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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)

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3 **A randomized controlled trial testing the feasibility of an exercise and nutrition intervention**
4
5 **for ovarian cancer patients during and after first-line chemotherapy (BENITA-study)**
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59

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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

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2
3 the study (completion rate, 73.3%), one patient dropped-out due to loss of interest, one due
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5 to poor health, one was lost to follow-up and one patient died.
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9 **Conclusion:** The BENITA study demonstrated the safety and acceptance of an exercise and
10
11 nutrition intervention integrated into first line therapy and follow-up care of ovarian cancer.
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13 A large multicenter RCT is planned to investigate the effectiveness of the intervention on
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15 HRQoL, CRF, and survival and to establish means of implementation into oncology guidelines
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17 and clinic routine.
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22 **Trial registration:** The study was registered at the German study registry for clinical studies
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24 (DRKS00013231).
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30 31 **Strength and limitations**

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

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3 prevent deterioration due to treatment as well as support maintenance of lifestyle changes
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5 thereafter.
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9 It was the aim of this study to determine the feasibility of a combined exercise and nutrition
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11 intervention for ovarian cancer patients during and after first-line chemotherapy. Main
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13 endpoints of the pilot trial were recruitment rate, adherence, completion rate as well as
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15 adverse events (safety). Furthermore, in-person assessments as planned for a main trial were
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17 conducted (e.g. HRQoL, CRF, muscular strength and quality, nutrition habits and quality) to
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19 investigate acceptance and safety in ovarian cancer patients.
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28 **Methods**

29 ***Study design, setting and participants***

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31 This pilot study was a monocentric 1:1 RCT with an intervention (IG) and a control group (CG).
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33 The ethics committee of the Faculty of Medicine at Hamburg University approved the study
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35 protocol. The trial was registered at the German Study Registry for Clinical Studies
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37 (DRKS00013231). Participants were recruited from the department of Gynecology at the
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39 University Medical Center Hamburg Eppendorf (UKE), Germany at diagnosis. Eligibility criteria
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41 included women ≥ 18 years of age, diagnosed with ovarian cancer, tubal cancer, or peritoneal
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43 cancer and primary or interval debulking, scheduled but not started adjuvant or neoadjuvant
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45 chemotherapy, and sufficient German language skills. Exclusion criteria were an Eastern
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47 Cooperative Oncology Group (ECOG) status of two or worse, any physical or mental condition
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49 that would hinder execution or completion of the training program and study procedures, a
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3 private engagement in exercise training above the WHO recommendation of 150 minutes of
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5 moderate-intensity activity per week (15), or a diagnosis of an eating disorder.
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11 ***Patient and public involvement***

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

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30 Two gynecologists identified and approached participants meeting inclusion criteria. After
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32 written informed consent, patients were randomized into the intervention group (IG) to
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34 receive a 12-months exercise and nutrition program or the control group (CG) to receive usual
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36 care. Group allocation was performed by a statistician not involved in data collection.
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38 Information on group allocation was conveyed to the study coordination responsible for
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40 making an appointment with the patients for the baseline assessment.
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45 In-person assessments were conducted independent of study arm at baseline (T0), mid-
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47 chemotherapy (T1), after completion of chemotherapy (T2), and at one-year follow-up (T3).
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49 Assessments include HRQoL (European Organisation for Research and Treatment of Cancer
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51 (EORTC)-QLQ-C30 (16) (16), CRF (Multidimensional Fatigue Inventory (MFI-20)) (17),
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53 nutritional risk (Nutritional Risk Score (NRS)-2002) (18), physical activity (Short Questionnaire
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55 to Assess Health enhancing physical activity (SQUASH)) (19), performance diagnostics
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57 including six-minute walk test (20), hand grip strength (Kern MAP 80k1) (21), and body
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3 composition (bioelectric impedance analysis (BIA), “AKERN BIA 101 Anniversary”) (22). A
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5 detailed overview on scheduled in-person assessments is described elsewhere (23). Safety of
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7 the program was analyzed through adverse events linked to the intervention during all phases
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9 of the study. All analyses were performed using STATA MP in version 16.
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17 ***Intervention***

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20 Participants received personalized exercise and nutrition programs and counselling that were
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22 tailored to different phases of patient’s treatment and recovery as well as individual needs
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24 throughout the trial. In both phases of the exercise intervention patients are given instructions
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26 and encouraged to participate in a daily 15-30 minute home-based training that includes
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28 endurance, resistance, and balance exercises to be performed in gradual increments.
29
30 Exercises using abdominal muscles will not be included till full recovery from surgery. The
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32 nutritional intervention in phase I aimed to reduce malnutrition risk by increasing protein and
33
34 calorie intake. In phase II (weeks 19-52) after chemotherapy, nutrition counselling focused on
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36 the Mediterranean diet, shown to reduce cancer risk. To monitor adherence and progress in
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38 phase I, participants received a weekly telephone call by a sports scientist, and triweekly by a
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40 nutritionist. In phase II patients received monthly counseling by telephone or in person. The
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42 intervention is described in more detail elsewhere (23).
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54 ***Measures***

