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

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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/m^2 (IQR: 22–29), 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], $P = 0.548$); weight – median % change from baseline to endpoint, per trial arm (experimental 1%[IQR: −3 to 3], control −0.5% [IQR: −3 to 1], $P = 0.184$); 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 −7593.53 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.[1] Indeed the number of people living with cancer is increasing by approximately 3% every year with life expectancies of several months to years.[2] Further, with population aging, people with incurable cancer are increasingly older, living longer, and have more co-morbidities.

Langbaum 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'.[1] This view is being increasingly acknowledged by learned societies with the European Society of Medical Oncology (ESMO)[3] and American Society of Clinical Oncology (ASCO),[4] supporting rehabilitation as a key component of cancer care. Optimizing overall function has been purported to improve quality of life, tolerability 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.[5–8] 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. Termed 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 were 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/WS/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*.[9] The trial was registered at ClinicalTrials.gov: NCT03316157. The rationale and trial design have been previously described.[10]

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, ILL, USA) and advised to take two per day. Each 220 mL supplement contained 1 g of eicosapentaenoic acid (EPA) and

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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 dietitian 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 amounts 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 the Research and Treatment of Cancer Quality of Life Questionnaire – C15PAL (EORTC QLQ-C15PAL),[18] the EQ-5DL, 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-5L[20] and EQ-VAS patient completed questionnaire, healthcare utilization, and out of pocket expenses.[19] 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.[21] 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/ukcc/].

Unit costs were assigned to resource use items using standard national costing sources such as PSSRU[22] and NHS reference costs,[23] 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 (VoI) analysis, implemented using the bootstrap method (1000 replications). For the PSA and for the VoI 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

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was not necessary.[26] Our justification for the sample size of 40 patients was supported by our previous work,[6] our potential pool of eligible patients (estimated at 1300 per year), consensus in the sample size of feasibility trials,[27] and based on this, we estimated we would be able to express the percentage completing the study protocol to within ±9% 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 on 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,[28] 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

