BMJ Open

A randomized controlled trial testing the feasibility of an exercise and nutrition intervention for ovarian cancer patients during and after first-line chemotherapy (BENITA-study)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054091
Article Type:	Original research
Date Submitted by the Author:	09-Jun-2021
Complete List of Authors:	Maurer, Tabea; University Medical Center Hamburg-Eppendorf, Cancer Epidemiology, University Cancer Center Hamburg (UCCH) Belau, Matthias; University Medical Center Hamburg-Eppendorf, Institute for Medical Biometry and Epidemiology von Grundherr, Julia; University Medical Center Hamburg-Eppendorf, Department of Oncology, Hematology, BMT with Section Pneumology, Hubertus Wald Tumour Center, University Cancer Center Hamburg (UCCH), Schlemmer, Zoe; University Medical Center Hamburg-Eppendorf, Department of Gynaecology and Gynaecologic Oncology Patra, Stefan; University Medical Center Hamburg-Eppendorf, Universitäres Kompetenzzentrum für Sport- und Bewegungsmedizin (Athleticum) Becher, Heiko; University Medical Center Hamburg-Eppendorf, Medical Biometry and Epidemiology Schulz, Karl-Heinz; University Medical Center Hamburg-Eppendorf, Universitäres Kompetenzzentrum für Sport- und Bewegungsmedizin (Athleticum) Zyriax, Birgit-Christiane; University Medical Center Hamburg-Eppendorf, Midwifery Science – Health Care Research and Prevention, Institute for Health Services Research in Dermatology and Nursing (IVDP) Schmalfeldt, Barbara; University Medical Center Hamburg-Eppendorf, Germany, Department of Gynaecology and Gynaecologic Oncology Chang-Claude, Jenny; University Medical Center Hamburg-Eppendorf; DKFZ, Division of Cancer Epidemiology
Keywords:	Adult oncology < ONCOLOGY, Epidemiology < ONCOLOGY, Gynaecological oncology < ONCOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A randomized controlled trial testing the feasibility of an exercise and nutrition intervention for ovarian cancer patients during and after first-line chemotherapy (BENITA-study)

T. Maurer[†1], M. Belau[†2], J. von Grundherr[3], Z. Schlemmer[4], S. Patra[5], H. Becher[2], K-H. Schulz[5], B-C. Zyriax[6], B. Schmalfeldt[4], J. Chang-Claude[17]

1 Cancer Epidemiology Group, University Cancer Center Hamburg (UCCH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany

2 Institute for Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

3 Department of Oncology, Hematology, BMT with Section Pneumology, Hubertus Wald Tumour Center, University Cancer Center Hamburg (UCCH), University Medical Center Hamburg-Eppendorf,

Hamburg, Germany

4 Department of Gynecology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

5 Universitäres Kompetenzzentrum für Sport- und Bewegungsmedizin (Athleticum), University Medical Center Hamburg-Eppendorf, Hamburg, Germany

6 Midwifery Science – Health Care Research and Prevention, Institute for Health Services Research in Dermatology and Nursing (IVDP), University Medical Center Hamburg-Eppendorf, Hamburg, Germany

7 Division of Cancer Epidemiology, German Cancer Research Centre, Heidelberg, Germany

Heidelberg, Baden-Württemberg, DE

[†]Shared first authorship

Corresponding author:
Prof. Jenny Chang-Claude
Cancer Epidemiology Group
University Cancer Center Hamburg (UCCH)
University Medical Center Hamburg-Eppendorf
Martinistrasse 52
20251 Hamburg, Germany
j.chang-claude@uke.de

Keywords: Ovarian Cancer, Feasibility, Exercise, Nutrition, RCT, during chemotherapy

Word Count: 2771

Abstract

Objectives: Advanced ovarian cancer is a serious disease with major side effects caused by peritoneal carcinomatosis, ascites and gastrointestinal involvement as well as exhaustive treatment like debulking surgery and combination chemotherapy. Two most frequently reported side effects are muscle wasting and malnutrition leading to frailty, decreased health-related quality of life (HRQoL), and cancer related fatigue (CRF). As muscle wasting and malnutrition often commence during first-line chemotherapy and develop progressively into a refractory state, an early intervention is warranted. This pilot study aimed to evaluate the safety and acceptance of a combined exercise and nutrition intervention during and after first-line chemotherapy.

Design: The pilot study was conducted as a monocentric 1:1 randomized controlled trial (RCT) with an intervention (IG) and a control group (CG).

Intervention: The IG received a 12-month exercise and nutrition program, the CG continued to follow usual care.

Primary and secondary outcome measures: Primary outcomes were recruitment rate, adherence to intervention, completion rate, and adverse events. In addition, in-person assessments (e.g. HRQoL, CRF, muscle quality and function, and dietary intake and quality) were conducted at baseline (T0, before chemotherapy), week 9 (T1, mid-chemotherapy), week 19 (T2, after completion of chemotherapy), and after 12 months of intervention (T3).

Results: Of 60 eligible patients, fifteen patients signed informed consent (recruitment rate=25.0%) and were randomized into IG (n=8) and CG (n=7). Eleven participants completed

the study (completion rate, 73.3%), one patient dropped-out due to loss of interest, one due to poor health, one was lost to follow-up and one patient died.

Conclusion: The BENITA study demonstrated the safety and acceptance of an exercise and nutrition intervention integrated into first line therapy and follow-up care of ovarian cancer. A large multicenter RCT is planned to investigate the effectiveness of the intervention on HRQoL, CRF, and survival and to establish means of implementation into oncology guidelines and clinic routine.

Trial registration: The study was registered at the German study registry for clinical studies (DRKS00013231).

Strength and limitations

- The trial uses objective measures to evaluate the feasibility of an exercise and nutrition intervention in ovarian cancer patients
- The exercise and nutrition intervention commences during first-line chemotherapy and continues well into ovarian cancer survivorship
- The exercise and nutrition intervention has been developed by an interdisciplinary team of exercise and nutrition experts
- A blinded randomization process was not possible due to the study design

Introduction

Ovarian cancer is the second most common gynecologic cancer in women and has the fifth highest rate of cancer-related deaths for women in Germany (1) with only 43% alive 5 years after diagnosis (2). Two major side effects of ovarian cancer and its treatment are muscle wastage and malnutrition leading to frailty, decreased health-related quality of life (HRQoL), and cancer related fatigue (CRF). Weight loss as a consequence of malnourishment, metabolic, and endocrine changes, as well as activation of catabolic pathways before and especially during chemotherapy, is associated with reduced response rates to chemotherapy and increased toxicity, and is included as one of the key Common Terminology Criteria of Adverse Events (CTCAE) (3). Exercise equivalent has been shown to significantly improve CRF, cardio pulmonary fitness, HRQoL and even survival in breast and colon cancer (4, 5). Adherence to recommended dietary guidelines before diagnosis significantly improved HRQoL (6) and decreased risk of cancers (7). However, there is paucity of knowledge on post-diagnosis physical activity (PA) or nutrition behavior on prognosis or HRQoL in ovarian cancer patients. In observational studies, ovarian cancer patients with greater post-diagnosis physical activity were found to experience a significantly better HRQoL (8-10). As muscle wastage and malnutrition often coexist, as seen in cancer cachexia, improving malnourishment in patients with advanced cancer through nutrition counseling in combination with exercise interventions may be most effective (11, 12). Yet, Randomized controlled trials (RCTs) evaluating the benefits of a bimodal intervention on survival and HRQoL are rare. Two RCTs on bimodal exercise and nutrition programs for ovarian cancer patients are currently ongoing (13, 14). One commences intervention after completion of treatment (13) and one investigates the effect of an intervention during first-line chemotherapy (14). However, no current or previous RCT offers a care program during and after first-line chemotherapy, which is necessary to

prevent deterioration due to treatment as well as support maintenance of lifestyle changes thereafter.

It was the aim of this study to determine the feasibility of a combined exercise and nutrition intervention for ovarian cancer patients during and after first-line chemotherapy. Main endpoints of the pilot trial were recruitment rate, adherence, completion rate as well as adverse events (safety). Furthermore, in-person assessments as planned for a main trial were conducted (e.g. HRQoL, CRF, muscular strength and quality, nutrition habits and quality) to investigate acceptance and safety in ovarian cancer patients.

Methods

Study design, setting and participants

This pilot study was a monocentric 1:1 RCT with an intervention (IG) and a control group (CG). The ethics committee of the Faculty of Medicine at Hamburg University approved the study protocol. The trial was registered at the German Study Registry for Clinical Studies (DRKS00013231). Participants were recruited from the department of Gynecology at the University Medical Center Hamburg Eppendorf (UKE), Germany at diagnosis. Eligibility criteria included women ≥18 years of age, diagnosed with ovarian cancer, tubal cancer, or peritoneal cancer and primary or interval debulking, scheduled but not started adjuvant or neoadjuvant chemotherapy, and sufficient German language skills. Exclusion criteria were an Eastern Cooperative Oncology Group (ECOG) status of two or worse, any physical or mental condition that would hinder execution or completion of the training program and study procedures, a

private engagement in exercise training above the WHO recommendation of 150 minutes of moderate-intensity activity per week (15), or a diagnosis of an eating disorder.

Patient and public involvement

The ovarian cancer patient organization in Germany (Verein Eierstockkrebs Deutschland e.V. (VED)) represented by its first chairperson, Andrea Krull, has provided input to the project from a patient's perspective, reviewed ethical issues and commented on consent forms.

Procedure

Two gynecologists identified and approached participants meeting inclusion criteria. After written informed consent, patients were randomized into the intervention group (IG) to receive a 12-months exercise and nutrition program or the control group (CG) to receive usual care. Group allocation was performed by a statistician not involved in data collection. Information on group allocation was conveyed to the study coordination responsible for making an appointment with the patients for the baseline assessment.

In-person assessments were conducted independent of study arm at baseline (T0), mid-chemotherapy (T1), after completion of chemotherapy (T2), and at one-year follow-up (T3). Assessments include HRQoL (European Organisation for Research and Treatment of Cancer (EORTC)-QLQ-C30 (16) (16), CRF (Multidimensional Fatigue Inventory (MFI-20)) (17), nutritional risk (Nutritional Risk Score (NRS)-2002) (18), physical activity (Short Questionnaire to Assess Health enhancing physical activity (SQUASH)) (19), performance diagnostics including six-minute walk test (20), hand grip strength (Kern MAP 80k1) (21), and body

composition (bioelectric impedance analysis (BIA), "AKERN BIA 101 Anniversary") (22). A detailed overview on scheduled in-person assessments is described elsewhere (23). Safety of the program was analyzed through adverse events linked to the intervention during all phases of the study. All analyses were performed using STATA MP in version 16.

Intervention

Participants received personalized exercise and nutrition programs and counselling that were tailored to different phases of patient's treatment and recovery as well as individual needs throughout the trial. In both phases of the exercise intervention patients are given instructions and encouraged to participate in a daily 15-30 minute home-based training that includes endurance, resistance, and balance exercises to be performed in gradual increments. Exercises using abdominal muscles will not be included till full recovery from surgery. The nutritional intervention in phase I aimed to reduce malnutrition risk by increasing protein and calorie intake. In phase II (weeks 19-52) after chemotherapy, nutrition counselling focused on the Mediterranean diet, shown to reduce cancer risk. To monitor adherence and progress in phase I, participants received a weekly telephone call by a sports scientist, and triweekly by a nutritionist. In phase II patients received monthly counseling by telephone or in person. The intervention is described in more detail elsewhere (23).

Measures

The primary objectives of the pilot study were (1) to obtain estimates of recruitment rate, completion rate, as well as investigate reasons for study termination, (2) to investigate patient

adherence to the sport and nutrition program, (3) to determine intervention safety in terms of side effects especially during active treatment, as well as its practicability and acceptance. Recruitment rate was defined as the ratio of patients eligible to participate and patients who signed informed consent. Completion rate was defined as the ratio of patients who signed informed consent and those who completed the 12 months intervention. General adherence to the intervention was defined as the ratio of planned and completed interventions, adherence to the sports program was further assessed using exercise diaries filled out every week until week 18 and once a months until 12 months follow-up. Adherence to the nutrition intervention in phase I was described in terms of changes in protein and caloric intake compared to baseline. During phase II adherence to the nutrition intervention was interpreted in terms of changes in MEDAS (Mediterranean Diet Adherence Screener) score points between T0 and T3 (24).

Results

Characteristics and feasibility

Of 67 patients with initial diagnosis of ovarian cancer from April 2018 to Sept 2019 screened for eligibility, 60 patients met inclusion criteria and were invited into the study. 45 refused to participate in the study. Main reasons were personal reasons, residence outside of Hamburg, not willing to be randomized and no interest in the research. Fifteen patients signed informed consent (recruitment rate, 25.0%) and were randomized into IG (n=8) and CG (n=7). Eleven participants completed the study (completion rate, 73.3%), one patient dropped-out due to loss of interest, one patient due to poor health (recurrence), one patient was lost to follow-

up (could not be reached via phone or mail) and one patient died. Fig. 1 provides flow of participants through the study.

Table 1 summarizes the baseline characteristics of participants by group assignment. The mean age of the participants was 56.5 ± 14.4 years ranging from 21 to 77 years, with an average of 33.9 ± 17.0 days since initial diagnosis. The majority (73.3%) of patients was diagnosed as having advanced stage disease. After surgery, eight patients had no residual tumor, five patients' tumors were resected to smaller than 1 centimeter and two patients' tumors had residual tumor larger than 1cm.