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57 The primary objectives of the pilot study were (1) to obtain estimates of recruitment rate,
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59 completion rate, as well as investigate reasons for study termination, (2) to investigate patient
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3 adherence to the sport and nutrition program, (3) to determine intervention safety in terms
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5 of side effects especially during active treatment, as well as its practicability and acceptance.
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8 Recruitment rate was defined as the ratio of patients eligible to participate and patients who
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10 signed informed consent. Completion rate was defined as the ratio of patients who signed
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12 informed consent and those who completed the 12 months intervention. General adherence
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14 to the intervention was defined as the ratio of planned and completed interventions,
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16 adherence to the sports program was further assessed using exercise diaries filled out every
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18 week until week 18 and once a months until 12 months follow-up. Adherence to the nutrition
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20 intervention in phase I was described in terms of changes in protein and caloric intake
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22 compared to baseline. During phase II adherence to the nutrition intervention was interpreted
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24 in terms of changes in MEDAS (Mediterranean Diet Adherence Screener) score points
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26 between T0 and T3 (24).
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37 **Results**

38 *39 Characteristics and feasibility*

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43 Of 67 patients with initial diagnosis of ovarian cancer from April 2018 to Sept 2019 screened
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45 for eligibility, 60 patients met inclusion criteria and were invited into the study. 45 refused to
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47 participate in the study. Main reasons were personal reasons, residence outside of Hamburg,
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49 not willing to be randomized and no interest in the research. Fifteen patients signed informed
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51 consent (recruitment rate, 25.0%) and were randomized into IG (n=8) and CG (n=7). Eleven
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53 participants completed the study (completion rate, 73.3%), one patient dropped-out due to
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55 loss of interest, one patient due to poor health (recurrence), one patient was lost to follow-
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3 up (could not be reached via phone or mail) and one patient died. Fig. 1 provides flow of
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5 participants through the study.
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9 Table 1 summarizes the baseline characteristics of participants by group assignment. The
10
11 mean age of the participants was 56.5 ± 14.4 years ranging from 21 to 77 years, with an
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13 average of 33.9 ± 17.0 days since initial diagnosis. The majority (73.3%) of patients was
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15 diagnosed as having advanced stage disease. After surgery, eight patients had no residual
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17 tumor, five patients' tumors were resected to smaller than 1 centimeter and two patients'
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19 tumors had residual tumor larger than 1cm.
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Table 1: Baseline characteristics of participants by group assignment

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

^aCASMIN classification (25); ^bSQUASH physical activity questionnaire (19); ^cFIGO classification (26)

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3 All 15 participants enrolled in the study completed T0 and T1 assessments. Between T1 and
4
5 T2 one patient in the intervention group died and another dropped out due to loss of interest.
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8 The remaining 13 patients completed the T1 assessment. Between T2 and T3 a patient of the
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10 intervention group was lost to follow-up and a patient of the control group dropped-out due
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12 to a recurrence. All eleven patients still enrolled in the study completed the final assessment.
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14
15 Table 2 provides detailed information on adherence to different assessments and time points
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17 by group assignment. Adherence to the sports intervention in terms of completed
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19 intervention sessions (face-to-face, by telephone) was 83.7% for exercise intervention (phase
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21 I, 83.2%; phase II, 85.1%) and 76.8% for nutrition intervention (phase I, 92.3%; phase II, 59.6%).
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25
26 Adherence to the exercise and nutrition program is shown in table 3. During phase I five out
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28 of eight patients documented their weekly home-based exercise for a total of 14-18 weeks.
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30 One patient documented their daily home-based exercise for ten weeks, another patient
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32 dropped out after six weeks, and one patient died during phase I without documentation of
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34 home-based training. Patients trained between 90 and 180 minutes per week. In phase II three
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36 patients documented their exercise for 30-34 weeks. Two patients stopped their
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38 documentation after 12 and 4 weeks, respectively. Two patients dropped out of the study and
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40 one patient did not continue to document their daily practice, but remained in the study. In
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42 phase II most patients trained for up to 90 minutes per week.
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49 Adherence to the nutrition intervention in phase I was interpreted in terms of increase in
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51 protein and caloric intake. Patients of the intervention group increased their protein intake
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53 from 65.8 gram (g) per day at baseline (T0) to 107.9g per day at T2. The calorie intake increased
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55 from 1860g per day at T0 to 2389g per day at T2. In phase II adherence to the nutrition
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57 intervention based on the MEDAS score showed that patients of the intervention group
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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

			<i>All participants</i>		<i>Intervention group</i>		<i>Control group</i>	
			<i>N^a</i>	<i>%</i>	<i>N^a</i>	<i>%</i>	<i>N^a</i>	<i>%</i>
Sport assessment	<i>Performance diagnostics</i>	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
	<i>Accelerometer</i>	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

^anumber of participants assessed/number eligible

^bT0 = 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

^adied in hospital; ^bdropped out; ^clost to follow-up, ^dMEDAS 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

