® alongside trial supplements for the duration of the intervention.
Table 9: Aerobic exercise comparison between intervention and arms

<table>
<thead>
<tr>
<th>Intervention Arm</th>
<th>Control Arm</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) Minutes per week</td>
<td>Median (IQR) Minutes per week</td>
<td>Mean (SD) Minutes per week</td>
</tr>
<tr>
<td>153 (237)</td>
<td>90 (66-141)</td>
<td>197 (167)</td>
</tr>
</tbody>
</table>

*Mann Whitney U-Test
5.4. Impact on physical function

Physical function was measured in terms of step count (baseline and endpoint), TUG, TMWT, LSA and KPS (measured at baseline, midpoint and endpoint). Steps were calculated by taking the values of steps on days where the PAM was worn all day, therefore excluding Wednesdays (day of PAM issue) and weekend days (due to the need to charge the PAM at the weekend and weekend variation in activity levels). Where data were missing for a particular day, mean weekly steps were re-calculated by dividing total steps by number of days full step data were recorded.

Table 10 details the median [IQR] for steps, TUG, TMWT and LSA between arms of the trial, as well as statistical significance comparing change between baseline and endpoint scores.

Change in participant baseline and endpoint measurements per arm for mean step count, TUG and TMWT times are illustrated as waterfall plots in Figures 26, 27 and 28.

There were no trends or significant differences in KPS scores from baseline to endpoint between arms and these data are presented graphically using scatter plots in Figure 29.
Table 10: Secondary endpoints examining physical function

<table>
<thead>
<tr>
<th></th>
<th>Intervention Arm</th>
<th>Control Arm</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td></td>
</tr>
<tr>
<td>Daily step count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2954 (2168-4143)</td>
<td>2294 (591-3821)</td>
<td></td>
</tr>
<tr>
<td>Endpoint</td>
<td>2898 (1055-5005)</td>
<td>2478 (727-3645)</td>
<td>0.548</td>
</tr>
<tr>
<td>Difference</td>
<td>-476 (-1592-1882)</td>
<td>6 (-860-335)</td>
<td>12</td>
</tr>
<tr>
<td>Difference %</td>
<td>-18.5 (-61 to 65)</td>
<td>5 (-32 to 50)</td>
<td>12</td>
</tr>
<tr>
<td>Timed up-and go test (seconds)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>13 (11-17)</td>
<td>15  (11-24.3)</td>
<td>22</td>
</tr>
<tr>
<td>Midpoint</td>
<td>15 (11.5-17.5)</td>
<td>14 (11-27)</td>
<td>15</td>
</tr>
<tr>
<td>Endpoint</td>
<td>14 (12-21.8)</td>
<td>14.5 (12-22.8)</td>
<td>0.767</td>
</tr>
<tr>
<td>Difference</td>
<td>-0.5 (-3-3.5)</td>
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<td>4.5 (-3.1-11.6)</td>
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<td>Two minute walk test (metres)</td>
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<tr>
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<td>104 (66-122)</td>
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<td>Midpoint</td>
<td>115 (77-136)</td>
<td>107 (52-137)</td>
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<tr>
<td>Endpoint</td>
<td>116 (75-138)</td>
<td>106 (68-122)</td>
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<tr>
<td>Difference</td>
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<td>52.0 (32.3-65.5)</td>
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<td>48.0 (33.5-58.0)</td>
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<tr>
<td>Difference</td>
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<tr>
<td>Difference %</td>
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<td>-4.5 (-19.1-17)</td>
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*Mann Whitney U-Test
Figure 26: Waterfall plot showing change in step counts
Figure 27: Waterfall plot showing change in timed up and go times
Figure 28: Waterfall plot showing change in two minute walk test distance
Figure 29 Scatter plots showing change in KPS score
5.5. Impact on nutritional status

Although not statistically significant, there was an increase in weight in the intervention arm from baseline to endpoint, and there was a decrease in weight in the control arm over the same time period.

There was no significant difference between baseline and endpoint aPG-SGA or AveS scores between arms.

Table 11 details changes in weight, aPG-SGA and AveS scores over the course of the trial. Figure 30 is a waterfall plot which illustrates the distribution of weight change comparing the two arms.
Table 11: Nutritional outcomes

<table>
<thead>
<tr>
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<th>Intervention Arm</th>
<th>Control Arm</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>n=</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>71.2 (59.8-79.2)</td>
<td>23</td>
<td>70.8 (62.4-85.7)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>76.2 (63.2-85.3)</td>
<td>17</td>
<td>68.2 (61.4-89)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>72.9 (62.3-88.1)</td>
<td>16</td>
<td>67.4 (57.4-87.1)</td>
</tr>
<tr>
<td>Difference</td>
<td>0.95 (-1.75-1.97)</td>
<td>16</td>
<td>-3.0 (-1.7-0.4)</td>
</tr>
<tr>
<td>Difference %</td>
<td>1.0 (-3-3)</td>
<td>16</td>
<td>-0.5 (-2.6-0.64)</td>
</tr>
<tr>
<td></td>
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<td>0.184</td>
</tr>
<tr>
<td>aPG-SGA score (0-36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.0 (1.0-9.0)</td>
<td>23</td>
<td>7.5 (3.0-13)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>5.0 (1.0-16)</td>
<td>18</td>
<td>7.0 (1.0-10)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>7.5 (1.3-13)</td>
<td>16</td>
<td>5.0 (1.0-7.0)</td>
</tr>
<tr>
<td>Difference</td>
<td>1.0 (-2.3-4.5)</td>
<td>16</td>
<td>-2.0 (-4.0-3.0)</td>
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<tr>
<td>Difference %</td>
<td>27.3 (-18-300)</td>
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<td>-41.7 (-73.3-117)</td>
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<td>0.249</td>
</tr>
<tr>
<td>AveS score (0-10)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>8.0 (5.0-8.0)</td>
<td>23</td>
<td>6.5 (5.0-8.3)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>7.0 (4.8-9.3)</td>
<td>18</td>
<td>8.0 (6.3-10.0)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>7.0 (4.0-9.8)</td>
<td>16</td>
<td>8.0 (6.5-9.5)</td>
</tr>
<tr>
<td>Difference</td>
<td>0.0 (-1.0-1.0)</td>
<td>16</td>
<td>0.0 (-1.5-2.0)</td>
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<td>Difference %</td>
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<td>16</td>
<td>0.0 (-16-31)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.398</td>
</tr>
</tbody>
</table>

*Mann Whitney U-Test

aPG-SGA scores range from 0 (no problem) to 36 (worst problem)

AveS asks participants: “If you consider at times when you are in good health, you eat 10/10, how much do you currently eat on a scale of 0-10?”
Change in weight (kg) per participant comparing baseline to endpoint

Figure 30 Waterfall plot showing change in weight
5.6. Impact on participant and carer quality of life

Participant QoL was assessed using the EORTC-QLQ-C15-PAL at baseline, midpoint and endpoint. This questionnaire is split into two functional scales (physical and emotional) and seven symptom scales: pain; fatigue; dyspnoea; insomnia; lack of appetite; nausea; constipation as well as a global QoL question. The EORTC-QLQ-C15-PAL scores from 0-100: for a functional scale 100 represents best function, whereas for a symptom scale 100 represents the worst/ highest level of symptoms.

No significant differences were identified between domains between arms with the exception of ‘emotional functioning’ which remained significantly higher in the intervention arm compared to the control arm (P=0.006). Table 12 details the results of this questionnaire.

Partner-carer QoL was assessed by the CQOLC questionnaire. Twenty-one partner carers completed a total of 46 questionnaires from 21 patients (11 from the intervention and 10 from the control arm). There was a non-significant trend towards improved QoL in partner carers of the intervention arm compared to a worsening of QoL scores in carers of participants in the control arm [Table 13].
### Table 12: EORTC-QLQ-C15-PAL questionnaire

<table>
<thead>
<tr>
<th></th>
<th>Intervention Arm</th>
<th>Control Arm</th>
<th>P*</th>
<th>Intervention Arm</th>
<th>Control Arm</th>
<th>P*</th>
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<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>n</td>
<td></td>
<td></td>
<td>n</td>
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<tr>
<td>Midpoint</td>
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<td>18</td>
<td>16</td>
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<td></td>
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</tr>
<tr>
<td>Endpoint</td>
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<td>16</td>
<td>16</td>
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<td></td>
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<tr>
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<tr>
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<td>13</td>
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<tr>
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<tr>
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<td><strong>Fatigue</strong></td>
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<tr>
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<td>22</td>
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<tr>
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<td>13</td>
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<tr>
<td>Difference %</td>
<td>10 (-33-100)</td>
<td>16</td>
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</table>

*Mann Whitney U-Test*
Table 13: Caregiver quality of life index-cancer scale

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<th>Overall QoL</th>
<th>Intervention Arm</th>
<th>Control Arm</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>n</td>
<td>Median (IQR)</td>
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<tr>
<td>Baseline</td>
<td>51 (41.8-62.3)</td>
<td>6</td>
<td>42 (29.3-47.3)</td>
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<tr>
<td>Midpoint</td>
<td>38 (32.8-68.8)</td>
<td>6</td>
<td>70 (34)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>39 (28.8-55.3)</td>
<td>4</td>
<td>56.5 (50)</td>
</tr>
<tr>
<td>Difference</td>
<td>-9 (-12)</td>
<td>3</td>
<td>1 (1.0-1.0)</td>
</tr>
<tr>
<td>Difference %</td>
<td>-13 (-24.5)</td>
<td>3</td>
<td>2 (2.0-2.0)</td>
</tr>
</tbody>
</table>

*Mann Whitney U-Test

CQOLC is scored from 0 to 140. A higher score represents a poorer QoL
5.7. Sleep

Sleep was assessed as part of the QoL component of the study. Sleep data included: minutes asleep, minutes awake (during sleep), number of awakenings and time in bed. Data were recorded at baseline and endpoints. Minutes asleep and time in bed increased in both arms of the trial from baseline to endpoint and there were no significant changes between arms of the trial. Sleep data are presented in Table 14.
Table 14: Sleep

<table>
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<th>Intervention Arm</th>
<th>Control Arm</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>n</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td><strong>Minutes asleep</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>478.7 (418.6-571.6)</td>
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<td>414.9 (301.9-500.3)</td>
</tr>
<tr>
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<td>532.4 (439.6-585.1)</td>
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<td>449.4 (283.3-534.5)</td>
</tr>
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<td>Difference</td>
<td>86.9 (-80.3-111.3)</td>
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<td>24.2 (-59.5-97.8)</td>
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<tr>
<td>Difference %</td>
<td>17.5 (-13.1-67.6)</td>
<td>14</td>
<td>7.8 (-10.9-40.2)</td>
</tr>
<tr>
<td><strong>Minutes awake (during sleep)</strong></td>
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</tr>
<tr>
<td>Baseline</td>
<td>33.6 (24.1-43)</td>
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<td>22.0 (11.0-28.7)</td>
</tr>
<tr>
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<td>34.0 (19.1-46.9)</td>
<td>15</td>
<td>11.9 (8.0-42.6)</td>
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<tr>
<td>Difference</td>
<td>4.5 (-3.5-14.8)</td>
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<td>-3.9 (-9.9-11.8)</td>
</tr>
<tr>
<td>Difference %</td>
<td>10.4 (-20.9-84.5)</td>
<td>14</td>
<td>-28.0 (-61.0-105.3)</td>
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<tr>
<td><strong>Awakenings</strong></td>
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</tr>
<tr>
<td>Baseline</td>
<td>2.6 (2.0-3.6)</td>
<td>20</td>
<td>2.4 (1.4-3.7)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>2.7 (1.7-3.7)</td>
<td>15</td>
<td>1.7 (1.0-2.1)</td>
</tr>
<tr>
<td>Difference</td>
<td>0.1 (-0.6-0.9)</td>
<td>14</td>
<td>-0.6 (-1.5 to -0.3)</td>
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<tr>
<td>Difference %</td>
<td>6.6 (-25.8-44.3)</td>
<td>14</td>
<td>-30.5 (-53.8 to -13.0)</td>
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<tr>
<td><strong>Time in bed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>517.7 (456-613.6)</td>
<td>21</td>
<td>436.6 (320.8-536.5)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>576.7 (470.9-635.1)</td>
<td>15</td>
<td>466.6 (291.3-578.8)</td>
</tr>
<tr>
<td>Difference</td>
<td>90.7 (-84.2-129.2)</td>
<td>14</td>
<td>19.4 (-73.5-112.6)</td>
</tr>
<tr>
<td>Difference %</td>
<td>16.4 (-14.8-68.5)</td>
<td>14</td>
<td>6.3 (-12.7-46.0)</td>
</tr>
</tbody>
</table>

*Mann Whitney U-Test
5.8. Survival

Of 45 participants, 25 completed the trial and 23 were still alive at the time of trial closure (3rd July 2019): 12 from the intervention arm and 11 from the control arm.

Twenty-two participants died before trial closure, 11 from each trial arm. Of participants who died before trial closure, 4 (36%) from the intervention arm and 5 (45%) from the control arm died less than 90 days after enrolment (inclusion criteria was clinician estimated prognosis >3 months).

Of those who died in each arm, there were no significant differences in survival (days) from date of enrolment as illustrated in Table 15.
Table 15: Survival: participants who died during trial period

<table>
<thead>
<tr>
<th>Survival (days) from date of randomisation</th>
<th>Intervention Arm</th>
<th>Control Arm</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>122 (56.2)</td>
<td>126 (78-171)</td>
<td>11</td>
</tr>
</tbody>
</table>

*Mann Whitney U-Test
5.9. Adverse or significant adverse events

There were 39 AEs recorded in total, 20 in the treatment arm (51%) and 19 in the control arm (49%). There were no SAEs.

Of AEs in the treatment arm, 9 (45%) were related to the ONS (described in chapter 4.3.1), 9 (45%) related to the underlying cancer diagnosis and 2 (10%) were due to non-cancer related issues. These AEs related either to pre-existing medical conditions or were not serious enough to constitute an SAE. In the control arm there were 12 cancer-related AEs (63%) and 7 (37%) relating to pre-existing medical conditions or not serious enough to constitute an SAE.

Table 16 details AEs in both arms of the trial.
Table 16: Adverse events

<table>
<thead>
<tr>
<th>AE type</th>
<th>Intervention Arm (n=23)</th>
<th>Control Arm (n=22)</th>
</tr>
</thead>
</table>
| **AE relating to ONS**       | 9 - Flatus/ gurgling from stoma  
- Flatulence/ stool frequency  
- Flatulence/ gurgling from bowel  
- Flatulence and abdominal cramps  
- Flatulence  
- Nausea x2  
- Diarrhoea  
- Overactive stoma         | N/A |
| **AE related to cancer**     | 9 - Pressure sore  
- Chest infection x2  
- Sub-hepatic haematoma  
- Intrahepatic bleed  
- Oesophageal bolus obstruction (tablet)  
- Falls (recurrent)  
- Admission to hospice-reduced mobility  
- Duodenal obstruction | 12 - Deep Vein Thrombosis  
- Hypercalcaemia  
- Fall x3  
- Chest infection x2  
- Delirium  
- Rectal bleeding  
- Pathological fracture  
- Pressure sore  
- Dysphagia |
| **AE Unrelated to Cancer**   | 2 - Urinary tract infection  
- Diarrhoea and vomiting | 7 - Tooth abscess  
- Atrial fibrillation x2  
- Cardiovascular complication  
- Diarrhoea  
- Wound infection  
- Diarrhoea and vomiting |
Chapter 6. Discussion

6.1. Introduction

This thesis set out to examine the feasibility of an exercise and nutritional rehabilitation programme in patients with incurable cancer. Chapter two examined the evidence for combined exercise and nutritional rehabilitation programmes in patients with incurable cancer. The findings showed that although there is limited evidence, there are multiple potential benefits from rehabilitation programmes incorporating exercise and nutrition. Most notable was evidence for improvements in physical function and measures of depression (Hall et al., 2019).

The second and third aims of the thesis were to establish if a combined exercise and nutritional rehabilitation programme was feasible and/or effective for a general population of patients with incurable cancer. The ENeRgy trial was successfully undertaken, and the results are discussed below in relation to previous trials. Suggestions and implications for future research are explored, as well as limitations of the present research.

Results of the ENeRgy trial

6.2. Trial population

6.2.1. Demographics

Comparing demographics of recruited participants in the present trial to previous trials in this area is of interest. It is notable that a greater proportion of males to females was also seen in similar studies. There are three previous trials where comparison is helpful:
- Solheim et al's feasibility trial of a multimodal exercise, nutrition and anti-inflammatory programme comprised 56% of males (Solheim et al., 2017b).

- Naito et al,'s ‘Nutrition and Exercise Treatment for Advanced Cancer’ (NEXTAC-1) feasibility trial for elderly patients with advanced cancer recruited a ratio of 2:1 males: females (Naito et al., 2019).

- In 2017 the RCT by Uster et al investigating the effects of a nutrition and physical exercise intervention in palliative cancer patients, 40 males and 18 females were recruited (Uster et al., 2017).

Although this male preponderance may be by chance, or due to a higher proportion of males being affected in the target cancer populations, it is also possible that terminology could have impacted on recruitment to these trials. Participants are attracted to trials involving the term ‘exercise’ due to perceptions of potential benefit, but similarly they may be put off by fear, lack of self-confidence, impact of symptoms (especially fatigue), as well as the misguided (but well-intentioned) support from carers promoting rest (Granger et al., 2017). Some participants are attracted to potential benefits around ‘fitness’ whereas some may find this less relevant in the context of advanced cancer and more willing to participate if programmes are promoted to help them continue normal routines and roles in life, to improve their mental wellbeing or remain ‘active’ (Wong et al., 2018).

People have different responses to the term ‘exercise’; some see it as intimidating, especially if they were not an active or ‘fit’ person pre-morbidly, or they have a high symptom burden. Perceptions of exercise and what it entails vary: some see walking and being active as exercise, yet to others, exercise is something more structured and vigorous, done at a gym or in a class, which can be off putting or seen as ‘boring’. People who do not see themselves as ‘exercisers’ may be less motivated to participate, and programmes using modalities such as walking may be more appealing (Granger et al., 2017).
Could it be possible that the term ‘exercise’ appeals more to males than females? It has previously been highlighted that an awareness by professionals of a person’s interests and preferences facilitates optimal uptake of physical activity interventions, and personalised exercises tailored to the individual are preferable (Granger et al., 2017, Bayly et al., 2018). With this in mind, it is very important that the particular interests of any potential participant are sought and that any ‘exercise’ or physical activity component of the programme be tailored to the individual’s goals.

A suggestion for future studies is therefore to consider re-branding the physical activity or ‘exercise’ component as a ‘tailored physical activity programme’ or an ‘individual activity (or fitness) programme’. This may also counteract the frequent criticism of this type of study: that only ‘fitter’ individuals volunteer for such studies, resulting in selection bias.

6.2.2. Cancer type and recruitment

As expected for a more morbid population of participants with incurable cancer (post anti-cancer treatment) there were more participants in the lower KPS (60-80) group (65% and 64% respectively) than the KPS 90-100 group. There was a higher proportion of GI cancers in the intervention arm than the control arm (52% versus 27%), yet fewer breast (9% versus 18%) and urological/gynaecological cancers (17% versus 27%) in the intervention arm compared to the control. Overall, however, there was a good distribution of different cancer types in each arm, considering the small study population.

The population of patients recruited in the ENeRgy trial does reflect the population of patients served by palliative care services within the UK. Using death rates for hospice populations as a proxy for the population of patients under hospice care, mortality data from within hospices in England from 1993 to 2012 is notable. Of these deaths, the highest numbers were from cancers of the breast and ovary, followed by cancers of the GI tract, liver/ pancreas.
and the lowest numbers of deaths were from the haematological malignancies (Sleeman et al., 2016). The highest numbers of patients in both arms recruited to ENeRgy came from the GI tract (52% intervention and 27% control), followed by urological/ gynaecological malignancies (17% intervention, 27% control) and then breast cancers (9% intervention, 18% control). There was a higher representation of patients with myeloma recruited to the ENeRgy trial (9% intervention and 14% of the control arms) than would usually be seen in the hospice population. The relatively high numbers of patients recruited with breast/ urological (including prostate cancers) may have been due to the inclusion criteria favouring recruitment of patients with tumours that are often well controlled with hormonal treatments. The relatively high numbers of patients recruited with myeloma may have been for two reasons: firstly myeloma treatment often results in periods of relative quiescence where good function is retained. This may create a pool of patients for whom this type of rehabilitation programme appeals to. The relatively high proportion of myeloma patients recruited may have also reflected recruitment bias as an education session was given specifically to the NHS Lothian haematology consultants (we were unable to deliver the equivalent session to all recruiting Oncologists in NHS Lothian). This may have therefore generated a greater number of referrals, and highlights the importance of delivering targeted education sessions for key groups of recruiting clinicians in the future phase three trial.

It is worth comparing demographics of the present trial with previous trials. Of note, studies examining similar interventions have previously targeted patients with lung and pancreatic cancer, due to the higher proportion of cachexia in these cancers.

The goal of the ENeRgy trial was to apply the principles of a multimodal intervention to a general population of patients with cancer. In all there were only a small proportion of participants with thoracic cancers recruited in both arms (4 and 9% in intervention and control arms respectively). Had
recruitment been limited to lung and GI cancers alone, the trial may not have recruited to target.

Other trials have had this problem including Uster et al in 2017, whose trial suffered from early closure due to poor recruitment. An affiliated group has recently published a trial of a leucine rich ONS in combination with an exercise and nutritional programme for advanced cancer patients. The initial plan was to recruit participants with lung and GI cancers, but due to slow recruitment, inclusion criteria were widened to breast, ovarian, prostate, renal cell and bladder cancers. In spite of this they did not recruit to target (88) resulting in an underpowered study with 53 participants in total. No significant improvement was seen in their primary endpoint (physical function measured by the short physical performance battery, SPPB), yet a significant improvement was seen in HGS. The most common reason for lack of eligibility in their trial was survival less than 6 months (Storck et al., 2020).

In the present trial, six patients were referred for the ENeRgy trial by a lung oncologist at the local cancer centre. Two of these patients did not meet the inclusion criteria due to short prognosis and being on anti-cancer treatment. The trial was discussed with the remaining four patients, yet all of them declined to take part. Reasons for declining to take part were: too symptomatic to undertake the interventions (breathlessness and fatigue); or they felt that travel to the hospice would be too burdensome.

This may be reflective of the fact that patients with end-stage thoracic malignancies have significant symptom burden. With the evolution of newer immunotherapies for stage IV disease, there is a potential for patients to remain on anti-cancer treatments for much longer. Newer therapies such as tyrosine kinase inhibitors (TKIs) including erlotinib can be used in metastatic lung and pancreatic cancers (Zhang et al., 2019, Lakkakula et al., 2019). By the time these patients complete SACT they may be too symptomatic to participate in rehabilitation trials.
The evolution of newer treatments, including TKIs for metastatic lung and pancreatic cancer, has implications for design of rehabilitation trials. Should trials wish to recruit these patients, eligibility criteria may need to be widened to include participants receiving anti-cancer treatments. Alternatively, trials should consider recruiting participants with any cancer type to avoid the same issues.

6.2.3. Body mass index and weight

The mean BMI for all participants in the ENeRgy trial was 25.7 and the mean BMIs for intervention and control arms were 24.2 and 27.2. It is acknowledged that a greater proportion of participants were in the heavier 25.1-30 and >30 BMI ranges in the control arm than the intervention arm (41% versus 30%) and (23% versus 13%) respectively.

The ENeRgy trial population from south-east Scotland is comparable to other international trials; for example, Storck et al. (2020) cited a mean participant BMI of 25.4 recruited from a Swiss cancer centre, and Solheim et al (2017) cited a mean participant population BMI of 24 from a population of Norwegian and Scottish patients.

This finding may reflect the increasing levels of obesity in western society and it would be remiss not to mention the increase in frequency of sarcopenic obesity (SO). SO is the presence of sarcopenia (a high degree of depletion of skeletal muscle mass that negatively affects health), alongside obesity - defined by the WHO as a BMI >30 (Baracos and Arribas, 2018). Loss of skeletal muscle mass often occurs in these patients (particularly in pancreatic and thoracic malignancies) long before weight loss and emaciated appearances traditionally associated with cachexia. SO is associated with greater mortality, post-surgical complications and toxicities from chemotherapy (Baracos and Arribas, 2018).
The ENeRgy trial was a rehabilitation trial, not a cancer cachexia trial, and thus clinical markers of cachexia were not necessary for inclusion. Measurements of muscle mass were also not included. The definition of cancer cachexia most often includes involuntary weight loss of >5% from historical weight over six months, a body mass index (BMI) <20kg/m² with any degree of weight loss >2%, or a skeletal muscle index consistent with sarcopenia with any degree of weight loss >2% (Fearon et al., 2011). It is predicted that 50-80% of patients with advanced cancer will have evidence of cancer cachexia (von Haehling et al., 2016).

Using estimated weight change from aPG-SGA in the present trial, 30% of the intervention and 41% of the control arm had lost >5% body weight in the six months prior to enrolment. Considering the missing data from these questions (up to 27% as participants were often ‘unsure’) this figure may have been higher and closer to the estimates of cachexia prevalence cited by Von Haehling et al. It is acknowledged that within the present trial there was no formal stratification or categorisation of participants in terms of cachectic status. This, in turn, makes differentiation of participants who responded and did not respond to the intervention (fundamentally designed on a multi-modal intervention for cachexia) more challenging.

It would be of interest in a future phase three trial to not only stratify patients based on their performance status, but also to stratify according to stage of cachexia or the level of SIR- e.g. grouping patients by mGPS. It would then be possible to analyse the response to exercise and nutritional interventions according to inflammatory status, which may reveal interesting results and explain why a ‘one size fits all’ intervention may have its limitations. The ability to gain muscle is impaired by increased inflammation (the ‘anabolic blockade’) (Fearon, 2008), and there is also an association between symptoms such as pain, symptom clusters and levels of systemic inflammation (Laird et al., 2011a, Laird et al., 2011b). It therefore follows that
for such a heterogeneous group of patents, the multi-modal intervention will be more effective in some than others. Stratifying by mGPS may help to elucidate which aspects of the intervention are impactful and why— for example why some patient groups have a good response to the interventions in terms of physical function and mood and others do not.

There has been some light shed recently into why at times an increase in muscle mass does not correlate with an improvement in muscle function. It has been suggested that there is a non-linear correlation between gains in muscle mass and muscle function (Ramage and Skipworth, 2018). For patients in the later stages of cancer cachexia (cachexia and refractory cachexia), gains in muscle mass may be initiated in advance of gains in muscle function, hence the need to stratify patients into cachexia/inflammatory groups. This may explain the failure of some large international phase three trials to demonstrate an increase in physical function where an increase in muscle mass is seen in the case of anamorelin and the ROMANA 1 and 2 trials (Temel et al., 2016).

In designing the phase three follow on trial- ENeRgise, measurement of baseline and serial CRP and albumin measurements (to calculate mGPS) will be undertaken as well as body composition analysis by BIA. This will allow further insights into the impact of a multi-modal intervention in these specific patient subgroups.
Primary endpoints
Discussion of the primary (feasibility) endpoints of the ENeRgy trial as detailed in chapter four of this thesis are included below.

6.3. Feasibility of trial procedures

6.3.1. Questionnaires

Although there were a number of questionnaires for participants to complete on test weeks, no participants were unwilling or did not complete questionnaires.

A retrospective meta-analysis examining compliance for patient-reported outcome (PRO) questionnaire completion in oncology trials previously has shown that PRO data is frequently missing where questionnaires are sent to participants for completion and are not returned (37% of non-compliant PRO's) (Atherton et al., 2016). The ENeRgy trial researchers guided participants through the PRO questionnaires, and warned participants prior to test weeks (weeks 0, 5 and 9) that these would be longer visits. These factors may have been helpful for compliance and should be considered in future trial design to maximise PRO data capture.

The CQOLC questionnaire was generally completed well by partner-carers, (46 questionnaires by 21 partner-carers). The question most frequently left unanswered was “I am satisfied with my sex life” (33% unanswered). It is possible that respondents may have found this question to be too intrusive or personal or not applicable if they were in a platonic relationship. Although the CQOLC is a validated tool (Weitzner et al., 1999), for family-carers, the ENeRgy trial offered it only to partner-carers due to the intimate nature of some of the questions. This may have limited the numbers of carers eligible to complete it and limited the data gathered.
Future studies may wish to consider the use of this CQOLC questionnaire for all family-carers, with the instruction to mark questions not applicable with “N/A”, or consider use of a questionnaire more suited to adult informal carers such as the adult carers quality of life questionnaire (AC-QoL) (Joseph, 2012).

6.3.2. Physical testing

Compliance with the physical tests employed in the ENeRgy trial (the TUG and the TMWT) was good with 98% of participants completing the TUG and 88% of participants completing the full TMWT. The most common reasons for not completing the TMWT was dyspnoea (55% non-completers) followed by fatigue (45% non-completers).

Other trials with similar interventions have employed other outcome measures including the six minute walk test (Uster et al., 2017, Naito et al., 2019), as well as the SPPB (Storck et al., 2020) which have been feasible but have yielded mixed results.