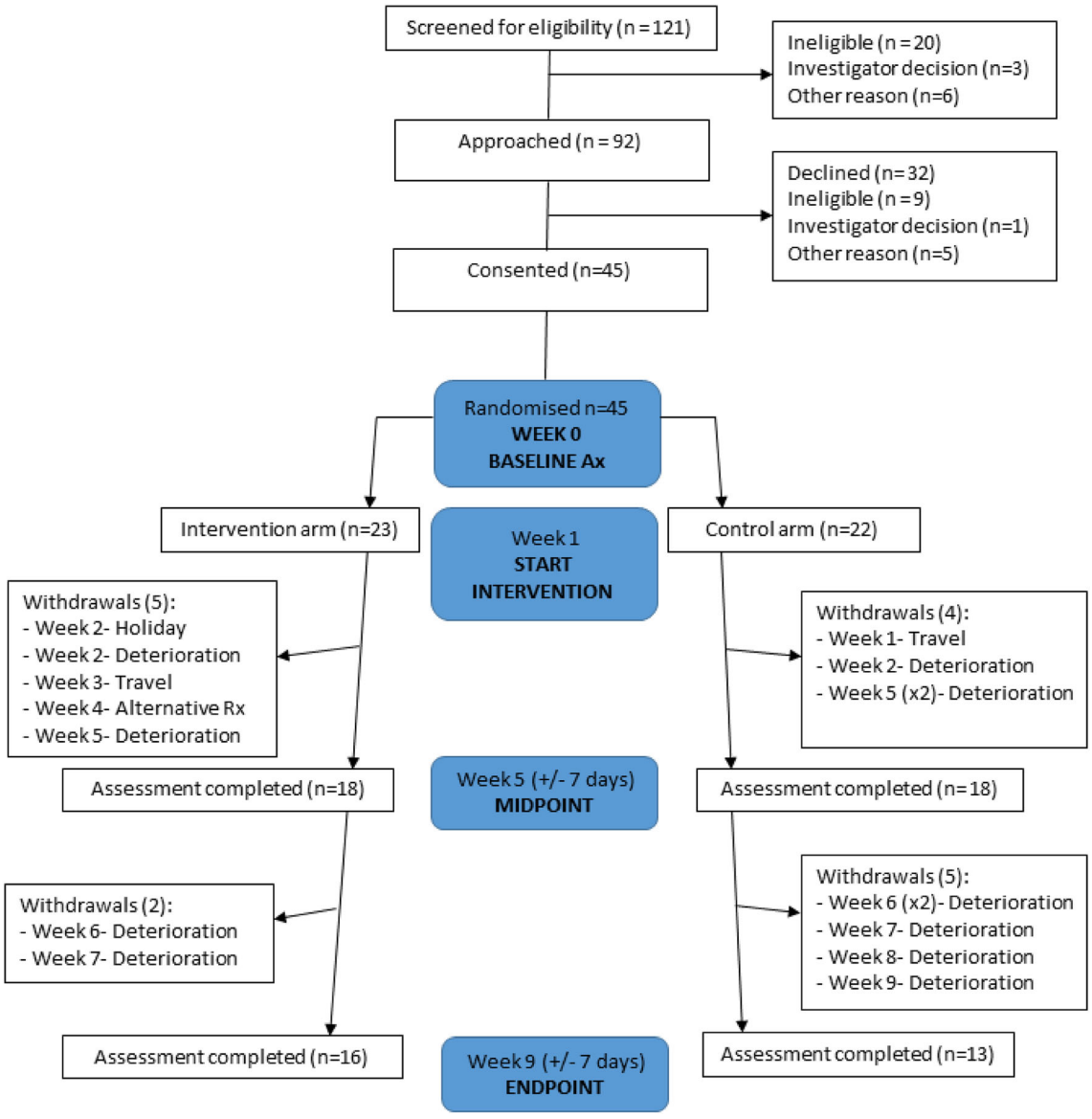

Figure 1 Trial profile.

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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/m^2 (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 18 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.[29,30] 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

Table 1 Patient characteristics

	Experimental arm (n = 23)		Control arm (n = 22)	
	n	%	*n*	%
Age <55 /55–65/ >65	6 /3 /14	26 /13/ 61	2 /4 /16	9 /18/ 73
Male gender	14	61	12	55
Primary cancer				
Gastrointestinal	12	52	6	27
Thoracic	1	4	2	9
Breast	2	9	4	18
Urological/Gyn	4	17	6	27
Myeloma	2	9	3	14
Head and neck	1	4	0	0
Other: (Endocrine)	1	4	1	5
Cancer stage				
Loco-regionally	8	35	8	36
Metastatic	15	65	14	64
Current cancer treatment				
Hormonal	5	22	7	32
Bisphosphonate	2	9	2	9
Steroids	6	26	7	32
Performance status				
60–80%	15	65	14	64
90–100%	8	35	8	36
Body mass index				
<18.5	4	17	2	9
18.5–25	9	39	6	27
25.1–30	7	30	9	41
>30.1	3	13	5	23
Weight change at baseline(<1 month)				
Weight gained	4	17	3	14
Loss 0–5%	18	78	14	64
Loss >5%	0	0	5	23
Unknown	1	4	0	0
Weight change at baseline (<6 months)				
Weight gained	2	9	2	9
Loss 0–5%	10	43	5	23
Loss >5%	7	30	9	41
Unknown	4	17	6	27