		<i>All participants</i>		<i>Intervention group</i>		<i>Control group</i>	
		<i>Mean (SD)</i>	<i>Median</i>	<i>Mean (SD)</i>	<i>Median</i>	<i>Mean (SD)</i>	<i>Median</i>
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
Mediterranean 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 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

^aT0 = baseline, T1 = mid-chemotherapy, T2 = after completion of chemotherapy, T3 = one year FU;

^bdominant hand; ^cMEDAS; ^dNRS-2002; ^eEORTC QLQ-C30; ^fMFI-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

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3 completed counseling sessions was higher than reported by previous studies (10) with 83.7%
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5 for exercise intervention (phase I, 83.2%; phase II, 85.1%) and 76.8% for nutrition intervention
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7 (phase I, 92.3%; phase II, 59.6%). There were no adverse events associated with the
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9 intervention documented throughout the trial. Therefore, this study to our knowledge is the
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11 first to show that a combined nutrition and exercise intervention in ovarian cancer patients
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13 during and after first-line chemotherapy is feasible, safe and accepted.
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17 To date few RCTs on exercise and/or nutrition in ovarian cancer exist and those few available
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19 mainly recruited patients after completion of treatment. Thus, these studies in principle
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21 predominantly recruited patients in remission free of progression. The WALC (29) trial, a six
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23 months exercise intervention in ovarian cancer, for example, included patients up to four
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25 years following initial diagnosis and the patients sample was therefore heterogeneous. The
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27 REACT study (5) including a few ovarian cancer patients among other cancer survivors used a
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29 12 week exercise intervention without combined nutrition counselling shortly after
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31 completion of treatment. The currently ongoing LIVES study (13) also investigates the effect
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33 of a 24 months lifestyle intervention after treatment for ovarian cancer patients. Only the
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35 ongoing PADOVA study offers a combined exercise and nutrition intervention during first-line
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37 chemotherapy (30). However, the exercise and nutrition intervention is limited to the duration
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39 of chemotherapy only, whereas our study aims to start with chemotherapy and to continue
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41 well into ovarian cancer survivorship to ensure maintenance of the recommended lifestyle.
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51 Previous studies on post-diagnosis exercise in ovarian cancer have shown that exercise lead
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53 to improvements in HRQOL, fatigue and additional physical and psychological outcomes (10).
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55 The few feasibility studies on exercise and/or nutrition interventions during first-line
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57 chemotherapy reported increased moderate to strenuous physical activity to be correlated
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59 with improvements in quality of life (31-33) and physical functioning (e.g. muscular strength,
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2
3 6-minute walking test) (31-33) as well as reduced fatigue (32, 33). Our study showed similar
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5 tendencies for the 6-minute walking test, physical fatigue as well as global health. However,
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7 these results are descriptive only and no RCT exists to prove effectiveness of a combined
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9 exercise and nutrition intervention during and/or after primary care in ovarian cancer
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11 patients.
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17 **Conclusion**

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20 To date guidelines on care programs for ovarian cancer patients in Germany are based solely
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22 on expert consensus (34). Although aftercare programs for ovarian cancer survivors to
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24 improve HRQoL and CRF are recommended, current treatment guidelines include a further
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26 15-24 months maintenance therapy after completion of chemotherapy, which renders it
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28 difficult for patients to receive inpatient rehabilitation after first-line therapy (34). Therefore,
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30 of about a third of patients that survive for more than eight years up to 70% will suffer long-
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32 term sequelae of cancer treatment, including reduced HRQoL and CRF (35). A home-based
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34 personalized standardized care intervention program beginning already during chemotherapy
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36 and continued post-treatment will enable the majority of patients to participate and further
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38 empower them to achieve long-term adherence to recommended exercise and nutrition
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40 behavior.
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47 Thus following this pilot study, it will be important to conduct a multicenter RCT to (1) provide
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49 evidence of the effectiveness of a personalized combined exercise and nutrition intervention
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51 during adjuvant and maintenance chemotherapy compared to standard care to improve
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53 HRQoL and reduce CRF in ovarian cancer patients and (2) to establish an exercise and nutrition
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55 program ready for implementation into routine clinical practice for ovarian cancer patients.
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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.