Table 1: Baseline characteristics of participants by group assignment

		All participants		***Intervention group***		***Control group***	
		N (=15)	*%*	*N (=8)*	*%*	*N (=7)*	*%*
Age	*median (range)*	*58 (21-77)*		52 (21-64)		65 (48-77)	
Education[a]	*Low*	*1*	*6.7*	0	0.0	1	14.3
	Medium	*8*	*53.3*	5	62.5	3	42.9
	High	*6*	*40.0*	3	37.5	3	42.9
Smoking status	*Never smoker*	*8*	*53.3*	4	50.0	4	57.1
	Former smoker	*5*	*33.3*	3	37.5	2	28.6
	Current smoker	*2*	*13.3*	1	12.5	1	14.3
Alcohol use *per week*	*<1g*	*5*	*33.3*	3	37.5	2	28.6
	1-12g	*1*	*6.7*	0	0.0	1	14.3
	13-24g	*3*	*20.0*	3	37.5	0	0.0
	25-48g	*4*	*26.7*	1	12.5	3	42.9
	49-60g	*2*	*13.3*	1	12.5	1	14.3
Body mass index	*Underweight (<18.5)*	*1*	*6.7*	1	12.5	0	0.0
	Normal weight (18.5-24.9)	*9*	*60.0*	4	50.0	5	71.4
	Overweight (25.0-29.9)	*2*	*13.3*	1	12.5	1	14.3
	Obesity (≥30.0)	*3*	*20.0*	2	25.0	1	14.3
Sports[b]	*0-4 MET h/week*	*9*	*60.0*	6	75.0	3	42.9
	5-10 MET h/week	*1*	*6.7*	1	12.5	0	0.0
	>10 MET h/week	*5*	*33.3*	1	12.5	4	57.1
Cancer stage[c]	*I*	*2*	*13.3*	1	12.5	1	14.3
	II	*2*	*13.3*	0	0.0	2	28.6
	III	*9*	*60.0*	6	75.0	3	42.9
	IV	*2*	*13.3*	1	12.5	1	14.3
Tumor size *post-op*	*Tumor-free*	*8*	*53.3*	4	50.0	4	57.1
	<1cm	*5*	*33.3*	2	25.0	3	42.9
	>1cm	*2*	*13.3*	2	25.0	0	0.0
Treatment	*Adjuvant chemotherapy*	*12*	*80.0*	6	75.0	6	85.7
	Neo-adjuvant chemotherapy	*3*	*20.0*	2	25.0	*1*	*14.3*

[a]CASMIN classification (25); [b]SQUASH physical activity questionnaire (19); [c]FIGO classification (26)

All 15 participants enrolled in the study completed T0 and T1 assessments. Between T1 and T2 one patient in the intervention group died and another dropped out due to loss of interest. The remaining 13 patients completed the T1 assessment. Between T2 and T3 a patient of the intervention group was lost to follow-up and a patient of the control group dropped-out due to a recurrence. All eleven patients still enrolled in the study completed the final assessment. Table 2 provides detailed information on adherence to different assessments and time points by group assignment. Adherence to the sports intervention in terms of completed intervention sessions (face-to-face, by telephone) was 83.7% for exercise intervention (phase I, 83.2%; phase II, 85.1%) and 76.8% for nutrition intervention (phase I, 92.3%; phase II, 59.6%).

Adherence to the exercise and nutrition program is shown in table 3. During phase I five out of eight patients documented their weekly home-based exercise for a total of 14-18 weeks. One patient documented their daily home-based exercise for ten weeks, another patient dropped out after six weeks, and one patient died during phase I without documentation of home-based training. Patients trained between 90 and 180 minutes per week. In phase II three patients documented their exercise for 30-34 weeks. Two patients stopped their documentation after 12 and 4 weeks, respectively. Two patients dropped out of the study and one patient did not continue to document their daily practice, but remained in the study. In phase II most patients trained for up to 90 minutes per week.

Adherence to the nutrition intervention in phase I was interpreted in terms of increase in protein and caloric intake. Patients of the intervention group increased their protein intake from 65.8 gram (g) per day at baseline (T0) to 107.9g per day at T2. The calorie intake increased from 1860g per day at T0 to 2389g per day at T2. In phase II adherence to the nutrition intervention based on the MEDAS score showed that patients of the intervention group

increased their MEDAS scores from a median of 7.0 at baseline to a median of 10 score points at week 52 (T3).

There were no adverse events due to the intervention or in-person assessments.

Table 2: Adherence to assessment time points

			All participants		***Intervention group***		***Control group***	
			N[a]	*%*	*N[a]*	*%*	*N[a]*	*%*
Sport assessment	*Performance diagnostics*	***T0[b]***	*14/15*	*93.3*	*7/8*	*87.5*	*7/7*	*100.0*
		T1	*11/15*	*73.3*	*6/8*	*75.0*	*5/7*	*71.4*
		T2	*12/13*	*92.3*	*6/6*	*100.0*	*6/7*	*85.7*
		T3	*11/11*	*100.0*	*5/5*	*100.0*	*6/6*	*100.0*
		T0 – T3	*48/54*	*88.9*	*24/27*	*88.9*	*24/27*	*88.9*
	Accelerometer	***T0***	*13/15*	*86.7*	*6/8*	*75.0*	*7/7*	*100.0*
		T1	*11/15*	*73.3*	*6/8*	*75.0*	*5/7*	*71.4*
		T2	*10/13*	*76.9*	*5/6*	*83.3*	*5/7*	*71.4*
		T3	*11/11*	*100.0*	*5/5*	*100.0*	*6/6*	*100.0*
		T0 – T3	*45/54*	*83.3*	*22/27*	*81.5*	*23/27*	*85.2*
Nutrition diagnostics		***T0***	*14/15*	*93.3*	*8/8*	*100.0*	*6/7*	*85.7*
		T1	*15/15*	*100.0*	*8/8*	*100.0*	*7/7*	*100.0*
		T2	*12/13*	*92.3*	*6/6*	*100.0*	*6/7*	*85.7*
		T3	*11/11*	*100.0*	*5/5*	*100.0*	*6/6*	*100.0*
		T0 – T3	*52/54*	*96.3*	*27/27*	*100.0*	*25/27*	*92.6*
Case report form		***T0***	*15/15*	*100.0*	*8/8*	*100.0*	*7/7*	*100.0*
		T1	*15/15*	*100.0*	*8/8*	*100.0*	*7/7*	*100.0*
		T2	*12/13*	*92.3*	*6/6*	*100.0*	*6/7*	*85.7*
		T3	*11/11*	*100.0*	*5/5*	*100.0*	*6/6*	*100.0*
		T0 – T3	*53/54*	*98.2*	*27/27*	*100.0*	*26/27*	*96.3*

[a]number of participants assessed/number eligible

[b]T0 = baseline, T1 = mid-chemotherapy, T2 = after completion of chemotherapy, T3 = one year follow-up

Table 3: Adherence to the implementation of sports and nutrition program among participants from the intervention group

Sports program					
	Participant	***Number of weeks reported***	***Days per week*** Median	***Minutes per week***	***Rating of perceived exertion*** BORG scale
Phase I (week 1 - 18)	*P1*	*15*	*5.2*	*up to 90 minutes*	*Very light to light (9-11)*
	P2	*18*	*5.7*	*up to 90 minutes*	*Light to somewhat hard (11-13)*
	P3	*6*	*4.3*	*up to 90 minutes*	*Light to somewhat hard (11-13)*
	P4	*14*	*5.4*	*90 to 180 minutes*	*Light to somewhat hard (11-13)*
	P5	*10*	*5.4*	*up to 90 minutes*	*Somewhat hard to hard (13-15)*
	P6	*18*	*3.8*	*90 to 180 minutes*	*Light to somewhat hard (11-13)*
	P7	*18*	*5.1*	*up to 90 minutes*	*Very light to light (9-11)*
	P8[a]	*0*	*0.0*	-	-
Phase II (week 19 - 52)	*P1*[b]	*0*	*0.0*	-	-
	P2	*32*	*4.1*	*up to 90 minutes*	*Light to somewhat hard (11-13)*
	P3[c]	*0*	*0.0*	-	-
	P4	*4*	*5.0*	*90 to 180 minutes*	*Light to somewhat hard (11-13)*
	P5	*12*	*2.0*	*up to 90 minutes*	*Light to somewhat hard (11-13)*
	P6	*34*	*2.0*	*up to 90 minutes*	*Somewhat hard (13)*
	P7	*34*	*6.1*	*up to 90 minutes*	*Somewhat hard (13)*
	P8[a]	*0*	*0.0*	-	-

Nutrition program					
		Protein intake (Gram per day)		***Mediterranean diet***[d] (Sum score)	
		Mean (SD)	Median	Mean (SD)	Median
Phase I (week 1 - 18)	*Week 1*	*65.8 (16.4)*	*64.8*	*7.0 (2.3)*	*7.0*
	Week 9	*96.7 (29.4)*	*90.3*	*7.8 (2.1)*	*8.0*
Phase II (week 19 - 52)	*Week 19*	*107.9 (18.1)*	*113.5*	*8.7 (1.0)*	*9.0*
	Week 52	*90.9 (9.1)*	*93.1*	*9.2 (1.6)*	*10.0*

[a]died in hospital; [b]dropped out; [c]lost to follow-up, [d]MEDAS sum score

Descriptive statistics of in-person assessments

Table 4 and figure 2 display descriptive results of in-person assessments at different time points by group assignment. Participants who received personalized exercise and nutrition programs increased their median six-minute walk distance from 411 meters (m) at baseline to 475m at T3, whereas members of the control groups decreased their distance from 440m to 380m. Patients of the intervention group increased their hand grip strength from 22.0 kilogram (kg) to 24.8kg (median), the control group showed a slightly lower increase (from 21.8 to 22.4kg). In terms of nutrition, calorie intake during chemotherapy increased in both IG and CG. The IG showed a larger increase in protein intake from baseline to T1 and T2 compared to controls. Adherence to Mediterranean diet or nutritional risk were comparable in IG and CG.

The HRQoL increased from baseline to T3 from 37.5 to 70.8 score points in the IG and from 41.7 to 50.0 score points in the CG. Both total and physical fatigue decreased from T0 to T3 and was somewhat stronger in IG than CG for physical fatigue.