One-off volitional measurements such as HGS are feasible (Solheim et al., 2017b, Storck et al., 2020) but as an outcome measure their use has been cast in doubt by varied results in trials. For example, Storck et. al (2020) showed a significant improvement in the secondary outcome of HGS but not the primary outcome of SPPB. Additionally, the findings from the ROMANA1/ROMANA2 trials (investigating the novel ghrelin receptor agonist Anamorelin) showed a significant increase in LBM but no significant difference in HGS (Temel et al., 2016). It is not clear therefore whether HGS is a good marker of muscle function and therefore an appropriate surrogate for ‘physical function’.

The ENeRgy trial was not adequately powered to demonstrate significant change in physical performance (secondary) outcomes. Design of a larger
phase three trial should take into account the appropriateness/applicability of the physical testing outcome to the trial population as well as the burden that it places on participants. Judging by the compliance levels with the TMWT in this trial, they would suggest it is an appropriate and feasible measure. Employing longer walk tests (such as the 6MWT) may be overly burdensome for this participant group and result in a higher drop-out rate, rendering data less reliable.

6.3.3. Physical activity meters

The PAM chosen for the ENErgy trial (the Fitbit® Flex 2) was a consumer-based, rather than research grade, monitor. It uses a tri-axial accelerometer (a measure of acceleration in three dimensions of space) to estimate steps. It has been shown as reliable in both healthy adults (Lee et al., 2014) and people with stroke and traumatic brain injury (Fulk et al., 2014).

Increasingly wearable activity monitors are being used in Oncology trials as they provide an objective measure of activity levels in the participant’s own surroundings (Gresham et al., 2018). Objective measures of function such as step count show promise in clinical trials as they have the potential to eliminate performance bias (seen in one-off volitional measurements), and poor inter-rater reliability seen in clinician-measures of function such as performance status (Broderick et al., 2019, Ando et al., 2001). However, minimum clinically important differences are yet to be established and understood for some of these parameters (Maddocks and Granger, 2018).

The Fitbit® Flex 2 monitor was selected due to its small size, water resistance, light weight (and therefore comfort), minimalistic display (four small LEDs which were easily masked with tape to avoid any ‘motivational effect’ of the monitor for participants) and its ease of use and charging. A PAM participant information leaflet was designed and approved by the ethical
committee [Appendix 7] and given to all participants to instruct them how to use and charge the PAM.

Vibrating alerts were switched off (monitors can be set to vibrate to alert the wearer when they pass a fraction of the daily step goal). Consumer-based PAMs have been shown to have similar accuracy for physical activity data when compared to research grade monitors such as the Actigraph® (Imboden et al., 2018). Advantages and disadvantages of consumer monitors and a comparison of the size of the Flex 2 with the Actigraph® are shown in Table 17 and Figure 31.
Table 17: Advantages and disadvantages of consumer based physical activity monitors compared to research grade monitors

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost low due to consumer demand</td>
<td>Validity still being explored in cancer populations</td>
</tr>
<tr>
<td>Accessible on multiple devices</td>
<td>Shorter battery life</td>
</tr>
<tr>
<td>User friendly</td>
<td>Proprietary algorithms- lack of control</td>
</tr>
<tr>
<td>More comfortable (smaller size)</td>
<td>Less easily blinded</td>
</tr>
<tr>
<td>Aesthetically pleasing</td>
<td>Compliance &amp; adherence can be issues when participants need to wear for a</td>
</tr>
<tr>
<td></td>
<td>certain timespan per day</td>
</tr>
<tr>
<td>Availability of more advanced analytic software</td>
<td>Variability between consumer devices making comparison between monitors</td>
</tr>
<tr>
<td>(eg. Fitbase®)</td>
<td>less reliable</td>
</tr>
<tr>
<td>Accurate- comparable with research grade monitors (Imboden et al., 2018)</td>
<td>Measurement reactivity ie. change in activity due to awareness of being</td>
</tr>
<tr>
<td></td>
<td>monitored (applies to both consumer and research monitors)</td>
</tr>
<tr>
<td>Brand/Model</td>
<td>Actigraph® wGT3X-BT</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Cost</td>
<td>$225 = approx. £179</td>
</tr>
<tr>
<td>Size</td>
<td>4.6cm x 3.3cm x 1.5cm</td>
</tr>
<tr>
<td>Battery life</td>
<td>25 days</td>
</tr>
<tr>
<td>Water resistance</td>
<td>To 1 metre/ 3 mins</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Brand/Model</th>
<th>Fitbit® Flex 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>£55</td>
</tr>
<tr>
<td>Size</td>
<td>31.7 x 8.9 x 6.8 mm</td>
</tr>
<tr>
<td>Battery life</td>
<td>5 days</td>
</tr>
<tr>
<td>Water resistance</td>
<td>50 feet/ unlimited</td>
</tr>
</tbody>
</table>

Figure 31: Actigraph® wGT3X-BT versus Fitbit® Flex 2

Discussion
6.3.3.1. PAM data retrieval

Data retrieval from the PAMs was good, with 82% complete data for all participants (ie. all steps/ sleep data retrieved). There were no reports of the devices being uncomfortable or too bulky; however, some participants reported that the bracelet was difficult to do up; they had problems with dexterity (such as arthritis/ peripheral neuropathy) and some reported having to ask a family member to assist them.

6.3.3.2. Participant PAM issues

The most frequent participant issue reported with the PAM (seven instances) was reinserting the sensor upside down. Although this was illustrated in the PAM leaflet [Appendix 7], reinserting the sensor upside down did not necessarily affect the data recorded. The next most commonly reported device issue was participants forgetting to charge the monitor. Interestingly, although the monitor battery life was quoted as five days in the product literature, where participants forgot to charge their device there was invariably seven days' worth of data retrieved and this may have been due to the settings used (reduced functionality with vibrating alerts switched off, for example) which may have helped to preserve battery life.

6.3.3.3. PAM data capture

One of the difficulties faced during trial design was deciding when to ask participants to charge their monitors. For the ENeRgy trial, participants were asked to charge the PAM for 3-4 hours on one weekend day (either Saturday or Sunday) to preserve battery life and prevent data loss. Weekend data were disregarded for this reason and also due to variability seen in weekend activity levels (ie. participants undertaking more activity associated with social interactions at weekends) which can skew step count results. This decision (put forward by Matthew Maddocks, lead physiotherapist) caused
much discussion at the TMG meetings. Previous literature reports that due to inherent biological variability in step counts, in order to be valid, measurements should be made over three to seven days to attain reliable measurements (Bassett et al., 2017). The ENeRgy trial therefore analysed step counts recorded on Thursday, Friday, Monday and Tuesdays only. In future trials, however, with the knowledge that the PAM battery lasts for seven days, it would be feasible to collect data over the full week.

A disadvantage of consumer PAMs is that they have proprietary algorithms and data can only be downloaded in a pre-programmed format. One of the unforeseen technical aspects with the Flex 2 monitors which affected the collection of sleep data (five instances), was loss of sleep data where monitors were worn for over seven days or there was a delay returning the monitor (therefore a delay in data download).

Although step data were recorded on the sensor and stored on the internal memory (much like a removable drive/ ‘memory stick’), sleep data seemed to only be retained for the seven days immediately prior to data download. Where participants wore PAMs for more than seven days, sleep data for the trial week were often missing. The same scenario was true where the sensor was not returned on day seven (for example two participants lost their PAM only to find it and return it weeks later). In these cases, step data were recovered but sleep data lost.

6.3.3.4. Other PAM issues

For one participant, step count data were consistently much lower than reported activity levels. It was noted by the researchers that this participant mobilised using a wheeled walking frame. This highlighted another unexpected device issue with this type of consumer-based monitor: the monitor is pre-programmed (proprietary algorithm) to record periods of ‘cycling’ activity. Therefore, step counts for this participant were falsely low as
the monitor had recorded much of her activity as ‘cycling’ rather than walking. This may have negatively skewed results for steps in this dataset with relatively few participants.

This is a disadvantage of this type of PAM, and lack of sensitivity to non-ambulatory physical activities including cycling, swimming and fitness training has been previously documented (Purswani et al., 2018).

Although there are drawbacks to consumer PAMs, including proprietary algorithms and battery life, the Fitbit® Flex 2 PAM provided a feasible, reliable, comfortable and easy to use option for measuring activity levels during the trial. Of note, the Flex-2 is no longer available at the time of writing and this is another consideration regarding longer term use of PAMs in future trials.

6.4. Feasibility of interventions

The primary endpoint of the ENeRgy trial was to evaluate the feasibility of delivering an exercise and nutritional rehabilitation programme at a hospice outpatient setting for patients with cancer. Feasibility was assessed by measuring compliance with the rehabilitation programme, firstly by numbers of intervention components managed versus those prescribed. Compliance with trial procedures was also measured, including completion of diaries & questionnaires, percentage withdrawal, completion of physical tests and completeness of PAM data.

When designing the trial, a threshold level above which compliance was defined was deliberately not set, as this would be arbitrary at best. In previous trials, compliance has been defined as >50% of components in >50% of participants (Solheim et al., 2017b). Solheim et al also regarded a 10% recruitment rate and an attrition rate of less than 26% as feasible, citing previous literature from Stone and Hui (Stone et al., 2013, Hui et al., 2013).
In a 2019 systematic review of exercise interventions for patients with advanced cancer mean recruitment rate was 49% and levels of adherence to exercise interventions ranged from 44 to 95% (Sheill et al., 2019).

Compared with these compliance standards, compliance with prescribed interventions in the ENeRgy trial was high. Therefore, it can be concluded that the ENeRgy trial interventions were feasible and manageable in the proposed timescale for this population of patients.

6.4.1. Oral nutritional supplements

ONS overall compliance was 76% with 16 of 21 participants taking a median of >80% of ONS prescribed during the whole trial. Two participants withdrew at week one therefore n=21. Ten of 21 participants (48%) managed to take the full ONS prescription (two per day) for the full duration of the trial, though one of these participants described an increase in flatulence relating to the product.

Not all participants were able to take the full prescription for the duration of the trial. Seven participants had ONS related AEs (33%), one participant was unable to take the omega-three rich ONS due to it containing soy (5%) and three participants (14%) had difficulties managing the ONS prescription due to symptoms relating to their underlying condition.

6.4.1.1. Nutritional impact symptoms and participants with stomas

Of three participants who were unable to tolerate the ONS due to underlying conditions, all dropped out in spite of ONS dose reductions soon afterwards due to deteriorating health: one participant described longstanding nausea; one had early satiety and one experienced a change in taste after an acute illness (and ONS became unpalatable).
It is perhaps not unexpected that these participants struggled to take their ONS as they had pre-existing nutritional impact symptoms (NIS). NIS are a broad spectrum of impediments to oral nutritional intake that are commonly found in patients with advanced cancer. These include taste and smell alterations, mucositis, nausea, constipation and pain (Omlin et al., 2013). An evaluation of the PG-SGA in 46 patients with advanced cancer showed that the most common NIS were anorexia (47%), early satiety (43%), nausea (20%) and abnormal taste (20%) (Thoresen et al., 2002).

Due to the high prevalence of NIS in this population of patients, it is perhaps not unexpected that in the ENeRgy trial, nine AEs were reported for seven participants in relation to trial ONS. Of these AEs, the most common was flatulence or flatus (five AEs). This was associated in some participants with other symptoms including abdominal colic, loose stools or increased stoma activity. Flatulence/ flatus improved in the majority of cases (80%) with a dose reduction to one ONS per day. Although this symptom was not significantly distressing in the main part, for two participants with stomas it caused more distress. This was due to the flatus causing the stoma bags to swell with a risk of them ‘bursting’ if not emptied regularly. For one participant, this symptom resolved with the dose reduction, but the other participant refused to trial a dose reduction and stopped the ONS at week three. Symptoms did resolve after cessation of the ONS but additional reassurance and education was sought from a community stoma nurse.

It is therefore recommended that future studies should screen for the symptom of flatulence and particular attention be paid to participants with stomas. These participants may require early referral to community allied health professionals such as stoma nurses to improve compliance and prevent symptoms impacting on QoL or risking participant attrition.
6.4.1.2. Ω-3 rich ONS compliance and impact of the trial dietitian

Compliance issues have previously been documented with Ω-3 enriched ONS in similar studies. In a systematic review of the role of fish oil for the treatment of cachexia, AEs including abdominal discomfort, fish belching, fish aftertaste, nausea and diarrhoea were reported with low incidence. These AEs were not serious enough to constitute SAEs (as was the case for the ENeRgy trial) but may have impacted on QoL (Ries et al., 2012).

In more recent years the formulation of ProSure® has been modified to combat some of these symptoms. Indeed, there were no reports of fish belching or aftertaste for ENeRgy trial participants. In the feasibility trial reported by Solheim et al in 2017 ProSure® was used at the same dosage, with overall compliance of 48% (less than their cut off for compliance). The authors reported that participants tended to take either the whole prescription as prescribed or not at all, and the most common reason for non-compliance was the supplement being unpalatable. The ENeRgy trial had much higher compliance rate for the ONS than that of Solheim et al, and it is worth examining some of the differences between these two trials, as this may help to inform future study design.

One major difference between the aforementioned trials is that the ENeRgy trial nutritional intervention was led by a dietitian as opposed to a research nurse. Due to the high level of NIS, the dietitian’s level of expertise in managing these may have been beneficial to improve compliance.

For example, where participants described NIS such as early satiety or altered taste, alternative methods of taking the ONS were advised. Examples included advising participants to ‘shot’ their ONS in small increments over the course of one to two hours rather than drinking them all in one sitting. Freezing the supplements and having them as an ice-cream type dessert was also helpful to a number of participants.
In addition, rather than generic dietary fortification advice, the dietitian was able to use her expertise to suggest alternative ways to improve an individual’s nutritional intake, meaning that even with the ONS (at full or reduced prescription), caloric intake was always optimised. Frequently, participants would require extensive education, led by the dietitian to undo life-long “healthy eating” habits. Reassurance was frequently given to participants that the foods they were being advised add to fortify their diet with were ‘safe’ to eat (including full fat/ sugar high calorie snacks) due to the need for higher caloric intake in advanced cancer. For many of the trial participants, this was the first time they had been reviewed by a dietitian in their entire cancer treatment journey, and nutritional intake is often an overlooked component of optimising the health of patients with cancer.

6.4.2. Timing of ENeRgy interventions and potential impact on compliance

The other reason the ENeRgy trial may have had better compliance was the timing of the trial intervention in relation to diagnosis and trajectory of the patient’s illness. For example, in Solheim et al (2017) intervention was given to patients with stage III/IV non-small cell lung cancer and inoperable pancreatic cancer, relatively soon after diagnosis and before starting chemotherapy. In contrast, the ENeRgy trial intervention was given to participants who had completed their anti-cancer therapy and were otherwise for ‘best supportive care’ with less frequent hospital clinics to attend.

The amount of information for patients to take in after a new diagnosis of cancer (especially prior to treatment) is considerable, and it is possible that participants in the trial of Solheim et al struggled to retain or understand the need for the multi-modal intervention at this time. For the ENeRgy trial on the other hand, participants had often completed their Oncology follow up, and one could argue that they may have more capacity, motivation or time to focus solely on the proposed trial interventions without competing demands.
If this is the case, this could have implications for future rehabilitation trial design when starting earlier in a participant’s cancer/ treatment journey, and that additional ways of reinforcing instructions/ modes of improving compliance may be required.

Overall the level of compliance with the ONS was such that it can be concluded that the dietary elements of the intervention (ONS and dietary fortification advice) were feasible for this population of patients. Future studies should take into consideration the need for screening for AEs, including flatulence, which usually resolve with dose reductions, and be particularly vigilant in participants with stomas.

6.4.3. Exercise

Eighteen of 21 of participants (86%) in the treatment arm achieved the target of at least 60 minutes of aerobic exercise per week, and 17 of 21 (81%) of participants completed a median of over 80% of resistance exercises prescribed. Levels of adherence to home supervised exercise programmes for patients with advanced cancer have been reported as ranging from 44 to 95% (Sheill et al., 2019). Adherence rates for the ENeRgy trial are therefore at the upper end of this spectrum.

6.4.3.1. Participant compliance facilitators

Exercises were prescribed on an individual basis according to an assessment by the trial physiotherapy assistant, and recording of exercise was done via participant diaries and therefore relied upon participants recording and reporting accurately. On a few occasions participants had recorded exercise incorrectly, but this was quickly identified at the weekly assessments. For example, rather than recording numbers of different exercise types completed, some participants recorded the numbers of individual repetitions. To improve compliance, the box on each diary was
completed at clinics to remind participants of the number of exercises prescribed each week [see intervention arm diary- Appendix 5.1]. Participants could also annotate their intervention booklet [Appendix 5] to remind them of their weekly exercise prescription.

The booklet was frequently reported as helpful by participants. On a number of occasions diaries were completed by the participant's partner or relative, and this was reported as a motivating factor, especially where the relative had participated along with the exercises or had 'supervised' them. This was generally (though not always!) reported as a positive influence by participants and may have also had an impact on compliance.

The reliance on honest reporting from participants and/or family members to complete information is a downside of diaries due to the potential for reporter bias. Diary use can lead to problems with recall bias, and diary fatigue which can affect data quality (Zanni, 2007). However, for this trial, the home-based exercise regimen, in combination with regular clinic reviews, meant that diary fatigue was minimised.

Alternative designs have shown that supervised exercise classes can have high levels of compliance (75% in the RCT by Uster et al in 2017). A mixture of supervised and home exercise programmes can also be effective (70.7% and 95% adherence respectively reported by Storck et al. 2020). The emerging use of wearable PAMs may have a role to play in objectively recording participants’ participation in home exercise regimens; indeed, in the NEXTAC-2 trial (results awaited) the authors propose to record physical activity during protocol-defined assessment intervals with an accelerometer (Lifecorder®).

The other positive benefit to home-based exercises guided by a booklet was that no fitness equipment was required. This makes the design transferrable to any outpatient setting at zero cost. The exercises used bodyweight as
resistance (e.g. squats and wall-press ups) and where additional resistance was required (for example, in upper body exercises) participants were advised to use ONS for weights (220mL= 220grams). Upwards from this, participants were instructed to use 500mL water bottles (=500grams). The majority of participants found this suitable and if additional weight was required participants were advised to purchase handheld dumbbells to increase resistance.

6.4.3.2. Motivating factors

Participants frequently reported enjoying the routine of having ‘a plan to follow’ and this was a motivating factor for them. One participant reported feeling ‘lost’ after completion of her Oncology treatment, and ‘not sure what to do’, in particular feeling uncertain whether it was safe to exercise or if they ought to be ‘resting’. She described this insecurity as leading to social isolation and causing a deterioration in her mental health. She took to the intervention with vigour, and by the end of the trial, described being able to move more freely, and was notably brighter in mood. She described to the team that she felt as if “a sack of coal had been lifted” from her shoulders, that she had enjoyed her exercise (gardening mostly) and was referred on to the hospice day therapies group on completion of the trial.

This feedback was entirely in keeping with the findings of our systematic review, which showed that improvements in physical function and mood were most likely seen following combined exercise and nutritional rehabilitation programmes (Hall et al., 2019). Participants who completed exercise regimens with family members, reported positive social benefits. Taking walks outside with family members, and in another case a man who started walking to the pub again, were reported as positive social benefits of the programme. Surprisingly, no AEs were reported relating to the exercise intervention, such as increased fatigue or myalgia. This is promising in terms of future rehabilitation trial design, and highlights that an individually tailored
exercise intervention, taking participant’s goals and limitations into consideration is not only feasible, but may also confer social and psychological benefits.

### 6.4.3.3. Participant experience and social elements

Participant experiences were captured in the accompanying qualitative study ‘ENeRgy- Q’. Fourteen participants were interviewed after completion of the ENeRgy trial intervention. Benefits reported were classified into major themes. Participants reported a motivation to partake in the trial to help others (ie. altruistic intent) but also with the hope of improving their own wellbeing. Both have previously been documented as a major motivator for participants taking part in rehabilitation trials (Payne et al., 2018). Some participants reported positive physical benefits: weight gain was often regarded as positive in the context of incurable cancer. Others described being able to ‘do a bit more’ for example, getting into the shower without feeling as breathless as before. Participants reported social benefits relating to their involvement with the research team, having a regular ‘focus’ (ie. weekly visits to the clinic), as well as the positive benefits of family members becoming involved. Participants did not find the interventions overly burdensome; indeed the opposite was described by the majority of participants. The only negative comment was that a participant hoped the exercise would involve meeting and socialising with other participants (unpublished data).

In future the design of rehabilitation trials may benefit from incorporating an element of social interaction between participants which may improve participant recruitment, experience and may also have a beneficial psychological impact.

Overall, the exercise components (both home-based resistance exercises guided by a booklet and weekly clinic review, as well as 60 minutes aerobic
exercise per week) are feasible for outpatients with incurable cancer. The reason most commonly cited by participants for non-completion of either aerobic or resistance exercises was fatigue. Future trials should therefore consider incorporating strategies to manage fatigue into the design of their regimens, such as specified 'rest days’ after exercise, to avoid over-exertion.

**Secondary endpoints**

Discussion of the secondary (exploratory) endpoints of the ENeRgy trial as detailed in chapter five are discussed below.

### 6.5. Recruitment and retention

The ENeRgy trial recruitment rate was 37% (45 of 121 screened). Recruitment rates for exercise interventions for patients with advanced cancer range from 15 to 74% with a mean (SD) of 49% (17%) (Sheill et al., 2019). Solheim et al (2017) recruited 46 of 399 (11.5%) patients with advanced non-small cell lung cancer or inoperable pancreatic cancer to their multi-modal feasibility trial, while Naito et al in 2018 recruited 30 of 46 screened (65%) for an exercise and nutritional intervention in the over 70’s.

It has previously been noted that for trials of exercise interventions in patients with advanced cancer, a positive correlation exists between older age and recruitment ($r = 0.4$, $p< 0.05$) (Sheill et al., 2019). The median age of 78 in the present trial was older than that reported by Solheim (63 and 59 in intervention and control arms respectively) and the recruitment rates are in keeping with this observation. Sheill et al (2019) reported that recruitment to exercise trials in the advanced cancer population was not influenced by duration of recruitment period or by duration of the exercise programs. The frequency of the exercise programme in the present trial was comparable to studies included in this systematic review (2-3x weekly).
6.5.1. Facilitators to recruitment

In order to maximise recruitment, the research team took measures to ensure recruiting teams had a thorough understanding of the trial and the target participants.

Education sessions were given in-person by the researchers to all clinical teams in the form of PowerPoint presentations. These were delivered to all four community palliative care teams, at three team meetings for Oncologists at the local tertiary referral centre, as well as at St Columba’s Hospice to all clinical staff.

Resources were designed and given to recruiting teams including a ‘pocket sized’ reference guide which was laminated and given to community palliative care nurses to be carried with them on visits. It detailed inclusion and exclusion criteria and highlighted what information the person making first contact would give to the potential participants [Appendix 8].

Telephone contact and in-person visits were made (where possible) with team leads on a weekly basis by the trial research nurse to prompt for referrals and teams were encouraged to screen for participants at their MDT meetings. As an additional measure, the research team liaised with the base hospice administrative team to screen all external referrals to St Columba’s Hospice for eligibility.

Partner education (in particular personal and repeated contact with referral sources) is known to be a key factor in maintaining enthusiasm and motivation throughout a study, as well as a way of being able to address any concerns that may develop (Dunleavy et al., 2018), and it was possible that these factors were a positive influence on trial recruitment for the ENErGy trial.
6.5.2. Sources of recruitment and the benefit of staff education

On closer examination of the recruitment figures, the highest number of referrals came from St Columba’s Hospice’s own or closely affiliated teams. The hospice’s community palliative care team recruited the greatest number of participants (27 referrals and 15 (56%) recruited), followed by the regional pain clinic - run by the CI of the trial, (eight referrals, seven (88%) recruited) - followed by the hospice’s East Lothian palliative care team (nine referred, four (44%) recruited). The St Columba’s hospice IPU was a source of five referrals, of which three (60%) were recruited.

These findings are perhaps not unexpected as the research team had the greatest day-to-day contact with their own affiliated teams. The additional measures taken by the research team of screening all external referrals resulted in many potential participants (52) but only eight (16%) recruited to the trial. This proved to be a time-consuming commitment for the research team with relatively small net gain. However, it did still identify participants who would otherwise have ‘slipped through the net’ and may be a valid screening tool to use in future trials, depending on available resources.

It is commonplace that trials recruit best at their own sites, and in a recent paper eight new reasons for recruitment failure were identified for RCTs from interviews with an international delegate of clinical trial stakeholders (Briel et al., 2021). Some of these points are relatable to issues encountered with the ENeRgy trial and its affiliated sites, where recruitment figures were poorer. New reasons identified within this paper included: funding related (either initially insufficient or ongoing funding not unavailable); research environment related (high quality healthcare systems with many options available - therefore a lack of incentive), design related (research question insufficiently compelling, or too few recruiting sites planned/ too few study staff and lack of patient engagement in trial design/ planning). Lack of staff competence, training and experience (including inadequate planning, “enthusiasm” lacking,
and issues with staff turnover and “trial fatigue”). Indeed, when initially proposing the trial at the second Edinburgh Hospice, there was a palpable sense of trial fatigue which I suspect may have contributed to lack of engagement. This is a point which is important to bear in mind for a future multi-centre study, though I believe trial fatigue was offset by the subsequent enthusiasm shown when staff were given face-to-face education about the ENEnergy trial, its rationale and potential impact. This, as well as the fact that there will be PPI involvement in the larger phase three trial design, should ensure that the research question remains relevant and attractive to potential participants.

Although the research team gave education sessions at three Oncology team meetings on separate occasions between March and June 2018, there remained relatively few referrals to the trial from this source (six patients over the duration of the recruitment period). Of these referrals, no patients were recruited to the trial. Reasons for this included: two patients who were ineligible (one due to short prognosis and the other on anti-cancer treatment), one participant declined due to travel concerns and another gave no reason. Two participants declined due to ‘other’ reasons: one was feeling too unwell and the other reason was not clearly documented.

Although these teams were contacted by the research nurse via a link person (for example hospital research nurse) it was often difficult to contact the referrer directly and as such, less regular prompting of these teams was possible.

In future studies, a way around this may be for a member of the research team to attend hospital MDT meetings to prompt and/or try to identify potential participants. Again, this may be limited by resources and highlights the need for good, consistent communication with referring teams as well as the benefits of building a good rapport with key staff at an early stage.
6.5.3. Overcoming barriers to recruitment

Barriers to recruitment are not uncommon, and one of the most difficult to overcome is that of professional gatekeeping (Dunleavy et al., 2018).

Gatekeeping in this context is when healthcare professionals prevent researchers from approaching their patients and/or carers from taking part in a study. Multiple factors contribute to this, as outlined by Dunleavy et al, including fears of overburdening, seeing patients as being too unwell, lack of belief in the intervention and concerns regarding randomisation. Numerous examples of these same barriers were encountered during the ENeRgy trial, and some of these undoubtedly influenced recruitment rates. For example, the plan was to recruit the majority of participants from the two hospice community palliative care teams in Edinburgh. In spite of meeting with the second hospice five months prior to the opening of the trial, (August 2017) consent was not gained to begin recruitment until almost a year later. This came after multiple meetings and negotiation of terms.

Reasons cited by the second site for not being able to facilitate recruitment for the ENeRgy trial included: concerns over travel distance for their patients; concerns over access of participants to hospice outpatient classes (including one physical exercise and one fatigue, anxiety and breathlessness class); concerns that their patients would be too unwell (<3 month prognosis) and that patients would ineligible as they may be undergoing anti-cancer treatments. The hospice stated that they were already committed to other research activities and there was the concern that the ENeRgy trial would overburden staff. The hospice initially proposed that they would allow recruitment only if the study could be run at their own hospice, and provided their patients had access to all of their therapy groups. These terms were eventually negotiated and an agreement was reached on 27th June 2018. The earliest date for an education session was one month later meaning that recruitment from this source did not begin until six months after the trial opening date. There were also concerns from the second site over conflicting
studies for their West Lothian community palliative care team. Recruitment permission was eventually granted for this team in February 2019, 13 months into trial recruitment.

6.5.4. Recruitment rates from different sites

Overall recruitment levels for participants referred by community palliative care teams ranged from 44-67%. Comparing referral rates per month between the two hospice teams showed that the trial home site had a consistent referral rate of 1.6 to 1.8 patients per month. The referral rate from the second site’s team remained low for the duration at 0.3 patients per month (3 patients in total over 9 months). Once the West Lothian community palliative care team were enabled to recruit, the team showed great enthusiasm from the outset and referred four patients in two months.

Reasons for the differences in recruitment between the two sites are not clear. It is possible that different levels of engagement from the trial research teams and resource issues may have played a role. Compared with weekly face-to-face visits at the home site, weekly phone calls to the second site team lead resulted in only a very small number of patients being referred. It was also not possible to screen all referrals for the other sites as was done at St Columba’s Hospice.