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21 providing them with the validated German version of the MEDAS questionnaire.
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29 **Figure 1:** Flow diagram of participant recruitment and randomization
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32 **Figure 2:** Descriptive results of in-person assessments at baseline (T0), mid-chemotherapy
33 (T1), after completion of chemotherapy (T2) and one year follow-up (T3) by group assignment
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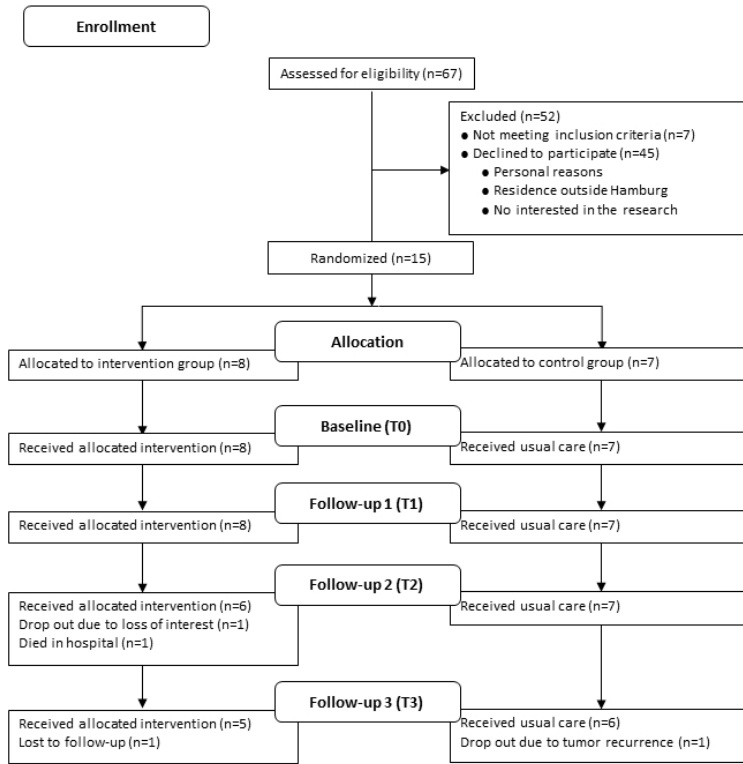


Figure 1: Flow diagram of participant recruitment and randomization

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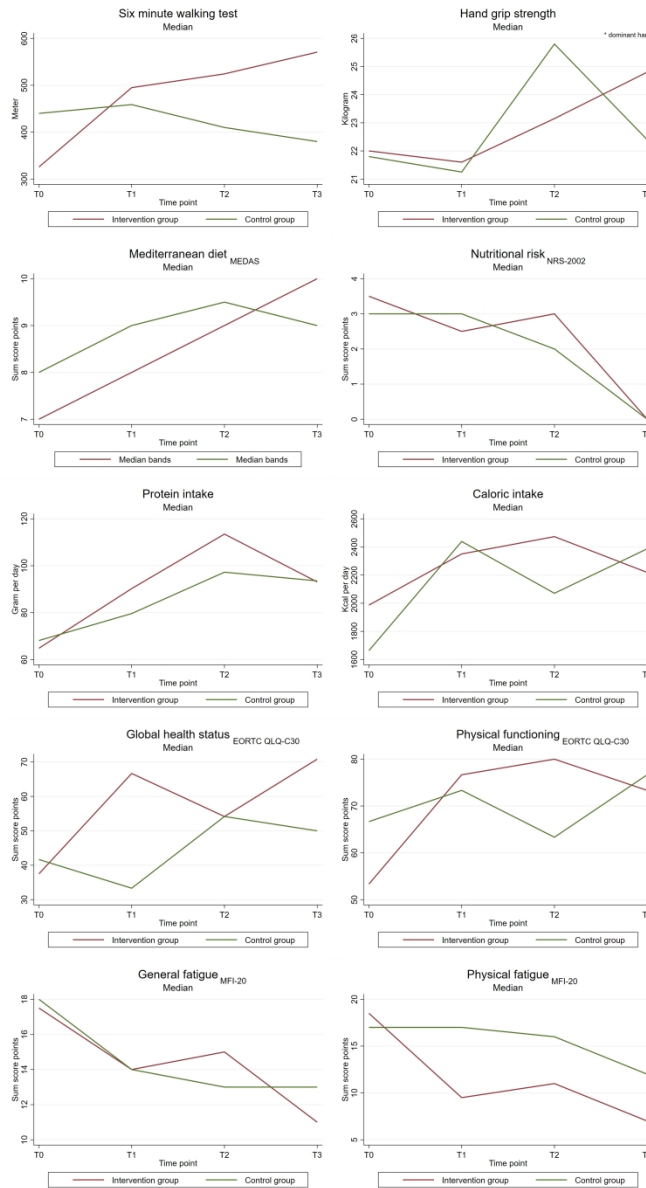


Figure 2: Descriptive results of in-person assessments at baseline (T0), mid-chemotherapy (T1), after completion of chemotherapy (T2) and one year follow-up (T3) by group assignment

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

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1	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Doesn't apply
2				
3		11b	If relevant, description of the similarity of interventions	Doesn't apply
4	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6-7
5		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6-7
6				
7	Results			
8	Participant flow (a	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and	7-8
9	diagram is strongly		were analysed for the primary outcome	
10	recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	7-8
11	Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
12		14b	Why the trial ended or was stopped	Doesn't apply
13	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9
14	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was	8
15			by original assigned groups	
16	Outcomes and	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its	No inferential
17	estimation		precision (such as 95% confidence interval)	statistics
18				(feasibility)
19		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Doesn't apply
20	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	13-16
21			pre-specified from exploratory	
22	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	No adverse
23				events
24	Discussion			
25	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17
26	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	17 ff
27	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	18-19
28	Other information			
29	Registration	23	Registration number and name of trial registry	3
30	Protocol	24	Where the full trial protocol can be accessed, if available	Published
31				(IJGC)
32	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	21

1 *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
2 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.
3 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.
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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)