Table 4: Results of assessments at different time points by group assignment

		All participants		***Intervention group***		***Control group***	
		Mean (SD)	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*
6 minute walking test *meter*	***T0***[a]	*397.5 (109.8)*	*411.0*	*369.7 (126.3)*	*325.7*	*436.4 (77.3)*	*440.0*
	T1	*489.0 (95.5)*	*490.0*	*483.9 (96.2)*	*495.0*	*495.1 (105.6)*	*458.8*
	T2	*496.2 (116.5)*	*507.7*	*511.9 (80.9)*	*524.4*	*477.4 (157.8)*	*410.0*
	T3	*492.8 (134.6)*	*475.0*	*542.4 (91.1)*	*570.7*	*451.5 (158.4)*	*380.0*
Hand grip strength[b] *kilogram*	***T0***	*22.4 (7.0)*	*21.9*	*22.2 (8.7)*	*22.0*	*22.6 (4.7)*	*21.8*
	T1	*24.1 (7.5)*	*21.6*	*23.5 (6.4)*	*21.6*	*25.0 (9.9)*	*21.3*
	T2	*25.2 (6.9)*	*24.6*	*23.0 (6.0)*	*23.2*	*27.8 (7.6)*	*25.8*
	T3	*25.6 (6.7)*	*24.8*	*26.3 (5.9)*	*24.8*	*25.1 (7.8)*	*22.4*
Mediterra-nean diet[c] *sum core*	***T0***	*7.0 (1.9)*	*8.0*	*7.0 (2.3)*	*7.0*	*7.0 (1.4)*	*8.0*
	T1	*8.4 (2.2)*	*9.0*	*7.8 (2.1)*	*8.0*	*9.1 (2.2)*	*9.0*
	T2	*9.0 (1.8)*	*9.0*	*8.7 (1.0)*	*9.0*	*9.3 (2.3)*	*9.5*
	T3	*9.2 (1.9)*	*10.0*	*9.2 (1.6)*	*10.0*	*9.2 (2.3)*	*9.0*
Nutritional risk[d] *risk score*	***T0***	*3.4 (1.1)*	*3.0*	*3.5 (1.2)*	*3.5*	*3.3 (1.1)*	*3.0*
	T1	*3.1 (1.3)*	*3.0*	*3.0 (1.5)*	*2.5*	*3.3 (1.1)*	*3.0*
	T2	*2.4 (1.8)*	*2.5*	*2.5 (2.1)*	*3.0*	*2.3 (1.6)*	*2.0*
	T3	*0.4 (0.7)*	*0.0*	*0.2 (0.5)*	*0.0*	*0.5 (0.8)*	*0.0*
Protein intake 8 *gram per day*	***T0***	*68.0 (13.3)*	*64.8*	*65.8 (16.4)*	*64.8*	*70.6 (9.1)*	*68.1*
	T1	*89.6 (30.4)*	*87.0*	*96.7 (29.4)*	*90.3*	*78.2 (31.4)*	*79.6*
	T2	*104.0 (23.5)*	*113.3*	*107.9 (18.1)*	*113.5*	*100.1 (29.1)*	*97.3*
	T3	*89.3 (23.0)*	*93.1*	*90.9 (9.1)*	*93.1*	*87.9 (31.4)*	*93.6*
Caloric intake *Kcal per day*	***T0***	*1830 (382)*	*1816*	*1860 (388)*	*1987*	*1795 (409)*	*1663*
	T1	*2237 (612)*	*2439*	*2380 (429)*	*2350*	*2010 (835)*	*2439*
	T2	*2237 (513)*	*2439*	*2389 (372)*	*2474*	*2147 (635)*	*2071*
	T3	*2206 (548)*	*2355*	*2105 (398)*	*2219*	*2291 (675)*	*2387*
HRQoL[e]							
Global health status	***T0***	*40.0 (10.5)*	*41.7*	*40.6 (8.3)*	*37.5*	*39.3 (13.4)*	*41.7*
	T1	*55.6 (27.8)*	*66.7*	*62.5 (20.4)*	*66.7*	*47.6 (34.3)*	*33.3*
	T2	*59.7 (20.7)*	*54.2*	*58.3 (14.9)*	*54.2*	*61.1 (26.7)*	*54.2*
	T3	*65.8 (19.8)*	*66.7*	*72.9 (8.0)*	*70.8*	*61.1 (24.5)*	*50.0*
Physical functioning	***T0***	*59.1 (25.1)*	*66.7*	*54.2 (27.5)*	*53.3*	*64.8 (22.7)*	*66.7*
	T1	*69.3 (23.1)*	*73.3*	*66.7 (23.9)*	*76.7*	*72.4 (23.5)*	*73.3*
	T2	*70.6 (21.9)*	*76.7*	*76.7 (12.5)*	*80.0*	*64.4 (28.5)*	*63.3*
	T3	*78.2 (16.9)*	*73.3*	*76.0 (17.4)*	*73.3*	*80.0 (17.9)*	*76.7*
CRF[f]							
General fatigue score	***T0***	*17.6 (5.3)*	*18.0*	*18.6 (5.2)*	*17.5*	*16.6 (5.7)*	*18.0*
	T1	*14.9 (6.3)*	*14.0*	*13.9 (5.1)*	*14.0*	*16.1 (7.7)*	*14.0*
	T2	*14.5 (6.2)*	*15.0*	*15.2 (6.1)*	*15.0*	*13.8 (7.0)*	*13.0*
	T3	*12.8 (6.2)*	*12.0*	*13.8 (7.2)*	*11.0*	*11.8 (5.6)*	*13.0*
Physical fatigue	***T0***	*18.5 (6.0)*	*17.0*	*19.1 (6.7)*	*18.5*	*17.7 (5.5)*	*17.0*
	T1	*14.0 (7.1)*	*15.0*	*12.3 (7.4)*	*9.5*	*16.0 (6.6)*	*17.0*
	T2	*12.9 (5.8)*	*12.0*	*12.0 (4.9)*	*11.0*	*14.0 (7.3)*	*16.0*
	T3	*11.6 (5.9)*	*9.5*	*11.0 (6.4)*	*7.0*	*12.2 (5.9)*	*12.0*

[a]T0 = baseline, T1 = mid-chemotherapy, T2 = after completion of chemotherapy, T3 = one year FU; [b]dominant hand; [c]MEDAS; [d]NRS-2002; [e]EORTC QLQ-C30; [f] MFI-20

Discussion

Patients with ovarian cancer are not only seriously ill, but undergo exhausting abdominal surgery and chemotherapy. Therefore, it is not surprising that the majority of patients with ovarian cancer report an inactive lifestyle and do not meet recommendations after diagnosis and treatment (27). Common side-effects of ovarian cancer and its treatment are muscle wasting and malnourishment. Both can be targeted by nutrition and exercise programs (11). Consequently, it can be assumed that ovarian cancer patients may benefit from an individualized exercise and/or nutrition intervention to an even greater extent than already demonstrated in breast and colon cancer patients (4, 5).

As ovarian cancer is often diagnosed at a late stage of disease and the median age at initial diagnosis is 62 years, it was anticipated that the recruitment and completion rate would be lower than that reported in studies including cancer patients diagnosed at an early stage or at a younger age (28). In our randomized feasibility trial recruitment rate was 25.0%, which is in line with recruitment rates of 16 - 63% and a retention rates of 70 - 100 stated a recent review (10). Reported reasons for refusal of participation were symptoms, illness and exhaustion (10). These reasons hold true for our study as well. In addition, many patients declined to take part due to a distant residence, which was also the reason for not undergoing chemotherapy at UKE, thus requiring separate trips to UKE for the study. Others did not participate because they were not willing to risk randomization into the control group. Patients who consented to participate in the study showed a high commitment, and only two patient(s) dropped out, leading to a completion rate of 73.3%. Adherence to the exercise intervention in terms of

completed counseling sessions was higher than reported by previous studies (10) with 83.7% for exercise intervention (phase I, 83.2%; phase II, 85.1%) and 76.8% for nutrition intervention (phase I, 92.3%; phase II, 59.6%). There were no adverse events associated with the intervention documented throughout the trial. Therefore, this study to our knowledge is the first to show that a combined nutrition and exercise intervention in ovarian cancer patients during and after first-line chemotherapy is feasible, safe and accepted.

To date few RCTs on exercise and/or nutrition in ovarian cancer exist and those few available mainly recruited patients after completion of treatment. Thus, these studies in principle predominantly recruited patients in remission free of progression. The WALC (29) trial, a six months exercise intervention in ovarian cancer, for example, included patients up to four years following initial diagnosis and the patients sample was therefore heterogeneous. The REACT study (5) including a few ovarian cancer patients among other cancer survivors used a 12 week exercise intervention without combined nutrition counselling shortly after completion of treatment. The currently ongoing LIVES study (13) also investigates the effect of a 24 months lifestyle intervention after treatment for ovarian cancer patients. Only the ongoing PADOVA study offers a combined exercise and nutrition intervention during first-line chemotherapy (30). However, the exercise and nutrition intervention is limited to the duration of chemotherapy only, whereas our study aims to start with chemotherapy and to continue well into ovarian cancer survivorship to ensure maintenance of the recommended lifestyle.

Previous studies on post-diagnosis exercise in ovarian cancer have shown that exercise lead to improvements in HRQOL, fatigue and additional physical and psychological outcomes (10). The few feasibility studies on exercise and/or nutrition interventions during first-line chemotherapy reported increased moderate to strenuous physical activity to be correlated with improvements in quality of life (31-33) and physical functioning (e.g. muscular strength,

6-minute walking test) (31-33) as well as reduced fatigue (32, 33). Our study showed similar tendencies for the 6-minute walking test, physical fatigue as well as global health. However, these results are descriptive only and no RCT exists to prove effectiveness of a combined exercise and nutrition intervention during and/or after primary care in ovarian cancer patients.

Conclusion

To date guidelines on care programs for ovarian cancer patients in Germany are based solely on expert consensus (34). Although aftercare programs for ovarian cancer survivors to improve HRQoL and CRF are recommended, current treatment guidelines include a further 15-24 months maintenance therapy after completion of chemotherapy, which renders it difficult for patients to receive inpatient rehabilitation after first-line therapy (34). Therefore, of about a third of patients that survive for more than eight years up to 70% will suffer long-term sequelae of cancer treatment, including reduced HRQoL and CRF (35). A home-based personalized standardized care intervention program beginning already during chemotherapy and continued post-treatment will enable the majority of patients to participate and further empower them to achieve long-term adherence to recommended exercise and nutrition behavior.

Thus following this pilot study, it will be important to conduct a multicenter RCT to (1) provide evidence of the effectiveness of a personalized combined exercise and nutrition intervention during adjuvant and maintenance chemotherapy compared to standard care to improve HRQoL and reduce CRF in ovarian cancer patients and (2) to establish an exercise and nutrition program ready for implementation into routine clinical practice for ovarian cancer patients.

Data Statement

Data cannot be made publicly available for legal reasons. Due to data privacy rules and according to German law (§ 75 SGB X) access to the data is granted only to responsible scientific personnel at UKE, Hamburg, Germany within the framework of the respective research project. It is not permitted to give third parties access to the data without a proposal approved by the principal investigator.

Authors Statement

TM, JvG, SP, KHS, BS, BCZ, and JCC contributed to study conception and design. TM, BM, JvG, and ZS contributed to data and sample collection. JCC obtained funding for the pilot project. TM, BM and JCC drafted the first version of the manuscript. BM is responsible for data management of pilot study. HB performed the sample size calculations and supervised randomization process. All authors revised the protocol critically for important intellectual content and read and approved the final version of the protocol.

Conflict of interest

The authors declare no conflict of interest.

Funding

The pilot phase of the BENITA study has been funded for 2 years by the Hamburger Krebsgesellschaft (grant number: not applicable). There is no pharmaceutical industry funding and there are no commercial interests.

Acknowledgement

We would like to thank all patients who participated in the BENITA study as well as Andrea Krull (Verein Eierstockkrebs Deutschland e.V.) for her helpful advice on the study plan.

The authors would also like to thank Professor Dr S C Bischoff of the University Hohenheim for providing them with the validated German version of the MEDAS questionnaire.

Figure 1: Flow diagram of participant recruitment and randomization

Figure 2: Descriptive results of in-person assessments at baseline (T0), mid-chemotherapy (T1), after completion of chemotherapy (T2) and one year follow-up (T3) by group assignment

Literature

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-403.
2. Krebs in Deutschland 2015/2016. Berlin: Robert Koch-Institute; 2019.
3. Institute UDoHaHSNIoHNC. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. [Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.
4. McNeely ML, Campbell KL, Rowe BH, Klassen TP, Mackey JR, Courneya KS. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2006;175(1):34-41.
5. Kampshoff CS, Chinapaw MJ, Brug J, Twisk JW, Schep G, Nijziel MR, et al. Randomized controlled trial of the effects of high intensity and low-to-moderate intensity exercise on physical fitness and fatigue in cancer survivors: results of the Resistance and Endurance exercise After ChemoTherapy (REACT) study. BMC Med. 2015;13:275.

6. Blanchard CM, Courneya KS, Stein K. Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer Society's SCS-II. J Clin Oncol. 2008;26(13):2198-204.
7. McCullough ML, Patel AV, Kushi LH, Patel R, Willett WC, Doyle C, et al. Following cancer prevention guidelines reduces risk of cancer, cardiovascular disease, and all-cause mortality. Cancer Epidemiol Biomarkers Prev. 2011;20(6):1089-97.
8. Smits A, Smits E, Lopes A, Das N, Hughes G, Talaat A, et al. Body mass index, physical activity and quality of life of ovarian cancer survivors: time to get moving? Gynecol Oncol. 2015;139(1):148-54.
9. Stevinson C, Faught W, Steed H, Tonkin K, Ladha AB, Vallance JK, et al. Associations between physical activity and quality of life in ovarian cancer survivors. Gynecol Oncol. 2007;106(1):244-50.
10. Jones TL, Sandler CX, Spence RR, Hayes SC. Physical activity and exercise in women with ovarian cancer: A systematic review. Gynecol Oncol. 2020;158(3):803-11.
11. Fearon KC. Cancer cachexia: developing multimodal therapy for a multidimensional problem. Eur J Cancer. 2008;44(8):1124-32.
12. Johns DJ, Hartmann-Boyce J, Jebb SA, Aveyard P. Diet or exercise interventions vs combined behavioral weight management programs: a systematic review and meta-analysis of direct comparisons. Journal of the Academy of Nutrition and Dietetics. 2014;114(10):1557-68.
13. Thomson CA, Crane TE, Miller A, Garcia DO, Basen-Engquist K, Alberts DS. A randomized trial of diet and physical activity in women treated for stage II-IV ovarian cancer: Rationale and design of the Lifestyle Intervention for Ovarian Cancer Enhanced Survival (LIVES): An NRG Oncology/Gynecologic Oncology Group (GOG-225) Study. Contemp Clin Trials. 2016;49:181-9.
14. Stelten S, Hoedjes M, Kenter GG, Kampman E, Huijsmans RJ, van Lonkhuijzen LR, et al. Rationale and study protocol of the Physical Activity and Dietary intervention in women with OVArian cancer (PADOVA) study: a randomised controlled trial to evaluate effectiveness of a tailored exercise and dietary intervention on body composition, physical function and fatigue in women with ovarian cancer undergoing chemotherapy. BMJ open. 2020;10(11):e036854.
15. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The Physical Activity Guidelines for Americans. Jama. 2018;320(19):2020-8.
16. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
17. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995;39(3):315-25.
18. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;22(3):321-36.
19. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003;56(12):1163-9.
20. Agarwala P, Salzman SH. Six-Minute Walk Test: Clinical Role, Technique, Coding, and Reimbursement. Chest. 2020;157(3):603-11.
21. Butte NF, Ekelund U, Westerterp KR. Assessing physical activity using wearable monitors: measures of physical activity. Medicine and science in sports and exercise. 2012;44(1 Suppl 1):S5-12.
22. Cotogni P, Monge T, Fadda M, De Francesco A. Bioelectrical impedance analysis for monitoring cancer patients receiving chemotherapy and home parenteral nutrition. BMC cancer. 2018;18(1):990.
23. Maurer T, von Grundherr J, Patra S, Jaeger A, Becher H, Schmalfeldt B, et al. An exercise and nutrition intervention for ovarian cancer patients during and after first-line chemotherapy (BENITA study): a randomized controlled pilot trial. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2020;30(4):541-5.