Clinical teams may feel over-burdened and therefore lack engagement with clinical trials. Research may be seen as an additional demand, competing with busy clinical workloads. Staff may not see research as part of their job role or and may not have research in their job description (Turner and Payne, 2009). Clinical staff often report that they are ‘too busy’ to identify participants for research trials and this is a known barrier to recruitment rates (Dunleavy et al., 2018).

Hospices have historically been challenging places to instigate research, and in 2013 a report by Hospice UK identified barriers to research including a
culture of hospices not always being open to research, and at times an apathy and even hostility towards research. This can be amplified by a lack of funding, and made more challenging by lack of affiliation with NHS or university sectors. Although barriers to promoting research within hospices exist, these can be overcome by fostering a culture shift toward including research as a core component of hospice activity (Payne, 2013).

6.5.5. Other challenges

As well as barriers encountered with partner sites, there were administrative and governance hurdles to be crossed setting up the research at the base hospice. These hurdles required negotiation skills and diplomacy, for example, finding adequate room space and negotiations with the Day Therapies Manager as to when these rooms could be used. Multiple risk assessments were required, for example, to assess the risks of participants performing walking tests. None of these hurdles was insurmountable and the tasks were tackled with enthusiasm as they arose. These issues are not unique and have been documented in the past as some of the hurdles to hospice based research (Dunleavy et al., 2011).

Involving key staff from the trial’s conception was a vital strategy (in this case including the hospice Medical Director, Day Therapies and Clinical Services Manager) and helped to promote collaborations for the duration of the trial which, along with regular face-to-face engagement with collaborating sites, are factors which may prove beneficial for setting up and improving recruitment for future studies.

In terms of overall recruitment rate, the ENeRgy trial recruited 49% of patients approached who were eligible (45 of 92). This level is much higher than some other feasibility trials, for example 11.5% quoted by Solheim et al in 2017, but lower than others, for example Naito et al (2019) who recruited 30 of 46 screened patients (65%).
6.5.6. Reasons participants declined and mitigating factors

Where participants were approached and declined to take part (47 of 92 approached = 51%) the most frequent reason was due to the time commitment required for the trial. Indeed, this was a concern mentioned by the second hospice site as a potential barrier to recruitment, but only accounted for four participants (4%) of 92 approached. The next most cited reason was fatigue (as well as ‘reason not-specified’), and equal third place was concerns over travel and participants feeling too unwell. The least cited reason was concerns over taking the ONS.

These findings are in keeping with barriers to recruiting patients with advanced cancer to exercise trials: the most commonly cited reason being a lack of time which can be a barrier in up to 50% of patients approached (Cheville et al., 2010). The next most cited reasons for declining to participate are multiple hospital commitments, transport issues or lack of interest in exercise or research (Sheill et al., 2019). Fatigue is often cited as a barrier to recruitment to exercise trials, in one trial of a six week mixed exercise programme for patients with incurable (GI and other) cancer, the recruitment rate was just 15% due to 52 of 61 potential participants feeling too fatigued to take part (Lowe et al., 2013).

Due to the significant symptom burden in patients with incurable cancer, and the potentially short prognosis, it is entirely understandable that these concerns were prevalent. Elements of the trial were designed to specifically mitigate these factors, including offering free transport by taxi to/from the hospice for trial-related activity and giving participants the option of undertaking assessments by telephone if they felt too unwell to come in. Flexible (two weekly) windows were built in for trial assessments in case participants had conflicting demands or felt too unwell to attend. For participants who felt unable to take ONS there was the option of taking equipotent doses of Ω-3 fatty acid capsules. By incorporating these elements
into the trial design, concerns raised by participants at the point of recruitment could often be quickly addressed, and it is possible that this helped aid recruitment and retention.

During the ENeRgy trial there was also good support from the base Hospice, who publicised it proudly. The trial was featured in a number of hospice publications including ‘Life’ magazine, and the trial featured on the hospice website, alongside a list of affiliated publications from the research team members. There was deliberate creation of a positive brand logo for the trial, and the team members wore ENeRgy logo branded polo shirts. Some participants commented that this attire was ‘less intimidating’ than hospital style healthcare uniforms, and put them at ease. Some also remarked that the trial had changed their perception of the hospice, which to some had always been affiliated with end-of-life care. Participants were issued with canvas bags sporting the trial logo: this was deliberate, and with a view to making participants feel that they were involved in something positive and unique. Creating a positive brand for trials is a use of a marketing strategy which can help to create a ‘brand value’ and helps to communicate a perception of a trial’s promise (Francis et al., 2007). It is possible that this factor helped with recruitment and retention of participants in the trial [Figure 32].
The ENeRgy trial logo is designed to bring a sense of positivity and a ‘brand value’.

Figure 32: ENeRgy trial branding

ENeRgy research team members wearing branded polo shirts in one of the hospice Day Therapy rooms overlooking the Forth of Firth, from left to right: Dr Charlie Hall (Medical Research Fellow), Honor Blackwood (Trial Dietitian), Valerie Gibson (Trial Physiotherapy Assistant) and Dr Barry Laird (Chief Investigator).
6.5.7. Timing considerations

There was a decision made by the TMG group to extend recruitment by two months (from 13 to 15 months) in total, due primarily to a reduction in recruitment rates over the festive period. For participants with incurable cancer, enrolling in such a trial prior to what may be their last Christmas is a big commitment so it understandable that recruitment rates dropped in the lead up. A similar phenomenon has been shown in recruitment to paediatric clinical trials (Kaur et al., 2016). However, in spite of the extension to the recruitment period, the number of participants enrolled into the study by the 13 month stage (original recruitment period) was still 37 out of a target of 40. Therefore, even without the extension to recruitment, it can be concluded that the recruitment rate to the trial was feasible.

Key factors to be taken forward to future trials are early engagement of key staff and face-to-face education sessions for recruiters. Regular (ideally face-to-face) prompting and plenty of motivation/enthusiasm from the research team are helpful. Ensuring that features of the trial design are favourable to the participant population, and adjusting recruitment targets to take into consideration public holidays may also help to recruit and retain participants, and may improve the chance of future trial recruitment targets being met in this population.

6.6. Attrition

The overall attrition rate for the trial was 36% (16 of 45 participants recruited). This is less than has been previously quoted for similar patient populations - as described below.
6.6.1. Causes of attrition

In a secondary analysis of 18 prospective interventional supportive care and palliative oncology trials by Hui et al (2013), median attrition rates prior to study endpoint were as high as 44%. The main reasons for attrition were mostly due to participant withdrawal (48-52%) and clinical deterioration (23-35%). The authors found a positive correlation between participants who had higher levels of fatigue, and that longer trial designs and outpatient studies had a higher attrition rate (47% compared to 6% for inpatient studies).

In trials of exercise interventions for patients with advanced cancer, attrition rates ranged from 10 to 42% with a mean of 24%. Advancing disease was the most commonly cited reason for dropout from exercise interventions. Other reasons cited included family commitments, unrelated medical conditions, hospitalisation, feeling too ill or overwhelmed (Sheill et al., 2019). In one palliative care trial of an exercise intervention, the attrition rate was 66%, due to patients being admitted to hospital, feeling overwhelmed or due to poorly controlled symptoms (Lowe et al., 2013), though this was a small trial (n=9).

The reasons for attrition in the ENeRgy trial were in keeping with these findings: the most common reason (12 of 16 participants, 75%) for withdrawal was due to deteriorating health and the remainder of withdrawals were due to travel distance (two participants, 12.5%) and two participants (12.5%) for ‘other’ reasons: one who left the country to seek alternate treatments; the other left on holiday and was lost to follow up.

6.6.2. Comparison of attrition between arms

Examining the attrition rates more closely between both arms of the ENeRgy trial, there was a higher attrition rate in the control arm compared to the intervention arm (41% compared to 30%). In addition, a greater proportion of those who dropped out from the control arm were due to deteriorating health
compared to the intervention arm (89% compared to 57%). Although the study was not powered to show significance in the secondary endpoints and thus this finding may have occurred by chance, this is a notable difference.

Importantly, aside from travel reasons, there were no participants who withdrew from the trial because it was overly burdensome, or too long. Indeed in a systematic review of exercise interventions for patients with advanced cancer, the frequency, number and duration of exercise sessions did not correlate with attrition rates ($r=0.001$, $P=0.069$) (Sheill et al., 2019).

This implies that the trial design was feasible in terms of trial length and that the interventions were not unduly burdensome. Means of reducing concerns about travel may be mitigated in future studies if multiple study sites are available, so that participants do not have to travel any further than the distance they would expect to travel to their own local hospice.

6.7. Contamination

Compared to some trial designs where plasma fatty acids are gathered and analysed to give evidence of exogenous EPA supplementation (Solheim et al., 2017b), the ENeRgy trial attempted to gauge contamination by participants voluntarily disclosing any non-trial supplements or additional exercise.

In the control arm, there was one participant who started taking Fortisip one week after enrolment, and another who increased their ONS prescription from one type of supplement to two types per day after the same time scale. Although this may have been by chance, there is a possibility that this was evidence of contamination; however without evidence of plasma EPA levels, there is no other objective evidence of exogenous EPA supplementation. EPA supplements are widely advertised and easily available over the
counter; however, to achieve equipotent doses, the participants would have required to take a very large number of conventionally available capsules.

In terms of nutritional outcomes, there was no evidence of increased AVeS or reduced aPG-SGA scores in the control arm compared to the intervention arm. There was a higher mean and median average weekly minutes aerobic exercise in the control arm compared to the intervention arm, which may indicate that there were participants in the control arm who were exercising significant amounts. However, there was an outlier in the control arm who may have skewed these values with such a small sample size (an ex-wrestler who did significant amounts of exercise).

Future trial designs may wish to include measurement of other blood/plasma parameters (such as markers of systemic inflammation) and measurement of plasma fatty acids could potentially be added to the array of tests done. If there was contamination in the present trial, it appears to have been minimal and was not significant enough to have invalidated the differences between intervention and control arms.

6.8. Impact on physical function

Physical function measures included comparison of the change from baseline to endpoint of the following: mean daily step counts, TUG time (seconds), TMWT (metres) Life Space Assessment scores and KPS.

The trial was not adequately powered to expect any significant differences in these secondary (exploratory) outcomes as was the case when analysing the data for these parameters. There were marked differences in mean and median step counts meaning that the data for steps were abnormally distributed as evidenced by large inter-quartile ranges (IQR) [Table 10, chapter 5.4] because there were individuals in each arm with significant
changes (both increases and decreases in daily step counts) between baseline and endpoints of the trial.

6.8.1. Daily step count

The waterfall plot [Figure 26], in chapter 5.4 shows that there was a mix of participants whose individual step counts dropped in both arms of the trial. The largest drop in mean daily step count in each arm was similar (-7759 steps in the intervention arm and -6788 steps in the control arm) and there was a larger proportion of participants from both arms of the trial whose step counts declined from baseline to endpoint. This is perhaps not unexpected as the demographics of the trial population showed a higher proportion of participants with a KPS score in the 60-80% category whose function was already compromised.

Participants’ ability to endure progressively less sustained periods of activity due to disease and with lower performance status has been noted previously (Dahele et al., 2007, Maddocks and Wilcock, 2012). Thus, over the course of eight-weeks, progressive disease was most likely the cause of the deterioration in physical function (irrespective of the intervention). However, looking at the numbers of participants whose step counts increased from baseline to endpoint, there was a greater number of participants in the intervention arm with a mean increase of >1000 steps per day.

Although the minimally important clinical differences (MCID) for step counts are yet to be established in patients with incurable cancer, it has been noted that patients with advanced disease prior to palliative chemotherapy take 45% fewer steps (3947 ± 2885 vs. 7239 ± 2885) and spend an extra 2.8 hours per day sitting or lying compared to patients with early disease (P= 0.001) (Ferriolli et al., 2012). Categories of MCID have been previously established in COPD. Two studies have examined the MCID for step counts in patients with COPD and the association with adverse medical events and
time to hospitalisation after rehabilitation. One study showed that a reduction in daily step count of between 350-1100 steps/day was associated with adverse medical events (Teylan, 2018). Another study showed that for patients with COPD undergoing pulmonary rehabilitation, an increase in daily step count of between 600 to 1100 steps per day resulted in a reduced risk of hospital admission.

There is the need for future trials to ascertain the MCID in terms of daily step counts that correlate to health outcomes for patients with incurable cancer. This is particularly relevant due to the emerging number of clinical trials using PAMs (Purswani et al., 2018).

Ferriolli et al in 2012 found that step count per day measured by ActivPAL™ PAM showed significant correlations between both ECOG-PS score and KPS score. They demonstrated that daily step counts reduced significantly with worsening ECOG-PS and KPS in patients with upper GI malignancies (P=0.002 and P=0.016 respectively). Of note, the group also reported that in a subgroup of patients (including patients receiving palliative chemotherapy), step count was significantly associated with certain domains of self-reported QoL (physical function, role function and fatigue domains of the EORTC-QLQ-C30 questionnaire).

Another study looking at physical activity (PA) in patients with cancer showed similar results to the ENeRgy trial in terms of daily step counts for patients with advanced cancer: Maddocks et al in 2012 examined relationships between PA and ECOG-PS for a population of patients with incurable thoracic malignancies. An ActivPAL™ PAM recorded aspects of PA including time spent sitting or lying, sit-to-stand transitions and step count. The group identified that there were significant differences between ECOG-PS groups in all aspects of PA excluding sit-to-stand transitions. Participants with an ECOG-PS 0 (=KPS 100: ‘fully active, able to carry on pre-disease performance without restriction’) had a mean (SD) daily step count of 8126
(3334) steps. Participants with an ECOG-PS 1 (=KPS 80-90: ‘restricted in physically strenuous activity but ambulatory and able to carry out work of light or sedentary nature’) had a mean (SD) daily step count of 3791 (2064). Finally, participants with ECOG-PS 2 (=KPS 60-70: ‘ambulatory and capable of self-care but unable to carry out work activities, up >50% of waking hours’) had a mean (SD) daily step count of 2307 (1518) (Oken et al., 1982, Maddocks and Wilcock, 2012). These step counts correlate closely to the mean daily step counts in the ENeRgy trial: for example, the majority of participants in the KPS 60-80 category (=ECOG-PS 1-2) had mean daily step counts between 2700 and 3300.

Of note, both of these trials and the ENErgy trial showed large standard deviations in step counts reflective of wide variations between participants in activity levels, even within the same performance status group. This does mean that in order for future trials to reliably ascertain differences between step counts and MCID, much larger sample sizes would be required. There is also the suggestion that due to the large decline (>30%) in step counts between ECOG-PS groups, objective measures of PA including step counts could provide more detailed and discriminate assessment of physical function than ECOG-PS (Maddocks and Wilcock, 2012).

Future post-hoc analysis of the ENeRgy trial data may provide insights into whether any correlation exists between step count and other PRO such as QoL scores, or whether step count and KPS are in any way linked to predictors of trial completion or attrition.

6.8.2. Timed up and go and two-minute walk test

There were no statistically significant differences seen between baseline and endpoint TUG and TMWT for participants in either arm of the trial (P=0.767 and P=0.484 respectively). However, once again examining individual
changes in participant performance illustrated by the waterfall plots [Figures 27 and 28, chapter 5.4] there are trends worth noting.

There was a greater median increase (ie. worsening performance) in TUG times in the intervention (21%) compared to the control arm (5%). However, there were a greater number of participants who reduced their TUG times from baseline to endpoint in the intervention arm (eight participants) compared to the control arm (three). Due to outlying values, data were not normally distributed and this was reflected in a marked difference between mean and median values. For example, the mean value of the intervention arm was pulled in to the positive due to one participant who had a very large deterioration in their TUG time. The median difference (%) between arms was therefore felt to be a more reliable indicator of true change and this reflects that there was a small, but nonetheless notable trend towards improvement in TUG times in the intervention arm (-4.5%) compared to the control arm (+4.5%).

TMWT distances showed no significant difference between arms of the trial and were similarly abnormally distributed due to the small sample size and the presence of outliers, for example, participants whose performance dropped significantly from baseline to endpoint. It was notable however that there were many more participants who achieved both measurements (due to less attrition) in the intervention arm (n=16) compared to the control arm (n=10). Again, a much larger sample size will be required to ascertain whether this is of statistical significance and can be attributed to the intervention rather than just chance.

Multiple other trials testing exercise and nutritional interventions have shown trends towards improvement in physical testing as evidenced by the findings of the systematic review (chapter 2.3.3). In six studies, although trial quality rated ‘low’, due to the overall magnitude of effect seen with improvement in physical endurance and power, the GRADE score of evidence for
improvements in physical endurance/power was upgraded to ‘moderate’ [Table 3 chapter 2.3.7] (Hall et al., 2019).

### 6.8.3. Life space assessment

The scores for LSA were more normally distributed for both arms of the trial, and there were no statistically significant differences between scores at baseline and endpoint in either arm of the trial (P=0.1).

The LSA is designed to measure a participant's movement within their own environment, by asking where and how often subjects travel and whether they have needed any assistance in the four weeks prior to assessment. The advantage of this assessment is that it asks what a person has actually done rather than asking what they could do. It is applicable to palliative care populations (Phillips et al., 2014). This measure is appropriate to use in such a trial and it should be considered for future larger-trial designs.

Goals of ‘rehabilitation’ in the context of patients with incurable cancer are most often ‘supportive’ or ‘palliative’ as per Dietz’ classification system [Table 1, chapter 1.3.3]. Supportive or palliative rehabilitation goals relate to maximising a participant’s functional independence or involvement in activities (in the context of established impairments) and adapting where there is irreversible loss of function. With this in mind, a person with incurable cancer is likely to have goals that are set to achieving ‘normality’ or managing ‘usual activities’ such as getting out in the garden or to the shops or visiting other family members. The LSA as a functional measure can therefore capture increase in frequency of these types of normal activity. It is therefore potentially useful in reflecting a person’s functional improvements or achievements in this participant group and should be considered as an outcome measure in future trials.
6.8.4. Karnofsky performance status

There were no trends or significant changes evident in KPS scores between arms of the trial, probably due to the relatively small sample size: any difference may become apparent in a larger phase three trial. The median baseline KPS for both arms of the trial was 80 (IQR 60-60), and the median endpoint KPS for both arms was also 80 (IQR 60-60). There was a dip in the median midpoint KPS for the control arm to 70 compared to 80 in the intervention arm.

The scatter plots [Figure 29, chapter 5.4] illustrate changes in individual participant KPS from baseline to endpoint: there were similar numbers of participants whose KPS improved, remained static or dropped throughout the course of the trial in both arms. However, there were more pre-post comparisons available for the intervention arm (n=16) than the control arm (n=13) due to the higher rate of attrition in the control arm. A suggestion for a future post-hoc analysis would be to examine whether there is a correlation between KPS scores of those participants who dropped out of the trial, and whether a certain change in score, perhaps a reduction of 20 points from baseline, was a predictor of attrition.

6.9. Impact on nutritional status

There was a non-significant (P=0.184) trend towards weight stabilisation/gain in the intervention arm (median change +1% body weight baseline to endpoint) compared to the control arm (mean change -0.48% body weight baseline to endpoint). Comparison of aPG-SGA scores and AveS scores between baseline and endpoint revealed no significant differences (P=0.244 and P=0.398 respectively).

Looking at these results in light of previous studies, Solheim et al (2017) showed that participants in the treatment arm of the six-week multi-modal intervention combining exercise, omega-3 rich ONS and oral celecoxib...
gained 1.29% body weight, whereas those in the control arm lost 3.19% (P=<0.001). The ENeRgy trial revealed a trend similar to this trial; however, it used the omega-3 rich ONS alone without NSAIDs. Although Solheim et al reported a significant difference in weight, there was no significant difference shown in muscle mass in these arms nor physical function. Similar also to the ENeRgy trial, their 2017 feasibility trial was not adequately powered for secondary outcomes, and thus the authors highlighted that the results should be interpreted with caution.

Weight loss is a key component of cancer cachexia and is associated with psychosocial distress, depression and anxiety in patients with advanced cancer (Rhondali et al., 2013). It is not implausible that there is a link between the improvement in depression scores, for which there is moderate evidence (Hall et al., 2019) and the improvement or stabilisation of weight described in patients undergoing combined exercise and nutritional rehabilitation programmes [chapter 2.3.4]. The concept of putting on or maintaining weight was one of the themes described as a factor important to participants as their motivation for taking part in the ENeRgy trial, as described in the sister qualitative trial ENeRgy-Q (unpublished data). Multiple participants described maintenance or gain of weight as being associated with wellness in the context of advancing cancer, and that loss of weight was worrying for them. Participants described the importance of the dietitian, particularly relating to the dietary fortification aspect of the intervention. The dietary advice they were able to access from the dietitian and the reassurance that was needed was vital for some participants. One participant described the difficulty of changing life-long ‘healthy’ eating habits (associated with the goal of weight loss), as opposed to the advice given in the context of advanced cancer, where the aim is to gain or maintain weight. [unpublished data].

The importance of the role of the dietitian in facilitating the dietary elements of the ENeRgy trial cannot be overstated. For many participants enrolled in
the trial, this was their first meeting with a dietitian in their whole cancer journey. Future trials should ensure that the dietary interventions are delivered by a registered dietitian to ensure compliance with dietary modification and ONS prescriptions are maximised.

It has been suggested that weight and physical function are meaningful outcomes to use in future cachexia trials; however, there are issues with weight as a measure, and whether increases in weight can be caused by other factors such as fluid retention - especially where NSAIDS are used as part of the intervention (Schlondorff, 1993). The use of bioelectrical impedance analysis (BIA) to allow for estimations of total body water (Bauer et al., 2005) or CT imaging to calculate muscle mass (Solheim et al., 2017b) can overcome this issue but the appropriateness of these procedures and the burden on patients with advanced cancer undertaking rehabilitation trials must be weighed up in future trial designs.

6.10. Impact on participant and carer quality of life

6.10.1. EORTC-QLQ-C15-PAL questionnaire

The questionnaire looks at participant QoL and is split into domains including physical and emotional function, as well as QoL single score and specific symptom scores. There was one statistically significant finding within the major domains of the questionnaire: a significant difference (P=0.006) in emotional functioning between the intervention and control arm. No other aspects of the questionnaire showed significant improvements.

Firstly, it is important to say that, as the trial was not powered to prove secondary endpoints these results should be interpreted with caution. However, the emotional functioning component, was made up of questions 13-14 of the questionnaire (during the past week) “did you feel tense?” and “did you feel depressed?”. The difference seen was due to a maintenance in
median score of 100 in the intervention arm compared to a drop of 16.7% from 100 to a median of 83.3 in the control arm. In spite of the low numbers this change was enough to be statistically significant, in keeping with the findings from the systematic review, which showed the strongest evidence for improvements in depression scores (and physical function) after multi-modal rehabilitation programmes containing nutritional components, as described in [chapter 2.3.6] (Hall et al., 2019). Strong consideration should therefore be given to placing the emotional function sub-category of the EORTC-QLQ-C15-PAL as a primary outcome for a larger phase three trial.

Mood is a very important component of QoL, and although not enough in itself to influence the overall score of the EORTC questionnaire, in a larger trial it may be significantly influenced if improvements in other domains are also experienced preferentially by the intervention arm (such as physical function).

6.10.2. Caregiver quality of life index-cancer questionnaire

There was a non-significant trend towards improvement in carer QoL for carers of patients in the intervention arm compared to a reduction in QoL for the control arm (P=0.5).

To date there are no studies involving rehabilitation interventions which have examined carer QoL using the CQOLC and in a subsequent larger trial, it would be very interesting to show whether this trend became statistically significant. Consideration should be given to extending the remit of the CQOLC questionnaire to include all family carers rather than just partner-carers as discussed in chapter 6.4.1. This would potentially increase the number of carers eligible to complete the CQOLC questionnaire and give more statistical power. In the present study, although many partner-carers agreed to participate in the study, the numbers of completed CQOLC questionnaires was low: six and four questionnaires at baseline for
intervention and control arms respectively, and four and two at endpoint, which makes the validity of these conclusions less reliable.

6.10.3. Sleep

Sleep parameters were measured by the PAM at baseline and endpoint during the test weeks and data analysed using means of all nights of the week. There were no significant differences in sleep parameters. The trends in the data were interesting and some are in keeping with what may be expected for patients with advanced cancer over 10 weeks. Both arms increased the overall number of minutes asleep from baseline to endpoint and both arms had an increase in time in bed. This may not be unexpected in a person with advancing disease - to be more sedentary or require increasing periods of sleep.

One of the issues with these sleep data is that there are not at present any MCID established for sleep parameters. For example, how many minutes of additional sleep does it take for a participant to feel more ‘well/rested’- or indeed is this the correct measurement? Would the number of awakenings at night be more important to participants in the context of sleep quality in a person with advanced cancer, due to symptoms such as pain?

Alternatives are subjective or PRO measures of sleep quality, for example in the study by Cheville et al in 2013. In this RCT, participants with stage four colorectal and lung cancer were randomly assigned to receive an eight-week home-based exercise programme. Sleep quality was assessed using the M.D. Anderson symptom inventory, which uses a numeric rating scale (0-10) to assess sleep quality. According to this trial, participants receiving the intervention had significantly improved sleep quality (P=0.05) compared to controls (Cheville et al., 2013).
Although more work is required to establish MCID for accelerometer-based data (Maddocks and Granger, 2018), sleep parameters for the Fitbit have recently been validated in studies comparing them to research grade activity monitors (the accepted alternative to polysomnography) (Hamill et al., 2020). However, the authors advise that caution be taken when interpreting the sleep data as the technology is still in infancy.

Future trial designs should consider incorporating dual outcomes to assess sleep quality combining wearable activity monitors with a PRO enquiring after the participant’s subjective evaluation of sleep quality (Brooks et al., 1993, Hamill et al., 2020). This may not only help to correlate sleep data with participant experience but may also help define MCID for sleep data in the future.

### 6.11. Survival

There was no significant difference in survival data for participants in the different arms of the trial; indeed, there was an equal number of deaths prior to trial closure in both arms (11 each). There was a higher number of deaths for participants in the lower (60-80%) KPS category in both arms of the trial (63% of deaths in the intervention arm and 73% in the control arm). This is not unexpected, as lower performance status is also correlated with poorer survival, first demonstrated over 30 years ago (Evans and McCarthy, 1985). Of those who died prior to trial closure, between 36% (intervention arm) and 45% (control arm) died before 90 days, the minimum expected survival for participants to be eligible for inclusion.

A barrier to success of palliative care trials is failure to recruit due to complex inclusion criteria: this includes estimates of survival (Dunleavy et al., 2018). These data reflect that fact - it can be extremely difficult for clinicians to prognosticate accurately in patients with advanced cancer. Prognostic tools using inflammatory markers are becoming used more widely, including the
mGPS which can help to identify patients who are more likely to have a prognosis of less than three months (McMillan, 2013), and this may be usefully employed in stratifying patients in a larger phase three trial. Markers of systemic inflammation were not measured in the ENeRgy trial. However, future trials should consider whether measurement of CRP and albumin to calculate mGPS scores to stratify participants may be beneficial. This could have the benefit not only of aiding to identify those participants at greatest risk of attrition, but may further help to identify whether certain groups (eg. with lower or higher levels of systemic inflammation) gain any greater benefit from multi-modal rehabilitation programmes using the cancer cachexia treatment paradigm.

6.12. Adverse events

Although not strictly a secondary endpoint, AEs were monitored as part of the trial and warrant discussion in relation to the feasibility of the trial and implications for future trial design. Although there were 39 AEs for participants throughout the trial (20 in the intervention and 19 in the control arm) there were no SAEs. AEs which were serious enough to warrant admission were always related either to the underlying cancer or pre-existing conditions and therefore did not meet the criteria for an SAE.

Within the treatment arm, although there were nine AEs relating to the ONS (discussed in chapter 6.5.1), there were no AEs relating to the exercise element of the intervention which is in contrast to the trial by Naito et al (2019) where participants suffered AEs relating to the intervention (home based low intensity exercise training and counselling to promote physical activity), including muscle pain, arthralgia, dyspnoea on exertion and plantar aponeurosis (Naito et al., 2019).
Chapter 7. Phase three trial proposal: ‘ENeRgise’

7.1. Introduction

Following on from the success of the ENeRgy trial, there are plans to proceed with a follow-on phase three trial, entitled ‘ENeRgise’. Funding applications are currently in progress for this study from organisations including the World Cancer Research Fund. This chapter describes the plan for the future trial in terms of the following: endpoints; interventions; population; stratification and length/ types of interventions, and aims to describe how the work and lessons learned from the SR and ENeRgy trial will be taken forward and incorporated in to this larger multicentre trial. Results of the ENeRgy feasibility trial and discussions of limitations have fed directly in to the design of ENeRgise, including outcomes, plans for data collection (including inflammatory status of participants), recruitment strategies and trial procedures. Importantly, it is worth noting that although the information below is a proposal, there is still scope to discuss some of the final outcomes to be used in the trial protocol (such as physical function measures alongside step count). The results of the SR will be taken in to consideration when choosing these, and may influence the final choice of outcomes for ENeRgise in a way that it did not for the ENeRgy trial (further discussed in chapter 8.1).