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3 1 **A randomized controlled trial testing the feasibility of an exercise and nutrition intervention**
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5 2 **for ovarian cancer patients during and after first-line chemotherapy (BENITA-study)**
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50 30 **Keywords:** Ovarian Cancer, Feasibility, Exercise, Nutrition, RCT, during chemotherapy

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3 **1 Abstract**
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6 **2 Objectives:** Advanced ovarian cancer is a severe disease with major side effects caused by
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3 peritoneal carcinomatosis, ascites and gastrointestinal involvement as well as exhaustive
4 treatment like debulking surgery and combination chemotherapy. Two most frequently
5 reported side effects are muscle wasting and malnutrition leading to frailty, decreased health-
6 related quality of life (HRQoL), and cancer related fatigue (CRF). As muscle wasting and
7 malnutrition often commence during first-line chemotherapy and develop progressively into
8 a refractory state, an early intervention is warranted. This pilot study aimed to evaluate the
9 safety and acceptance of a combined exercise and nutrition intervention during and after first-
10 line chemotherapy.

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

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

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

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3 1 **Primary and secondary outcome measures:** Primary outcomes were recruitment rate,
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5 2 adherence to intervention, completion rate, and adverse events. In addition, in-person
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7 3 assessments (e.g. HRQoL, CRF, muscle quality and function, and dietary intake and quality)
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9 4 were conducted at baseline (T0, before chemotherapy), week 9 (T1, mid-chemotherapy),
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11 5 week 19 (T2, after completion of chemotherapy), and after 12 months of intervention (T3).
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16 6 **Results:** Of 60 eligible patients, fifteen patients signed informed consent (recruitment
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18 7 rate=25.0%) and were randomized into IG (n=8) and CG (n=7). Eleven participants completed
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20 8 the study (completion rate, 73.3%), one patient dropped-out due to loss of interest, one due
21
22 9 to poor health, one was lost to follow-up and one patient died.
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27 10 **Conclusion:** The BENITA study demonstrated the safety and acceptance of an exercise and
28
29 11 nutrition intervention integrated into first line therapy and follow-up care of ovarian cancer.
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31 12 A large multicenter RCT is planned to investigate the effectiveness of the intervention on
32
33 13 HRQoL, CRF, and survival and to establish means of implementation into oncology guidelines
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35 14 and clinic routine.
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40 15 **Trial registration:** The study was registered at the German study registry for clinical studies
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42 16 (DRKS00013231).
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45 17 **Funding:** Hamburger Krebsgesellschaft e.V. (grant number: not applicable)
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58 21 **Strength and limitations**
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- 3 1 • The trial uses objective measures to evaluate the feasibility of an exercise and nutrition
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- 5 2 intervention in ovarian cancer patients
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- 8 3 • The exercise and nutrition intervention commences during first-line chemotherapy and
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- 10 4 continues well into ovarian cancer survivorship
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- 12 5 • The exercise and nutrition intervention has been developed by an interdisciplinary team of
- 13
- 14 6 sport and nutrition experts
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- 17 7 • Sport and nutrition experts conducting the intervention and assessing the outcome in both
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- 19 8 groups could not be blinded due to the study design
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23 Introduction

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3 1 Ovarian cancer is the second most common gynecologic cancer in women and has the fifth
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5 2 highest rate of cancer-related deaths for women in Germany (1) with only 43% alive 5 years
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7 3 after diagnosis (2). Major side effects of ovarian cancer and its treatment are cancer cachexia,
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10 4 sarcopenia, frailty, and malnutrition. All are leading to either loss of skeletal muscle mass
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12 5 and/or fat mass of the patient and are associated with decreased health-related quality of life
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14 6 (HRQoL), cancer related fatigue (CRF) and poorer outcome (3, 4). As these syndromes share
15
16 7 similar etiological factors such as reduced food intake, inflammation, hormonal changes,
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18 8 increased energy requirements and reduced physical activity (5) more than one can be present
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20 9 in the same patient at the same time. Hence, a combined intervention consisting of an exercise
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23 10 and nutrition program may be most successful to address these syndromes in patients with
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26 11 advanced cancer (6, 7). Exercise has been shown to significantly improve CRF,
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28 12 cardiorespiratory fitness, HRQoL and even survival in breast and colon cancer (8, 9).
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30 13 Adherence to lifestyle recommendations such as physical activity and nutrition before
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33 14 diagnosis was associated with a significantly higher HRQoL (10) and decreased risk of cancers
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35 15 (11). However, there is paucity of knowledge on post-diagnosis physical activity (PA) or
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38 16 nutrition behavior on prognosis or HRQoL in ovarian cancer patients. In observational studies,
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40 17 ovarian cancer patients with greater post-diagnosis physical activity were found to experience
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43 18 a significantly better HRQoL (12-14). Yet, randomized controlled trials (RCTs) evaluating the
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45 19 benefits of an exercise and nutrition intervention on survival and HRQoL are rare. Two RCTs
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48 20 on bimodal exercise and nutrition programs for ovarian cancer patients are currently ongoing
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50 21 (15, 16). One commences intervention after completion of treatment (15) and one
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53 22 investigates the effect of an intervention during first-line chemotherapy (16). However, no
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56 23 current or previous RCT offers a care program during and after first-line chemotherapy, which
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1 is necessary to prevent deterioration due to treatment as well as support maintenance of
2 lifestyle changes thereafter.