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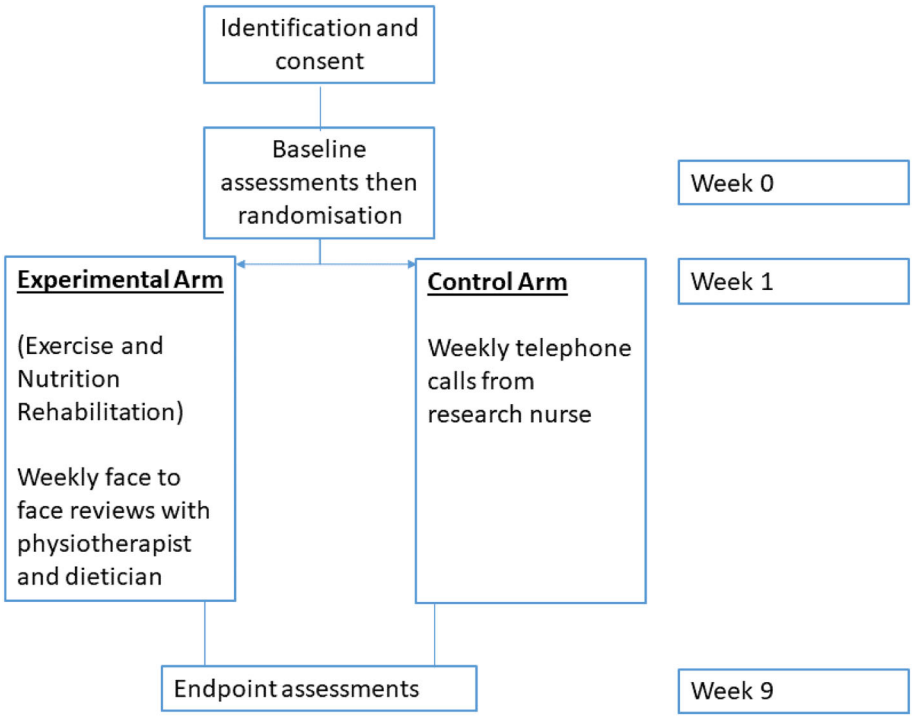

Figure 2 Trial schematic.

Table 2 Primary endpoint: adherence to the experimental arm

Adherence to individual intervention components (n = 21)[a]			<50%		≥50–79%		≥80%	
			n	(%)	*n*	(%)	*n*	(%)
Oral nutritional supplement (n = 21)			1	(5)	4	(19)	16	(76)
Resistance (n = 21)			1	(5)	3	(14)	17	(81)
Aerobic (n = 21)			1	(5)	2	(10)	18	(86)
Adherence to combined intervention components			<50%		≥50%		≥80%	
Aerobic	Resistance		1	(5)	4	(19)	16	(76)
Aerobic	ONS		1	(5)	6	(29)	14	(67)
Resistance	ONS		1	(5)	7	(33)	13	(62)
Aerobic	Resistance	ONS	1	(5)	8	(38)	12	(57)

[a]Two patients withdrew from the trial post randomization.

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 = 0.548), 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-C15 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 carer-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 (10%) were due to non-cancer-related issues.

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Table 3 Exploratory endpoints examining physical function, weight, and nutrition

		Experimental arm		Control arm		
		N	Median (IQR)	*n*	Median (IQR)	*P*
Daily step count[a]	Baseline	22	2954 (2168–4143)	22	2294 (591–3821)	
	Endpoint	16	2898 (1055–5005)	12	2478 (727–3645)	
	Difference	15	−476 (−1592–1882)	12	6 (−860–335)	
	Difference %	15	−19 (−61 to 65)	12	5 (−32 to 50)	0.548*
Timed up-and go test (s)	Baseline	23	13 (11–17)	22	16 (11–24)	
	Midpoint	17	15 (12–18)	15	14 (11–27)	
	Endpoint	16	14 (12–21.8)	12	15 (12–23)	
	Difference	16	−0.5 (−3–4)	12	0.5 (−1–2)	
	Difference %	16	−5 (−18–20)	12	4.5 (−3–12)	0.767*
2 min walk test (m)	Baseline	23	114 (76–144)	21	104 (66–122)	
	Midpoint	17	115 (77–136)	13	107 (52–137)	
	Endpoint	16	116 (75–138)	10	106 (68–122)	
	Difference	16	9 (−5–18)	10	2 (−10–12)	
	Difference %	16	6 (−4–27)	10	2 (−10–15)	0.484*
Life space assessment (max score 120)	Baseline	21	53 (32–81)	22	37(31–52)	
	Midpoint	18	38 (34–60)	16	52 (32–66)	
	Endpoint	16	50 (35–64)	13	48 (34–58)	
	Difference	16	0 (−16–11)	13	−2 (−10–5)	
	Difference %	16	0 (−21–41)	13	−5 (−19–17)	1.00*
Weight	Baseline	23	71 (60–79)	22	70.8 (62–86)	
	Midpoint	17	76 (63–85)	15	68 (61–89)	
	Endpoint	16	80 (62–88)	13	67(57–87)	
	Difference	16	1 (−2–2)	13	−3 (−2–0)	
	Difference %	16	1 (−3–3)	13	−0.5 (−3–1)	0.184*
aPG-SGA score (0–36)	Baseline	23	4 (1–9)	22	6 (2–11)	
	Midpoint	18	5 (1–16)	15	6 (1–14)	
	Endpoint	16	8 (1–13)	13	6 (1–10)	
	Difference	16	1 (−2–5)	13	1 (−3–3)	
	Difference %	16	27 (−18–300)	13	−42 (−73–117)	0.249*
AveS score (0–10)	Baseline	23	8 (5–8)	22	7 (5–8)	
	Midpoint	18	7 (5–9)	16	8 (6–10)	
	Endpoint	16	7 (4–10)	13	8 (7–10)	
	Difference	16	0 (−1–1)	13	0 (−2–2)	
	Difference %	16	0 (−25–22)	13	0 (−16–31)	0.398*