7.2. Design

The trial will be an international, open label randomised trial of an Exercise and Nutrition based Rehabilitation programme (ENeRgise), delivered by healthcare professionals, versus standard care for patients with life limiting cancer. Following consent (baseline) and wearing of an activity monitor (this will most likely be a commercially available monitor such as the Fitbit® rather than a research grade monitor for the reasons discussed in chapter 6.3.3) for
seven days. Participants will then be randomised into the intervention or standard care (control) arm for eight weeks (endpoint). Patients will then wear the activity monitor for a further seven days (total trial duration ten weeks).

7.2.1. Trial Centres

1) Edinburgh Cancer Centre, Edinburgh, UK: Dr Barry Laird, Professor Marie Fallon. 2) St James Hospital/ Our Lady’s Hospice, Dublin, Ireland: Professor Andrew Davies. 3) St Olav’s Hospital, Trondheim, Norway: Professor Tora Solheim. 4) Maastricht University Hospital, Maastricht, Netherlands: Professor Annemie Scholls. 5) St Wilfred’s/ St Michael’s Hospice, East Sussex Healthcare NHS Trust, Eastbourne/ Hastings, UK: Dr Farida Malik. 6) Prince and Princess of Wales Hospice, Glasgow, UK: Dr Alistair McKeown.

Choice of centres has been informed by three aspects: trial centres have a history of high quality research in nutrition and rehabilitation as well as the necessary infrastructure to support the trial. Secondly the trial centres include a mix of cancer centres and specialist palliative care units (hospices) to optimise recruitment and generate a mix of patients receiving hospital and palliative care. Lastly, several sites (Edinburgh, Dublin, Trondheim and Maastricht) have world leading researchers in nutrition and supportive care. Education sessions will be delivered at each of the trial centres and early involvement of key stakeholders and recruiting teams will be vital.

7.2.2. Hypothesis

The hypothesis for ENeRgise is that an exercise and nutrition-based rehabilitation programme improves quality of life in people with life limiting cancer.
7.3. Participants

7.3.1. Inclusion criteria:
1. Community dwelling (ambulatory) adults (≥ 18 years)
2. Diagnosis of cancer (histological, cytological, radiological and/or multidisciplinary consensus) with life limiting prognosis
3. ECOG performance status score 0-3
4. Life expectancy of >3 months based on judgement of treating clinician
5. Able to comply with trial interventions (in the opinion of the referring clinician) e.g. willing and able to do light exercise and take an ONS
6. Provide written informed consent
7. Weight loss >2% in the previous two months

7.3.2. Exclusion criteria:
1. Patients with breast cancer*
2. Patients receiving parenteral nutrition or enteral nutrition via feeding tube
3. Patients with dysphagia
4. Corticosteroids are allowed if on a stable or tapering dose for two weeks prior to enrolment. Patients taking inhaled corticosteroids are permitted.

* Patients with breast cancer will be excluded due to a body of evidence which exists showing that SACT and rehabilitation can improve QoL in these patients, therefore potentially confounding the results.

7.3.3. Participant pathway and stratification
- Day 0 (T0): baseline trial assessments done and activity meter worn for 7 days
- Day 7 (T1): randomisation to either intervention or control arm. Patients will be stratified according both to ECOG group and also
inflammatory status (according to mGPS score combining baseline CRP and albumin)

- Weekly review appointments (intervention arm)
- Weekly telephone calls (control arm)
- Day 63 (+/- 7) (T2): endpoint trial assessments done and activity monitor worn for 7 days.

### 7.3.4. Intervention Arm

The intervention is an exercise and nutrition based rehabilitation programme. After screening, participants give informed consent. Following baseline assessment and randomisation, participants have an interview with the trial dietitian and physiotherapist. Based on this interview they will be given personalised advice on nutrition and exercise. Consideration will be given as to whether to re-name the exercise intervention a ‘tailored physical activity programme’ rather than ‘exercise programme’ for reasons discussed in chapter 6.2.1.

The exercise component will be similar to that delivered in the ENeRgy trial: a home based programme consisting of aerobic and resistance components in divided intervals as per patient choice and capability. The aerobic component will total 60 minutes of aerobic exercise per week (e.g. walking at an intensity consistent with ‘warm and slightly out of breath’ i.e. 3-4 on Modified Borg rating). The resistance component will be tailored to the individual by the physiotherapist and advised three times per week. The exercises will focus on major muscle groups in the upper and lower body using own body weight exercises such as half squats, standing press ups and shoulder thrusts and will be similar to those used in the ENeRgy trial. Due consideration will be given when the protocol is finalised, as to whether to add lifestyle coaching to the physical activity intervention. Reasons for this are discussed in more detail in chapter 8.2.4.
The nutrition component aims to ensure optimal nutritional intake and will consist of dietitian-led counselling (individualised for each patient) taking into account dietary preferences. Patients will also be provided with an energy dense, protein enriched ONS. At the present time it has not been confirmed whether this ONS will also include high dose omega three fatty acids as per the ENeRgy trial.

Written participant information will support the information given and adherence will be monitored at weekly follow up clinics, and designed using input from PPI representatives to ensure this is acceptable and easily usable from the patient perspective. During weekly clinics, regimens will be adjusted and tailored to the individual as needed, to support adherence. Flexibility will be built in to clinic reviews as they were previously in the ENeRgy trial for this reason. For example weekly reviews for those in the intervention group can be done by phone if participants are unable to attend in person and endpoint assessments can be done within seven days before or after trial completion.

7.3.5. Control Arm

The control arm will continue to receive ongoing usual care which will include ongoing specialist palliative care follow up or input from allied healthcare professionals, as per individual patient need.

The control arm will receive weekly phone calls from the research team to ensure adherence to trial related data collection and record any (non-trial) nutritional interventions and amounts of exercise undertaken. The control arm will be offered the trial intervention at the end of their involvement to minimise the chances of contamination.
7.4. Outcomes

7.4.1. Primary

The primary outcome will measure patient reported quality of life using the EORTC-QLQ-C15 PAL, emotional functioning subscale. This outcome was chosen as a result of the findings of the ENeRgy trial where emotional functioning remained significantly higher in the intervention arm (p=0.006) compared to the control arm.

7.4.2. Secondary

a) Physical activity. This will be assessed using step count measured by physical activity monitors worn at baseline and endpoint for 7 days. Other measures of physical activity are yet to be confirmed, however in view of the results of the SR, is a strong argument for including the 6MWT over the 2MWT.

b) Body weight. This remains an important and meaningful outcome to patients and clinicians with the acknowledgement that increase or reduction does not necessarily correlate directly with functional change. This as a measure in tandem with body composition and inflammatory status data (below), will allow more detailed analysis and interpretation of changes in the context of cachexia.

7.4.3. Tertiary

a) Nutritional intake- assessed using the aPG-SGA

b) Quality of life (assessed using the EORTC-QLQ C30 [summary score] and C15 PAL overall QoL score

c) Performance status (ECOG criteria)

d) Healthcare utility (assessed using the EQ-5DL questionnaire), healthcare utilisation and cost- consequences (the main indicator being inpatient days)
e) Biomarkers (bloods will be taken for blood bank and include specific assessment of CRP and albumin to generate mGPS scores)

f) Body composition (assessed using bio-impedance analysis)

All endpoints will be assessed at baseline (T0) and endpoint (T2)

7.5. Anticipated effect size

While we anticipate that the rehabilitation programme offered in the ENeRgise trial may improve patient reported QoL, it is more likely, (based on the results of ENeRgy) that a slowing will be seen in the deterioration of the intervention arm, with stabilisation of the emotional functioning aspect of health related QoL, in comparison to continued deterioration in the control arm. Previous literature states that the MCID in the emotional functioning subscale of the EORTC-QLQ-C15 PAL is nine points (Laird et al., 2016). For 90% power and an alpha 0.05, and based on the common standard deviation of 15 from previous feasibility trials (Solheim et al., 2017a, Hall et al., 2021), 60 participants per arm will be required. Due to deteriorating health we would anticipate a follow up of 70%, which gives a total target sample size of 172 participants.

7.5.1. Recruitment strategy and back up sites

It is acknowledged that there is a risk that recruitment targets are not met and this risk is mitigated by including large scale oncology centres with established clinical trial portfolios. The principle investigators within each trial sites also have an interest in the area and no competing clinical trials which will facilitate recruitment. A milestone for recruitment has been added specifically at 16 months with a target of 33% recruitment (n=57) and if this is not met two reserve sites have been identified to also add to the trial centres (St Columba’s Hospice, Edinburgh and one of the two hospices in East Sussex) to facilitate recruitment.
7.6. Analyses

The trial will be reported in accordance with consort guidelines and according to statistical analysis plan prior to data lock, approved by the trial steering committee. Analysis of the primary outcome at eight weeks will compare the two randomised groups using a linear model. This will also include an indicator variable for treatment and terms for any pre-specified baseline prognostic factors such as baseline inflammatory status (assessed using the mGPS and CRP/albumin blood results), performance status and recruiting centre. Any differences between groups will be reported with associated 95% confidence intervals and the analysis will be according to the intention to treat principle rather than per-protocol.

A health economic analysis will be performed using the method of cost consequences analysis, which has been used previously in rehabilitation studies (Gage et al., 2006). Cost-effectiveness per QALY will also be calculated, however this will not be the primary analysis due to previous criticism of this outcome in the palliative care setting (Normand, 2009). A bespoke data collection template developed and tested for the ENeRgy feasibility trial will be utilised, refined and adapted with country-specific modifiers to capture the main drivers of cost impact.

7.7. Impact and future directions

If the findings of ENeRgise are positive there would be a strong rationale for integration of nutritional and activity-related guidance in to routine care of people with life-limiting cancer. The next steps would be to proceed to implementation studies in healthcare settings around the world to assess the practicalities of introducing the intervention in to routine care, and our recommendation would be that funding for such work would be at the national or international (EU) level.
The study would generate the potential for international professional training and educational opportunities, which could be coordinated by national cancer research organisations such as the National Cancer Research Institute (NCRI) in the UK and the National Cancer Institute (NCI) in the USA. Furthermore, global collaborations to maximise the impact of this study could be managed by a consortium of international bodies such as ESPEN, the World Cancer Research Fund (WCRF) and the European Society for Medical Oncology (ESMO).

The implications of a positive result of the ENeRgise trial would be to challenge the preconception held by many healthcare professionals and patients: that nutritional and functional decline are merely irreversible consequences of cancer. By targeting these aspects, we may, in turn improve quality of life: thereby facilitating people living with cancer to live as fully as possible, as Dame Cicely Saunders advocated all those years ago.
Chapter 8. Limitations

8.1. Systematic review limitations

The search strategy may have precluded relevant articles due to stringency of the search criteria. One such factor was exclusion of studies reporting results for ‘cancer survivors’. The definition of this term is very broad, from initial diagnosis to death, and may also include family, friends or caregivers (National_Cancer_Institute, 2006).

Application of the GRADE criteria can be advantageous due to transparency of judgements about quality; however, limitations of the system (including its use for assessment of individual studies) are acknowledged (Guyatt et al., 2011b). A further challenge with GRADE is the complexity which can result in poor-to-moderate inter-rater agreement (Hartling et al., 2012). Our GRADE checklist was designed to improve this, and though effective, was not a validated tool.

The lack of RCTs (two studies) meant that meta-analysis was not possible. However, use of the robustly validated GRADE system (Meader et al., 2014, Schünemann, 2013, Atkins et al., 2004) ensured that conclusions drawn were as accurate as possible.

On reflection, the timing of the systematic review (i.e. this was started after the ENeRgy trial protocol was written) may have in turn, been a limitation to the design and/or effectiveness of the ENeRgy trial. In many cases, a systematic review of the literature is done prior to a clinical trial, to inform the design in terms of inclusion criteria, interventions used and outcomes measured (Abbas et al., 2008). In this case, the SR revealed the strongest body of evidence pertaining to changes in physical function and mood for participants of combined exercise and nutritional rehabilitation programmes. Although this would not have changed the primary (feasibility) outcomes for
ENeRgy, it may have impacted the choice of secondary (exploratory) outcomes used in the trial. Within the SR, the majority of outcomes measuring both physical activity and mood were different to the outcomes utilised in the ENeRgy trial. This may have contributed to some of the negative results of the ENeRgy trial. For example, within the SR many trials used the 6MWT (chapter 2.3.3) to measure changes in physical function, rather than the 2MWT which was chosen in ENeRgy. For measures of depression, trials within the SR frequently used the ESAS symptom scale, or the HADs score (chapter 2.3.6). Again, these were not outcome measures used within the ENeRgy trial. Therefore albeit this is not a limitation of the SR per-se, the timing of the SR, may have contributed to some of the negative results seen in the ENeRgy trial.

On reflection, it will be important to acknowledge the findings of the SR when finalising the outcomes for ENeRgise (trial proposal detailed in chapter seven). The primary outcome of ENeRgise at present is measurement of emotional functioning (a proxy for mood) from a subscale of the EORTC-QLQ-C15 PAL questionnaire. This was informed by the results of the ENeRgy feasibility trial, but there is also a strong argument for the use of the ESAS or HADs scales to measure changes in mood, informed by the findings of the SR. Physical function outcomes have not yet been fully decided upon for ENeRgise: based on the findings of the SR, there would also be a strong argument in favour of choosing the 6MWT over the 2MWT due to its previous extensive validation and widespread use in this patient population.

8.2. ENeRgy trial limitations

8.2.1. Trial design

The unblinded design of the ENeRgy trial could be perceived as a limitation to its methodology. However, the possibility of contamination in the control arm has been considered throughout and where possible, captured, and was
Limitations

minimal. Other trials where plasma lipid concentrations have been measured have still only revealed low levels of contamination (Solheim et al., 2017b). It has been suggested that participants could be given an inert unlabelled ONS of similar consistency, with no added nutritional value to blind this element. However, although this aspect of the intervention may be blinded to participants, it would not be possible to blind participants to the exercise component of the trial unless those in the control arm were given sets of stretching exercises as an alternative to resistance and aerobic exercise.

Systemic inflammation was not measured in the present trial. The ENeRgy trial was a feasibility study designed to test the intervention of a multi-modal rehabilitation programme with the potential for use in the management of people with a diagnosis of any cancer type. The interventions chosen were justified by clinical science, including the frequent presence of systemic inflammation and/or cancer cachexia in this patient group, which necessitates a multi-modal intervention. However, inflammatory status of participants was not measured and neither was it a prerequisite for enrolment. The aim of the present trial was not to assess the effects of the intervention on biochemical parameters (such as CRP), but rather to focus on the feasibility of such a trial as well as the holistic effects of the intervention on the participants in a ‘real world’ setting. The outcomes measured were focused therefore on whether the intervention is feasible in this patient group (primary outcomes), and preliminary assessment of any impact of the intervention on QoL and other parameters (secondary outcomes).

Measurements of systemic inflammation would not have provided any meaningful information for this feasibility trial. Although academically this may be of interest, to the participants undergoing the trial, these results would not be meaningful. The use of ‘surrogate outcomes’ are discouraged according to the internationally acknowledged GRADE system: “Outcomes of interest should be those important to patients: if patient-important outcomes are represented by a surrogate, they will frequently require rating down the
quality of evidence for indirectness” (Guyatt et al., 2011a). A surrogate outcome is one which may be of scientific or academic interest, yet meaningless to the patient. In this case, to focus on measuring inflammatory markers before and after the multi-modal intervention rather than the effect of the intervention on a person’s function, QoL or survival would potentially reduce the validity of the evidence produced in this trial.

Furthermore, the additional burden of bleeding this group of patients could prove a further barrier to recruitment. This group of people have completed their SACT and for most, their goals of care would now be for comfort and QoL, and as such, the idea of further blood tests may be unappealing. This, alongside the potential difficulties in obtaining blood samples in patients with potentially difficult venous access, the logistics of training research staff to undertake the tests and the associated cost of running the laboratory specimens, contributed to the decision not to measure biochemical markers of inflammation in this phase two study.

There would be a strong case for measuring inflammatory markers (e.g. serum CRP/ albumin) in a larger phase three study. In this case the greater study power might provide adequate data to determine whether stratifying patients based on their inflammatory state, alongside other measures such as KPS is useful clinically.

**8.2.2. Hidden bias**

The successful recruitment and retention to the trial may have been in part due to the recruiters being from the same centre as that in which the trial was designed, and therefore being highly motivated. This may have resulted in hidden bias, whereby the researchers tried to ensure that targets were met and participants had the best experience. Although all hospices advocate person centred care, the care and attention offered by the original research
team within the research centre may not be fully reproducible in a multi-
centre trial.

However, following the presentation of selected ENeRgy trial results at
national conferences (Including two Hospice UK annual conferences-
2018/2019), there was a very positive response from sites around the UK,
and many hospices have expressed enthusiasm and interest in being a host
centre for a subsequent larger phase three study. It will be important that
some of the methodologies including trial branding, use of research
volunteers and flexible windows of assessment, for example, are not lost as
these may have contributed to improved participant experience.

8.2.3. Reporting and recall bias

There is the potential that some methodologies employed in the ENeRgy trial
could be subject to reporting bias. For example, a participant’s interpretation
of the duration of aerobic exercise they have undertaken as well as its
intensity (the equivalent to an intensity of 3-4 rating of perceived exertion on
a modified Borg Scale).

In addition, the use of participant diaries can lead to recall and reporting bias,
particularly where a relationship has been formed with the researchers and
participants not wishing to ‘disappoint’ if they have not undertaken the target
level of exercise.

One way around this for future trials is the consideration of newer
technologies which can be used to avoid recall bias (for example recording
exercise after each session using a phone app). Otherwise, trials using
supervised exercise classes have been shown to be feasible (Uster et in
2017); however, this type of design brings with it inherent difficulties when
up-scaling to multiple sites, where the availability of equipment or space to
undertake supervised classes may be limited. Therefore, the home-based, equipment-free exercise programme has significant advantages.

8.2.4. Limitations of exercise interventions without coaching

Another limitation of the ENeRgy trial was that the exercise intervention did not include an accompanying lifestyle coaching intervention. In other diseases, particularly in COPD, evidence has shown that exercise interventions alone, do not always result in increased physical activity (Cindy Ng et al., 2012). The importance of coaching alongside exercise interventions cannot be underestimated, particularly if the benefits of an exercise intervention are to be maintained. Due to this, in pulmonary rehabilitation, there is now good evidence that exercise or physical activity programmes should be accompanied by coaching, and doing so results in significant improvements in physical activity (Demeyer et al., 2017). Coaching interventions can be delivered using newer technology, for example in the study by Demeyer et al, a smartphone app was utilised to set individualised daily goals alongside a pedometer and weekly phone calls by the researchers resulted in significantly improved 6MWT distances and functional state compared to usual care controls. Another trial has shown that sedentary behaviour is reduced and physical activity is increased in participants with COPD receiving a home based telephone coaching intervention (Coulteras et al., 2018).

The importance of learning and translating research from other disease models cannot be understated, and this aspect will be given full consideration when the ENeRgise phase three trial protocol is finalised.
Chapter 9. Conclusion

The aims of this thesis were firstly to examine the evidence for combined exercise and nutritional rehabilitation programmes in patients with incurable cancer. Secondly, to undertake a randomised controlled trial and to assess the primary (feasibility) endpoints of an eight-week exercise and nutritional rehabilitation programme (ENeRgy) versus standard care for patients with incurable cancer. Thirdly, to analyse secondary (exploratory) endpoints of the trial to ascertain any impact on physical function, nutritional status, QoL and survival.

The first aim of this thesis was achieved by undertaking a SR of the literature (presented in chapter two). It demonstrated that in spite of limited data, multi-modal rehabilitation programmes incorporating exercise and nutritional interventions improve many outcomes that are important to patients with incurable cancer, the greatest quality of evidence pertaining to physical endurance and depression scores (Hall et al., 2019). This finding lends support to the argument that exercise and nutritional interventions should form integral components of cancer rehabilitation in the future.

The second aim of this thesis was to assess the feasibility of an eight-week exercise and nutritional rehabilitation programme (ENeRgy) versus standard care for outpatients with incurable cancer. The ENeRgy trial has shown that a multimodal intervention combining an eight-week, home-based rehabilitation programme incorporating resistance and aerobic exercise, as well as dietary fortification and omega three rich ONS is feasible for a general population of patients with advanced cancer (chapter four). Trial procedures including the use of a commercially available PAM (the Flex 2 Fitbit®), weekly visits to the hospice, and the completion of trial assessments were also feasible.

The third and final aim of the thesis was to analyse secondary (exploratory) endpoints including the impact of the intervention on physical function,
nutritional status, QoL and survival (presented in chapter five). No significant differences were seen in physical function or nutritional status, though there was a non-significant trend toward weight stabilisation in the intervention arm. Although there was no significant difference in overall QoL, a significant difference (P=0.006) was seen in emotional functioning in favour of the intervention arm compared to the control arm. There was a non-significant trend towards improved carer QoL. No differences were seen in survival between arms. The trial was not powered to assess these outcomes, therefore P values for secondary outcomes should be interpreted with caution.

There are multiple opportunities to improve patient wellbeing throughout all phases of cancer care: from the point of diagnosis, prior to treatment, as well as during the advanced stages of incurable disease (Silver et al., 2015, Silver et al., 2013). Modern palliative care should now encompass rehabilitation (Tiberini R, 2015) as well as forming an integral and concurrent element of active cancer care (Ferrell et al., 2017).

We have shown that combined exercise and nutritional rehabilitation is feasible for patients with incurable cancer. Furthermore, it has the potential to improve other important aspects of QoL, including emotional and physical functioning for patients and their carers.

A future phase three clinical trial of the ENeRgy rehabilitation programme will further elucidate whether this model is effective and can be applied to patients with incurable cancer more widely. This shift towards a joint rehabilitative-palliative approach throughout the cancer trajectory shines a light in the dark for cancer patients of the future.
Appendices

Appendix 1: Combined exercise and nutritional rehabilitation in outpatients with incurable cancer: a systematic review

Introduction

Patients with cancer are living longer than ever before; indeed, in many cases, cancer is now considered a chronic disease [1]. While this is clearly a positive development, the consequences of patients living longer with cancer are wide and varied. With longer survival comes an increase in morbidity and associated healthcare costs with associated socioeconomic implications [3]. There is a need to take a proactive approach to this evolving situation and to optimise the overall condition of patients living with cancer, including those with incurable disease [4]. Rehabilitation may be one such way of optimising the function and overall quality of life (QoL) of this patient population.

Rehabilitation is a concept widely embraced by Western medicine for the management of acute and chronic illness and has recently been advocated for patients with incurable cancer, including those receiving treatment with palliative intent [5–7]. Although ‘rehabilitation’ for patients with incurable cancer may seem paradoxical, there is a plausible argument that patients whose overall condition is compromised...

have the most to gain from appropriately tailored intervention [7]. In patients with advanced disease, rehabilitation aims at improving and/or maintaining function where the effects of the illness or its treatment threaten to cause decline, or to ease the transition toward dependency when functional deterioration is inevitable. Promoting patients’ own interests and social engagement and optimising functional independence are fundamental [7]. It is acknowledged widely that rehabilitation in patients with incurable cancer should be multi-modal and tailored [5, 7, 8] yet, there is a lack of evidence as to the most efficacious components of a rehabilitation programme for this patient population [2].

The emerging principles of optimising physical and nutritional function in patients with cancer cachexia would seem appropriate to be applied to a broader rehabilitation concept in all patients with cancer. Cachexia is defined as ‘an ongoing loss of skeletal muscle mass (with or without fat mass) that cannot be fully reversed by conventional nutritional support and leads to protein breakdown, and resultant loss of muscle mass and functional decline’ [9]. It is common in solid tumours, which account for over 50% of cancer deaths worldwide and affects over half of all patients with advanced cancer [10]. Cachexia adversely affects function and QoL and is an independent predictor of poorer treatment response, side-effect profiles and shorter survival [11–13]. The high prevalence of cachexia in patients with incurable cancer alone means that any rehabilitation intervention for this group should consider key components of cachexia.

Cachexia is characterised by involuntary weight loss and a negative energy balance created by reduced oral intake, alterations in body metabolism and inflammation [10]. Dietary interventions alone are not effective in reversing cancer-related cachexia, [11, 14] due to metabolic alterations including elevated energy expenditure, excess catabolism and inflammation [10], which together prevent muscle anabolism (the ‘anabolic blockade’) [11]. Exercise stimulates skeletal muscle anabolism, leading to increased muscle mass and strength; however, supra-normal protein intake is required to achieve the same post-prandial anabolic effects in cachectic patients [11]. Introducing exercise without nutritional support in this group of patients may exacerbate the negative energy balance. Work to date has demonstrated that cancer cachexia is best targeted through a pro-active, multi-modal intervention that aims to improve lean mass (muscle), physical function and overall QoL [11, 15]. This pro-active and multi-modal approach advocated for cancer cachexia has the potential to be adopted usefully as a rehabilitation approach for patients with incurable cancer.

Patients with incurable cancer frequently suffer from symptom clusters (SCs), where two or more interrelated symptoms present together, independent of other SCs: raising the possibly of a common aetiology or mechanism [16]. Examples include the fatigue/anorexia-cachexia and the fatigue/neuro-psychological clusters, which have been clinically and statistically defined. Proinflammatory cytokines may play a role in the aetiology of SCs [17], and thus, the multi-modal rehabilitation approach advocated for cancer cachexia may also play a useful role in the management of SCs.

Exercise is feasible in patients with incurable cancer and has multiple beneficial effects on physical well-being, fatigue and depression, all impacting on overall QoL [2, 18]. Based on work to date, there is a strong rationale that exercise and nutrition in combination should be key constituents of any rehabilitation programme for patients with cancer; however, the details of any such programmes remain to be elucidated [5]. The aim of this systematic review is therefore to examine current evidence for combined exercise and nutritional rehabilitation interventions in patients with incurable cancer.

Materials and methods

Ethical approval was not required for this systematic review. The following databases were searched electronically: MEDLINE, EMBASE and the Cochrane Library. The time frame was 1990 to current. The keywords and search strategy are outlined in Appendix 1. The literature search was performed between February 26, 2018 and March 5, 2018. A consort diagram (Fig. 1) was performed as per PRISMA guidelines.

Eligibility criteria

Studies met the following inclusion criteria: patients with incurable cancer (defined as metastatic cancer [histological, cytological or radiological evidence] or locally advanced cancer being treated with palliative intent); rehabilitation programmes including both exercise and nutritional components; all methodologies; studies in humans; and English language.

Studies were excluded if they met any of the following criteria: studies of cancer survivors or carers of cancer patients; unimodal rehabilitation interventions; reviews; protocols; case reports; retrospective case note reviews; conference abstracts; and rehabilitation/prehabilitation for cancers managed with curative intent.

Appraisal process

Titles were reviewed by CH then relevant abstracts screened by CH and BL. Abstracts deemed relevant or requiring clarification were reviewed at full text. Full texts were screened by CH and BL and thematic analysis applied by JC and CH. Estimates of effect extracted from studies included change scores (pre-post measurements), effect sizes and P values. Values were synthesised according to patient-important
outcomes (see below) as well as outcomes of methodological interest for future study design: feasibility, dropout rates, predictors of completion and cost-effectiveness.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) analyses were undertaken by CH and JC. Due to the complexity and to improve inter-rater reliability, a checklist was developed [Supplementary material on request] based on the GRADE handbook and a validated checklist for meta-analyses [19–21]. This was applied to individual studies then to the body of evidence for patient-important outcomes, which were decided a priori between authors and ranked in order of importance. Where GRADE discrepancies existed, these were discussed among the authors and a consensus reached.

Results

Figure 1 shows the literature review process. The following numbers of articles were retrieved from each database: 781 (MEDLINE), 1625 (EMBASE) and 18 (Cochrane Database of Systematic Reviews).

A summary of the included studies is detailed in Table 1. Eight studies were eligible enrolling a total of 685 participants. Studies included two randomised control trials (RCTs) [22, 23], three prospective studies [24–26], two secondary analyses of quasi-experimental data [1, 27] and one exploratory study [28]. All interventions were outpatient-based rehabilitation programmes: seven in hospitals and one hospice-based.

Three studies examined the 8 to 12-week McGill Cancer Nutrition Rehabilitation Programme (CNRP) [24–26], and three studies examined the 8-week Ottawa Palliative Rehabilitation Programme (PRP) [1, 27]. Two studies examined novel rehabilitation programmes in the UK [23] and Switzerland [22]. All programmes were interdisciplinary and were individually tailored. Seven studies included core components combining dietary modification/supplementation and exercise [1, 22, 24–28]. The remaining study included dietary and physiotherapy interventions as an optional (non-core) element dependent on patient goal; it was not possible to ascertain numbers of participants receiving input from both these specialists [22].

Studies and patient-important outcomes and were evaluated using the GRADE approach. Consensus was reached on the quality of evidence for each patient-important outcome, presented in Tables 2 and 3.