24. Hebestreit K, Yahiaoui-Doktor M, Engel C, Vetter W, Siniatchkin M, Erickson N, et al. Validation of the German version of the Mediterranean Diet Adherence Screener (MEDAS) questionnaire. BMC Cancer. 2017;17(1):341.
25. Brauns H. SS, Steinmann S. The CASMIN Educational Classification in International Comparative. Research. In: Hoffmeyer-Zlotnik J.H.P. WCe, editor. Boston, MA.: Springer; 2003.
26. Prat J. FIGO's staging classification for cancer of the ovary, fallopian tube, and peritoneum: abridged republication. Journal of gynecologic oncology. 2015;26(2):87-9.
27. Mizrahi D, Naumann F, Broderick C, Samara J, Ryan M, Friedlander M. Quantifying physical activity and the associated barriers for women with ovarian cancer. Int J Gynecol Cancer. 2015;25(4):577-83.
28. Sheill G, Guinan E, Brady L, Hevey D, Hussey J. Exercise interventions for patients with advanced cancer: A systematic review of recruitment, attrition, and exercise adherence rates. Palliative & supportive care. 2019;17(6):686-96.
29. Zhou Y, Gottlieb L, B. C, Li F, Ercolano EA, Harrigan M, et al. Randomized trial of exercise on quality of life and fatigue in women diagnosed with ovarian cancer: The Women's Activity and Lifestyle Study in Connecticut (WALC). . Journal of Clinical Oncology. 2015 33(15_suppl):9505-.
30. Stelten S, Hoedjes M, Kenter GG, Kampman E, Huijsmans RJ, van Lonkhuijzen LR, et al. Rationale and study protocol of the Physical Activity and Dietary intervention in women with OVArian cancer (PADOVA) study: a randomised controlled trial to evaluate effectiveness of a tailored exercise and dietary intervention on body composition, physical function and fatigue in women with ovarian cancer undergoing chemotherapy. BMJ Open. 2020;10(11):e036854.
31. Newton MJ, Hayes SC, Janda M, Webb PM, Obermair A, Eakin EG, et al. Safety, feasibility and effects of an individualised walking intervention for women undergoing chemotherapy for ovarian cancer: a pilot study. BMC Cancer. 2011;11:389.
32. Mizrahi D, Broderick C, Friedlander M, Ryan M, Harrison M, Pumpa K, et al. An Exercise Intervention During Chemotherapy for Women With Recurrent Ovarian Cancer: A Feasibility Study. Int J Gynecol Cancer. 2015;25(6):985-92.
33. von Gruenigen VE, Frasure HE, Kavanagh MB, Lerner E, Waggoner SE, Courneya KS. Feasibility of a lifestyle intervention for ovarian cancer patients receiving adjuvant chemotherapy. Gynecol Oncol. 2011;122(2):328-33.
34. Wagner U, Harter P, Hilpert F, Mahner S, Reuß A, du Bois A, et al. S3-Guideline on Diagnostics, Therapy and Follow-up of Malignant Ovarian Tumours: Short version 1.0 - AWMF registration number: 032/035OL, June 2013. Geburtshilfe und Frauenheilkunde. 2013;73(9):874-89.
35. Joly F, Ahmed-Lecheheb D, Kalbacher E, Heutte N, Clarisse B, Grellard JM, et al. Long-term fatigue and quality of life among epithelial ovarian cancer survivors: a GINECO case/control VIVROVAIRE I study. Annals of oncology : official journal of the European Society for Medical Oncology. 2019;30(5):845-52.

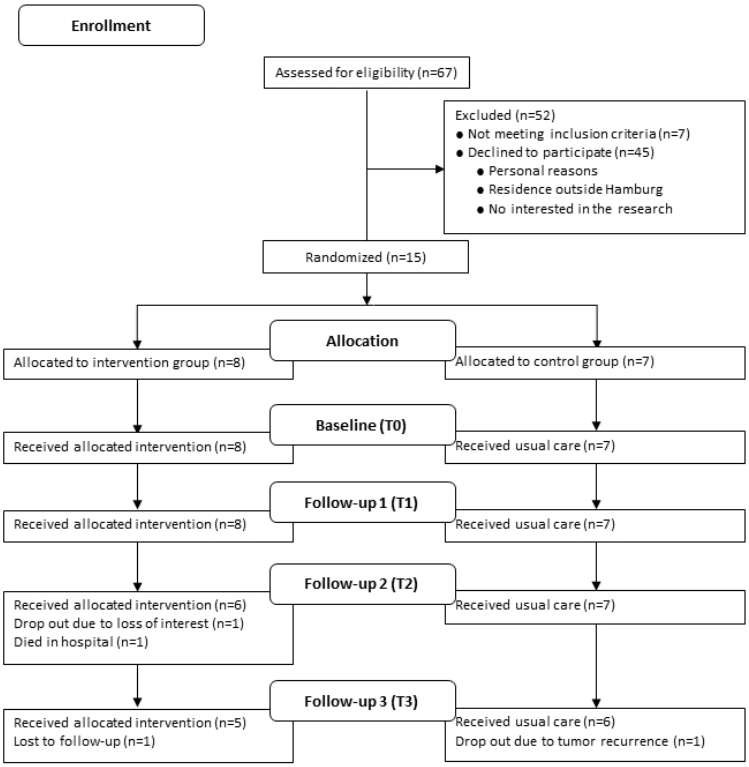

Figure 1: Flow diagram of participant recruitment and randomization

190x275mm (96 x 96 DPI)

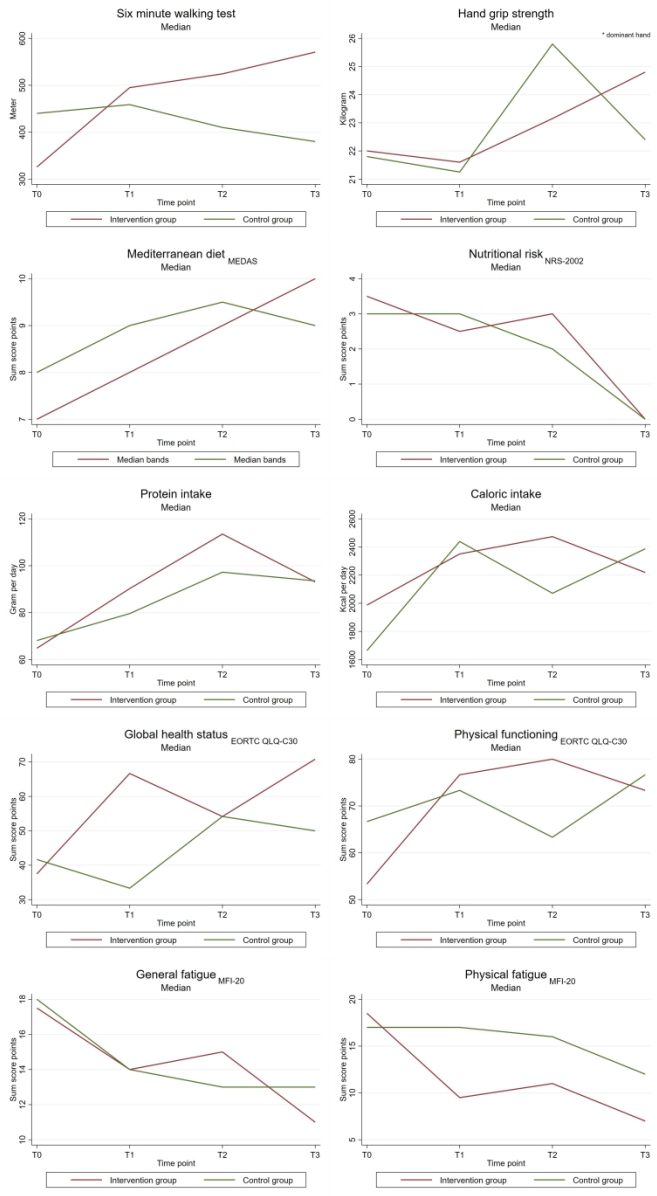

Figure 2: Descriptive results of in-person assessments at baseline (T0), mid-chemotherapy (T1), after completion of chemotherapy (T2) and one year follow-up (T3) by group assignment

1017x1849mm (72 x 72 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4-5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Doesn't apply
Participants	4a	Eligibility criteria for participants	4-5
	4b	Settings and locations where the data were collected	4-5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6-7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Doesn't apply
Sample size	7a	How sample size was determined	Described in study protocol
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Doesn't apply
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Described in study protocol
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Doesn't apply
	11b	If relevant, description of the similarity of interventions	Doesn't apply
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6-7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6-7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7-8
	13b	For each group, losses and exclusions after randomisation, together with reasons	7-8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the trial ended or was stopped	Doesn't apply
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	No inferential statistics (feasibility)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Doesn't apply
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	13-16
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	No adverse events
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	17 ff
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	18-19
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	Published (IJGC)
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	21

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

A randomized controlled trial testing the feasibility of an exercise and nutrition intervention for ovarian cancer patients during and after first-line chemotherapy (BENITA-study)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054091.R1
Article Type:	Original research
Date Submitted by the Author:	11-Dec-2021
Complete List of Authors:	Maurer, Tabea; University Medical Center Hamburg-Eppendorf, Cancer Epidemiology, University Cancer Center Hamburg (UCCH) Belau, Matthias; University Medical Center Hamburg-Eppendorf von Grundherr, Julia; University Medical Center Hamburg-Eppendorf, Department of Oncology, Hematology, BMT with Section Pneumology, Hubertus Wald Tumour Center, University Cancer Center Hamburg (UCCH), Schlemmer, Zoe; University Medical Center Hamburg-Eppendorf, Department of Gynaecology and Gynaecologic Oncology Patra, Stefan; University Medical Center Hamburg-Eppendorf, Universitäres Kompetenzzentrum für Sport- und Bewegungsmedizin (Athleticum) Becher, Heiko; University Medical Center Hamburg-Eppendorf, Medical Biometry and Epidemiology Schulz, Karl-Heinz; University Medical Center Hamburg-Eppendorf, Universitäres Kompetenzzentrum für Sport- und Bewegungsmedizin (Athleticum) Zyriax, Birgit-Christiane; University Medical Center Hamburg-Eppendorf, Midwifery Science – Health Care Research and Prevention, Institute for Health Services Research in Dermatology and Nursing (IVDP) Schmalfeldt, Barbara; University Medical Center Hamburg-Eppendorf, Germany, Department of Gynaecology and Gynaecologic Oncology Chang-Claude, Jenny; University Medical Center Hamburg-Eppendorf; DKFZ, Division of Cancer Epidemiology
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Adult oncology < ONCOLOGY, Epidemiology < ONCOLOGY, Gynaecological oncology < ONCOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A randomized controlled trial testing the feasibility of an exercise and nutrition intervention for ovarian cancer patients during and after first-line chemotherapy (BENITA-study)

T. Maurer[†1], M.H. Belau[†2], J. von Grundherr[3], Z. Schlemmer[4], S. Patra[5], H. Becher[2], K-H. Schulz[5], B-C. Zyriax[6], B. Schmalfeldt[4], J. Chang-Claude[17]

1 Cancer Epidemiology Group, University Cancer Center Hamburg (UCCH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany

2 Institute for Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

3 Department of Oncology, Hematology, BMT with Section Pneumology, Hubertus Wald Tumour Center, University Cancer Center Hamburg (UCCH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany

4 Department of Gynecology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

5 Institute for Medical Psychology and Competence center for sports and exercise medicine (Athleticum),University Medical Center Hamburg-Eppendorf, Hamburg, Germany

6 Midwifery Science – Health Care Research and Prevention, Institute for Health Services Research in Dermatology and Nursing (IVDP), University Medical Center Hamburg-Eppendorf, Hamburg, Germany

7 Division of Cancer Epidemiology, German Cancer Research Centre, Heidelberg, Germany

[†]Shared first authorship

Corresponding author:
Prof. Jenny Chang-Claude
Cancer Epidemiology Group
University Cancer Center Hamburg (UCCH)
University Medical Center Hamburg-Eppendorf
Martinistraße 52
20251 Hamburg, Germany
j.chang-claude@uke.de

Keywords: Ovarian Cancer, Feasibility, Exercise, Nutrition, RCT, during chemotherapy

Word Count: 2771

Abstract

Objectives: Advanced ovarian cancer is a severe disease with major side effects caused by peritoneal carcinomatosis, ascites and gastrointestinal involvement as well as exhaustive treatment like debulking surgery and combination chemotherapy. Two most frequently reported side effects are muscle wasting and malnutrition leading to frailty, decreased health-related quality of life (HRQoL), and cancer related fatigue (CRF). As muscle wasting and malnutrition often commence during first-line chemotherapy and develop progressively into a refractory state, an early intervention is warranted. This pilot study aimed to evaluate the safety and acceptance of a combined exercise and nutrition intervention during and after first-line chemotherapy.

Design: The pilot study was conducted as a monocentric 1:1 randomized controlled trial (RCT) with an intervention (IG) and a control group (CG). Participants were divided by chance into IG or CG. Information on group allocation was conveyed to the study coordinator responsible for making an appointment with the patients for the baseline assessment as well as the physiotherapist and nutritionist responsible for the intervention, and outcome assessment in both groups.