*Mann–Whitney *U*-test.
[a]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 (OOH) services, and travel costs. The mean incremental cost of the experimental arm versus control is £-319.51 [CI −7593.53 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 −0.021, 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.

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Table 4 Exploratory endpoints examining patient reported outcomes of quality of life

		Experimental arm		Control arm				Experimental arm		Control arm		
		n	Median (IQR)	*n*	Median (IQR)	*P*		*n*	Median (IQR)	*n*	Median (IQR)	*P*
Overall QoL	Baseline	23	66.7 (50–83.3)	22	50 (45.8–70.8)		**Dyspnoea**	23	50 (16.7–66.7)	22	33.3 (16.7–70.8)	
	Midpoint	18	75.0 (50–83.3)	16	50 (50–66.7)			18	33.3 (29.2–54.2)	16	33.3 (16.7–62.5)	
	Endpoint	16	66.7 (50–83.3)	13	66.7 (50–66.7)			16	50 (33.3–66.7)	13	33.3 (16.7–41.7)	
	Difference	16	0.0 (−16.7–12.5)	13	0.0 (−16.7–16.7)			16	8.3 (−16.7–16.7)	13	0.0 (−16.7–16.7)	
	Difference %	16	0.0 (−20–18.8)	13	0.0 (−22.5–33.3)	0.846		16	10 (−33–100)	13	0.0 (−50–75)	0.589
Physical	Baseline	23	88.9 (66.7–100)	22	83.3 (66.7–100)		**Insomnia**	23	33 (0.0–66.7)	22	33.3 (0.0–33.3)	
	Midpoint	18	88.9 (77.8–100)	16	88.9 (77.8–100)			18	33.3 (0.0–41.7)	16	0 (0.0–33.3)	
	Endpoint	16	83.3 (66.7–100)	13	88.9 (83.3–100)			16	16.7 (0.0–66.7)	13	0 (0–0)	
	Difference	16	0.0 (0.0–8.3)	13	0.0 (0.0–11.1)			16	0 (0–0)	13	0 (−16.7–16.7)	
	Difference %	16	0.0 (0.0–9.4	13	0.0 (0.0–18.3)	0.268		8	0 (−37.5–75)	13	−100 (−100 to-75)	0.92
Emotional	Baseline	23	100 (83.3–100)	22	100 (83.3–100)		**Appetite**	23	0 (0.0–33.3)	22	33.3 (0.0–66.7)	
	Midpoint	18	100 (95.8–100)	16	100 (66.7–100)			18	16.7 (0.0–66.7)	16	33.3 (0.0–58.3)	
	Endpoint	16	100 (100–100)	13	83.3 (83.3–100)			16	16.7 (0.0–33.3)	13	0 (0.0–33.3)	
	Difference	16	0.0 (0.0–16.7)	13	−16.7 (−16.7–0.0)			16	0 (0.0–25)	13	0 (−33–0.0)	
	Difference %	16	0.0 (0.0–20)	13	−16.7 (−16.7-)_	0.006		16	0 (−50–25)	13	−50 (−100–0.0)	0.268
Pain	Baseline	23	33.3 (16.7–66.7)	22	33.3 (16.7–54.2)		**Nausea**	23	0 (0.0–33.3)	22	0 (0.0–33.3)	
	Midpoint	18	33.3 (16.7–70.8)	16	16.7 (0.0–33.3)			18	0 (0.0–66.7)	16	0 (0.0–25)	
	Endpoint	16	33.3 (16.7–66.7)	13	16.7 (0.0–41.7)			16	0 (0.0–33.3)	13	0 (0.0–33.3)	
	Difference	16	0.0 (−16.7–0.0)	13	0.0 (−16.7–16.7)			16	0 (0.0–0.0)	13	0 (0.0–0.0)	
	Difference %	13	0.0 (−58.3–0.0)	13	0.0 (−100–50)	0.714		16	−66 (−100–0.0)	13	0 (−100–0.0)	0.812
Fatigue	Baseline	23	50 (16.7–66.7)	22	33.3 (16.7–70.8)		**Constipation**	23	0 (0.0–33.3)	22	33.3 (0.0–66.7)	
	Midpoint	18	33.3 (29.2–54.2)	16	33.3 (16.7–62.5)			18	16.7 (0.0–33.3)	16	0 (0.0–33.3)	
	Endpoint	16	50 (33.3–66.7)	13	33.3 (16.7–41.7)			16	0 (0.0–0.0)	13	33.3 (0.0–33.3)	
	Difference	16	8.3 (−16.7–16.7)	13	0.0 (−16.7–16.7)			16	0 (−25–0.0)	13	0 (−16.7–16.7)	
	Difference %	16	10 (−33–100)	13	0.0 (−50–75)	0.449		16	−100 (−100–16.7)	13	0.0 (−100–0.0)	0.714