Feasibility and adverse events

Three studies (n = 300) commented on feasibility of the rehabilitation programmes or constituents of their interventions. Patients attended a mean of 67% of bi-weekly exercise

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Appendices
<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Design</th>
<th>Participants</th>
<th>Setting</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Aim(s)</th>
<th>Outcome measures (time points)</th>
<th>Main findings and effects (sub-headings relate to the &quot;Results&quot; section)</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chau et al. 2009</td>
<td>Observational study</td>
<td>N=53, stage 2-4 gastric-oesophageal cancer</td>
<td>Outpatient Clinic (Montreal, Canada)</td>
<td>8-week CRP</td>
<td>Nil</td>
<td>Evaluate whether an individualized rehabilitation programme affects symptoms and quality of life</td>
<td>ESAS - PG-SGA - BHS - DT - SRTW</td>
<td>Physical function/improvement; Significant improvement in appetite, strength, nutrition, pain, depression, constipation, and nausea; Non-significant improvement in mood; SRTW was below 1 clinical level.</td>
<td>D*</td>
</tr>
<tr>
<td>Chau et al. 2003</td>
<td>Exploratory study</td>
<td>N=116, stage 3-4 heterogeneous cancer (completed anti-cancer treatments)</td>
<td>Outpatient Clinic (Ottawa, Canada)</td>
<td>8-week PEP</td>
<td>Nil</td>
<td>1. Effect of the PEP on physical, emotional, social, and psychological functioning. 2. Determine medical factors associated with programme completion.</td>
<td>ESAS - MD Anderson Symptom Index - PG-SGA - BHS - Functional mood test - TUG - Grop test - ECOG PS - FBC - serum albumin, CEA, PS, TSH, free T4, LHR</td>
<td>Physical function/overall function; Significant improvement in ECOG PS, endurance, mobility, nutrition, general health, and physical function. Moderate non-significant improvements in walking, balance, and HGS.</td>
<td>C*</td>
</tr>
<tr>
<td>Feldman et al. 2006</td>
<td>Secondary analysis of quasi-experimental data</td>
<td>N=131, stage 3-4 heterogeneous cancer</td>
<td>Outpatient Clinic (Ottawa, Canada)</td>
<td>8-week PEP</td>
<td>Nil</td>
<td>To examine the impact of three aspects of the PEP: tolerance, self-efficacy and exercise on depression, quality of life</td>
<td>LSMR CRP - ECOG PS - BHS - Depression scale</td>
<td>Physical function/mortality; Significant increase in exercise (SRTW). Depression: Significant increase in self-efficacy. Significant decrease in depression scores, but below 1 clinical level. Predicted variables accounted for 15% change in depression scores. Of the three variables only change in self-efficacy accounted for a significant (11%) change.</td>
<td>D*</td>
</tr>
</tbody>
</table>
Table 1 (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>N =</th>
<th>Stage (Response to Treatment)</th>
<th>Primary Endpoints</th>
<th>Secondary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feldstein et al.</td>
<td>Secondary analysis of quas-experimental data</td>
<td>44</td>
<td>3-4</td>
<td>Increase in depression score within 3 months post PRP completion</td>
<td>Depression symptoms, no significant contribution from exercise/CPR.</td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dropout rate: 39% completed the programme (18% disease progression, 19% personal)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>deaths 1%, 1% geographically inaccessible, 1% active treatment.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Depression: statistically and clinically significant decrease in reported depressive symptoms between T1, T2 and T3 indicating the PRP helps reduce residual depressive symptoms and is maintained at 6 months post.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dropout rate: 47% (46%) eligible participants included in analysis. Non-compliance, 14% unrecorded and 40% non-respondents.</td>
</tr>
<tr>
<td>O'connor et al.</td>
<td>Uncontrolled prospective intervention study</td>
<td>188</td>
<td>3-4</td>
<td>Increase in depression score within 10-12 weeks CNRP completion</td>
<td>Depression symptoms, no significant contribution from exercise/CPR.</td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td></td>
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<td></td>
<td>Dropout rate: 47% (46%) eligible participants included in analysis. Non-compliance, 14% unrecorded and 40% non-respondents.</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Depression symptoms, no significant contribution from exercise/CPR.</td>
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<td></td>
<td>Dropout rate: 47% (46%) eligible participants included in analysis. Non-compliance, 14% unrecorded and 40% non-respondents.</td>
</tr>
<tr>
<td>Giart et al.</td>
<td>Prospective study</td>
<td>54</td>
<td>3-4</td>
<td>Increase in depression score within 3 months post PRP completion</td>
<td>Depression symptoms, no significant contribution from exercise/CPR.</td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dropout rate: 47% (46%) eligible participants included in analysis. Non-compliance, 14% unrecorded and 40% non-respondents.</td>
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<td></td>
<td>Depression symptoms, no significant contribution from exercise/CPR.</td>
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<td>Dropout rate: 47% (46%) eligible participants included in analysis. Non-compliance, 14% unrecorded and 40% non-respondents.</td>
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</table>

Appendices
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Outcomes</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>Additional Outcomes</th>
</tr>
</thead>
</table>
| Juran et al. 2013 | Two-arm randomized control trial | N = 41, patients at end of treatment or with active progressive, recurrent haematological or breast cancer, Recruited from Oncology services. | 3-month rehabilitation programme: core components, outpatient clinic, nurse led clinic, day suite, volunteer support and education groups. Other interventions dependent on needs/goals. | Usual care (identical intervention after 3 months) | To test the incremental cost-effectiveness of the rehabilitation intervention: 1. Psychological subscales of supportive care needs survey long form 2. Other SCNS domains, psychological status, continuity of care and EQ-5D. Economic evaluation based on EQ-5D score.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Outcomes</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>Additional Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usar et al. 2017</td>
<td>Parallel group randomized control trial</td>
<td>N = 58, metastatic or locally advanced O or lung cancer</td>
<td>3-month nutrition and physical exercise programme</td>
<td>Standard cancer centre medical therapy</td>
<td>To test the effects of the programme in terms of: 1. Global health status/QoL, Scale 2. Dietary intake</td>
</tr>
</tbody>
</table>
Table 1 (continued)

<table>
<thead>
<tr>
<th>Glossary of Terms:</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBS, Berg Balance Scale</td>
<td>(high) evidence quality due to study type</td>
</tr>
<tr>
<td>BIA, bioelectrical impedance analysis</td>
<td>GRADE score reduced (+1) due to high dropout rate (58% dropout rate), variable intervention, small sample size, small numbers included in analysis. Although effect consistent with rapid effect, GRADE score not increased due to these limitations.</td>
</tr>
<tr>
<td>BFI, brief fatigue inventory</td>
<td>GRADE score reduced (+1) due to high dropout rate (%), incomplete analysis of enrolled patients, variable intervention. GRADE score increased (+1) due to magnitude of effect and rapidity across subjects with larger sample size.</td>
</tr>
<tr>
<td>BMI, body mass index</td>
<td>GRADE score reduced (+1) due to dropout rate (39%), missing data (unquantified), variable interventions in relation to the primary outcome, surrogate outcome measure (HADS) with limited diagnostic sensitivity for clinical vs. subclinical depression. GRADE score not increased due to these limitations.</td>
</tr>
<tr>
<td>BMT, bone marrow transplant</td>
<td>GRADE score reduced (+1) due to large losses to follow-up and small numbers of participants, sample bias and variable interventions given. GRADE score increased (+1) due to rapidity and consistency of effect as well due to attempts to analyse demographic of non-responders (confounding)</td>
</tr>
<tr>
<td>C-SPCT, C-reactive protein</td>
<td>GRADE score reduced (+1) due to use of non-validated tools, variable interventions, explained absence of data for outcomes. GRADE score increased (+1) due to large magnitude and consistency of effect which was rapid.</td>
</tr>
<tr>
<td>CT, coping thermometer</td>
<td>GRADE score reduced (+1) due to high dropout rate, variable intervention, lack of adequate control for confounding (67% on chemotherapy), small sample size and missing data. GRADE score not increased due to these limitations.</td>
</tr>
<tr>
<td>ECOG-PS, Eastern Cooperative Oncology Group Performance Status</td>
<td>GRADE score reduced (+1) due to low numbers (1% predicted recruitment), variability of interventions, wide confidence intervals due to small sample size. GRADE score not increased due to these limitations.</td>
</tr>
<tr>
<td>EQ-5D-5L, EQ-5D-5 Dimensions</td>
<td>GRADE score reduced (+1) for selection bias and failure to adequately control for confounding and small sample size. GRADE score not increased due to these limitations.</td>
</tr>
</tbody>
</table>

**Notes:**
- All started as GRADE: C (low) evidence quality due to study type
- *Started as A (high) evidence quality due to study type

**Support Care in Cancer**

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<table>
<thead>
<tr>
<th>Patient/important outcomes</th>
<th>Studies</th>
<th>N=total participants* (breakdown per outcome measure)</th>
<th>Quality of the body of evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life</td>
<td>3 [22, 23, 26]</td>
<td>N=214 159 (ESAS) 41 (EQ-VAS) 44 (HORTC C30)</td>
<td>Low (C)</td>
<td>Two moderate-quality studies with conflicting results, one low-quality study showing improvement; studies have limitations and inconsistencies in outcome variables.</td>
</tr>
<tr>
<td>Overall function</td>
<td>2 [25, 26]</td>
<td>N=81 56 (ECOG PS) 25 (KPS)</td>
<td>Very low (D)</td>
<td>Two studies with low and very low-quality examined changes in functional status scores, one finding significant and one non-significant improvements. Sparse data with limitations.</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 [22, 24, 26, 28]</td>
<td>N=203 22 (10%) 137 (MDFI) 44 (HORTC QL-Q-C30)</td>
<td>Low (C)</td>
<td>Two low, one very low-quality studies with limitations showing significant improvements in fatigue in spite of sparse data, and one high-quality (underpowered) study showing non-significant improvements in intervention group compared to control.</td>
</tr>
<tr>
<td>Physical endurance/strength</td>
<td>6 [22, 24–28]</td>
<td>N=342 6MWT (342) HGS (64 within two of the above studies)</td>
<td>Moderate (B)</td>
<td>Six studies with quality overall low quality, with limitations: variable consistency in significance levels and overall magnitude of effect seen was improvement in spite of low statistical power of studies; GRADE of evidence increased (+2).</td>
</tr>
<tr>
<td>Depression</td>
<td>6 [1, 23, 24, 26–28]</td>
<td>N=371 211 (ESAS) 124 (HADS) 36 (cNHS-LFS)</td>
<td>Moderate (B)</td>
<td>Overall low-quality studies with limitations but GRADE of evidence increased (+2) due to studies all showing consistent significant improvements in depression/psychological subscales.</td>
</tr>
<tr>
<td>Nutrition/weight</td>
<td>5 [24, 26, 28]</td>
<td>N=285 107 (PG-SGA) 178 (weight)</td>
<td>Very low (D)</td>
<td>Five studies of overall low quality with serious limitations and indirectness (variable interventions). Two low-quality very low-quality studies showed improved PG-SGA scores but the highest-quality RCT showed only significant increases in protein intake. Evidence not strong enough to be upgraded.</td>
</tr>
</tbody>
</table>

*Total participants include numbers actually analysed within studies for each outcome as opposed to Table 3 showing ‘N’ as numbers enrolled into each trial.

Training classes over 3 months, and all patients managed at least half of the ONS after each training session in one RCT [22]. Similarly, for a 10–12-week CNERP, patients attended 82% of prescribed exercise sessions [26]. No adverse effects were reported, but this was only mentioned in one study [22]. In the same trial, 3-month dropout rates due to death or withdrawal were lower in the intervention group compared to the control group: 4% vs. 24%, indicating feasibility. Over 90% of patients reported the CNRP as important to them; however, introducing this programme in a busy cancer centre was labour-intensive, requiring a nurse, administrative and financial support to be viable [25].

Table 3  GRADE Definitions

<table>
<thead>
<tr>
<th>GRADE (from [20])</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (A)</td>
<td>We are very confident that the true effect is close to that of the estimate of the effect.</td>
</tr>
<tr>
<td>Moderate (B)</td>
<td>We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>Low (C)</td>
<td>Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>Very low (D)</td>
<td>We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.</td>
</tr>
</tbody>
</table>

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status and better nutritional status [26]. Glare et al. [25] cited a baseline 6-min walk test (6MWT) >420 m, i.e. better endurance as a predictor of programme completion. Although within this study programme completers demonstrated improvements in multiple domains, high dropout rates (>50%) meant that earlier identification of the population who would best respond was recommended.

**Physical endurance, strength and overall function**

Studies used multiple outcome measures; however, the 6MWT was frequently cited as a marker of endurance and mean distances improved in six studies (n = 342). Two studies reported performance status (ECOG/KPS) as primary endpoints (n = 81). Feldstein and Chasen [27, 28] reported significant increase in mean 6MWT distance (179 m) = 3.91, P < 0.001 [27] and d = 0.80, i.e. moderate-to-large effect size, P < 0.001 [28] after the PRP. Studies utilising the CNRP quoted improvements in mean 6MWT distances between 41 m (95% CI 29–52 m: effect size 0.7, P not reported [26]) and 58 m [24] (non-significant, median 6MWT increase: P = 0.01). Glare and Uster [22, 25] reported non-significant increases in 6MWT (n = 25, median 441 m (186–675) to 570 m (range not reported) [25], data presented graphically [22]) and other physical parameters, though both studies were underpowered. Chasen [28] reported an improvement in ECOG PS (P < 0.001, t = 6.43, d = 0.90) from mean 1.8 (±0.7) to 1.29 (±0.46) for patients completing the PRP, and Glare [25] reported non-significant improvements in median KPS score (n = 25) from 70% (score ≥ 50%;100%) to 80% (score ≥ 50%;100%) in programme completers.

**Fatigue, weakness and insomnia**

Four studies described changes in fatigue (n = 211) using the Brief Fatigue Inventory (BFI) [21], the Multidimensional Fatigue Inventory (MDFI) [26, 28] and the European Organisation for Research and Treatment of Cancer (EORTC QLC-C30) symptom scales [22]. Chasen [24] described improvements in BFI usual fatigue (5.0 (1–10) to 3.0 (1–10); P = 0.03) and fatigue now (5.0 (0–10)–3.0 (0–10); P = 0.05). Furthermore, in 2013, using the MDFI, reductions in general and physical fatigue (d = 0.61 and 0.55, both P < 0.001) were reported [28]. Gagnon reported strong improvements in MDFI activity and physical fatigue (mean 4.6 [95% CI 3.6–5.6] to 3.7 [95% CI 2.6–4.7], respectively, both P < 0.001, effect size 0.8–1.1), moderate reductions in general fatigue (mean change 2.8 [95% CI 1.8–3.8], P < 0.0001, effect size 0.7) and small but significant improvements in motivation and mental fatigue (mean change 1.6 [95% CI 0.8–2.5], P = 0.0004 and 1.7 [95% CI 0.8–2.6], P = 0.0005: effect size both 0.4). Reductions were seen in weakness (mean change 1.5 [95% CI 1.1–1.8], P < 0.0001, effect size 0.7) as well as reductions in sleepiness and insomnia (mean change 1.1 [95% CI 0.6–1.6], P < 0.0001 and mean change 1.0 [95% CI 0.5–1.4], P = 0.0001 effect size both 0.4) [26].

**Effects on depression and quality of life**

Six studies included endpoints examining depression (n = 371) using the Edmonton Symptom Assessment Scale (ESAS) [24, 26, 28], the Hospital Anxiety and Depression Scale (HADS) [1, 27] and the psychological subscale of the Supportive Care Needs Survey Long Form (SCNS-LF59) [23]. Studies frequently mentioned QoL, but only three studies reported a QoL outcome using questions from the ESAS [26], EORTC QLC-C30 [22] and EQ-5D/EQ-VAS questionnaires [23]. Chasen reported improvements in (ESAS) nervousness and depression (4.5 (0–10)–1.5 (0–5); P = 0.02 and (3.0 (0–9)–2.0 (0–7); P = 0.04 respectively) in 2010 [24] and depression scores for those completing the PRP in 2013 (P = 0.005, d = 0.37) [28]. Similarly, Gagnon [26] reported reductions in (ESAS) depression scores (mean change 1.4 (95% CI 1.1–1.8) P < 0.0001, effect size 0.7) as well as reduced (DT) distress (mean change 1.4 (95% CI 0.9–1.9) P < 0.0001, effect size 0.5), improved (CT) coping (mean change 1.8 (95% CI 1.2–2.4) P < 0.0001, effect size 0.7) and (ESAS) QoL (mean change 1.0 (95% CI 0.6–1.3) P < 0.0001, effect size 0.5) after the CNRP. One RCT demonstrated reduced unmet psychological support needs on the psychological subscale of the SCNS compared with controls (adjusted difference = 16.8 points (95% CI 28.34 to −5.3) P = 0.060) and improvements in (EQ-5D) self-reported health state (12.8, (95% CI 3.2–22.4) P = 0.01) [23]. Conversely, the other RCT [22] showed no difference global QoL. There was no significant trend toward improvement; however, this trial was curtailed due to poor recruitment and lacking power. Feldstein [27] described increased self-efficacy (27.86 (SD = 6.16) to 31.22 units (SD = 5.77), P = 0.001) and reduced depression scores (7.14 (SD = 3.91) to 5.95 units (SD = 3.51), P = 0.002) after the PRP. Changes in self-efficacy (the perception that one can influence life events) quality of functioning) accounted for the greatest change (11%) in depression scores. In a subsequent study [1], depression score improvements were maintained 3 months post-PRP (mean difference T1–T3 = 2.21, SE 0.78, P = 0.007).

**NUTRITIONAL STATUS**

Two studies measured weight as an outcome [22, 26], two used the Patient-Generated Subjective Global Assessment (PG-SGA) [24, 28] and one used a combination of both [25]. Comparison between studies is hampered by lack of detail on nutritional interventions, heterogeneity of subjects and varied outcome measures. Nutritional counselling, dietary advice and oral nutritional supplements (ONS) are mentioned by most. Details of dietary interventions varied: 72% saw the

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The content above is a continuation of the text from the previous page. It appears to be a continuation of the discussion on physical endurance, strength, and overall function, along with various studies and outcomes related to depression, quality of life, and nutritional status. The text is precise and informative, focusing on various parameters and their changes over time in the context of supportive care interventions.
physician, physiotherapist and dietitian, with 25% seeing the physician and dietitian only in one [25]; 60–70% saw the dietitian in another [1]; and in another, 94.7% received dietary counselling, with 80.2% receiving ONS [26]. One RCT ensured patients received >1.2 g protein/kg/day and encouraged protein dense ONS (18–20 g in 125–200 mL) after exercise. Significant improvements in protein intake ($P < 0.01$), but no significant differences in energy intake or nutritional status were seen between arms; indeed, weight increased in both [22]. Patients undergoing nutritional interventions within multidisciplinary programmes maintained (77% within 2 kg) [26] or increased their weight [22], although longitudinal data is lacking. Increases in protein intake were not maintained 3 months post-intervention, dropping below baseline in both groups, more so in the control group [22].

PG-SGA score improvements (median baseline 12.0 (2–24), to 9.0 (1–18) at completion $P = 0.05$) were reported following the CNRP [24] and also post-PRP (baseline mean (± SD) 8.15 (± 5.29) to 5.98 (± 4.14), $i = 3.49$, $P = 0.001$, $d = 0.46$ [28]. There was a higher mean PG-SGA score (89% ≥ 9 versus 70% ≥ 9) in dropouts of than those who returned for their 2-month CNRP follow-up [25].

Cost-effectiveness

One RCT (n = 41) examined the cost-effectiveness of a 3-month, complex hospice-based rehabilitation programme plus usual care versus usual care alone [23]. The intervention was associated with greater total costs (mean difference £955, 95% CI £822–£1,975) and greater QoL (mean difference 0.05 QALYs, 95% CI 0.000–0.112) resulting in an incremental cost-effectiveness ratio (ICER) of £19,391 per quality-adjusted life year (QALY) gained. The cost per QALY was only calculated over the 3-month (intervention) period and was close to the £20,000 threshold often used for incorporation of an intervention into the UK National Health Service. The authors postulated that if the benefits of the programme were maintained for 1 year, the ICER would decrease to approximately £4,000 making the projection cost-effective in 92.7% of simulations at a threshold of £20,000 per QALY.

Discussion

There are few data available for multi-modal rehabilitation programmes incorporating exercise and nutritional interventions for patients with incurable cancer. However, of those outcomes important to patients, many showed improvements following the interventions described. Factors associated with programme completion are higher baseline nutritional or functional status and lower levels of inflammation. Of the studies analysed, methodological quality was frequently limited by study design and statistical power. Heterogeneity of study design (including interventions and outcome measures) meant meta-analysis was not appropriate.

In patients with incurable cancer, the highest quality of evidence pertains to improvements in depression and physical endurance following multi-modal rehabilitation programmes including exercise and nutritional support. Depression is one of the commonest mental health problems in patients with advanced cancer [29]. Six studies showed improvements in depression scores, using outcomes including the Hospital Anxiety and Depression Scale (HADS). This scale, however, does not differentiate clinical depression from sub-threshold symptomatology, which is a limitation to its use in this patient population [27].

A high level of evidence exists for exercise in rehabilitation trials [2, 30], and this review suggests that the combination of exercise and nutritional support also improves physical endurance in patients with incurable cancer. Evidence for change in overall function remains very low due to serious limitations in the evidence (Table 2). Plausibly however, improvements in physical endurance may impact on overall function via reductions in dependency.

Evidence for improved fatigue remains low. This finding is in keeping with the lack of interventions for fatigue in advanced incurable disease. Rehabilitation studies in patients with cancer are at risk of selection bias as patients recruited may be more motivated, acknowledged by Uster [22]. Three studies measured QoL, but overall evidence for improvement remained low. Cancer negatively affects QoL by many modalities hence, the necessity of a multi-modal approach in this patient group. Results for nutritional parameters were variable, and it was difficult to make comparisons, resulting in a very low rating of evidence. Weight is a key feature of cachexia and (as an outcome) is meaningful to both patients and clinicians [31], but does not take into account body composition. PG-SGA scores reflect changes in weight but also symptoms so may not reflect alterations in nutritional status alone. Furthermore, patients with incurable cancer are more likely to be at a ‘refractory’ stage of cachexia that is poorly responsive to treatment; therefore, this level of evidence is unsurprising [9]. A further confounding factor is that of contamination, whereby the control group mimics the intervention. Both groups gained weight and improved hand grip strength within Uster’s RCT, which may have contributed to a lack of statistical significance [22].

Cancer rehabilitation trials are frequently limited by design and sample size and high attrition rates are common [32]. Recruitment issues were encountered in both RCTs; one cut short due to poor recruitment [22], the other recruiting just 17% of expected patients. In this RCT, 189 eligible patients were not approached, and interviews with recruiting clinicians revealed reasons including discomfort with the trial design, lack of confidence discussing prognosis and anxieties about delivering the intervention at a hospice [23]. Other barriers to recruitment include difficulties identifying participants.
(complex inclusion criteria) and high refusal rates (competing priorities, fear of randomisation to non-preferred arm, lack of acceptable control). Healthcare professional gatekeeping is one of the significant barriers to recruitment [33]; however, patients find symptom control trials beneficial irrespective of whether they obtain improvements in their symptoms [34].

Some of the findings presented herein are worthy of comparison to other diseases. The importance of exercise and nutritional intervention is acknowledged in models of rehabilitation for non-malignant disease, where cachexia may be present. Pulmonary rehabilitation (PR) has included exercise as a cornerstone for many years. Research on muscle dysfunction in patients with chronic obstructive pulmonary disease (COPD) has shown that multi-modal interventions including exercise and nutritional supplementation can have beneficial effects on body weight, exercise tolerance, physical activity, depression and survival [35, 36]. There is now a shift toward earlier PR to improve exercise tolerance and physical activity and to promote self-efficacy and behavioural change while reducing exacerbations [36]. These observations provide further grounds for optimism that exercise and nutrition-based rehabilitation programmes in patients with incurable cancer are viable.

It is clear from work to date that the principles employed in the treatment of cancer cachexia may be useful in rehabilitation. Work is ongoing to define the best approach to target cachexia at all stages of disease: including ‘prehabilitation’ for patients undergoing cancer surgery [37], and a phase 3 trial is underway of a multi-modal cachexia treatment (exercise, nutrition plus anti-inflammatories) for patients undergoing chemotherapy [31]. A feasibility trial of a multi-modal rehabilitation programme combining exercise and nutritional support for hospice outpatients with incurable cancer is also in progress [38]. There is a growing body of evidence for the use of new technologies in oncology trials such as physical activity monitors, which provide an objective measurement of patient activity in their usual environment [39]. There is now strong international consensus that cachexia is a multi-modal problem which requires multi-modal treatment [10, 11]. One of the challenges in cancer cachexia, however, is that the optimal endpoints are not clear, and this appears similar in cancer rehabilitation studies where consensus on endpoints is not evident [40]. Potential outcomes are numerous, though it is important that measures are validated and clinically meaningful [30]. GRADE discourages the use of ‘surrogate outcomes’, which can result in downgrading of evidence for indirectness [20]. The aforementioned difficulties in comparing trials due to the clinical and methodological heterogeneity of interventions and outcomes may be one reason for the slow growth of evidence in this field. There are inherent difficulties however, performing clinical trials in a field where personalised care makes standardising interventions challenging [30].

For patients with incurable cancer, concerns about nutrition, loss of function and increased dependency are commonplace. Loss of independence can compromise a person’s sense of dignity and fear of functional decline can surpass fears of impending death [41]. As the population changes, with improvements in anti-cancer treatment and greater numbers of patients treated under the umbrella of palliative care, there is the need to enable patients to live their lives as fully as possible, while minimising social-care costs. This approach, incorporating rehabilitation, places living before dying and is at the heart of palliative care [6].

Limitations

The search strategy may have precluded relevant articles due to stringency of the search criteria. One such factor was exclusion of studies reporting results for ‘cancer survivors’. The definition of this term is very broad, encompassing patients from initial diagnosis to death, and may also include family, friends or caregivers [42]. Application of the GRADE criteria may be advantageous due to transparency of judgements about quality; however, limitations of the system (including its use for assessment of individual studies) are acknowledged [43]. A further challenge with GRADE is the complexity which can result in poor-to-moderate inter-rater agreement [44]. Our GRADE checklist was designed to improve this and, though effective, it is not a validated tool. The lack of randomised control trials (two studies) meant that meta-analysis was not possible. However, the use of the robustly validated GRADE system of analysis [19–21] ensured that conclusions drawn were as accurate as possible.

Conclusion

This review demonstrates that in spite of limited data, multi-modal rehabilitation programmes incorporating exercise and nutritional interventions improve many outcomes that are important to patients with incurable cancer, most notably those relating to physical endurance and depression. This finding, along with factors associated with programme completion, lends further support to the argument that exercise and nutritional intervention should form integral components of cancer rehabilitation. Multi-modal treatments are evolving for cancer cachexia, and these may be usefully adapted to cancer rehabilitation.

There are multiple opportunities to improve patient wellbeing throughout all phases of cancer care: from the point of diagnosis, prior to treatment and at the advanced stages of incurable disease [4, 8]. Modern palliative care should now encompass rehabilitation [6] as well as forming an integral and concurrent element of active cancer care [45]. Rehabilitation for patients with incurable cancer has the potential to significantly improve functional status and QoL for the ever-increasing numbers of patients ‘living with cancer’.

Appendices
with potentially large socio-economic benefits. Further, carefully
designed high-quality trials are needed, but the current
shift toward a joint rehabilitative-palliative approach through-
out the cancer trajectory shines a light in the dark for cancer
patients of the future.

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of Edinburgh for supporting this work as part of Dr Hal’s position as
Medical Research Fellow.

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Hal’s MD as Medical Research fellow.

Compliance with ethical standards

The authors have control of the data contained within this review and this
may be reviewed by the journal on request.

Conflict of interest. The authors declare that they have no conflict of
interest.

Appendix. Search Strategy

All terms searched within ‘Title’, ‘Limit to: Human subjects,
English language, year 1990-current.