Participants: Eligibility criteria included women ≥18 years of age, diagnosed with ovarian cancer, tubal cancer, or peritoneal cancer and primary or interval debulking, scheduled but not started adjuvant or neoadjuvant chemotherapy, and sufficient German language skills.

Intervention: The IG received a 12-month exercise and nutrition program, the CG continued to follow usual care.

Primary and secondary outcome measures: Primary outcomes were recruitment rate, adherence to intervention, completion rate, and adverse events. In addition, in-person assessments (e.g. HRQoL, CRF, muscle quality and function, and dietary intake and quality) were conducted at baseline (T0, before chemotherapy), week 9 (T1, mid-chemotherapy), week 19 (T2, after completion of chemotherapy), and after 12 months of intervention (T3).

Results: Of 60 eligible patients, fifteen patients signed informed consent (recruitment rate=25.0%) and were randomized into IG (n=8) and CG (n=7). Eleven participants completed the study (completion rate, 73.3%), one patient dropped-out due to loss of interest, one due to poor health, one was lost to follow-up and one patient died.

Conclusion: The BENITA study demonstrated the safety and acceptance of an exercise and nutrition intervention integrated into first line therapy and follow-up care of ovarian cancer. A large multicenter RCT is planned to investigate the effectiveness of the intervention on HRQoL, CRF, and survival and to establish means of implementation into oncology guidelines and clinic routine.

Trial registration: The study was registered at the German study registry for clinical studies (DRKS00013231).

Funding: Hamburger Krebsgesellschaft e.V. (grant number: not applicable)

Strength and limitations

- The trial uses objective measures to evaluate the feasibility of an exercise and nutrition intervention in ovarian cancer patients
- The exercise and nutrition intervention commences during first-line chemotherapy and continues well into ovarian cancer survivorship
- The exercise and nutrition intervention has been developed by an interdisciplinary team of sport and nutrition experts
- Sport and nutrition experts conducting the intervention and assessing the outcome in both groups could not be blinded due to the study design

Introduction

Ovarian cancer is the second most common gynecologic cancer in women and has the fifth highest rate of cancer-related deaths for women in Germany (1) with only 43% alive 5 years after diagnosis (2). Major side effects of ovarian cancer and its treatment are cancer cachexia, sarcopenia, frailty, and malnutrition. All are leading to either loss of skeletal muscle mass and/or fat mass of the patient and are associated with decreased health-related quality of life (HRQoL), cancer related fatigue (CRF) and poorer outcome (3, 4). As these syndromes share similar etiological factors such as reduced food intake, inflammation, hormonal changes, increased energy requirements and reduced physical activity (5) more than one can be present in the same patient at the same time. Hence, a combined intervention consisting of an exercise and nutrition program may be most successful to address these syndromes in patients with advanced cancer (6, 7). Exercise has been shown to significantly improve CRF, cardiorespiratory fitness, HRQoL and even survival in breast and colon cancer (8, 9). Adherence to lifestyle recommendations such as physical activity and nutrition before diagnosis was associated with a significantly higher HRQoL (10) and decreased risk of cancers (11). However, there is paucity of knowledge on post-diagnosis physical activity (PA) or nutrition behavior on prognosis or HRQoL in ovarian cancer patients. In observational studies, ovarian cancer patients with greater post-diagnosis physical activity were found to experience a significantly better HRQoL (12-14). Yet, randomized controlled trials (RCTs) evaluating the benefits of an exercise and nutrition intervention on survival and HRQoL are rare. Two RCTs on bimodal exercise and nutrition programs for ovarian cancer patients are currently ongoing (15, 16). One commences intervention after completion of treatment (15) and one investigates the effect of an intervention during first-line chemotherapy (16). However, no current or previous RCT offers a care program during and after first-line chemotherapy, which

is necessary to prevent deterioration due to treatment as well as support maintenance of lifestyle changes thereafter.

It was the aim of this study to determine the feasibility of a combined exercise and nutrition intervention for ovarian cancer patients during and after first-line chemotherapy. Main endpoints of the pilot trial were recruitment rate, adherence, completion rate as well as adverse events (safety). Furthermore, assessments requiring visits to the hospital (in-person assessments) as planned for a main trial were conducted (e.g. HRQoL, CRF, muscular strength and quality, nutrition habits and quality) to investigate acceptance and safety in ovarian cancer patients.

Methods

Study design, setting and participants

This pilot study was a monocentric 1:1 RCT with an intervention (IG) and a control group (CG). The ethics committee of the Faculty of Medicine at Hamburg University approved the study protocol. The trial was registered at the German Study Registry for Clinical Studies (DRKS00013231). Participants were recruited from the department of Gynecology at the University Medical Center Hamburg Eppendorf (UKE), Germany at diagnosis. Eligibility criteria included women ≥18 years of age, diagnosed with ovarian cancer, tubal cancer, or peritoneal cancer and primary or interval debulking, scheduled but not started adjuvant or neoadjuvant chemotherapy, and sufficient German language skills. Exclusion criteria were an Eastern Cooperative Oncology Group (ECOG) status of two or worse, any physical or mental condition that would hinder execution or completion of the training program and study procedures, a

private engagement in exercise training above the WHO recommendation of 150 minutes of moderate-intensity activity per week (17), or a diagnosis of an eating disorder.

Patient and public involvement

The ovarian cancer patient organization in Germany (Verein Eierstockkrebs Deutschland e.V. (VED)) represented by its first chairperson, Andrea Krull, has provided input to the project from a patient's perspective, reviewed ethical issues and commented on consent forms.

Procedure

Two gynecologists identified and approached participants meeting inclusion criteria. After written informed consent, patients were randomized into the intervention group (IG) to receive a 12-months exercise and nutrition program or the control group (CG) to receive usual care. Group allocation was performed by a statistician not involved in data collection. Information on group allocation was conveyed to the study coordinator responsible for making an appointment with the patients for the baseline assessment as well as the physiotherapist and nutritionist responsible for the intervention, and outcome assessment in both groups.

In-person assessments were conducted independent of study arm at baseline (T0), mid-chemotherapy (T1), after completion of chemotherapy (T2), and at one-year follow-up (T3). Assessments include HRQoL (European Organisation for Research and Treatment of Cancer (EORTC)-QLQ-C30 (16), CRF (Multidimensional Fatigue Inventory (MFI-20)) (18), nutritional risk (Nutritional Risk Score (NRS)-2002) (19), physical activity (Short Questionnaire to Assess

Health enhancing physical activity (SQUASH)) (20), performance diagnostics including six-minute walk test (21), hand grip strength (Kern MAP 80k1) (22), accelerometer ("Actigraph wGT3X-BT"), and body composition (bioelectric impedance analysis (BIA), "AKERN BIA 101 Anniversary") (23). A detailed overview on scheduled in-person assessments is described elsewhere (24). Safety of the program was analyzed through adverse events linked to the intervention during all phases of the study. All analyses were performed using STATA MP, version 17.

Intervention

Participants received personalized exercise and nutrition programs and counselling that were tailored to different phases of patient's treatment and recovery as well as individual needs throughout the trial. In both phases of the exercise intervention patients are given instructions and encouraged to participate in a daily 15-30 minute unsupervised home-based training that includes endurance, resistance, and balance exercises to be performed in gradual increments. An exercise catalogue was developed by sports scientists and all exercises were categorized based on their intensity. Each patient received an individually adapted program consisting of exercises that are part of the catalogue. The program was adjusted each week (phase I) or every other week (phase II) if needed based on the patients' individual abilities and current needs. Exercises using abdominal muscles were not included till full recovery from surgery. The exercise catalogue used to build the exercise programs can be found in the supplements. The nutrition intervention in phase I aimed to reduce malnutrition risk by increasing protein and calorie intake. During chemotherapy, patients were supervised by a nutritionist every three weeks. Those who were in need of an increased calorie and protein intake were advised

to consume several smaller meals throughout the day and, if necessary, to increase the use of oils and butter if necessary. Furthermore, patients were educated about suitable types of foods and drinks that are high in protein, fat or energy. If deemed necessary oral sip feeding was suggested. These recommendations were based on the patients' development in weight as well as other body composition parameters derived from BIA measurements (e.g. phase angle, muscle mass). In phase II (weeks 19-52) after chemotherapy, monthly nutrition counselling focused on the Mediterranean diet, shown to reduce malnutrition and cancer risk. To monitor adherence and progress in phase I, participants received a weekly telephone call by a sports scientist, and triweekly by a nutritionist. In phase II patients received monthly counseling by telephone or in person. The intervention is described in more detail elsewhere (24).

Statistical methods

Recruitment rate was defined as the ratio of patients eligible to participate and patients who signed informed consent. Completion rate was defined as the ratio of patients who signed informed consent and those who completed the 12 months intervention. General adherence to the intervention was defined as the ratio of planned and completed counseling sessions. Adherence to the exercise program was further assessed using exercise diaries filled out every week until week 18 and once a months until 12 months follow-up. Adherence to the nutrition intervention in phase I was described in terms of changes in protein and caloric intake compared to baseline. During phase II adherence to the nutrition intervention was interpreted in terms of changes in MEDAS (Mediterranean Diet Adherence Screener) score points between T0 and T3 (25). Descriptive analyses were conducted for all parameters assessed

during the study. No inferential statistics were used as this feasibility trial was not powered for this purpose.

Results

Characteristics and feasibility

Of 67 patients with initial diagnosis of ovarian cancer from April 2018 to Sept 2019 screened for eligibility, 60 patients met inclusion criteria and were invited into the study. 45 refused to participate in the study. Main reasons were personal reasons, residence outside of Hamburg, not willing to be randomized and no interest in the research. Fifteen patients signed informed consent (recruitment rate, 25.0%) and were randomized into IG (n=8) and CG (n=7). Eleven participants completed the study (completion rate, 73.3%), one patient dropped-out due to loss of interest, one patient due to poor health (recurrence), one patient was lost to follow-up (could not be reached via phone or mail) and one patient died. Fig. 1 provides flow of participants through the study.

Table 1 summarizes the baseline characteristics of participants by group assignment. The mean age of the participants was 56.5 ± 14.4 years ranging from 21 to 77 years, with an average of 33.9 ± 17.0 days since initial diagnosis. The majority (73.3%) of patients was diagnosed as having advanced stage disease (stage III or IV). After surgery, eight patients had no residual tumor, five patients' tumors were resected to smaller than 1 centimeter and two patients' tumors had residual tumor larger than 1 centimeter.

Table 1: Baseline characteristics of participants by group assignment

		All participants		***Intervention group***		***Control group***	
		N (=15)	*%*	*N (=8)*	*%*	*N (=7)*	*%*
Age	*median (range)*	*58 (21-77)*		52 (21-64)		65 (48-77)	
Education[a]	*Low*	*1*	*6.7*	0	0.0	1	14.3
	Medium	*8*	*53.3*	5	62.5	3	42.9
	High	*6*	*40.0*	3	37.5	3	42.9
Smoking status	*Never smoker*	*8*	*53.3*	4	50.0	4	57.1
	Former smoker	*5*	*33.3*	3	37.5	2	28.6
	Current smoker	*2*	*13.3*	1	12.5	1	14.3
Alcohol use *per week*	*<1g*	*5*	*33.3*	3	37.5	2	28.6
	1-12g	*1*	*6.7*	0	0.0	1	14.3
	13-24g	*3*	*20.0*	3	37.5	0	0.0
	25-48g	*4*	*26.7*	1	12.5	3	42.9
	49-60g	*2*	*13.3*	1	12.5	1	14.3
Body mass index	*Underweight (<18.5)*	*1*	*6.7*	1	12.5	0	0.0
	Normal weight (18.5-24.9)	*9*	*60.0*	4	50.0	5	71.4
	Overweight (25.0-29.9)	*2*	*13.3*	1	12.5	1	14.3
	Obesity (≥30.0)	*3*	*20.0*	2	25.0	1	14.3
Sports[b]	*0-4 MET h/week*	*9*	*60.0*	6	75.0	3	42.9
	5-10 MET h/week	*1*	*6.7*	1	12.5	0	0.0
	>10 MET h/week	*5*	*33.3*	1	12.5	4	57.1
Cancer stage[c]	*I*	*2*	*13.3*	1	12.5	1	14.3
	II	*2*	*13.3*	0	0.0	2	28.6
	III	*9*	*60.0*	6	75.0	3	42.9
	IV	*2*	*13.3*	1	12.5	1	14.3
Tumor size *post-op*	*Tumor-free*	*8*	*53.3*	4	50.0	4	57.1
	<1cm	*5*	*33.3*	2	25.0	3	42.9
	>1cm	*2*	*13.3*	2	25.0	0	0.0
Treatment	*Adjuvant chemotherapy*	*12*	*80.0*	6	75.0	6	85.7
	Neo-adjuvant chemotherapy	*3*	*20.0*	2	25.0	*1*	*14.3*

[a]CASMIN classification (26); [b]SQUASH questionnaire (20); [c]FIGO classification (27)

All 15 participants enrolled in the study completed T0 and T1 assessments. Between T1 and T2 one patient in the intervention group died and another dropped out due to loss of interest. The remaining 13 patients completed the T1 assessment. Between T2 and T3 a patient of the intervention group was lost to follow-up and a patient of the control group dropped-out due to a recurrence. All eleven patients still enrolled in the study completed the final assessment. Table 2 provides detailed information on adherence to different assessments and time points by group assignment. Adherence to the exercise intervention in terms of completed intervention sessions (face-to-face, by telephone) was 83.7% for exercise intervention (phase I, 83.2%; phase II, 85.1%) and 76.8% for nutrition intervention (phase I, 92.3%; phase II, 59.6%).