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

10

11 **Methods**

12 ***Study design, setting and participants***

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

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3 1 private engagement in exercise training above the WHO recommendation of 150 minutes of
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5 2 moderate-intensity activity per week (17), or a diagnosis of an eating disorder.
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10 4 ***Patient and public involvement***

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15 5 The ovarian cancer patient organization in Germany (Verein Eierstockkrebs Deutschland e.V.
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17 6 (VED)) represented by its first chairperson, Andrea Krull, has provided input to the project
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19 7 from a patient's perspective, reviewed ethical issues and commented on consent forms.
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26 10 ***Procedure***

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30 11 Two gynecologists identified and approached participants meeting inclusion criteria. After
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32 12 written informed consent, patients were randomized into the intervention group (IG) to
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34 13 receive a 12-months exercise and nutrition program or the control group (CG) to receive usual
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36 14 care. Group allocation was performed by a statistician not involved in data collection.
37
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39 15 Information on group allocation was conveyed to the study coordinator responsible for
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41 16 making an appointment with the patients for the baseline assessment as well as the
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43 17 physiotherapist and nutritionist responsible for the intervention, and outcome assessment in
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45 18 both groups.
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50 19 In-person assessments were conducted independent of study arm at baseline (T0), mid-
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52 20 chemotherapy (T1), after completion of chemotherapy (T2), and at one-year follow-up (T3).
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54 21 Assessments include HRQoL (European Organisation for Research and Treatment of Cancer
55
56 22 (EORTC)-QLQ-C30 (16), CRF (Multidimensional Fatigue Inventory (MFI-20)) (18), nutritional
57
58 23 risk (Nutritional Risk Score (NRS)-2002) (19), physical activity (Short Questionnaire to Assess
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3 1 Health enhancing physical activity (SQUASH)) (20), performance diagnostics including six-
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5 2 minute walk test (21), hand grip strength (Kern MAP 80k1) (22), accelerometer (“Actigraph
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7 3 wGT3X-BT”), and body composition (bioelectric impedance analysis (BIA), “AKERN BIA 101
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9 4 Anniversary”) (23). A detailed overview on scheduled in-person assessments is described
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11 5 elsewhere (24). Safety of the program was analyzed through adverse events linked to the
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13 6 intervention during all phases of the study. All analyses were performed using STATA MP,
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24 9 ***Intervention***

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27 10 Participants received personalized exercise and nutrition programs and counselling that were
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29 11 tailored to different phases of patient’s treatment and recovery as well as individual needs
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31 12 throughout the trial. In both phases of the exercise intervention patients are given instructions
32
33 13 and encouraged to participate in a daily 15-30 minute unsupervised home-based training that
34
35 14 includes endurance, resistance, and balance exercises to be performed in gradual increments.
36
37 15 An exercise catalogue was developed by sports scientists and all exercises were categorized
38
39 16 based on their intensity. Each patient received an individually adapted program consisting of
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41 17 exercises that are part of the catalogue. The program was adjusted each week (phase I) or
42
43 18 every other week (phase II) if needed based on the patients’ individual abilities and current
44
45 19 needs. Exercises using abdominal muscles were not included till full recovery from surgery.
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47 20 The exercise catalogue used to build the exercise programs can be found in the supplements.
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49 21 The nutrition intervention in phase I aimed to reduce malnutrition risk by increasing protein
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51 22 and calorie intake. During chemotherapy, patients were supervised by a nutritionist every
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53 23 three weeks. Those who were in need of an increased calorie and protein intake were advised
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3 1 to consume several smaller meals throughout the day and, if necessary, to increase the use of
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5 2 oils and butter if necessary. Furthermore, patients were educated about suitable types of
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7 3 foods and drinks that are high in protein, fat or energy. If deemed necessary oral sip feeding
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9 4 was suggested. These recommendations were based on the patients' development in weight
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11 5 as well as other body composition parameters derived from BIA measurements (e.g. phase
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13 6 angle, muscle mass). In phase II (weeks 19-52) after chemotherapy, monthly nutrition
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15 7 counselling focused on the Mediterranean diet, shown to reduce malnutrition and cancer risk.
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17 8 To monitor adherence and progress in phase I, participants received a weekly telephone call
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19 9 by a sports scientist, and triweekly by a nutritionist. In phase II patients received monthly
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21 10 counseling by telephone or in person. The intervention is described in more detail elsewhere
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23 11 (24).
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34 **Statistical methods**

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37 14 Recruitment rate was defined as the ratio of patients eligible to participate and patients who
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39 15 signed informed consent. Completion rate was defined as the ratio of patients who signed
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41 16 informed consent and those who completed the 12 months intervention. General adherence
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43 17 to the intervention was defined as the ratio of planned and completed counseling sessions.
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45 18 Adherence to the exercise program was further assessed using exercise diaries filled out every
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47 19 week until week 18 and once a months until 12 months follow-up. Adherence to the nutrition
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49 20 intervention in phase I was described in terms of changes in protein and caloric intake
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51 21 compared to baseline. During phase II adherence to the nutrition intervention was interpreted
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53 22 in terms of changes in MEDAS (Mediterranean Diet Adherence Screener) score points
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55 23 between T0 and T3 (25). Descriptive analyses were conducted for all parameters assessed
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1 during the study. No inferential statistics were used as this feasibility trial was not powered
2 for this purpose.