MEDLINE. Total 781

1. Rehabilitation + Cancer: (578)
2. Rehabilitation + Cancer + Exercise: (36)
3. Rehabilitation + Cancer + Nutrition: (3)
4. Rehabilitation + Cancer + Exercise + Nutrition: (0)
5. Exercise + Cancer + Nutrition: (21)
6. Palliative + Rehabilitation: (42)
7. Palliative + Exercise + Nutrition: (0)
8. Rehabilitation: (81)
9. Rehabilitation + Cancer: (18)
10. Rehabilitation + Cancer + Palliative: (0)
11. Rehabilitation + Palliative: (0)
12. Rehabilitation + Nutrition (2)

EMBASE. Total 1625

1. Rehabilitation + Cancer: (1168)
2. Rehabilitation + Cancer + Exercise: (65)
3. Rehabilitation + Cancer + Nutrition: (10)
4. Rehabilitation + Cancer + Exercise + Nutrition: (0)
5. Exercise + Cancer + Nutrition: (50)
6. Palliative + Rehabilitation: (96)
7. Palliative + Exercise + Nutrition: (3)
8. Rehabilitation: (180)
9. Rehabilitation + Cancer: (50)
10. Rehabilitation + Cancer + Palliative: (0)
11. Rehabilitation + Palliative: (0)

12. Rehabilitation + Nutrition (3)

Cochrane Library. Total 18

1. Rehabilitation + Cancer: (2)
2. Rehabilitation + Cancer + Exercise: (4)
3. Rehabilitation + Cancer + Nutrition: (0)
4. Rehabilitation + Cancer + Exercise + Nutrition: (0)
5. Exercise + Cancer + Nutrition: (1)
6. Palliative + Rehabilitation: (2)
7. Palliative + exercise + nutrition: (0)
8. Rehabilitation: (1)
9. Rehabilitation + Cancer: (8)
10. Rehabilitation + Cancer + Palliative: (0)
11. Rehabilitation + Palliative: (0)
12. Rehabilitation + Nutrition: (0)

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priate credit to the original authors and the source, provide a link to the
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References

symptomatology following a palliative rehabilitation program. Qual Life
1007/s11136-017-1531-7
bitation among patients with advanced cancer: a systematic re-
0284186X.2014.996661
rehabilitation: an essential component of quality care and survivor-
canj.2013.6
doi.org/10.1503/cmaj.131402
6. Tiberius RGH. Palliative rehabilitative care enabling people to live
fully until they die: a challenge for the 21st century. Hospice UK, St
Joseph’s Hospice, St Christopher’s, Burdett Trust for Nursing,
United Kingdom.
care approaches. 3rd edn. Oxford University Press
(2015) Cancer rehabilitation and palliative care: critical compo-
nents in the delivery of high-quality oncology services. Support
Care Cancer 23(12):3533–3543. https://doi.org/10.1007/s00520-
015-2916-3
9. Faasen K, Smass F, Askerd SK, Bosacan I, Brenner E, Faasen FRL,
Jost A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscariello M,
Olafy F, Radnich L, Ravasco P, Walsh D, Wilcock A, Kaus X, Bannin BE
(2011) Definition and classification of
36. Chen BP, Awadhi R, Sweet SN, Munsella EM, Bergdahl A, Sasta Mia D, Curi F, Sebedio-Bergdahl C (2017) Four-week probiotic program is sufficient to modify exercise behaviors and improve preoperative functional walking capacity in patients...

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Appendix 2: GRADE checklist

GRADE SCORE SHEET FOR SYSTEMATIC REVIEW: Adapted from (Meader et al., 2014)

<table>
<thead>
<tr>
<th>Study 1st Author/ Title/ Year</th>
<th>1. Rate Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• RCT/ Meta-analysis = High</td>
</tr>
<tr>
<td></td>
<td>• Non Randomised/ Observational Studies = Low</td>
</tr>
<tr>
<td></td>
<td>• Any other evidence = Very Low</td>
</tr>
</tbody>
</table>

Factors Decreasing Quality (five categories)

1. Study Limitations (risk of bias)* (Note fields marked with * are specific for RCTs so may not be applicable to other types of study).

   • *Was there Allocation concealment? (Lack of concealment from the researchers as to which group the next participant will be in)
   - Y ( ) N ( ) Unclear ( ) NA ( )

   • *Was random sequence allocation used? (to limit selection bias)
   - Y ( ) N ( ) Unclear ( ) NA ( )

   • *Was there blinding of participants and personnel? (To limit performance bias)
   - Y ( ) N ( ) Unclear ( ) NA ( )

   • *Was there blinding of outcome assessments?
   - Y ( ) N ( ) Unclear ( ) NA ( )

   • Failure to develop & apply appropriate eligibility criteria (e.g. selection of exposed/unexposed from different populations in cohort studies)
   - Y ( ) N ( ) Unclear ( ) NA ( )

   • Flawed measurement of both exposure and outcome (e.g. Recall bias/ different measurement for exposed/ non-exposed)
   - Y ( ) N ( ) Unclear ( ) NA ( )

   • Failure to adequately control confounding (failure to measure all known prognostic factors and/or adjust in statistical analysis)
   - Y ( ) N ( ) Unclear ( ) NA ( )

   • Incomplete or inadequately short follow up (Both groups should be followed up for the same length of time)
   - Y ( ) N ( ) Unclear ( ) NA ( )

   • Incomplete accounting of patients/ Outcome events (reporting bias) (loss to follow up, failure of Intention to treat principle- ie all patients enrolled are analysed- e.g. were >80% participants enrolled analysed?)
   - Y ( ) N ( ) Unclear ( ) NA ( )
### Appendices

- **Selective outcome reporting bias** *(incomplete or absent reporting of some outcomes and not others)*
- **Trial stopped early for benefit**
- **Use of unvalidated outcome measures** *(e.g. Patient reported outcomes)*

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</table>

### 2. Inconsistency of Results

- **Any unexplained* heterogeneity of results?** *(e.g. wide variance of point estimates [these are estimates of an unknown parameter from a sample of data, e.g. a Population mean], large I² value- see notes if required)*
- **Did confidence intervals overlap?** *(minimal or no overlap of confidence intervals suggests heterogeneity)*
- **Was the direction of effect consistent?**

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<tr>
<td>Y ( ) N ( ) Unclear ( ) NA ( )</td>
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</tbody>
</table>

### 3. Indirectness of Evidence

- **Is study population applicable to your population/ question/ decision** *(consider diffs in population e.g. animals, relevant intervention and relevant comparisons?)*
- **Were there differences in Interventions or delivery?** *(interventions that are indirectly related to the study can cause evidence to reduce, or if same intervention used but delivered differently)*
- **Were there differences in Outcome measures?** *(i.e. Surrogate outcomes used?)* *(Are the outcomes measured those of primary importance to patients? The use of surrogate endpoints e.g. HBA1c for diabetes rather than diabetic symptoms/ complications etc would result in downgrading- See grade notes p8)*
- **Any Indirect comparisons?** *(e.g. comparing drug A & B based on 2 other studies testing drug A vs. C and B vs. C. Is the outcome of interest?)*

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<td>Y ( ) N ( ) Unclear ( ) NA ( )</td>
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### 4. Imprecision of results (numbers involved)

- **Few patients/ small sample size?**
- **Few events/ studies?**
- **Very wide confidence intervals?**
- **Was the (dichotomous) outcome common** *(i.e. more than 1 in 100? - note this number can vary- see handbook for details)*

<table>
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</table>
5. **Publication Bias** (requires making inferences about missing evidence- see GRADE handbook notes, e.g.:

- All industry sponsored?
- Publication bias likely?

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<tr>
<th>Y ( )</th>
<th>N ( )</th>
<th>Unclear ( )</th>
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**Factors which can Increase confidence in the Evidence (x3)**

1. **Large magnitude of effect** *(Observational studies may only be upgraded if they are not downgraded for any of the 5 factors, or if there is a very large estimate of the magnitude of effect. More likely to upgrade due to magnitude of effect if:*

   - The effect is rapid/
   - The effect is consistent across subjects
   - The previous trajectory of disease is reversed?

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2. **Presence of a Dose Response Gradient?** *(i.e. bigger effect with increased intensity/ frequency/ input/ dosage?)*

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3. **Effect of Plausible Residual Confounding?** *(Meaning that after statistical analysis adjusts for confounding variables in observational studies, there will at times be another reason that the effect seen is small/ negligible or the opposite- SEE GRADE NOTES, eg, only a small effect but it was shown in the sickest patient group (eg profit vs non profit hospital death rates or condom use in HIV examples- helps to explain this!)*

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**Conclusion/ Rationales for GRADE level:**

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<th>Study score:</th>
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<th>Overall GRADE [ ]</th>
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References:

Appendix 3: A randomised, phase II, unblinded trial of an Exercise and Nutrition-based Rehabilitation programme (ENeRgy) versus standard care in patients with cancer: feasibility trial protocol
While there is evidence of the benefits of rehabilitation in non-malignant conditions, such as chronic respiratory disease [13], extrapolating these models to incurable cancer care needs evaluation. The majority of work to date in patients with incurable cancer has focused on exercise as a single intervention [15]. Although exercise is important, it has been argued that any rehabilitation programme in incurable cancer should also focus on nutritional aspects [11]. This would seem logical as approximately 20% of cancer deaths are directly attributable to cancer cachexia, and cachexia is highly prevalent in patients with advanced cancer [9, 16]. Cachexia is the multifactorial syndrome, defined by ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support, causing progressive functional impairment [17]. Optimising nutrition is fundamental to facilitate post-prandial anabolism, which is key to maintaining muscle and thus physical function [18]. There is a persuasive argument that exercise and nutrition should be considered as cornerstones of rehabilitation programmes in patients with incurable cancer [19]. However, this remains to be demonstrated in clinical practice.

Previous studies have demonstrated the detrimental effect of deteriorating physical function on survival [20]. It therefore follows that optimising physical function may have survival benefits. At the very least, it may enable patients to remain independent for longer periods. Previous work by our group has examined an exercise and nutrition-based intervention in oncology outpatients with lung and pancreatic cancer undergoing chemotherapy and demonstrated that such an intervention was feasible and had beneficial effects on physical function and weight [21]. A recent randomised control trial has shown good adherence to an exercise and nutritional intervention in palliative lung and gastrointestinal cancer patients, with beneficial effects on symptoms of nausea and vomiting and protein intake [22].

These findings are encouraging; however, the potential benefits of an exercise and nutrition-based rehabilitation programme in a general population of patients with incurable cancer remain unclear. The ENeRGy trial aims to determine whether an exercise and nutritional rehabilitation programme is feasible in a hospice outpatient setting for patients with incurable cancer. It aims to also examine changes in physical function, nutritional status and quality of life in these patients. Effects on partner-carer quality of life as well as healthcare resource utilisation will also be examined. A companion qualitative study ‘ENeRGy-Q’ will be undertaken to explore acceptability, compliance and the psychosocial impact of this rehabilitation programme for patients with incurable cancer in the hospice setting.

Methods
Design
This is a randomised, unblinded feasibility trial of an Exercise and Nutrition-based Rehabilitation programme (ENeRGy) versus standard care in patients with incurable cancer. Full ethical approval has been given (17/WS/0226), and the trial will be conducted according to principles of Good Clinical Practice and the Declaration of Helsinki.

Population
Eligible patients will meet the following key criteria: ≥18 years of age, Kardosky Performance Status (KPS) ≥60, diagnosis of incurable cancer (defined as metastatic or locally advanced cancer not amenable to curative treatment), not undergoing anti-cancer therapy (hormonal treatment or bisphosphonate treatments), using enteral nutrition, unable to swallow or co-enrolled in drug trials are excluded. Figure 1 details the trial schematic. The consent process will be opt in and, written informed consent will be obtained by the trial research nurse or doctor. After baseline assessments (which occur over 7 days; week 0), patients will be randomised (1:1 stratified by baseline KPS 60–80%, 90–100%) to receive either an 8-week exercise and nutrition-based rehabilitation programme (treatment arm) or standard care (control arm). Patients randomised to the control arm will be offered the study intervention after trial completion.

The trial is being conducted in a single centre (a hospice) serving a geographically defined region in the UK with a population of approximately one million. Trial-related assessments will take place at an outpatient clinic at this hospice. Management of the trial will be overseen by a Trial Management Group (TMG). Patient and public involvement (PPI) for the trial has been provided by Marie Curie’s Expert Voices group, as well as an ex-carer of a patient with cancer. PPI input has been highly valued, ranging from design of trial documents to regular presence at TMG meetings.

Interventions
Treatment arm
The treatment arm is an exercise and nutrition-based rehabilitation programme. Patients allocated to this arm will have an interview with the trial physiotherapist and dietician at week 1. They will then be given an individualised exercise and nutrition-based rehabilitation
programme following this assessment. Key components of this include the following:

**Exercise** A home-based exercise programme is supported by a booklet. This will consist of aerobic and resistance exercise in divided sessions of the patient’s choosing. The aerobic component comprises a total of 60 min of physical activity over the course of each week at moderate intensity, i.e. feeling warm and getting slightly out of breath (able to talk), equivalent to an intensity of 3–4 rating of perceived exertion on a modified Borg scale [23]. Walking will be recommended as the main type of physical activity although cycling or more vocational forms of activity, e.g. heavy housework and gardening, can also be used as long as they provoke the desired level of exertion. The resistance component involves major muscle groups in the upper and lower body (e.g. half squats, standing press-ups, shoulder press) and will be recommended three times per week. Patient diaries will record the amount of resistance and aerobic exercise taken daily and any difficulties with particular exercises.

**Nutrition** The main goal of the nutritional intervention is to promote energy balance and to ensure optimal nutritional intake. The nutritional component consists of individual dietary counselling to enhance overall dietary intake [19, 21] and oral nutritional supplements (ONS). Individual dietary counselling will continue weekly throughout the trial by the trial dietitian. Dietary advice will be tailored and take into account any specific requirements, e.g. ethnic background. Patients will be instructed to take two ONS per day. One ONS portion (230 mL) contains 1 g of eicosapentaenoic acid (EPA), and the caloric distribution is relevant for cancer patients experiencing unintended weight loss. Patients not able to tolerate the ONS due to personal preference will be offered an alternative ONS plus capsules containing 2 g EPA. Patient information leaflets will detail varied ways to take the ONS to improve compliance, and diaries will record the numbers of ONS taken daily.

At weekly review appointments, patient diaries will be reviewed by the research nurse for healthcare-related resource use; adverse events will also be screened for and logged. The trial dietitian will review the patients’ dietary intake and compliance with the ONS, and the trial physiotherapist will review exercise progress, offer goal setting and prompt any changes needed to maintain compliance.

**Control arm**

Patients randomised to the control arm will continue to receive standard care from their GP and community palliative care team on an as required basis according to individual patient need. This care may also include referral to other members of the community-aided healthcare professional MDT team if required (e.g. example: counsellors, occupational therapist or social workers). The control group will be phoned at weekly intervals by the research nurse to ascertain levels of healthcare-related utility and adverse events. In the control group, patients will also have diaries to record any (non-trial) nutritional supplements they are taking as well as the amount and type of exercise undertaken each week. This will help gauge any degree of contamination in the control group.

Patients in the control arm will be offered the opportunity to undertake the rehabilitation programme at the end of their involvement in the trial if they wish to do so.
Outcomes

The primary endpoint is to evaluate the feasibility of delivering the exercise and nutritional rehabilitation programme in a hospice outpatient context. This will be assessed by measuring compliance with the rehabilitation programme (number of exercises and nutritional supplements versus those advised). Compliance with trial procedures will also be measured, including completion of diaries and questionnaires, percentage withdrawal, completion of physical tests and completeness of physical activity monitor data.

Secondary endpoints will examine the feasibility of recruitment and retention, evidence of contamination in the control group and change in physical function and nutritional status. Quality of life measures for patients (and partner-caregivers) and impact on patient healthcare-related resource use in terms of cost between sectors of the NHS, social services, third sector, patient expenses and carer costs will also be examined. All endpoints will be assessed at baseline (pre-randomisation—week 0) and at trial endpoint (week 9). Table 1 details a summary of trial-related assessments and time points.

Statistical considerations

The primary endpoint of this study is to assess the feasibility of the treatment (an exercise and nutrition-based rehabilitation programme). As such, a formal sample size calculation has not been performed. We plan to recruit over a 13-month period and expect to be able to obtain at least 40 participants over that timeframe. Intention-to-treat analysis will be performed.

The primary outcome measures will be presented descriptively using appropriate summary statistics with corresponding 95% confidence intervals. Demographic statistics and exploratory outcome measures shall also be presented using appropriate summary split by treatment group. Continuous outcome measures, for example, change in daily step count and change in weight, will be compared between treatment arms using two sample t-tests or non-parametric equivalent as appropriate. Rates of compliance will be reported along with completion rates for all other outcome measures. This feasibility trial is not powered to explore efficacy, but these estimates of variability will be used to inform the sample size and inform our choice of primary endpoint for the definitive trial. There are no plans to perform an interim analysis while recruitment is ongoing or before follow-up is completed. Estimation of economic parameters will rely on questionnaires designed to measure health-related utility, healthcare-related resource use and costs, administered at baseline and follow-up assessment time points. Unit costs will be assigned using standard national costing sources where available or through consultation with relevant service business managers. Costs

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<thead>
<tr>
<th>Table 1</th>
<th>Trial-related assessments and time points (both arms)</th>
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<tr>
<td><strong>Baseline measures (week 0)</strong></td>
<td><strong>Midpoint (week 5)</strong></td>
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<tr>
<td>Demographic</td>
<td>Gender, primary tumour site and tumour status; metastatic sites; current hormone/bisphosphonate or steroid treatment</td>
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<tr>
<td>Physical measures</td>
<td>Weight</td>
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<tr>
<td>Quality of life (QOL) measures</td>
<td>Patient QOL (EORTC QLQ-C30/PAL; questionnaire) [2-4]</td>
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<tr>
<td>Functional measures</td>
<td>KPM</td>
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<tr>
<td>Social-economic measures</td>
<td>Healthcare utilisation and expenses questionnaire</td>
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<tr>
<td>Physical activity</td>
<td>Physical Activity Measurement (PAM) continuously for 7 days*</td>
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*Partner-caregiver is a partner with whom the patient is married, cohabiting or receiving, and the patient also describes as their carer.
*PAM data for weekend days may be excluded to reduce potential variation.
will be summarised from the perspectives of (a) the NHS, (b) the charitable and third sector, (c) the patient and their carers and (d) wider society. A proof-of-concept health economic model will be constructed taking the form of a probabilistic decision model that simulates the passage of patients through the clinical pathway defined by discrete health states, allowing estimation of costs, quality of life and survival. The model will be parameterised using data from the feasibility study where possible, supplemented by data from the published literature. Cost-effectiveness will be presented as the incremental cost-effectiveness ratio (ICER), expressed as cost per QALY gained.

A computer-generated randomisation schedule will be produced using a random block size to allocate patients at random in a 1:1 ratio to either the treatment arm (personalised exercise and nutrition-based rehabilitation programme) or control arm (standard care) via sealed envelopes. The randomisation will be stratified by performance status due to its influence on prognosis to ensure that patients with differing prognoses are equally distributed between arms (KPS of 60-80% versus KPS 90-100%). Randomisation will occur at baseline (week 0) but will be blinded to patients until week 1 when it will be revealed by the research nurse so as not to influence baseline activity levels in either group during baseline assessments.

Paper case report forms (pCRF) will be used, and data will be entered directly into an electronic data base. A 10% check will be undertaken on all inputted data to ensure validity. Patients will be identified by a unique trial identification number, and patient identifiable data will be kept locked securely within the hospice. Standard operating procedures (SOPs) issued by the trial sponsor (ACCORD/NHS Lothian) will be adhered to for example reporting deviations from the protocol or serious adverse events (SAEs).

Discussion

One of the fundamental arguments supporting rehabilitation is the changing face of cancer. Although initially regarded as a terminal disease, cancer is now viewed as a chronic condition which in combination with its increasing incidence will mean that more patients are living with rather than dying from their cancer. Combined with an ageing population, this means that the population who will fit under the umbrella of palliative care is likely to rise considerably over the coming decades. It is important that in view of this potential increase in patient numbers, the overall condition of patients is optimised through maximisation of physical function and nutritional status.

The ENErgy trial is a key step in defining, developing and assessing the feasibility of an exercise and nutrition-based rehabilitation programme in this patient cohort. We will use the trial to test the mechanism of healthcare resource use data capture with a view to identifying key possible drivers of cost differences. The results of this trial and subsequent studies have the potential to significantly impact and influence the approach to rehabilitation for patients with incurable cancer in the future.

Trial status

The description of the trial is in keeping with the approved version of the trial protocol (version 3, date 15 April 2018). The trial has been open to recruitment from 30 January 2018, and recruitment is expected to last 13 months, ending on 28 February 2019.

Acknowledgements

The authors would like to thank Marie Curie and the Chief Scientist Office (CSO) for funding this work (MTRES/01-16-75), and we acknowledge the support offered from the trial sponsors (ACCORD & NHS Lothians Edinburgh, UK). Also the valued contributions from the Southport Hospital Clinical Trials Unit (UK), the Qtu Airways Institute of Palliative Care, Policy and Research, Kings College London (UK) as well colleagues from different institutes within Edinburgh University (UK). Thanks to all the St Columba’s staff who helped set the trial up, or added with the administration and the smooth running of the trial. Particular thanks to St Columba’s day therapies team especially Yvonne Whitehouse. Thanks to our dedicated palliative care volunteers, Gillian Reid and Tommy Dohleley for their commitment and help make our participants feel welcomed and at ease; and for keeping the clinics running smoothly. Thanks to the clinical administration team and both community nurse specialist teams who showed great enthusiasm in identifying potential participants. Thanks Marie Curie Hospice Edinburgh and the support from Dr. Emma Cockett (Marie Curie Glasgow) for their engagement and assistance with the trial. Thanks also to Abbott Nutrition, for supplying the oral nutritional supplements for the trial (Pulsan), also for support from the Abbott team, in particular Dr Emma Voss.

Funding

The trial was funded by Marie Curie and the Chief Scientist Office (CSO) (MTRES/01-16-75). The funding bodies specified where changes were required to the design of the trial (including incorporating the impact upon care and any health-economic impact as outcomes of the trial). The funding bodies will not otherwise be involved in the collection, analysis or interpretation of the trial data.

Availability of data and materials

Not applicable.

Trial sponsor

ACCORD/NHS Lothian Contact: Dr. Emma Cockett, Emma.Cockett@nhs.net.
Appendices
Appendix 4: Research and ethics committee approval

Dear Dr Laird

Study title: ENeRgy: Exercise and Nutritional Rehabilitation in patients with advanced cancer: randomised (1:1) unblinded feasibility trial of rehabilitation programme (exercise and nutrition) versus waiting list control, in patients with advanced cancer

REC reference: 17/WS/0226
Protocol number: AC17085
IRAS project ID: 233123

The Research Ethics Committee reviewed the above application at the meeting held on 3 November 2017. Thank you for attending to discuss the application along with Dr Charlie Hall.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.
Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study:

1. Please confirm that the informed consent process is opt-in.
2. Please amend the PIS as follows:-
   a. Change the title so that everything after the colon is deleted and also delete the word “advanced” in the first sentence, so that it reads: “Exercise and Nutritional Rehabilitation in patients with cancer”.
   b. In the section “What will being in the trial involve?”, reword the 2nd paragraph to include information about the control group. In the 1st sentence of this paragraph, change the phrase “completely at chance” to “completely by chance”.
   c. In the section “Will I need to stay in the hospice?”, include information that applies to the control group.
3. Please amend the GP letter as follows:-
   a. Change the title so that it matches that in the PIS.
   b. Include a short paragraph about the control group.
4. Please harmonise the consent form so that it matches the PIS and GP letter.

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).


Where a NHS organisation’s role in the study is limited to identifying and referring potential participants to research sites (“participant identification centre”), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.
Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 8 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non NHS sites (if applicable)

The Committee has not yet completed any site-specific assessment(s) (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Summary of discussion at the meeting

- **Care and protection of research participants: respect for potential and enrolled participants' welfare and dignity**

  The Committee was content that patients were permitted to withdraw at any stage and that appropriate measures were taken to protect confidentiality. They also noted that if patients lost the ability to consent or no longer had capacity, they would be removed from the study.

  The Committee asked the applicants why eight weeks had been chosen as the length of participation for those in the study.
The applicants responded that this duration was chosen because if it was much longer than this there was a risk that the attrition rate would be too high. They were trying to balance adequate time to get benefit from the treatment with avoiding too much attrition. The timescale was informed by a previous feasibility study in those with incurable lung and pancreatic cancer which was six weeks. They added that if it became apparent that eight weeks was not a realistic timescale, this could be adjusted in future to include healthier participants.

The Committee was reassured by this.

The Committee noted that the control group would have the option to take part in the rehabilitation programme after eight weeks, and asked who would assess if they were well enough to undertake this.

The applicants explained that it would be themselves, Dr Laird and Dr Hall, who would assess if they were well enough to take part in this. They added that if any participants wished to continue with the treatment after the study was finished, it would be possible to do this.

The Committee was content with this.

- Informed consent process and the adequacy and completeness of participant information

The Committee was unclear on the exact details of the consent process and sought further information from the applicants about this.

The applicants explained that those patients with incurable cancer based in Lothian would be eligible for participation. They would be approached via the community palliative care nursing teams in liaison with themselves and other members of the research team. Potential participants would be given the PIS at first contact by the community palliative care team or the nursing team. Potential participants would then come into the hospice to meet the research team and consent would be taken at this point.

The Committee asked if it was an opt-out or opt-in process.

The applicants confirmed that it was an opt-in process.

The Committee was satisfied with these responses.

Other ethical issues were raised and resolved in preliminary discussion before your attendance at the meeting.

Please contact the REC Manager if you feel that the above summary is not an accurate reflection of the discussion at the meeting.

Approved documents

The documents reviewed and approved at the meeting were:

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<td>Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)</td>
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Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/
With the Committee’s best wishes for the success of this project.

Yours sincerely

On behalf of
Dr Ken James
Chair

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

“After ethical review – guidance for researchers”

Copy to: Mr Chris Coner
Kenneth Scott, ACCORD
Appendix 5: Home based exercise information leaflet

Rehabilitation Arm Information Leaflet
TO THE PARTICIPANT

Thank you for agreeing to participate in the ENeRgy Trial.

Over the following 8 weeks, you are participating in a rehabilitation programme consisting of two parts:

1. **Doing a home-based exercise programme consisting of:**
   a) **Aerobic exercise**- (60 minutes per week)
   b) **Strength exercises** – (3 times per week)

2. **Drinking 2 bottles of a 220 ml oral nutritional supplement every day**
WHAT WILL WE DO?

We will aim to review you once a week at the hospice ENeRgy clinic to see how you are getting on with the rehabilitation programme. Here you will see the trial physiotherapist and dietitian, as well as the research nurse.

You can also contact us by phone, or e-mail if you have questions. Please let us know if you will not make it to any of your appointments in advance if possible.

CONTACT PERSONS:

Jane Cook (Research Nurse)
0131 551 1381
energytrial@stcolumbashospice.org.uk*

Dr Charlie Hall (Research Doctor)
0131 551 1381

*We value our participant's confidentiality, this is a research email address which will only be accessed by the research team, however we cannot guarantee it will be 100% secure. We are happy for you to email if you prefer, however if you wish to discuss sensitive issues you may prefer to discuss these by phone.

APPOINTMENT DATES FOR FOLLOWUP

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<td><strong>Week 2 review</strong></td>
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<td><strong>Week 3 review</strong></td>
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<td><strong>Week 4 review</strong></td>
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<td><strong>Week 5 (midpoint) review</strong></td>
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<td><strong>Week 8 review</strong></td>
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<td><strong>Week 9 (endpoint) review</strong></td>
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<td>and physical activity meter taken home for another 7 days. Arrangements made for collection</td>
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HOME-BASED EXERCISE PROGRAMME

You may have noticed that you have become less active in recent weeks. Quite naturally, you may do less to avoid feeling short of breath, tired or worn out.

As a result of this your muscles become weaker and less efficient. The aim of the home based exercise programme is to increase your muscle strength and activity level.

The study personnel will help you adjust the exercise programme to your level of physical function.

The home based exercise programme consists of two parts:

a) Aerobic exercise
   b) Strength exercises

A) AEROBIC EXERCISE

You can do any form of aerobic exercise you want, such as walking, swimming, gardening or demanding housework.

We would like you to complete 60 minutes of aerobic exercise over the course of each week. For example, you could exercise for 30 minutes twice per week, 20 minutes three times or 15 minutes four times per week and so on.

For example, you might want to walk as part of your aerobic exercise. Walking is a great way of being active. You can walk outside, indoors or on the spot. You can also combine your walking exercise with an everyday task, e.g. going to the shops.

Aerobic exercise should be a little exhausting, in other words you should feel warmer and breathe a little faster than when you are resting. To give you an idea of how hard we would like you to exercise, there is a scale described on page 13 – the level would be 12-15 on this scale.

B) STRENGTH EXERCISES

The strength exercise consists of eight exercises aimed at strengthening your large muscle groups. We would like you to complete three sets of these exercises over the course of each week. They are simple and require very little equipment. You can do the exercises at home in your living room, outdoors or when you are travelling. There are two parts to these exercises: first the warm up and then the main exercises.
WARM UP

We recommend that you do some kind of warm up before you start the strength exercises. You might take a walk or you can do a few warm up – exercises as suggested below.

1. SHOULDER ROLLS

Sitting with your hands relaxed in your lap
- Slowly circle your shoulders backwards
- Change direction and slowly circle your shoulders forwards
- Repeat _____x_____

![Diagram of shoulder rolls]
2. CHEST STRETCH

Sitting slightly forwards in your chair with your feet firmly on the floor
- Push your shoulders backwards and push your chest out
- Return slowly to the initial position
- Repeat ______x_______
3. TRUNK ROTATIONS

Sitting slightly forwards in your chair with your feet firmly on the floor
- Cross your arms over your chest
- Keep your hips/knees facing forwards
- Twist your shoulders round as far as possible to one side
- Use a suitable pace for you
- Twist your shoulders around as far as possible to the other side
- Repeat _____x_____

4. MARCHING ON THE SPOT

Standing

- Walk on the spot for _______ minutes
- Use support if needed
- Your body should start to feel warm and your breath and heart rate should have increased some.
THE MAIN EXERCISES

We would like you to pace yourself at moderate intensity until you feel warm and slightly out of breath during each exercise. You are aiming for a score of 12-15 on the intensity scale on page 13.