Adherence to the exercise and nutrition program is shown in table 3. During phase I five out of eight patients documented their weekly home-based exercise for a total of 14-18 weeks. One patient documented their daily home-based exercise for ten weeks, another patient dropped out after six weeks, and one patient died during phase I without documentation of home-based training. Patients trained between 90 and 180 minutes per week. In phase II three patients documented their exercise for 30-34 weeks. Two patients stopped their documentation after 12 and 4 weeks, respectively. Two patients dropped out of the study and one patient did not continue to document their daily practice, but remained in the study. In phase II most patients trained for up to 90 minutes per week.

Adherence to the nutrition intervention in terms of caloric and protein intake showed that, patients of the intervention group increased their protein intake from 65.8 gram (g) per day at baseline (T0) to 107.9g per day at T2. The calorie intake increased from 1860kcal per day at T0 to 2389kcal per day at T2. In phase II adherence to the nutrition intervention based on the MEDAS score showed that patients of the intervention group increased their MEDAS scores from a median of 7.0 at baseline to a median of 10 score points at week 52 (T3).

Safety of the intervention was defined through any adverse events that could be linked to either the exercise or the nutrition intervention. There were no adverse events reported to be due to the intervention or in-person assessments.

Table 2: Adherence to assessment time points

			All participants		***Intervention group***		***Control group***	
			N[a]	*%*	*N*[a]	*%*	*N*[a]	*%*
Exercise assessment	*Performance diagnostics*	***T0***[b]	*14/15*	*93.3*	*7/8*	*87.5*	*7/7*	*100.0*
		T1	*11/15*	*73.3*	*6/8*	*75.0*	*5/7*	*71.4*
		T2	*12/13*	*92.3*	*6/6*	*100.0*	*6/7*	*85.7*
		T3	*11/11*	*100.0*	*5/5*	*100.0*	*6/6*	*100.0*
		T0 – T3	*48/54*	*88.9*	*24/27*	*88.9*	*24/27*	*88.9*
	Accelerometer[c]	***T0***	*13/15*	*86.7*	*6/8*	*75.0*	*7/7*	*100.0*
		T1	*11/15*	*73.3*	*6/8*	*75.0*	*5/7*	*71.4*
		T2	*10/13*	*76.9*	*5/6*	*83.3*	*5/7*	*71.4*
		T3	*11/11*	*100.0*	*5/5*	*100.0*	*6/6*	*100.0*
		T0 – T3	*45/54*	*83.3*	*22/27*	*81.5*	*23/27*	*85.2*
Nutrition diagnostics		***T0***	*14/15*	*93.3*	*8/8*	*100.0*	*6/7*	*85.7*
		T1	*15/15*	*100.0*	*8/8*	*100.0*	*7/7*	*100.0*
		T2	*12/13*	*92.3*	*6/6*	*100.0*	*6/7*	*85.7*
		T3	*11/11*	*100.0*	*5/5*	*100.0*	*6/6*	*100.0*
		T0 – T3	*52/54*	*96.3*	*27/27*	*100.0*	*25/27*	*92.6*
Case report form[d]		***T0***	*15/15*	*100.0*	*8/8*	*100.0*	*7/7*	*100.0*
		T1	*15/15*	*100.0*	*8/8*	*100.0*	*7/7*	*100.0*
		T2	*12/13*	*92.3*	*6/6*	*100.0*	*6/7*	*85.7*
		T3	*11/11*	*100.0*	*5/5*	*100.0*	*6/6*	*100.0*
		T0 – T3	*53/54*	*98.2*	*27/27*	*100.0*	*26/27*	*96.3*

[a]number of participants assessed/number eligible

[b]T0 = baseline, T1 = mid-chemotherapy, T2 = after completion of chemotherapy, T3 = one year follow-up

[c] Worn at home for a week at each time of assessment

[d] Included all questionnaires applied In the study

Table 3: Adherence to the implementation of exercise and nutrition program among participants from the intervention group

Exercise program					
	Participant	***Number of weeks reported***	***Days per week*** Median	***Minutes per week***	***Rating of perceived exertion*** BORG scale
Phase I (week 1 - 18)	*P1*	*15*	*5.2*	*up to 90 minutes*	*Very light to light (9-11)*
	P2	*18*	*5.7*	*up to 90 minutes*	*Light to somewhat hard (11-13)*
	P3	*6*	*4.3*	*up to 90 minutes*	*Light to somewhat hard (11-13)*
	P4	*14*	*5.4*	*90 to 180 minutes*	*Light to somewhat hard (11-13)*
	P5	*10*	*5.4*	*up to 90 minutes*	*Somewhat hard to hard (13-15)*
	P6	*18*	*3.8*	*90 to 180 minutes*	*Light to somewhat hard (11-13)*
	P7	*18*	*5.1*	*up to 90 minutes*	*Very light to light (9-11)*
	P8[a]	*0*	*0.0*	-	-
Phase II (week 19 - 52)	*P1*[b]	*0*	*0.0*	-	-
	P2	*32*	*4.1*	*up to 90 minutes*	*Light to somewhat hard (11-13)*
	P3[c]	*0*	*0.0*	-	-
	P4	*4*	*5.0*	*90 to 180 minutes*	*Light to somewhat hard (11-13)*
	P5	*12*	*2.0*	*up to 90 minutes*	*Light to somewhat hard (11-13)*
	P6	*34*	*2.0*	*up to 90 minutes*	*Somewhat hard (13)*
	P7	*34*	*6.1*	*up to 90 minutes*	*Somewhat hard (13)*
	P8[a]	*0*	*0.0*	-	-

Nutrition program					
		Protein intake (Gram per day)		***Mediterranean diet***[d] (Sum score)	
		Mean (SD)	Median	Mean (SD)	Median
Phase I (week 1 - 18)	*Week 1*	*65.8 (16.4)*	*64.8*	*7.0 (2.3)*	*7.0*
	Week 9	*96.7 (29.4)*	*90.3*	*7.8 (2.1)*	*8.0*
Phase II (week 19 - 52)	*Week 19*	*107.9 (18.1)*	*113.5*	*8.7 (1.0)*	*9.0*
	Week 52	*90.9 (9.1)*	*93.1*	*9.2 (1.6)*	*10.0*

[a]died in hospital; [b]dropped out; [c]lost to follow-up, [d]MEDAS sum score

Descriptive statistics of in-person assessments

Table 4 and figures 2 and 3 display descriptive results of in-person assessments at different time points by group assignment. Participants who received personalized exercise and nutrition programs increased their median six-minute walk distance from 411 meters (m) at baseline to 475m at T3, whereas members of the control groups decreased their distance from 440m to 380m. Patients of the intervention group increased their hand grip strength from 22.0 kilogram (kg) to 24.8kg (median), the control group showed a slightly lower increase (from 21.8 to 22.4kg). In terms of nutrition, calorie intake during chemotherapy increased in both IG and CG. The IG showed a larger increase in protein intake from baseline to T1 and T2 compared to controls. Adherence to Mediterranean diet or nutritional risk were comparable in IG and CG.

The HRQoL increased from baseline to T3 from 37.5 to 70.8 score points in the IG and from 41.7 to 50.0 score points in the CG. Both total and physical fatigue decreased from T0 to T3 and was somewhat stronger in IG than CG for physical fatigue.

Table 4: Results of assessments at different time points by group assignment

		All participants		***Intervention group***		***Control group***	
		Mean (SD)	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*
6 minute walking test *meter*	***T0***[a]	*397.5 (109.8)*	*411.0*	*369.7 (126.3)*	*325.7*	*436.4 (77.3)*	*440.0*
	T1	*489.0 (95.5)*	*490.0*	*483.9 (96.2)*	*495.0*	*495.1 (105.6)*	*458.8*
	T2	*496.2 (116.5)*	*507.7*	*511.9 (80.9)*	*524.4*	*477.4 (157.8)*	*410.0*
	T3	*492.8 (134.6)*	*475.0*	*542.4 (91.1)*	*570.7*	*451.5 (158.4)*	*380.0*
Hand grip strength[b] *kilogram*	***T0***	*22.4 (7.0)*	*21.9*	*22.2 (8.7)*	*22.0*	*22.6 (4.7)*	*21.8*
	T1	*24.1 (7.5)*	*21.6*	*23.5 (6.4)*	*21.6*	*25.0 (9.9)*	*21.3*
	T2	*25.2 (6.9)*	*24.6*	*23.0 (6.0)*	*23.2*	*27.8 (7.6)*	*25.8*
	T3	*25.6 (6.7)*	*24.8*	*26.3 (5.9)*	*24.8*	*25.1 (7.8)*	*22.4*
Mediterra-nean diet[c] *sum core*	***T0***	*7.0 (1.9)*	*8.0*	*7.0 (2.3)*	*7.0*	*7.0 (1.4)*	*8.0*
	T1	*8.4 (2.2)*	*9.0*	*7.8 (2.1)*	*8.0*	*9.1 (2.2)*	*9.0*
	T2	*9.0 (1.8)*	*9.0*	*8.7 (1.0)*	*9.0*	*9.3 (2.3)*	*9.5*
	T3	*9.2 (1.9)*	*10.0*	*9.2 (1.6)*	*10.0*	*9.2 (2.3)*	*9.0*
Nutritional risk[d] *risk score*	***T0***	*3.4 (1.1)*	*3.0*	*3.5 (1.2)*	*3.5*	*3.3 (1.1)*	*3.0*
	T1	*3.1 (1.3)*	*3.0*	*3.0 (1.5)*	*2.5*	*3.3 (1.1)*	*3.0*
	T2	*2.4 (1.8)*	*2.5*	*2.5 (2.1)*	*3.0*	*2.3 (1.6)*	*2.0*
	T3	*0.4 (0.7)*	*0.0*	*0.2 (0.5)*	*0.0*	*0.5 (0.8)*	*0.0*
Protein intake *gram per day*	***T0***	*68.0 (13.3)*	*64.8*	*65.8 (16.4)*	*64.8*	*70.6 (9.1)*	*68.1*
	T1	*89.6 (30.4)*	*87.0*	*96.7 (29.4)*	*90.3*	*78.2 (31.4)*	*79.6*
	T2	*104.0 (23.5)*	*113.3*	*107.9 (18.1)*	*113.5*	*100.1 (29.1)*	*97.3*
	T3	*89.3 (23.0)*	*93.1*	*90.9 (9.1)*	*93.1*	*87.9 (31.4)*	*93.6*
Caloric intake *Kcal per day*	***T0***	*1830 (382)*	*1816*	*1860 (388)*	*1987*	*1795 (409)*	*1663*
	T1	*2237 (612)*	*2439*	*2380 (429)*	*2350*	*2010 (835)*	*2439*
	T2	*2237 (513)*	*2439*	*2389 (372)*	*2474*	*2147 (635)*	*2071*
	T3	*2206 (548)*	*2355*	*2105 (398)*	*2219*	*2291 (675)*	*2387*
HRQoL[e]							
Global health status	***T0***	*40.0 (10.5)*	*41.7*	*40.6 (8.3)*	*37.5*	*39.3 (13.4)*	*41.7*
	T1	*55.6 (27.8)*	*66.7*	*62.5 (20.4)*	*66.7*	*47.6 (34.3)*	*33.3*
	T2	*59.7 (20.7)*	*54.2*	*58.3 (14.9)*	*54.2*	*61.1 (26.7)*	*54.2*
	T3	*65.8 (19.8)*	*66.7*	*72.9 (8.0)*	*70.8*	*61.1 (24.5)*	*50.0*
Physical functioning	***T0***	*59.1 (25.1)*	*66.7*	*54.2 (27.5)*	*53.3*	*64.8 (22.7)*	*66.7*
	T1	*69.3 (23.1)*	*73.3*	*66.7 (23.9)*	*76.7*	*72.4 (23.5)*	*73.3*
	T2	*70.6 (21.9)*	*76.7*	*76.7 (12.5)*	*80.0*	*64.4 (28.5)*	*63.3*
	T3	*78.2 (16.9)*	*73.3*	*76.0 (17.4)*	*73.3*	*80.0 (17.9)*	*76.7*
CRF[f]							
General fatigue score	***T0***	*17.6 (5.3)*	*18.0*	*18.6 (5.2)*	*17.5*	*16.6 (5.7)*	*18.0*
	T1	*14.9 (6.3)*	*14.0*	*13.9 (5.1)*	*14.0*	*16.1 (7.7)*	*14.0*
	T2	*14.5 (6.2)*	*15.0*	*15.2 (6.1)*	*15.0*	*13.8 (7.0)*	*13.0*
	T3	*12.8 (6.2)*	*12.0*	*13.8 (7.2)*	*11.0*	*11.8 (5.6)*	*13.0*
Physical fatigue	***T0***	*18.5 (6.0)*	*17.0*	*19.1 (6.7)*	*18.5*	*17.7 (5.5)*	*17.0*
	T1	*14.0 (7.1)*	*15.0*	*12.3 (7.4)*	*9.5*	*16.0 (6.6)*	*17.0*
	T2	*12.9 (5.8)*	*12.0*	*12.0 (4.9)*	*11.0*	*14.0 (7.3)*	*16.0*
	T3	*11.6 (5.9)*	*9.5*	*11.0 (6.4)*	*7.0*	*12.2 (5.9)*	*12.0*

[a]T0 = baseline, T1 = mid-chemotherapy, T2 = after completion of chemotherapy, T3 = one year FU; [b]dominant hand; [c]MEDAS; [d]NRS-2002; [e]EORTC QLQ-C30; [f] MFI-20

Discussion

This pilot trial investigating the safety, acceptance and feasibility of a combined exercise and nutrition intervention during and after first-line chemotherapy in ovarian cancer patients demonstrated that patients were motivated to enroll and adhere to the program and that the exercise and nutrition intervention as early as during chemotherapy was save for this vulnerable patient group.