Table 5 Adverse events

AE type	Experimental arm (n = 23)	Control arm (n = 22)
AE relating to ONS	**9**	**N/A**
Description	- Flatus/gurgling from stoma - Flatulence/stool frequency - Flatulence/gurgling from bowel - Flatulence and abdominal cramps - Flatulence - Nausea ×2 - Diarrhoea - Overactive stoma	
AE related to cancer	**9**	**12**
Description	- Pressure sore - Chest infection ×2 - Sub-hepatic haematoma - Intrahepatic bleed - Oesophageal bolus obstruction (tablet) - Falls (recurrent) - Admission to hospice-reduced mobility - Duodenal obstruction	- Deep vein thrombosis - Hypercalcaemia - Fall ×3 - Chest infection ×2 - Delirium - Rectal bleeding - Pathological femur fracture - Pressure sore - Dysphagia
AE unrelated to cancer	**2**	**7**
Description	- Urinary tract infection - Diarrhoea and vomiting	- Tooth abscess - Atrial fibrillation ×2 - Cardiovascular complication - Diarrhoea - Oral antibiotics for skin wound - Diarrhoea and vomiting

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).[30] They demonstrated feasibility, and a randomized phase two trial is underway to further assess this approach.[31] Edbrooke and co-workers undertook a randomized trial assessing exercise and behavioural change strategies in 92 patients with inoperable lung cancer.[32] 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,[3] ASCO,[4] 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 cancer, 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

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mechanism by which interventions have an impact, and identifying ways of tailoring therapy to patient preference and type', and we agree.[33] 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,[34] as part of their clinical trial.[32]

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 wide spread integration into health care. 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 also 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).
Table S4: CRFs Start point-, Midpoint-, Endpoint Assessment.
Data S2. Supporting information.
Data S3. Supporting information.

Conflict of interest

B.L. has received honoraria and consultancy fees from Helsinn, Artelo and XBiotech. R.S. has received honoraria and consultancy fees from Helsinn 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.

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