You are advised to do a set of 6 to 10 repetitions for the first 3 weeks and to increase to 12 to 15 repetitions in weeks 4-6 when you are more accustomed to the exercises. For the last 2 weeks adjustments can be made to match your personal level of function.

For a weight we suggest using one of your supplement drink bottles (220mL=220g), a 500mL (=500g) bottle of water, or a large can of beans or similar.

1. HALF SQUAT

- Standing with your feet shoulder width apart
- Slowly bend your knees
- as if you are going to sit down on a chair, keeping your back upright
- Use support if needed
- Stand up straight again
- Repeat _____x______
2. PRESS UP

Facing a wall or closed door, stand an arm’s length away from the wall with your feet shoulder width apart

- Place your hands on the wall at shoulder height and width
- Your palms flat on the surface
- Keep your feet still and your back straight
- Slowly bend your elbows bringing your nose towards the surface
- Straighten your arms again so you are pushing your body weight back from the surface, keeping your back straight.
- Repeat ______x_______
3. KNEE LIFTS

Standing holding onto a secure object such as a chair or a kitchen worktop

- Stand straight, use support if needed.
- Lift your right knee upwards in front of you as far as is comfortable
- Lower at a suitable pace
- Lift your left knee upwards and lower in the same manner
- Repeat _______ x_______
4. SHOULDER PRESS

Sitting with your back supported and holding a weight e.g. a bottle of your supplement drink, a small water bottle or a tin of food

- Place the weight in your right hand
- Bend your elbow so that the weight is at shoulder level
- Slowly straighten your right arm lifting the weight towards the ceiling
- Slowly lower again
- Do the same with your left arm
- Repeat ________x_________
5. STEP UPS

Standing in front of a step or a stair case with a handle bar, if support is needed.

- Step up and down with your right foot first
- Repeat ________x________
- Step up and down with your left foot first
- Repeat ______x_______

If you do not have access to a step, you can replace this exercise with marching on the spot, but try and lift your knees up as high as possible as you march.
6. UP AND OVER

Sitting with your back supported, arms hanging loosely by your side and holding a weight
- Slowly lift both your arms out to the side and upwards, keeping your arms straight
- When your arms meet in the middle above your head, swap the weight over to the opposite hand
- Slowly lower again
- Swap the weights in the same way with the other hand
- Repeat ______x_______

7. SIT TO STAND

Sitting slightly forward in your chair with our feet shoulder width apart and flat on the floor
- Slowly stand up, if possible without using your arms
- Slowly and gently sit back down again
- Repeat ______x_______
8. BICEP CURLS

Sitting with your back supported and a weight in your hand (one or both at the same time). You should feel the muscle on the front of your upper arm doing the work.

- Slowly bend your right elbow
- Lifting the weight towards your right shoulder, stopping at a 45° angle
- Slowly and controlled lower the weight again
- Repeat with your left arm
- Repeat ______x_________

After these exercises try not to stop immediately. We suggest you repeat the warm up exercises to cool down.
**HOW HARD DO I EXERCISE?**

Whenever you exercise, try to use the Borg scale shown below in order to gain the most benefit from the activities. It can be used to help gauge how your breathing feels during an activity. **When exercising aim to be moderately breathless; a score of 12-15 on the Borg scale.**

<table>
<thead>
<tr>
<th>Borg scale</th>
<th>Level</th>
<th>Experience</th>
<th>Type of exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Extremely hard</td>
<td>In a few minutes you will need to stop.</td>
<td>Extremely hard</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Very hard</td>
<td>You breathe heavily, and can only respond with single words.</td>
<td>Very hard</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Somewhat hard</td>
<td>You can talk, but must take breaks to catch your breath. You can sing, but it does not sound particularly pretty.</td>
<td>Somewhat hard</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Light</td>
<td>You can speak relatively effortlessly, but it's a bit tiring to sing.</td>
<td>Light</td>
</tr>
<tr>
<td>12</td>
<td>Very light</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Extremely light</td>
<td>You can talk effortlessly, and you can sing along.</td>
<td>Warm up</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td>Cool down</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Rest</td>
<td></td>
<td>Before and after exercise</td>
</tr>
</tbody>
</table>
GENERAL TIPS ON EXERCISE

- Ensure you have a glass of water handy to take small sips to keep yourself hydrated throughout the session.

- Start gradually and build up slowly. Keep it simple, doing activities such as walking, lifting tins of beans, or practising sit to stand (getting up from a chair).

- You can do the exercise wearing your normal everyday clothing but it might feel more comfortable if the clothing is light and flexible to wear.

- Perform each exercise as demonstrated to you in this leaflet.

- Do the exercises at your own pace and take breaks if you need to. Exercising should not be painful! It is however normal to experience some muscle soreness 1-2 days after strength training as the muscles are adapting to the load. You may find it helpful to take a painkiller before you start your exercises.

- Being short of breath is not dangerous but you should not feel uncomfortable or unwell due to exercise.

- Most importantly listen to your body and enjoy your workout.
NUTRITION

Many people with cancer feel that their eating habits change. Eating enough food is important for everyone, but it is particularly important for people with cancer. If you eat well, you are more likely to feel better and your body is better able to handle the stresses of cancer. The main goal of this nutritional intervention is to try and achieve weight maintenance and to optimise your nutritional intake.

The following steps should be followed:

INCREASING YOUR NORMAL FOOD INTAKE

The best way to increase your overall food intake is with normal food. This can be achieved by eating more frequently and by eating food that is particularly high in energy.

EATING THE RIGHT TYPE OF FOOD

1. Use full-fat milk in preference to low-fat milk, drink milk based drinks such as milky coffee, hot chocolate and milk shakes
2. Avoid low-fat and low-sugar products
3. Enrich food and drinks such as cereals, milk pudding, canned fruit, potatoes, soups and vegetables with cream, butter, margarine, cheese, evaporated milk or sugar

WHAT TO DO WHEN YOU DON’T FEEL LIKE EATING

We recommend that you eat whatever you feel like – eating something is better than nothing. Try to eat several small meals or snacks throughout the day. Aim to go no longer than 2-3 hours without eating or having a nutritious drink. Try to eat at least two snacks between your regular main meals. The nutritional supplement works well as a snack or light meal and in addition you might try some of the suggested snacks below:

SWEETS

- Scones, pancakes, waffles or cakes with cream, jam, honey or lemon curd
- Pastries, buns, tarts, croissants, tea loaf etc
- Full-fat/thick and creamy yoghurt
- Dried fruits (apricots, mango, raisins)
- Tinned fruits with ice cream/whipped cream/evaporated milk
- Ice cream
- Chocolate, sweets, fudge
- Pudding (sponge, bread and butter) with custard or sauce, rice pudding,
Appendices

- cheesecake, semolina, trifle
- Jelly
- Porridge made with full-fat milk

**SAVOURY**

- Nuts, salted or unsalted (hazelnuts, almonds, peanuts, cashews, pistachios, walnuts)
- Chips or crisps, popcorn, pretzels, nachos, crackers
- Dip sauces - fresh or sour cream, quark, humous
- Full-fat cheese and biscuits
- Sandwiches, bagels, crackers, toast
- Avocado, olives, feta – cheese, haloumi
- Garlic bread
- Pizza
- Pies or sausage rolls
- Omelette, scrambled eggs, quiche
- Baked potato with butter, cheese, ham/sausage, sour cream or beans, egg
- mayonnaise, tuna mayonnaise
- Boiled eggs

**HOW TO ADD EXTRA CALORIES**

Adding extra calories in your meals can help to ensure that you get enough energy even though you may be eating small portions.
You can easily add extra calories to a meal with ingredients such as:

- Double cream in sauces, stews, desserts, porridges, soups or cocoa, omelettes, pancakes or waffles
- Sour cream or crème fraîche in sauces or dressings, porridges, stews, soups
- waffles or pancakes
- Full-fat cheese on pizza, sandwiches, lasagne, pasta, vegetable and béchamel sauce
- Full-fat butter on potatoes and cooked vegetables, in mashed potatoes, on bread and pasta
- Egg yolks in sauces, mashed potatoes

We recommend that you drink plenty of fluids daily, about 8 cups or 1.5-2 litres per day.
However, do not drink too much before and during your meals, as these can fill you up and stop you eating food. Try drinking energy-dense fluids such as fruit juices, soda, squash, milk, buttermilk, root beer, smoothies and cocoa or hot chocolate with whipped cream.
USING THE ORAL NUTRITIONAL SUPPLEMENT

In this study you are advised to take 2 bottles of a nutritional supplement every day in addition to your regular diet. This supplement has been approved for medical purposes for patients who experience unwanted weight loss. It is high in calories and it is a good source of protein and fibre. It contains omega-3 fatty acids from fish oil and some vitamins and minerals. Together with the other meals you eat during the day, the supplements will help you maintain a good nutritional status. To give the best chance of the supplement being effective, we recommend that you drink the entire two containers (each of 220 ml) every day and continue doing this for the 8 weeks of the study.

WHEN FIRST TAKING THE ORAL NUTRITIONAL SUPPLEMENT DRINK AT THE START OF THE STUDY

The nutritional supplement is rich in fibre, and it can take a little time for your body to adapt to the fibre if you are not used to a high-fibre diet. We recommend that you start by taking less than the full two bottles over the first few days, and work up to taking the full amount after about 5 days. The first few days can be considered an adjustment period.

The following is a schedule to help you begin drinking the oral nutritional supplement:

**Days 1-2:** Drink 1 bottle of the oral nutritional supplement (1/2 bottle twice a day).

**Days 3-4:** Drink ½ bottle three times a day (total 1½ bottles).

**Day 5:** Drink 2 bottles of the oral nutritional supplement (drink ½ bottle four times a day, or however you wish to spread the drink out).

Shake the oral nutritional supplement vigorously before opening.
LOOKING AFTER YOUR ORAL NUTRITIONAL SUPPLEMENT

If drinking a ½ bottle at a time, cover and refrigerate the remainder of the bottle until the next use. Use opened product within 24 hours. Carry the bottle of oral nutritional supplement with you if you go out or go on a holiday. The containers do not need to be refrigerated until they are opened.

HOW TO TAKE/ DRINK THE SUPPLEMENT

Drink the oral nutritional supplement in a covered container with a straw. Sip the oral nutritional supplement slowly (for example over 15 to 20 minutes). Avoid drinking more than 1 bottle at a time. Drink the oral nutritional supplement over the course of the day (for example drink ½ bottle of the oral nutritional supplement four times a day).

Try drinking the oral nutritional supplement chilled. You may also like to try adding coffee or juice, to the oral nutritional supplement to thin it.

You may like to try the oral nutritional supplement frozen. Pour the oral nutritional supplement into a bowl or shallow container and place it in the freezer until slushy or frozen (about 45 minutes to 1 hour). Eat the oral nutritional supplement with a spoon.

If the oral nutritional supplement seems too thick, consider drinking it at room temperature.

Try drinking the oral nutritional supplement warm (but do not let it come to a boil). For flavour variation, mix ½ bottle of the coffee flavour supplement with ½ bottle of the vanilla.

Add crushed or small pieces of fruit such as strawberries, bananas or peaches to the oral nutritional supplement.
EXAMPLES OF RECIPES USING YOUR NUTRITIONAL SUPPLEMENT

LEMON DRINK

1 bottle (220 mL) of vanilla oral nutritional supplement
4 tablespoons lemon curd
Dash of nutmeg or allspice
Place all ingredients in a tall glass
Stir until completely mixed

FULL-OF-FLAVOUR FRUIT SMOOTHIE

1 bottle (220 mL) of banana-flavoured oral nutritional supplement
10 whole strawberries
Sugar/honey to taste
1. Pour nutritional supplement into an ice cube tray and freeze.
2. Clean and freeze strawberries.
3. Blend the frozen oral nutritional supplement and strawberries in a blender until the mixture reaches the desired consistency.
4. Sweeten to taste.

YUMMY YOGURT COOLER

1 bottle (220 mL) of oral nutritional supplement
140 g (4 oz) yoghurt
Your favourite fruit granola
1. Blend oral nutritional supplement with yogurt.
2. Top with fruit and granola.

CHOCOLATE PUDDING

2 bottles (2x200ml) of Café au Lait or Vanilla oral nutritional supplement
1 small package of chocolate instant pudding
Place ingredients in a mixing bowl
Mix thoroughly with a hand mixer or wire whisk
Chill

- For lemon pudding, use vanilla oral nutritional supplement and lemon instant pudding in place of chocolate instant pudding.

- For banana pudding use banana oral nutritional supplement and banana instant pudding and add fresh sliced bananas
# Appendix 5.1: Intervention arm trial diary

## Section 1: Complete this study diary each day during the whole trial period

The weekly goal is to:
- Complete the exercise programme: strength exercise sessions three times per week and 60 minutes of aerobic exercise (e.g. 2x30 mins/ 3x20 mins)
- Drink two bottles of medical nutritional supplement daily

<table>
<thead>
<tr>
<th>Day 1 (Weds)</th>
<th>Day 2 (Thurs)</th>
<th>Day 3 (Fri)</th>
<th>Day 4 (Sat)</th>
<th>Day 5 (Sun)</th>
<th>Day 6 (Mon)</th>
<th>Day 7 (Tues)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: [ ]/[/ ] [ ]/[/ ] [ ]/[/ ] [ ]/[/ ] [ ]/[/ ] [ ]/[/ ] [ ]/[/ ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total minutes of aerobic exercise per day (Write '0' if you did no exercise that day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minutes</td>
<td>Minutes</td>
<td>Minutes</td>
<td>Minutes</td>
<td>Minutes</td>
<td>Minutes</td>
<td>Minutes</td>
</tr>
<tr>
<td>You have been prescribed [ ] strength exercises to complete per session. How many did you complete each day? (Write '0' if you did no exercises)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[ ]</td>
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<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Number of nutritional supplements taken per day (including halves)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[ ]</td>
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<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

Section 2: How you had any difficulties with supplements or exercises this week: Yes [ ] No [ ] If 'Yes': please describe:

EneRgy study diary 2. V3 24-01-18
Section 3: We would like to know any times you needed to use medical services. If you tick ‘Yes’ to any of the questions below, please answer the following questions.

Have you had any contact with health care services out of the study, e.g. GP, hospital, hospice, etc. in the past week?  Yes [ ]  No [ ]

*If you answer ‘Yes’ please answer the questions below and the research nurse may ask you some further details about each episode including any travel costs.*

(Tick if ‘Yes’)

1. Were you admitted to hospital for more than 24 hours? [ ]
   *If ‘Yes’ how many days were you in the hospital?* [ ]

2. Have you been to A&E but not admitted to hospital [ ]
   *If ‘Yes’ tell us how many times you went to A&E?* [ ]

3. Were you admitted to the hospice for more than 24 hours? [ ]
   *If ‘Yes’ how many days were you in the hospice?* [ ]

4. Did you call NHS 24 during the last week? [ ]
   - How many times did NHS 24 send a GP for a home visit? [ ]
   - How many times did NHS 24 offer you a GP out-of-hours appointment? [ ]

5. Have you been to a hospital or hospice outpatient clinic? [ ]
   *If ‘Yes’ how many appointments?* [ ]

6. Have you had appointments with your GP or practice nurse? [ ]
   *If ‘Yes’ how many appointments* [ ]

7. Have you had any contact with your district nurse? [ ]
   *If ‘Yes’ how many contacts?* [ ]

8. Have you had any contact with your Palliative Care Nurse? [ ]
   *If ‘Yes’ how many contacts?* [ ]

9. Have you had contact with any other healthcare professional not listed above? *If ‘Yes’ please make a note of who below and discuss with the research nurse at your next visit.*

______________________________
Appendix 5.2: Control arm trial diary

<table>
<thead>
<tr>
<th>Study Diary</th>
<th>Patient ID Number</th>
<th>Week number (circle)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
</table>

Complete this study diary each week during the whole trial period.
We are interested to know whether you are using any nutritional supplements (not as part of the trial) and how much exercise you are doing per week.

<table>
<thead>
<tr>
<th>Day 1 (Wed) Date: <strong>/</strong>/__</th>
<th>Day 2 (Thurs)</th>
<th>Day 3 (Fri)</th>
<th>Day 4 (Sat)</th>
<th>Day 5 (Sun)</th>
<th>Day 6 (Mon)</th>
<th>Day 7 (Tues)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you done any exercise today?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>What was the exercise? (e.g. Walking, swimming, gardening, vigorous housework)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If 'Yes', how many minutes?</td>
<td>Minutes</td>
<td>Minutes</td>
<td>Minutes</td>
<td>Minutes</td>
<td>Minutes</td>
<td>Minutes</td>
</tr>
<tr>
<td>Have you taken any nutritional supplements?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>(we do not request you to in this part of the study) if 'Yes' detail what they are and how many you take daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Section 3: We would like to know any times you needed to use medical services. If you tick ‘yes’ to any of the questions below, please answer the following questions.

Have you had any contact with health care services out with the study, e.g. GP, hospital, hospice, etc. in the past week?  Yes □ No □

*If you answer ‘yes’ please answer the questions below and the research nurse may ask you some further details about each episode including any travel costs.*

[Tick if yes]

1. Were you admitted to hospital for more than 24 hours? □ If ‘yes’ how many days were you in the hospital? □
2. Have you been to A&E but not admitted to hospital □ If ‘yes’ tell us how many times you went to A&E? □
3. Were you admitted to the hospice for more than 24 hours? □ If ‘yes’ how many days were you in the hospice? □
4. Did you call NHS 24 during the last week? □ If ‘yes’ how many times did you call them? □
   - How many times did NHS 24 send a GP for a home visit? □
   - How many times did NHS 24 offer you a GP out-of-hours appointment? □
5. Have you been to a hospital or hospice outpatient clinic? □ If ‘yes’ how many appointments? □
6. Have you had appointments with your GP or practice nurse? □ If ‘yes’ how many appointments □
7. Have you had any contact with your District Nurse? □ If ‘yes’ how many contacts? □
8. Have you had any contact with your Palliative Care Nurse? □ If ‘yes’ how many contacts? □
9. Have you had contact with any other healthcare professional not listed above? If ‘yes’ please make a note of who below and discuss with the research nurse at your next visit. ____________________________

Energy study diary 2. V3 24-01-10
Appendix 6: A randomised, feasibility trial of an Exercise and Nutrition-based Rehabilitation programme (ENeRgy) in people with cancer.

A randomized, feasibility trial of an exercise and nutrition-based rehabilitation programme (ENeRgy) in people with cancer

Charlie C. Hali, Richard J.E. Skipworth, Honor Blackwood, Duncan Brown, Jane Cook, Katharina Diermbelger, Elizabeth Dixon, Valerie Gibson, Catriona Graham, Peter Hall, Erne Haraldsdottir, Jane Hopkinson, Anna Lloyd, Matthew Maddocks, Lucy Norris, Sharon Tuck, Marie T. Fallon & Barry J.A. Laid

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Abstract

Background Despite rehabilitation being increasingly advocated for people living with incurable cancer, there is limited evidence supporting efficacy or component parts. The progressive decline in function and nutritional in this population would support an approach that targets these factors. This trial aimed to assess the feasibility of an exercise and nutrition-based rehabilitation programme in people with incurable cancer.

Methods We randomized community dwelling adults with incurable cancer to either a personalized exercise and nutrition-based programme (experimental arm) or standard care (control arm) for 8 weeks. Endpoints included feasibility, quality of life, physical activity (step count), and body weight. Qualitative and health economic analyses were also included.

Results Forty-five patients were recruited (23 experimental arm, 22 control arm). There were 26 men (58%), and the median age was 78 years (IQR: 69–84). At baseline, the median BMI was 26 kg/m² (IQR: 23–29), and median weight loss in the previous 6 months was 5% (IQR: −12% to 0%). Adherence to the experimental arm was >80% in 16/21 (76%) patients. There was no statistically significant difference in the following between trial arms: step count – median % change from baseline to endpoint, per trial arm (experimental –18.5% [IQR: −61 to 65], control 5% [IQR: −32 to 50], P = 0.54); weight – median % change from baseline to endpoint, per trial arm (experimental 1% [IQR: −3 to 3], control −0.5% [IQR: −3 to 1], P = 0.194); overall quality of life – median % change from baseline to endpoint, per trial arm (experimental 0% [IQR: −20 to 19], control 0% [IQR: −23 to 33], P = 0.846). Qualitative findings observed themes of capability, opportunity, and motivation amongst patients in the experimental arm. The mean incremental cost of the experimental arm versus control was £319.51 (CI: −759.53 to 6581.91), suggesting the experimental arm was less costly.

Conclusions An exercise and nutritional rehabilitation intervention is feasible and has potential benefits for people with incurable cancer. A larger trial is now warranted to test the efficacy of this approach.

Keywords Exercise; Nutrition; Cancer; Rehabilitation

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Introduction

Cancer is becoming more common, yet advances in treatment mean that more people are living longer with incurable disease than ever before. Indeed the number of people living with cancer is increasing by approximately 3% every year with life expectancies of several months to years. Further, with population aging, people with incurable cancer are increasingly older, living longer, and have more co-morbidities. Sroomanjaroen and Smith argue that ‘many people with cancer function fully for years, and it is commonplace for patients with chronic cancer to face the challenge of determining how to optimize their remaining time.’ This view is being increasingly acknowledged by learned societies with the European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO), supporting rehabilitation as a key component of cancer care. Optimising overall function has been purported to improve quality of life, tolerance of cancer therapies and reduce patient and caregiver distress. Furthermore, this may have positive benefits on health care resource allocation and use. Although these are laudable achievements there remains a paucity of evidence to directly support the benefits of rehabilitation in patients with incurable cancer and to guide the constituent parts of programmes.

It would seem logical that targeting physical and nutritional deficits should be the cornerstones of any rehabilitation intervention. Together, deterioration in physical function combined with loss of muscle and fat termed ‘cancer cachexia’, result in approximately 50% of cancer deaths, and becomes more prevalent as disease progresses. It has been advocated that to optimally address cachexia, any interventions should be multimodal and comprise nutritional support and exercise advice. However, to date, there is limited evidence to support this.

Therefore, a trial was undertaken to assess the feasibility of an exercise and nutritional rehabilitation programme in people with incurable cancer. Titled the ENErgy trial, this was a randomized, feasibility trial of an Exercise and Nutrition-based Rehabilitation programme (ENeRgy) versus standard care in people with cancer.

Methods

Study design and patients

We undertook a randomized, open label, feasibility trial at a specialist palliative care unit in the UK, serving a geographically defined population of approximately one million. Eligible patients met the following criteria: outpatients; age ≥18 years; Karnofsky performance status (KPS) ≥60; diagnosis of incurable cancer (defined as metastatic or locally advanced cancer not amenable to curative treatment); not undergoing anti-cancer therapy (hormonal treatment and/or bisphosphonates permitted); a clinician predicted survival of >3 months. Patients undergoing anti-cancer therapy (hormonal, bisphosphonates permitted), receiving parenteral nutritional support, who had dysphagia or who were co-enrolled in a clinical trial were excluded. Those who had received any systemic anti-cancer therapy in the preceding 4 weeks were not eligible.

The trial was conducted as per Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by an ethics committee for human research (ethics reference: 17/W5/0226). All patients provided written informed consent. The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia and Muscle. The trial was registered at ClinicalTrials.gov: NCT03316157. The rationale and trial design have been previously described.

Randomization

Patients were randomized centrally in a 1:1 ratio of experimental to control, using a block randomization with random block sizes and stratified for baseline KPS (60–80% or 90–100%).

Procedures

The experimental arm was an exercise and nutrition-based rehabilitation programme. Following baseline assessments and randomization, patients had an interview with the trial physiotherapist and dietitian. Based on this interview, they were given personalized advice on nutrition and exercise.

The exercise component, developed by the physiotherapist, was a home-based programme consisting of aerobic and resistance training in divided intervals as per patient choice and capability. The aerobic component totalled 60 min of exercise per week (e.g. walking) at moderate intensity (warm and slightly out of breath—modified Borg scale 3–4 rating). The resistance component focussed on major muscle groups in the upper and lower body, predominantly using body weight exercises including standing press ups, half squats and shoulder thrusts, with sets advised three times per week.

The nutrition component aimed to ensure optimal nutritional intake and consisted of dietitian-led counselling (personalized for each patient) taking into account dietary preferences. Patients were also supplied with an Oral Nutritional Supplement (ONS—ProSure®—Abbott Laboratories, IL, USA) and advised to take two per day. Each 220 ml supplement contained 1 g of eicosapentaenoic acid (EPA) and DHA.
1.5 kcal/mL. Patients who did not tolerate the ONS due to preference were offered an alternative ONS and oral capsules containing 2 g EPA.

Written information supporting the exercise and nutrition interventions were provided (Supporting Information, Data S3). The dietician and physiotherapist reviewed adherence to the relevant interventions during weekly clinic attendances by patients. At this time, progress was reviewed and the intervention modified if needed, to support adherence. A patient diary (paper) was used to record the number of minutes of aerobic exercise per day, the number of strength exercises performed per day, and the number of nutritional supplements taken per day, and this was discussed with the patient at their weekly visits.

Patients randomized to the control arm received their usual care which may have included ongoing specialist palliative care follow-up as per individual patient need. They were entitled to any additional support from allied health professionals if needed. Those in the control arm received weekly telephone calls from the research team to ensure adherence to trial-related data collection and record any nutritional interventions (dietitian and/or prescribed ONS) and exercise undertaken. These data were collected to assess any contamination of the control group (mimicking any aspect of the trial-related intervention). Patients in the control arm were offered the trial intervention at the end of their involvement in the trial.

Endpoints

The primary endpoint of the trial was to assess feasibility of the experimental arm (rehabilitation programme). Feasibility was assessed primarily by adherence to the intervention using the prescribed number of exercises/ONS prescribed versus actual undertaken. We recorded adherence by using the prescribed versus actual amount of exercise and nutritional supplements performed/taken. These data were obtained from patient recorded diaries (of which completion was supported by weekly telephone calls by research staff).

Secondary endpoints assessed other aspects of feasibility using recruitment rate (could we recruit our target sample within an acceptable time frame [18 months]), attrition rate (compared with similar studies in patients with advanced cancer), and contamination of the control arm (use of ONS outside the trial and exercise uptake). The acceptable attrition rate was defined as <44%, and this was informed by previous work in palliative and supportive care trials.11

The exploratory endpoints examined the following.

Physical function was assessed using a physical activity monitor (Fitbit®, San Francisco, USA). Patients wore this pre-randomization for 7 days then at the end of the trial for 7 days. We assessed mean daily step count at these time points. We also assessed physical function assessed using the timed up and go (TUG) test,12 2 min walk test (TMWT),13 and the Life Space Assessment (LSA) questionnaire.14 All of these were carried out at baseline (pre-randomization) and at the trial endpoint.

Performance status was assessed at baseline using Karnofsky performance status criteria.15 Nutritional status was assessed using the abridged Patient Generated Subjective Global Assessment (abPG-SGA),16 body weight, and assessment of nutritional intake using a 10-point scale (Aves).17

Quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – C15PQLQ (EORTC QLG-C15PQLQ),18 the EQ-SDL, and the EQ-VAS questionnaires.19 Quality of sleep was assessed using sleep data recorded by the physical activity monitor. Adverse events were also assessed and reported.

Health economic endpoints examined the potential impact on patient-reported health utility, healthcare-related resource use and costs. Health utility was assessed by the EQ-5D-5L20 and EQ-VAS patient completed questionnaire, healthcare utilization, and out of pocket expenses.21 Questionnaires were designed to measure health-related utility healthcare-related resource use and costs, administered at baseline and follow-up assessment time-points. Patient health-related quality of life was captured using a patient reported outcome measure; the EQ-5D-5L and EQ-VAS questionnaires. Utility values were assigned to responses using the standard UK value set.22 Healthcare utilization and costs were collected using a bespoke patient completed questionnaire, adapted from the UK Cancer Costs Questionnaire [citation: https://blogs.ed.ac.uk/ukcqc/].

Unit costs were assigned to resource use items using standard national costing sources such as PSSRU23 and NHS reference costs,24 or through consultation with relevant service business managers. Costs were summarized from the perspectives of the NHS, the charitable and 3rd sector and the patient and their carers. Cost-effectiveness was calculated as the Incremental Cost-effectiveness Ratio (ICER), expressed as cost per QALY gained.

A within-trial cost-effectiveness analysis was performed in accordance with the methodological specification of the NICE Guide to the Methods for Health Technology Assessment.24 Uncertainty was evaluated using probabilistic sensitivity analysis (PSA) and value of information (Vol) analysis, implemented using the bootstrap method (1000 replications). For the PSA and for the Vol Analysis, the SAVI Tool from the University of Sheffield was used.25

Statistical considerations

As the primary endpoint of this study was to assess the feasibility of the trial, rather than superiority of the experimental arm over the control arm, a formal sample size calculation

Appendices
was not necessary. Our justification for the sample size of 40 patients was supported by our previous work, our potential pool of eligible patients (estimated at 1300 per year), consensus in the sample size of feasibility trials, and based on this, we estimated we would be able to express the percentage completing the study protocol to within 20% assuming a two-sided 95% confidence interval (CI) around an expected percentage of 90% completion. Findings are presented descriptively split by trial arm and endpoints (e.g. change in daily step count and change in weight) are compared between trial arms using appropriate non-parametric tests (Mann-Whitney U test). No interim analysis was planned or undertaken. The analysis was performed using data from all patients recruited. SPSS v23 (Chicago, IL, USA) was used.