Patients with ovarian cancer are not only seriously ill, but undergo exhausting abdominal surgery and chemotherapy. Therefore, it is not surprising that the majority of patients with ovarian cancer report an inactive lifestyle and do not meet recommendations after diagnosis and treatment (28). Common side-effects of ovarian cancer and its treatment are muscle wasting and malnourishment. Both can be targeted by nutrition and exercise programs (6). Consequently, it can be assumed that ovarian cancer patients may benefit from an individualized exercise and/or nutrition intervention to an even greater extent than already demonstrated in breast and colon cancer patients (8, 9).

As ovarian cancer is often diagnosed at a late stage of disease and the median age at initial diagnosis is 62 years, it was anticipated that the recruitment and completion rate would be lower than that reported in studies including cancer patients diagnosed at an early stage or at a younger age (29). In our randomized feasibility trial recruitment rate was 25.0%, which is in line with recruitment rates of 16 - 63% and a retention rates of 70 - 100 stated in a recent review (14). Reported reasons for refusal of participation were symptoms, illness and exhaustion (14). These reasons hold true for our study as well. In addition, many patients declined to take part due to a distant residence, which was also the reason for not undergoing

chemotherapy at UKE, thus requiring separate trips to UKE for the study. Others did not participate because they were not willing to risk randomization into the control group. Patients who consented to participate in the study showed a high commitment, and only two patient(s) dropped out, leading to a completion rate of 73.3%. Adherence to the exercise intervention in terms of completed counseling sessions was higher than reported by a systematic review (14) with 83.7% for exercise intervention (phase I, 83.2%; phase II, 85.1%) and 76.8% for nutrition intervention (phase I, 92.3%; phase II, 59.6%). There were no adverse events associated with the intervention documented throughout the trial. Therefore, this study to our knowledge is the first to show that a combined nutrition and exercise intervention in ovarian cancer patients during and after first-line chemotherapy is feasible, safe and accepted.

To date few RCTs on exercise and/or nutrition in ovarian cancer exist and those few available mainly recruited patients after completion of treatment. Thus, these studies in principle predominantly recruited patients in remission free of progression. The WALC (30) trial, a six months exercise intervention in ovarian cancer, for example, included patients up to four years following initial diagnosis and the patients sample was therefore heterogeneous. The REACT study (9) including a few ovarian cancer patients among other cancer survivors used a 12 week exercise intervention without combined nutrition counselling shortly after completion of treatment. The currently ongoing LIVES study (15) also investigates the effect of a 24 months lifestyle intervention after treatment for ovarian cancer patients. Only the ongoing PADOVA study offers a combined exercise and nutrition intervention during first-line chemotherapy (31). However, the exercise and nutrition intervention is limited to the duration of chemotherapy only, whereas our study aims to start with chemotherapy and to continue well into ovarian cancer survivorship to ensure maintenance of the recommended lifestyle.

Previous studies on post-diagnosis exercise in ovarian cancer have shown that exercise lead to improvements in HRQOL, fatigue and additional physical and psychological outcomes (14). The few feasibility studies on exercise and/or nutrition interventions during first-line chemotherapy reported increased moderate to strenuous physical activity to be correlated with improvements in quality of life (32-34) and physical functioning (e.g. muscular strength, 6-minute walking test) (32-34) as well as reduced fatigue (33, 34). Our study showed similar tendencies for the 6-minute walking test, physical fatigue as well as global health. However, these results are descriptive only and no RCT exists to prove effectiveness of a combined exercise and nutrition intervention during and/or after primary care in ovarian cancer patients.

Conclusion

To date guidelines on care programs for ovarian cancer patients in Germany are based solely on expert consensus (35). Although aftercare programs for ovarian cancer survivors to improve HRQoL and CRF are recommended, current treatment guidelines include a further 15-24 months maintenance therapy after completion of chemotherapy, which renders it difficult for patients to receive inpatient rehabilitation after first-line therapy (35). Therefore, of about a third of patients that survive for more than eight years up to 70% will suffer long-term sequelae of cancer treatment, including reduced HRQoL and CRF (36). A home-based personalized standardized care intervention program beginning already during chemotherapy and continued post-treatment will enable the majority of patients to participate and further empower them to achieve long-term adherence to recommended exercise and nutrition behavior.

Thus following this pilot study, it will be important to conduct a multicenter RCT to 1) provide evidence of the effectiveness of a personalized combined exercise and nutrition intervention during adjuvant and maintenance chemotherapy compared to standard care to improve HRQoL and reduce CRF in ovarian cancer patients and 2) to establish an exercise and nutrition program ready for implementation into routine clinical practice for ovarian cancer patients.

Data Statement

Data cannot be made publicly available for legal reasons. Due to data privacy rules and according to German law (§ 75 SGB X) access to the data is granted only to responsible scientific personnel at UKE, Hamburg, Germany within the framework of the respective research project. It is not permitted to give third parties access to the data without a proposal approved by the principal investigator.

Authors Statement

TM, JvG, SP, KHS, BS, BCZ, and JCC contributed to study conception and design. TM, MHB, JvG, and ZS contributed to data and sample collection. JCC obtained funding for the pilot project. TM, MHB and JCC drafted the first version of the manuscript. MHB is responsible for data management of pilot study. HB performed the sample size calculations and supervised randomization process. All authors revised the protocol critically for important intellectual content and read and approved the final version of the protocol.

Conflict of interest

The authors declare no conflict of interest.

Funding

The pilot phase of the BENITA study has been funded for 2 years by the Hamburger Krebsgesellschaft e.V. (grant number: not applicable). There is no pharmaceutical industry funding and there are no commercial interests.

Acknowledgement

We would like to thank all patients who participated in the BENITA study as well as Andrea Krull (Verein Eierstockkrebs Deutschland e.V.) for her helpful advice on the study plan.

The authors would also like to thank Professor Dr S C Bischoff of the University Hohenheim for providing them with the validated German version of the MEDAS questionnaire.

Figure 1: Flow diagram of participant recruitment and randomization

Figure 2: Descriptive results of in-person assessments at baseline (T0), mid-chemotherapy (T1), after completion of chemotherapy (T2) and one year follow-up (T3) by group assignment

Figure 3: Descriptive results (continued) of in-person assessments at baseline (T0), mid-chemotherapy (T1), after completion of chemotherapy (T2) and one year follow-up (T3) by group assignment

Literature

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. European journal of cancer (Oxford, England : 1990). 2013;49(6):1374-403.
2. Krebs in Deutschland 2015/2016. Berlin: Robert Koch-Institute; 2019.
3. Rutten IJ, van Dijk DP, Kruitwagen RF, Beets-Tan RG, Olde Damink SW, van Gorp T. Loss of skeletal muscle during neoadjuvant chemotherapy is related to decreased survival in ovarian cancer patients. Journal of cachexia, sarcopenia and muscle. 2016;7(4):458-66.
4. Fearon KC, Barber MD, Moses AG. The cancer cachexia syndrome. Surgical oncology clinics of North America. 2001;10(1):109-26.
5. Gingrich A, Volkert D, Kiesswetter E, Thomanek M, Bach S, Sieber CC, et al. Prevalence and overlap of sarcopenia, frailty, cachexia and malnutrition in older medical inpatients. BMC geriatrics. 2019;19(1):120.
6. Fearon KC. Cancer cachexia: developing multimodal therapy for a multidimensional problem. European journal of cancer (Oxford, England : 1990). 2008;44(8):1124-32.
7. Johns DJ, Hartmann-Boyce J, Jebb SA, Aveyard P. Diet or exercise interventions vs combined behavioral weight management programs: a systematic review and meta-analysis of direct comparisons. J Acad Nutr Diet. 2014;114(10):1557-68.
8. McNeely ML, Campbell KL, Rowe BH, Klassen TP, Mackey JR, Courneya KS. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2006;175(1):34-41.
9. Kampshoff CS, Chinapaw MJ, Brug J, Twisk JW, Schep G, Nijziel MR, et al. Randomized controlled trial of the effects of high intensity and low-to-moderate intensity exercise on physical fitness and fatigue in cancer survivors: results of the Resistance and Endurance exercise After ChemoTherapy (REACT) study. BMC Med. 2015;13:275.
10. Blanchard CM, Courneya KS, Stein K. Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer Society's SCS-II. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(13):2198-204.
11. McCullough ML, Patel AV, Kushi LH, Patel R, Willett WC, Doyle C, et al. Following cancer prevention guidelines reduces risk of cancer, cardiovascular disease, and all-cause mortality. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2011;20(6):1089-97.
12. Smits A, Smits E, Lopes A, Das N, Hughes G, Talaat A, et al. Body mass index, physical activity and quality of life of ovarian cancer survivors: time to get moving? Gynecologic oncology. 2015;139(1):148-54.
13. Stevinson C, Faught W, Steed H, Tonkin K, Ladha AB, Vallance JK, et al. Associations between physical activity and quality of life in ovarian cancer survivors. Gynecologic oncology. 2007;106(1):244-50.
14. Jones TL, Sandler CX, Spence RR, Hayes SC. Physical activity and exercise in women with ovarian cancer: A systematic review. Gynecol Oncol. 2020;158(3):803-11.
15. Thomson CA, Crane TE, Miller A, Garcia DO, Basen-Engquist K, Alberts DS. A randomized trial of diet and physical activity in women treated for stage II-IV ovarian cancer: Rationale and design of the Lifestyle Intervention for Ovarian Cancer Enhanced Survival (LIVES): An NRG Oncology/Gynecologic Oncology Group (GOG-225) Study. Contemp Clin Trials. 2016;49:181-9.
16. Stelten S, Hoedjes M, Kenter GG, Kampman E, Huijsmans RJ, van Lonkhuijzen LR, et al. Rationale and study protocol of the Physical Activity and Dietary intervention in women with OVArian cancer (PADOVA) study: a randomised controlled trial to evaluate effectiveness of a tailored exercise and dietary intervention on body composition, physical function and fatigue in women with ovarian cancer undergoing chemotherapy. BMJ open. 2020;10(11):e036854.

17. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The Physical Activity Guidelines for Americans. Jama. 2018;320(19):2020-8.
18. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995;39(3):315-25.
19. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clinical nutrition (Edinburgh, Scotland). 2003;22(3):321-36.
20. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. Journal of clinical epidemiology. 2003;56(12):1163-9.
21. Agarwala P, Salzman SH. Six-Minute Walk Test: Clinical Role, Technique, Coding, and Reimbursement. Chest. 2020;157(3):603-11.
22. Butte NF, Ekelund U, Westerterp KR. Assessing physical activity using wearable monitors: measures of physical activity. Medicine and science in sports and exercise. 2012;44(1 Suppl 1):S5-12.
23. Cotogni P, Monge T, Fadda M, De Francesco A. Bioelectrical impedance analysis for monitoring cancer patients receiving chemotherapy and home parenteral nutrition. BMC cancer. 2018;18(1):990.
24. Maurer T, von Grundherr J, Patra S, Jaeger A, Becher H, Schmalfeldt B, et al. An exercise and nutrition intervention for ovarian cancer patients during and after first-line chemotherapy (BENITA study): a randomized controlled pilot trial. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2020;30(4):541-5.
25. Hebestreit K, Yahiaoui-Doktor M, Engel C, Vetter W, Siniatchkin M, Erickson N, et al. Validation of the German version of the Mediterranean Diet Adherence Screener (MEDAS) questionnaire. BMC Cancer. 2017;17(1):341.
26. Brauns H. SS, Steinmann S. The CASMIN Educational Classification in International Comparative. Research. In: Hoffmeyer-Zlotnik J.H.P. WCe, editor. Boston, MA.: Springer; 2003.
27. Prat J. FIGO's staging classification for cancer of the ovary, fallopian tube, and peritoneum: abridged republication. Journal of gynecologic oncology. 2015;26(2):87-9.
28. Mizrahi D, Naumann F, Broderick C, Samara J, Ryan M, Friedlander M. Quantifying physical activity and the associated barriers for women with ovarian cancer. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2015;25(4):577-83.
29. Sheill G, Guinan E, Brady L, Hevey D, Hussey J. Exercise interventions for patients with advanced cancer: A systematic review of recruitment, attrition, and exercise adherence rates. Palliative & supportive care. 2019;17(6):686-96.
30. Zhou Y, Gottlieb L, B. C, Li F, Ercolano EA, Harrigan M, et al. Randomized trial of exercise on quality of life and fatigue in women diagnosed with ovarian cancer: The Women's Activity and Lifestyle Study in Connecticut (WALC). . Journal of Clinical Oncology. 2015 33(15_suppl):9505-.
31. Stelten S, Hoedjes M, Kenter GG, Kampman E, Huijsmans RJ, van Lonkhuijzen LR, et al. Rationale and study protocol of the Physical Activity and Dietary intervention in women with OVArian cancer (PADOVA) study: a randomised controlled trial to evaluate effectiveness of a tailored exercise and dietary intervention on body composition, physical function and fatigue in women with ovarian cancer undergoing chemotherapy. BMJ Open. 2020;10(11):e036854.
32. Newton MJ, Hayes SC, Janda M, Webb PM, Obermair A, Eakin EG, et al. Safety, feasibility and effects of an individualised walking intervention for women undergoing chemotherapy for ovarian cancer: a pilot study. BMC Cancer. 2011;11:389.
33. Mizrahi D, Broderick C, Friedlander M, Ryan M, Harrison M, Pumpa K, et al. An Exercise Intervention During Chemotherapy for Women With Recurrent Ovarian Cancer: A Feasibility Study. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2015;25(6):985-92.