3 **Results**

4 ***Characteristics and feasibility***

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

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

20

1 **Table 1:** Baseline characteristics of participants by group assignment

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

2 ^aCASMIN classification (26); ^bSQUASH questionnaire (20); ^cFIGO classification (27)

1 All 15 participants enrolled in the study completed T0 and T1 assessments. Between T1 and
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1 All 15 participants enrolled in the study completed T0 and T1 assessments. Between T1 and
2 T2 one patient in the intervention group died and another dropped out due to loss of interest.
3 The remaining 13 patients completed the T1 assessment. Between T2 and T3 a patient of the
4 intervention group was lost to follow-up and a patient of the control group dropped-out due
5 to a recurrence. All eleven patients still enrolled in the study completed the final assessment.
6 Table 2 provides detailed information on adherence to different assessments and time points
7 by group assignment. Adherence to the exercise intervention in terms of completed
8 intervention sessions (face-to-face, by telephone) was 83.7% for exercise intervention (phase
9 I, 83.2%; phase II, 85.1%) and 76.8% for nutrition intervention (phase I, 92.3%; phase II, 59.6%).
10 Adherence to the exercise and nutrition program is shown in table 3. During phase I five out
11 of eight patients documented their weekly home-based exercise for a total of 14-18 weeks.
12 One patient documented their daily home-based exercise for ten weeks, another patient
13 dropped out after six weeks, and one patient died during phase I without documentation of
14 home-based training. Patients trained between 90 and 180 minutes per week. In phase II three
15 patients documented their exercise for 30-34 weeks. Two patients stopped their
16 documentation after 12 and 4 weeks, respectively. Two patients dropped out of the study and
17 one patient did not continue to document their daily practice, but remained in the study. In
18 phase II most patients trained for up to 90 minutes per week.
19 Adherence to the nutrition intervention in terms of caloric and protein intake showed that,
20 patients of the intervention group increased their protein intake from 65.8 gram (g) per day
21 at baseline (T0) to 107.9g per day at T2. The calorie intake increased from 1860kcal per day at
22 T0 to 2389kcal per day at T2. In phase II adherence to the nutrition intervention based on the
23 MEDAS score showed that patients of the intervention group increased their MEDAS scores
24 from a median of 7.0 at baseline to a median of 10 score points at week 52 (T3).

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

4
 5 **Table 2:** Adherence to assessment time points

			<i>All participants</i>		<i>Intervention group</i>		<i>Control group</i>	
			<i>N^a</i>	<i>%</i>	<i>N^a</i>	<i>%</i>	<i>N^a</i>	<i>%</i>
Exercise assessment	<i>Performance diagnostics</i>	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
	<i>Accelerometer^c</i>	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

6 ^anumber of participants assessed/number eligible

7 ^bT0 = baseline, T1 = mid-chemotherapy, T2 = after completion of chemotherapy, T3 = one year
 8 follow-up

9 ^cWorn at home for a week at each time of assessment

10 ^dIncluded 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

^adied in hospital; ^bdropped out; ^clost to follow-up, ^dMEDAS sum score

1 ***Descriptive statistics of in-person assessments***

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6 2 Table 4 and figures 2 and 3 display descriptive results of in-person assessments at different
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9 3 time points by group assignment. Participants who received personalized exercise and
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11 4 nutrition programs increased their median six-minute walk distance from 411 meters (m) at
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14 5 baseline to 475m at T3, whereas members of the control groups decreased their distance from
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16 6 440m to 380m. Patients of the intervention group increased their hand grip strength from
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18 7 22.0 kilogram (kg) to 24.8kg (median), the control group showed a slightly lower increase
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21 8 (from 21.8 to 22.4kg). In terms of nutrition, calorie intake during chemotherapy increased in
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24 9 both IG and CG. The IG showed a larger increase in protein intake from baseline to T1 and T2
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26 10 compared to controls. Adherence to Mediterranean diet or nutritional risk were comparable
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29 11 in IG and CG.

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32 12 The HRQoL increased from baseline to T3 from 37.5 to 70.8 score points in the IG and from
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34 13 41.7 to 50.0 score points in the CG. Both total and physical fatigue decreased from T0 to T3
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36 14 and was somewhat stronger in IG than CG for physical fatigue.