**Embedded qualitative study**

Interviews with a purposive sample of experimental arm patients were audio-recorded and transcribed verbatim. Coding of all transcribed data, conducted by two researchers blind to the trial results (A. L. and J. H.), was inductive and focused on the questions: “What is the experience of EneRgy?” and “What are the barriers to and facilitators of the physical activity and nutritional components of EneRgy?”

The analysis used the framework technique, which involves systematic and interconnected stages of sifting and charting coded qualitative data, then mapping patterns in a search for understanding and explanation. The pre-existing

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**Figure 1: Trial profile.**
framework, Capability, Opportunity, and Motivation together result in Behaviour (COM-B) was applied to the coded data. Coded data extracts were categorized (J. H.) as capability, opportunity, or motivation for physical activity or for nutritional intake. Data relevant to understanding the experience of and engagement with ENergy but falling outside the COM-B framework were also captured in a visual representation of the whole data set. Overarching patterns were identified that revealed factors influencing adherence/non-adherence to ENergy.

The trial was sponsored jointly by the University of Edinburgh and NHS Lothian.

Role of the funding source

This trial was funded by a grant from Marie Curie and the Chief Scientist Office (Scotland, UK). The oral nutritional supplement was provided free of charge by Abbott Laboratories. The funders and Abbott Laboratories had no involvement in the design, conduct or analysis of the trial. B. L., C. H., M. F., P. H., K. D., E. W., A. L., J. H., and C. G. had access to raw data. The corresponding author had final responsibility for the decision to submit the manuscript for publication.

Results

From 30 January 2018 to 24 April 2019 (15 months), 45 patients were recruited (23 experimental arm, 22 control arm) (Figure 1). Baseline characteristics are shown in Table 1. The median age was 78 years (IQR: 69–84) and 26 (58%) were male. The most common primary cancer site was gastrointestinal (18 [40%]), and patients had either metastatic (29 [64%]) or loco-regionally advanced disease (16 [36%]). Twenty-nine (65%) of patients had a Karnofsky performance score of 60–80. The median BMI at baseline was 26 kg/m² (IQR: 22–29), and the median weight loss in the previous 6 months was 5% (IQR: 12–0%) (Figure 2).

Table 2 details the primary endpoints of feasibility of the experimental arm (rehabilitation programme) assessed by adherence to the prescribed exercises/ONS versus actual undertaken. For the experimental arm, adherence was defined as excellent if this was ≥80%, good if this was 50–79% and poor if this was below 50%. For individual components of the experimental arm, excellent adherence was achieved by at least 16/21 (76%) of patients, and for adherence to all components, this was either good (8 [38%]) or excellent (12 [57%]) patients. Therefore, feasibility in terms of compliance to the experimental interventions was acceptable, and the trial was positive in this regard.

Secondary endpoints assessed other aspects of feasibility. The recruitment target was 40 patients over 15 months; however, accrual was better than expected, and 45 patients were recruited over 15 months, and then, recruitment was stopped. Of the 121 people screened, 29 were not eligible and were not assessed further. Of the remaining 92 who were further assessed for participation, 45 (49%) were recruited, 9 (10%) were ineligible, 32 (35%) declined, 1 (1%) was not recruited due to an investigator decision, and 5 (5%) for other reasons. The recruitment rate was 37% (45/121) which was similar to other trials in this patient population. The main reason for patients not participating was that they declined (32 [35%]).

Of the 45 patients recruited, 29 (64%) completed the trial resulting in an attrition rate of 36% (16/45). The attrition rate was 30% (7/23) and 41% (9/22) in the experimental and control arms respectively. The most common reason for attrition was deteriorating health (four patients—experimental; seven patients—control arm).

Contamination in the control arm was low; one patient in the control arm started an ONS and another increased their pre-trial ONS use. Patients in the control arm did not have...
Increased exercise based on self-reported measures and activity data.

Table 3 details the exploratory endpoints examining physical function, weight, and nutrition, assessed as part of the trial. There was no evidence of statistically significant differences in the % difference in daily step count ($P = 0.546$), timed up and go test ($P = 0.767$), 2-min walk test ($P = 0.484$), and life space assessment ($P = 1.00$) between the trial arms. Patients in the experimental arm gained a median of 1% (IQR: −3% to 3%) of weight versus those in the control arm who lost a median of 0.48% (IQR: −2.6% to 0.64%), $P = 0.184$.

Table 4 details the exploratory endpoints examining patient reported outcomes of quality of life measured using the EORTC QLQ-C30 PAL. With the exception of emotional functioning ($P = 0.006$), there were no statistically significant differences between the trial arms. There was no difference in cancer-related quality of life ($P = 0.5$) or any sleep parameters between the trial arms—data not presented.

Table 5 details adverse events. There were no SAEs for patients in the trial. There were 39 AEs recorded in total, 20 in the experimental arm (51%), and 19 in the control arm (49%). Of AEs in the experimental arm, nine (45%) were related to the ONS, nine (45%) related to the underlying cancer diagnosis, and two (1%) were due to non-cancer-related issues.

Table 2: Primary endpoint: adherence to the experimental arm

<table>
<thead>
<tr>
<th>Adherence to individual intervention components (n = 21)</th>
<th>&lt;50% n (%)</th>
<th>≥50–79% n (%)</th>
<th>≥80% n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral nutritional supplement (n = 21)</td>
<td>1 (5)</td>
<td>4 (19)</td>
<td>16 (76)</td>
</tr>
<tr>
<td>Resistance (n = 21)</td>
<td>1 (2)</td>
<td>3 (14)</td>
<td>17 (81)</td>
</tr>
<tr>
<td>Aerobic (n = 21)</td>
<td>1 (5)</td>
<td>2 (10)</td>
<td>18 (86)</td>
</tr>
<tr>
<td>Adherence to combined intervention components</td>
<td>&lt;50%</td>
<td>≥50%</td>
<td>≥80%</td>
</tr>
<tr>
<td>Aerobic</td>
<td>1 (5)</td>
<td>4 (19)</td>
<td>16 (76)</td>
</tr>
<tr>
<td>Aerobic ONS</td>
<td>1 (5)</td>
<td>6 (29)</td>
<td>14 (67)</td>
</tr>
<tr>
<td>Resistance ONS</td>
<td>1 (5)</td>
<td>7 (33)</td>
<td>13 (62)</td>
</tr>
<tr>
<td>Aerobic ONS</td>
<td>1 (5)</td>
<td>8 (38)</td>
<td>12 (27)</td>
</tr>
</tbody>
</table>

*Two patients withdrew from the trial post randomization.
Table 3  Exploratory endpoints examining physical function, weight, and nutrition

<table>
<thead>
<tr>
<th></th>
<th>Experimental arm</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Daily step count*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>22</td>
<td>2954 (2168–4143)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>16</td>
<td>2896 (1055–5005)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>15</td>
<td>–476 (–1592–1882)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>16</td>
<td>14 (12–21.8)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>–0.5 (–3–4)</td>
</tr>
<tr>
<td>Difference %</td>
<td>15</td>
<td>–19 (–61–65)</td>
</tr>
<tr>
<td>Timed up-and go test (s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23</td>
<td>13 (11–17)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>17</td>
<td>15 (12–18)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>16</td>
<td>14 (12–21.8)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>–0.5 (–3–4)</td>
</tr>
<tr>
<td>Difference %</td>
<td>16</td>
<td>–5 (–19–20)</td>
</tr>
<tr>
<td>2 min walk test (m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23</td>
<td>114 (76–144)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>17</td>
<td>115 (77–136)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>16</td>
<td>116 (75–138)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>–9 (–5–18)</td>
</tr>
<tr>
<td>Difference %</td>
<td>16</td>
<td>6 (–4–27)</td>
</tr>
<tr>
<td>Life space assessment (max score 120)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>21</td>
<td>33 (22–81)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>18</td>
<td>38 (34–60)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>16</td>
<td>50 (35–64)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>0 (–16–11)</td>
</tr>
<tr>
<td>Difference %</td>
<td>16</td>
<td>0 (–21–41)</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23</td>
<td>71 (60–79)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>17</td>
<td>76 (63–85)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>16</td>
<td>80 (62–88)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>4 (–3–3)</td>
</tr>
<tr>
<td>Difference %</td>
<td>16</td>
<td>1 (–3–3)</td>
</tr>
<tr>
<td>aPG-SGA score (0–36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23</td>
<td>4 (1–9)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>18</td>
<td>5 (1–16)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>16</td>
<td>8 (1–13)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>1 (–2–5)</td>
</tr>
<tr>
<td>Difference %</td>
<td>16</td>
<td>27 (–18–300)</td>
</tr>
<tr>
<td>AvoS score (0–10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23</td>
<td>8 (5–8)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>18</td>
<td>7 (5–6)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>16</td>
<td>7 (4–10)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>0 (–1–1)</td>
</tr>
<tr>
<td>Difference %</td>
<td>16</td>
<td>0 (–25–22)</td>
</tr>
</tbody>
</table>

* Mann-Whitney U test.
** Full 24 h periods.

In the control arm, there were 12 cancer-related AEs (63%) and seven unrelated AEs (37%), relating to pre-existing medical conditions or not serious enough to constitute an SAE.

Health economic results

Supporting Information, Data S1 contains the full health economic analysis results. In summary, the main drivers of costs were hospital inpatient stays and unscheduled hospice stays followed by community care, outpatient appointments, out of hours (ODH) services, and travel costs. The mean incremental cost of the experimental arm versus control is £319.51 [CI –7599.53 to 6581.91], suggesting the experimental arm is less costly. The mean incremental benefit of the experimental arm versus control was 0.00018 QALYs [CI –0.21, 0.023]. Probabilities of the intervention being cost saving and more beneficial compared with the control group were 0.544 and 0.517, respectively.

Qualitative analysis

Fourteen patients in the experimental arm had an end of trial interview. The factors influencing capability, opportunity, and motivation to adhere to ENErgy with supporting evidence (patient quotes) are reported in the Supporting Information, Data S2.

In summary, to engage with ENErgy patients had to perceive benefit, improvement in energy levels, increased physical or social activity, improved food intake, weight gain or, for one patient, an expectation of improved survival. For 10 of the patients, ENErgy was enjoyable and restorative. However, only some of these patients reported improvement in activity, physical strength, oral intake, or weight. Perception of benefit, such as a sense of achievement, knowing what to do, a sense of control, or hope of improvement, could motivate adherence. Family members and carers also influenced ability to and willingness to adhere to ENErgy. The four patients who did not report benefit ranged from mildly resistant to non-adherent. These patients revealed that ENErgy can have an unintended consequence of raising awareness of progressing disease and impending death.
Table 4  Exploratory endpoints examining patient reported outcomes of quality of life

<table>
<thead>
<tr>
<th></th>
<th>Experimental arm</th>
<th>Control arm</th>
<th>P</th>
<th>Experimental arm</th>
<th>Control arm</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall QoL</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23</td>
<td>66.7 (50–83.3)</td>
<td>22</td>
<td>50 (45.8–70.8)</td>
<td>23</td>
<td>50 (16.7–66.7)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>18</td>
<td>75.0 (50–83.3)</td>
<td>16</td>
<td>50 (50–66.7)</td>
<td>18</td>
<td>33.3 (29.2–54.2)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>16</td>
<td>66.7 (50–83.3)</td>
<td>13</td>
<td>66.7 (50–66.7)</td>
<td>16</td>
<td>50 (33.3–66.7)</td>
</tr>
<tr>
<td>Difference</td>
<td>16</td>
<td>0.0 (–16.7–12.5)</td>
<td>13</td>
<td>0.0 (–16.7–16.7)</td>
<td>16</td>
<td>8.3 (–16.7–16.7)</td>
</tr>
<tr>
<td>Difference %</td>
<td>16</td>
<td>0.0 (–20–18.8)</td>
<td>13</td>
<td>0.0 (–22.5–33.3)</td>
<td>16</td>
<td>10 (–33–100)</td>
</tr>
<tr>
<td><strong>Physical</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23</td>
<td>88.9 (66.7–100)</td>
<td>22</td>
<td>83.3 (66.7–100)</td>
<td>23</td>
<td>33 (0.0–66.7)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>18</td>
<td>88.9 (77.8–100)</td>
<td>16</td>
<td>88.9 (77.8–100)</td>
<td>18</td>
<td>33.3 (0.0–41.7)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>16</td>
<td>83.3 (66.7–100)</td>
<td>13</td>
<td>88.9 (83.3–100)</td>
<td>16</td>
<td>16.7 (0.0–66.7)</td>
</tr>
<tr>
<td>Difference</td>
<td>16</td>
<td>0.0 (0.0–8.3)</td>
<td>13</td>
<td>0.0 (0.0–11.1)</td>
<td>16</td>
<td>0.0 (0.0–0)</td>
</tr>
<tr>
<td>Difference %</td>
<td>16</td>
<td>0.0 (0.0–9.4)</td>
<td>13</td>
<td>0.0 (0.0–18.3)</td>
<td>8</td>
<td>0 (–37.5–75)</td>
</tr>
<tr>
<td><strong>Emotional</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23</td>
<td>100 (83.3–100)</td>
<td>22</td>
<td>100 (83.3–100)</td>
<td>23</td>
<td>0.0 (0.0–33.3)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>18</td>
<td>100 (95.8–100)</td>
<td>16</td>
<td>100 (66.7–100)</td>
<td>18</td>
<td>16.7 (0.0–66.7)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>16</td>
<td>100 (100–100)</td>
<td>13</td>
<td>83.3 (83.3–100)</td>
<td>16</td>
<td>16.7 (0.0–33.3)</td>
</tr>
<tr>
<td>Difference</td>
<td>16</td>
<td>0.0 (0.0–16.7)</td>
<td>13</td>
<td>–16.7 (–16.7–0.0)</td>
<td>16</td>
<td>0.0 (0.0–25)</td>
</tr>
<tr>
<td>Difference %</td>
<td>16</td>
<td>0.0 (0.0–20)</td>
<td>13</td>
<td>–16.7 (–16.7)</td>
<td>16</td>
<td>0 (–50–25)</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Baseline</td>
<td>23</td>
<td>33.3 (16.7–66.7)</td>
<td>22</td>
<td>33.3 (16.7–54.2)</td>
<td>23</td>
<td>0.0 (0.0–33.3)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>18</td>
<td>33.3 (16.7–70.8)</td>
<td>16</td>
<td>16.7 (0.0–33.8)</td>
<td>18</td>
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<td>Endpoint</td>
<td>16</td>
<td>33.3 (16.7–66.7)</td>
<td>13</td>
<td>16.7 (0.0–41.7)</td>
<td>16</td>
<td>0.0 (0.0–33.3)</td>
</tr>
<tr>
<td>Difference</td>
<td>16</td>
<td>0.0 (–16.7–0.0)</td>
<td>13</td>
<td>0.0 (–16.7–16.7)</td>
<td>16</td>
<td>0.0 (0.0–0)</td>
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<tr>
<td>Difference %</td>
<td>13</td>
<td>0.0 (–58.3–0.0)</td>
<td>13</td>
<td>0.0 (–100–50)</td>
<td>16</td>
<td>–66 (–100–0.0)</td>
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<tr>
<td><strong>Fatigue</strong></td>
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<tr>
<td>Baseline</td>
<td>23</td>
<td>50 (16.7–66.7)</td>
<td>22</td>
<td>33.3 (16.7–70.8)</td>
<td>23</td>
<td>0.0 (0.0–33.3)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>18</td>
<td>33.3 (29.2–54.2)</td>
<td>16</td>
<td>33.3 (16.7–62.5)</td>
<td>18</td>
<td>16.7 (0.0–33.3)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>16</td>
<td>50 (33.3–66.7)</td>
<td>13</td>
<td>33.3 (16.7–41.7)</td>
<td>16</td>
<td>0.0 (0.0–0)</td>
</tr>
<tr>
<td>Difference</td>
<td>16</td>
<td>8.3 (–16.7–16.7)</td>
<td>13</td>
<td>0.0 (–16.7–16.7)</td>
<td>16</td>
<td>0 (–25–0.0)</td>
</tr>
<tr>
<td>Difference %</td>
<td>16</td>
<td>1.0 (–33–100)</td>
<td>13</td>
<td>0.0 (–50–75)</td>
<td>16</td>
<td>–100 (–100–16.7)</td>
</tr>
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</table>
Discussion

Our findings demonstrate that delivering and testing a rehabilitation programme incorporating exercise and nutritional advice/supplementation, delivered in an outpatient setting to people with incurable cancer, is feasible. This trial recruited ahead of schedule and target, with an acceptable attrition rate in the setting of advanced cancer. The trial was not powered to assess the effects on nutritional, functional or quality of life outcomes, but encouraging changes in emotional functioning were observed, echoed by our qualitative findings. Our health economic analyses were also encouraging. There is a strong belief that rehabilitation should be an optional therapy for the management of people living with incurable cancer, yet trials supporting this viewpoint are scarce. The present trial provides a foundation for larger trials to assess the efficacy of such an approach.

There is limited similar research for comparison; however, two studies are notable. Naito and co-workers completed a single arm trial examining a multimodal intervention (exercise and nutrition) in 30 elderly patients with lung or pancreatic cancer (NEXTAC-ONE)\(^\text{[20]}\). They demonstrated feasibility, and a randomized phase two trial is underway to further assess this approach.\(^\text{[21]}\) Edbrooke and co-workers undertook a randomized trial assessing exercise and behaviourial change strategies in 92 patients with inoperable lung cancer.\(^\text{[22]}\) No improvement in exercise capacity was observed (primary outcome), but quality of life improved. These trials, along with the present trial, are well aligned with recommendations by ESMO,\(^\text{[5]}\) ASCO,\(^\text{[6]}\) and the UK National Institute for Clinical Excellence (NICE) for the care of people with incurable cancer. However, a rehabilitative approach, integrated into routine care, remains the exception rather than the norm. In the present study, the paradigm and design were informed by our previous work in cancer cachexia where the importance of a multimodal approach including exercise and optimal nutrition is advocated. Cancer cachexia remains the cause of death in approximately half of patients with cancers, and the combination of nutritional and functional deficits acts synergistically with devastating consequences. Previous work has focussed on uni-modal exercise approaches to rehabilitation with scarce attention to nutritional care scarce. Optimizing nutritional care alongside physical function may serve to optimize rehabilitative potential but also address cachexia as exercise itself has an anti-inflammatory effect. It is hoped that future work will elucidate this.

A key strength of our trial is the embedded qualitative analysis. Feasibility trials often do not progress to efficacy trials due to a lack of encouraging effects on exploratory endpoints, and as such, interventions may seem ineffective. However, we would argue that in feasibility trials, with modest sample sizes, it is unrealistic to expect a plethora of encouraging exploratory endpoint results. Richards and colleagues argue that ‘Applying mixed methods integration techniques to data or findings from studies involving both RCTs and qualitative research can yield insights that might be useful for understanding variation in outcomes, the
mechanism by which interventions have an impact, and identifying ways of tailoring therapy to patient preference and type, and we agree. The qualitative findings demonstrated the positive impact of the intervention and suggest continuation to a larger trial is worthwhile and will help refine aspects of the trial design. There are limited qualitative studies conducted as part of quantitative clinical trials in cancer rehabilitation; however, Edbrooke and co-workers are to be commended for assessing the patient experience of their exercise intervention, as part of their clinical trial.

The Health Economic Analysis undertaken suggested that the rehabilitation intervention was cost-saving compared with the control group. We focussed on the costs to the NHS, and community care with some indication of costs to the patients such as travel costs. One potential reason for the cost saving was that the care provided replaced or prevented community healthcare needs. It may have been due to patients having additional attention to their wider symptom control needs (e.g. pain management) or indirect psychological support from the trial team. The Health Economic Analysis is an important part as even if a rehabilitation intervention proves to be efficacious, excess costs may prohibit widespread integration into healthcare. Cost-effectiveness analyses may therefore support widespread integration.

The trial had several limitations including the sample size. This was small however in terms of a feasibility trial it was reasonable; however, any definitive conclusions on efficacy cannot be drawn. Further the sample size was underpowered for health economic analysis, particularly for estimation of costs and this will need further evaluated in any larger trial. We also acknowledge that the heterogeneous sample (age, tumour type, etc.) is a limitation. It was also difficult to standardize background care to ensure both arms received similar care with the exception of the rehabilitation intervention. This latter point is key, and we cannot rule out that improvements in emotional functioning seen in the intervention arm were as result of contact with trial staff rather than the intervention per se. Such aspects are difficult to disentangle yet represent key considerations in future trial design. We also acknowledge that while the intervention targeted physical function and nutrition, we did not quantify degree of cancer cachexia or incorporate specific measures of body composition (lean mass assessment) or measures of muscle function (e.g. hand grip strength). Rather, we focussed on generic measures of function (physical activity) and quality of life but accept that the former parameters would be of interest. Further, characterizing cachexia stage of participants at enrolment, in future trials, would be of interest.

Conclusion

A rehabilitation intervention targeting exercise and nutrition, in people with incurable cancer, is feasible and has potential benefits in terms of emotional function, motivation, capability attitudes, and costs. The trial was feasible and provides sufficient support for progression to a larger trial to assess efficacy. Such a trial, ENERGise, is in development and, along with similar trials, will serve to inform rehabilitation interventions in people living with incurable cancer.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Cost effectiveness plane. Table S1: Mean cumulative costs per patient at study end point for NHS, community care and travel. Table S2: Expected Value of Perfect Information (EVPI) per person. Table S3: Expected value of perfect parameter information (EVPPi).


Conflict of interest

B.L. has received honoraria and consultancy fees from Helsinn, Arteo and XBiotech. R.S. has received honoraria and consultancy fees from Hebins and Novartis. M.F. has received honoraria and consultancy fees from Pfizer. C.H., H.B., D.B., J.C., K.D., E.D., V.G., C.G., P.H., E.H., J.H., A.L., M.M., L.W., and S.T. have no conflicts of interest.

Journal of Cachexia, Sarcopenia and Muscle 2021
DOI: 10.1002/jcsm.12806

Appendices
References

23. NHS. NHS Reference Costs. (NICE) NHECE.

Journal of Cachexia, Sarcopenia and Muscle 2021
DOI: 10.1007/s00398-020-02838-6
Appendix 7: Physical activity monitor participant leaflet

THE PHYSICAL ACTIVITY METER (PAM)
WHAT IS A PHYSICAL ACTIVITY MONITOR?

It is a small battery charged sensor, inside a bracelet which monitors your movements during standing, walking or lying in bed.

HOW SHOULD I USE IT?

The monitor is a bracelet containing a sensor which should be worn on the wrist of your non-writing hand. We would like you to wear the bracelet for 7 days at the start of the trial, and again at the end (weeks 0 and 9). The monitor is waterproof and should be worn continuously day and night. The idea is to record your normal activity levels and sleep patterns. A member of the research team will tell you when to wear the bracelet and when to return it.
CHARGING THE BRACELET.

The battery in the sensor lasts for up to 5 days. Charging should occur **on a weekend** day for **at least 3 hours** and then the monitor replaced on the wrist.

To charge, the sensor must be removed from the bracelet and placed in the charger. Your research nurse will show you how to do this when you get it.

The sensor has a small diamond shape at one end (circled in red in the picture). This must be lined up with the corresponding diamond shape on the charger (see picture) with the three gold dots touching (facing downwards).

The charger may then be plugged in to the wall (or a computer if you prefer) in the same way as you would charge a mobile phone.

**Please charge your battery over the weekend for at least 3 hours.**
After charging is finished, remove the sensor from the charger and put it back in to the bracelet with the three gold dots facing your wrist (see picture).

Please do not hesitate to contact a member of the research team if you have any questions.

CONTACT PERSONS:

Jane Cook (Research Nurse)
0131 551 1381
energytrial@stcolumbashospice.org.uk*

Dr Charlie Hall (Research Doctor)
0131 551 1381

*We value our participant's confidentiality, this is a research email address which will only be accessed by the research team, however we cannot guarantee it will be 100% secure. We are happy for you to email if you prefer, however if you wish to discuss sensitive issues you may prefer to discuss these by phone.
Appendix 8: Recruiter ‘pocket guide’ for recruiting team members

The ENeRgy Trial
Exercise and Nutritional Rehabilitation in Patients with Cancer

Information for Healthcare Professionals making first contact with potential patients:

1. Does your patient meet the eligibility criteria?
2. If yes or unsure please phone us to discuss and confirm.
3. If your patient is eligible, all you need to explain is that the research team at the hospice are running a clinical trial. This is an exciting opportunity to take part in the first of its kind in the UK.
4. The trial involves giving patients with cancer a tailored programme of exercise and nutritional drinks.
5. (If the patient asks how will it benefit me?) Explain as follows: What we do know is that people who lose weight and lose physical function often do worse. The research team think that giving people exercise and a special diet is good for them, but at present we are not sure of this. We have designed this trial to try and answer this question.
6. If your patient is interested in finding out more or taking part in the trial, please explain that you will organise a meeting with the research team who will give the patient (+ their carers) more information.

Give us a call and we will organise an initial meeting with the patient (+ carer) and also give them a Patient Information Sheet.

Inclusion criteria:
• Diagnosis: locally advanced/ metastatic Ca
• Prognosis ≥ 3 months (based on your judgement)
• Outpatient/Community patients
• ≥18 years
• Karnofsky Performance Status ≥ 60 (may require some help but able to perform most personal requirements ie. ECOG 0-2)
• Agree to attend St Columba’s Hospice weekly (transport will be provided if needed)

Exclusion Criteria:
• Undergoing anti-cancer therapy (hormonal treatment or bisphosphonates permitted)
• Using enteral or parenteral nutrition
• Co-enrolment in drug trials
• Inability to swallow
Publications


4. Harding Z, **Hall C**, Lloyd A. Rehabilitation in palliative care: a qualitative study of team professionals BMJ Supportive & Palliative Care Published Online First: 30 December 2019. doi: 10.1136/bmjspcare-2019-002008


Presentations


2. Grand Round Western General Hospital, Edinburgh, March 2019: Oral presentation entitled: Functional and Nutritional Rehabilitation: Exercise and Nutritional Rehabilitation in Patients with Cancer (ENeRgy Trial)

3. Edinburgh University Institute of Genetics and Molecular Medicine Seminar June 2019: Oral presentation entitled: Exercise and Nutritional Rehabilitation in Patients with Cancer (ENeRgy Trial)


7. 6th International Cancer Cachexi conference: Bridging Molecular Advances to Clinical Care, Gainesville, Florida (virtual), August 2021: Poster presentation entitled: The ENeRgy Trial: Applying a potential cancer cachexia treatment paradigm to cancer rehabilitation. **Winner, 1st Prize Poster** within category: Clinical.
References:


Bibliography


DIETZ, J. 1981. Rehabilitation Oncology, United Kingdom, John Wiley and Sons.


and survival duration of patients with pancreatic cancer. *Cancer, 75*, 2077-82.


GAGNON, B., MURPHY, J., EADES, M., LEMOIGNAN, J., JELOWICKI, M., CARNEY, S., AMDOUNI, S., DI DIO, P., CHASEN, M. & MACDONALD, N. 2013. A prospective evaluation of an interdisciplinary nutrition-


HALL, J. C. 1948-2014 2014. RE: Advice from Mum on Life: "Just remember... This moment will pass, this day will pass as yesterday's passed and tomorrow will too... Nothing remains without change as life goes on.". Type to HALL, C.


IMBODEN, M. T., NELSON, M. B., KAMINSKY, L. A. & MONTOYE, A. H. 2018. Comparison of four Fitbit and Jawbone activity monitors with a research-


LAKKAKULA, B., FARRAN, B., LAKKAKULA, S., PEELA, S., YÄRLÄ, N. S., BRAMHACHARI, P. V., KAMAL, M. A., SADDALA, M. S. & NAGARAJU,


Bibliography


MOSES, A. W., SLATER, C., PRESTON, T., BARBER, M. D. & FEARON, K. C. 2004. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. *Br J Cancer*, 90, 996-1002.


PAYNE, S., PRESTON, N., TURNER, M., ROLLS, L. 2013. Research in Palliative Care: can Hospices afford not to be involved? : Help the Hospices commission into the future of hospice care.


RIES, A., TROTENBERG, P., ELSNER, F., STIEL, S., HAUGEN, D., KAASA, S. & RADBRUCH, L. 2012. A systematic review on the role of fish oil for...


TIBERINI R, R. H. 2015. Rehabilitative Palliative Care Enabling people to live fully until they die: A challenge for the 21st century. United Kingdom: Hospice UK, St Joseph’s Hospice, St Christopher’s, Burdett Trust for Nursing


Bibliography
care access inequalities: a systematic review and narrative synthesis. 
BMJ Support Palliat Care.