34. von Gruenigen VE, Frasure HE, Kavanagh MB, Lerner E, Waggoner SE, Courneya KS. Feasibility of a lifestyle intervention for ovarian cancer patients receiving adjuvant chemotherapy. Gynecologic oncology. 2011;122(2):328-33.

35. Wagner U, Harter P, Hilpert F, Mahner S, Reuß A, du Bois A, et al. S3-Guideline on Diagnostics, Therapy and Follow-up of Malignant Ovarian Tumours: Short version 1.0 - AWMF registration number: 032/035OL, June 2013. Geburtshilfe und Frauenheilkunde. 2013;73(9):874-89.

36. Joly F, Ahmed-Lecheheb D, Kalbacher E, Heutte N, Clarisse B, Grellard JM, et al. Long-term fatigue and quality of life among epithelial ovarian cancer survivors: a GINECO case/control VIVROVAIRE I study. Annals of oncology : official journal of the European Society for Medical Oncology. 2019;30(5):845-52.

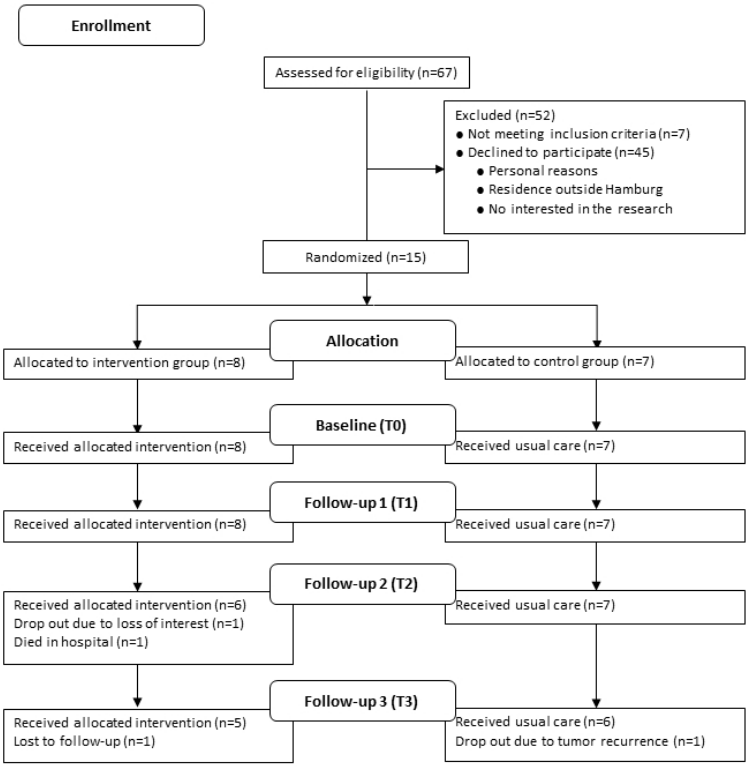

Figure 1: Flow diagram of participant recruitment and randomization

190x275mm (96 x 96 DPI)

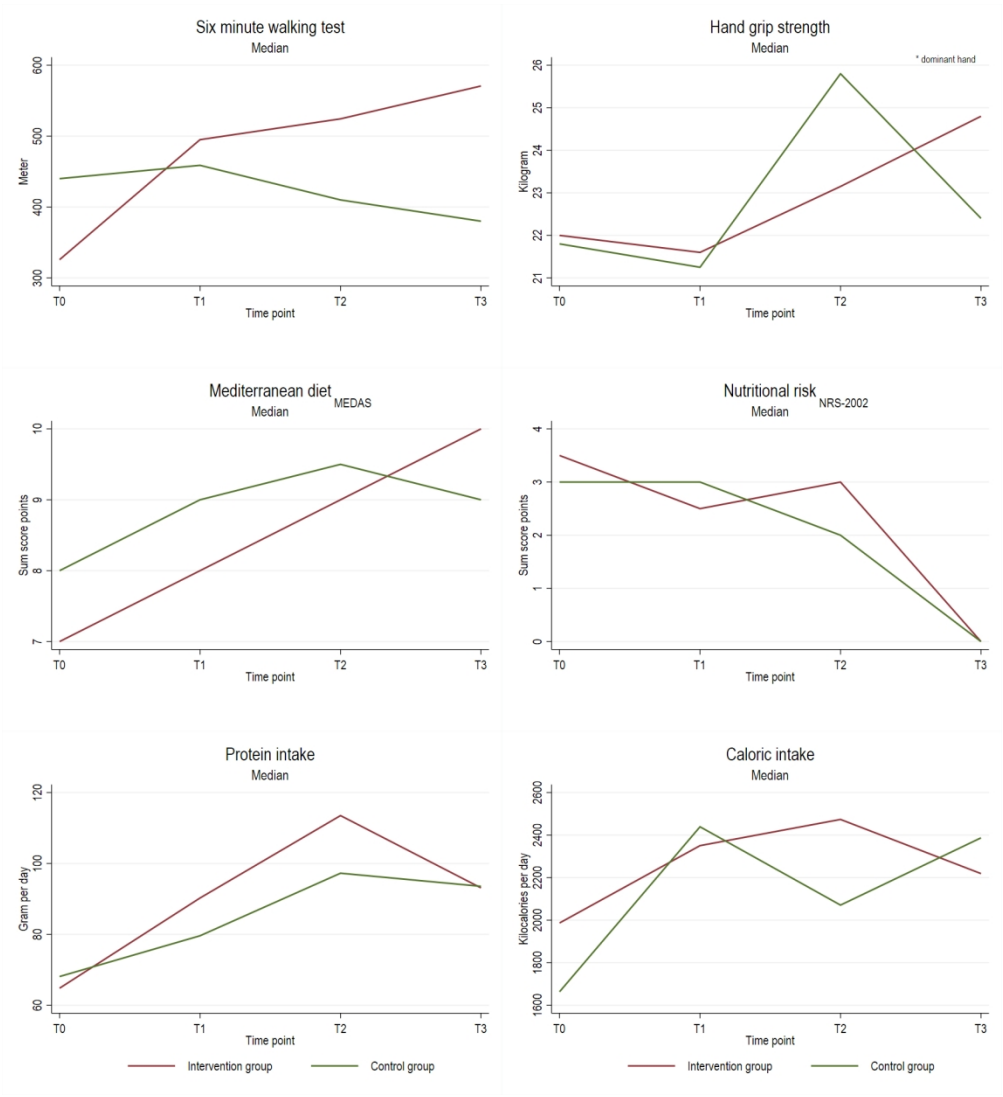

Figure 2: Descriptive results of in-person assessments at baseline (T0), mid-chemotherapy (T1), after completion of chemotherapy (T2) and one year follow-up (T3) by group assignment

632x688mm (72 x 72 DPI)

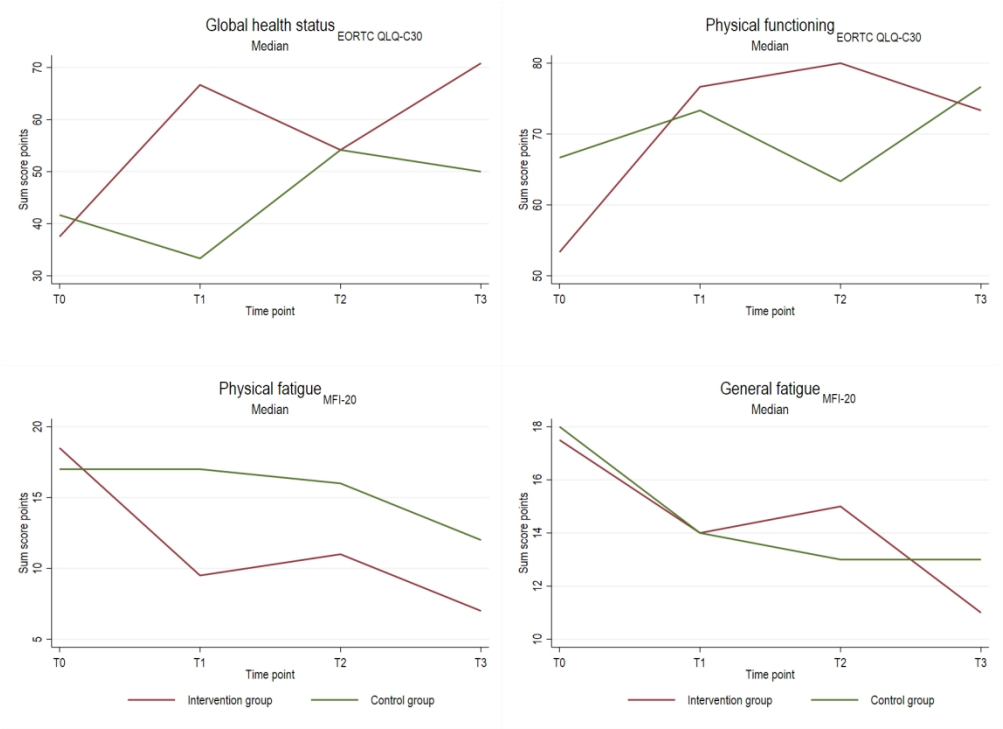

Figure 3: Descriptive results (continued) of in-person assessments at baseline (T0), mid-chemotherapy (T1), after completion of chemotherapy (T2) and one year follow-up (T3) by group assignment

632x459mm (72 x 72 DPI)

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of study as randomised pilot or feasibility trial	p.1, l. 1
Authors *	Contact details for the corresponding author	p.1, ll.21-28
Trial design	Description of pilot trial design (eg, parallel, cluster)	p.2, ll.11-12
Methods		
Participants	Eligibility criteria for participants and the settings where the pilot trial was conducted	p.2, ll.17-19
Interventions	Interventions intended for each group	p.2, ll.20-21
Objective	Specific objectives of the pilot trial	p.2, ll.8-10
Outcome	Prespecified assessment or measurement to address the pilot trial objectives**	p.3, ll.1-5
Randomization	How participants were allocated to interventions	p.2, ll.12-13
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	p.2, ll.13-16
Results		
Numbers randomized	Number of participants screened and randomised to each group for the pilot trial objectives**	p.3, l.7
Recruitment	Trial status†	
Numbers analysed	Number of participants analysed in each group for the pilot objectives**	p.3, l.7
Outcome	Results for the pilot objectives, including any expressions of uncertainty**	p.3, ll.8-12
Harms	Important adverse events or side effects	p.3, l.11
Conclusions	General interpretation of the results of pilot trial and their implications for the future definitive trial	p.3, ll.12-13
Trial registration	Registration number for pilot trial and name of trial register	p.3, ll.17-18
Funding	Source of funding for pilot trial	p.3, l.19

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

**this item is specific to conference abstracts*

***Space permitting, list all pilot trial objectives and give the results for each. Otherwise, report those that are a priori agreed as the most important to the decision to proceed with the future definitive RCT.*

†For conference abstracts.

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	5-6
	2b	Specific objectives or research questions for pilot trial	6
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	6-7
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	7-9
	4c	How participants were identified and consented	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-9
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	7-9
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	-
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	-
Sample size	7a	Rationale for numbers in the pilot trial	-
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	-
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	-
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	-

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6-7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	-
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	10
	13b	For each group, losses and exclusions after randomisation, together with reasons	10
Recruitment	14a	Dates defining the periods of recruitment and follow-up	10
	14b	Why the pilot trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	11
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	10-14
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	-
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
	19a	If relevant, other important unintended consequences	-
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	17-19
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	-
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	19
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	19
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	3, 6
Protocol	24	Where the pilot trial protocol can be accessed, if available	-
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	3, 21
	26	Ethical approval or approval by research review committee, confirmed with reference number	6

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4-5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Doesn't apply
Participants	4a	Eligibility criteria for participants	4-5
	4b	Settings and locations where the data were collected	4-5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6-7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Doesn't apply
Sample size	7a	How sample size was determined	Described in study protocol
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Doesn't apply
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Described in study protocol
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Doesn't apply
	11b	If relevant, description of the similarity of interventions	Doesn't apply
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6-7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6-7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7-8
	13b	For each group, losses and exclusions after randomisation, together with reasons	7-8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the trial ended or was stopped	Doesn't apply
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	No inferential statistics (feasibility)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Doesn't apply
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	13-16
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	No adverse events
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	17 ff
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	18-19
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	Published (IJGC)
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	21

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.