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

		<i>All participants</i>		<i>Intervention group</i>		<i>Control group</i>	
		<i>Mean (SD)</i>	<i>Median</i>	<i>Mean (SD)</i>	<i>Median</i>	<i>Mean (SD)</i>	<i>Median</i>
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
Mediterranean 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

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3 1 ^aT0 = baseline, T1 = mid-chemotherapy, T2 = after completion of chemotherapy, T3 = one year FU;
4 2 ^bdominant hand; ^cMEDAS; ^dNRS-2002; ^eEORTC QLQ-C30; ^f MFI-20

6 3 **Discussion**

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10 4 This pilot trial investigating the safety, acceptance and feasibility of a combined exercise and
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12 5 nutrition intervention during and after first-line chemotherapy in ovarian cancer patients
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14 6 demonstrated that patients were motivated to enroll and adhere to the program and that the
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16 7 exercise and nutrition intervention as early as during chemotherapy was save for this
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18 8 vulnerable patient group.

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22 9 Patients with ovarian cancer are not only seriously ill, but undergo exhausting abdominal
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24 10 surgery and chemotherapy. Therefore, it is not surprising that the majority of patients with
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26 11 ovarian cancer report an inactive lifestyle and do not meet recommendations after diagnosis
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28 12 and treatment (28). Common side-effects of ovarian cancer and its treatment are muscle
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30 13 wasting and malnourishment. Both can be targeted by nutrition and exercise programs (6).
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32 14 Consequently, it can be assumed that ovarian cancer patients may benefit from an
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34 15 individualized exercise and/or nutrition intervention to an even greater extent than already
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36 16 demonstrated in breast and colon cancer patients (8, 9).

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41 17 As ovarian cancer is often diagnosed at a late stage of disease and the median age at initial
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43 18 diagnosis is 62 years, it was anticipated that the recruitment and completion rate would be
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45 19 lower than that reported in studies including cancer patients diagnosed at an early stage or at
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47 20 a younger age (29). In our randomized feasibility trial recruitment rate was 25.0%, which is in
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49 21 line with recruitment rates of 16 - 63% and a retention rates of 70 - 100 stated in a recent
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51 22 review (14). Reported reasons for refusal of participation were symptoms, illness and
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53 23 exhaustion (14). These reasons hold true for our study as well. In addition, many patients
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55 24 declined to take part due to a distant residence, which was also the reason for not undergoing
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1 chemotherapy at UKE, thus requiring separate trips to UKE for the study. Others did not
2 participate because they were not willing to risk randomization into the control group.
3 Patients who consented to participate in the study showed a high commitment, and only two
4 patient(s) dropped out, leading to a completion rate of 73.3%. Adherence to the exercise
5 intervention in terms of completed counseling sessions was higher than reported by a
6 systematic review (14) with 83.7% for exercise intervention (phase I, 83.2%; phase II, 85.1%)
7 and 76.8% for nutrition intervention (phase I, 92.3%; phase II, 59.6%). There were no adverse
8 events associated with the intervention documented throughout the trial. Therefore, this
9 study to our knowledge is the first to show that a combined nutrition and exercise intervention
10 in ovarian cancer patients during and after first-line chemotherapy is feasible, safe and
11 accepted.

12 To date few RCTs on exercise and/or nutrition in ovarian cancer exist and those few available
13 mainly recruited patients after completion of treatment. Thus, these studies in principle
14 predominantly recruited patients in remission free of progression. The WALC (30) trial, a six
15 months exercise intervention in ovarian cancer, for example, included patients up to four
16 years following initial diagnosis and the patients sample was therefore heterogeneous. The
17 REACT study (9) including a few ovarian cancer patients among other cancer survivors used a
18 12 week exercise intervention without combined nutrition counselling shortly after
19 completion of treatment. The currently ongoing LIVES study (15) also investigates the effect
20 of a 24 months lifestyle intervention after treatment for ovarian cancer patients. Only the
21 ongoing PADOVA study offers a combined exercise and nutrition intervention during first-line
22 chemotherapy (31). However, the exercise and nutrition intervention is limited to the duration
23 of chemotherapy only, whereas our study aims to start with chemotherapy and to continue
24 well into ovarian cancer survivorship to ensure maintenance of the recommended lifestyle.

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3 1 Previous studies on post-diagnosis exercise in ovarian cancer have shown that exercise lead
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5 2 to improvements in HRQOL, fatigue and additional physical and psychological outcomes (14).
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8 3 The few feasibility studies on exercise and/or nutrition interventions during first-line
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10 4 chemotherapy reported increased moderate to strenuous physical activity to be correlated
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12 5 with improvements in quality of life (32-34) and physical functioning (e.g. muscular strength,
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14 6 6-minute walking test) (32-34) as well as reduced fatigue (33, 34). Our study showed similar
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16 7 tendencies for the 6-minute walking test, physical fatigue as well as global health. However,
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18 8 these results are descriptive only and no RCT exists to prove effectiveness of a combined
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20 9 exercise and nutrition intervention during and/or after primary care in ovarian cancer
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22 10 patients.
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30 **Conclusion**

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32 13 To date guidelines on care programs for ovarian cancer patients in Germany are based solely
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34 14 on expert consensus (35). Although aftercare programs for ovarian cancer survivors to
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36 15 improve HRQoL and CRF are recommended, current treatment guidelines include a further
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38 16 15-24 months maintenance therapy after completion of chemotherapy, which renders it
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40 17 difficult for patients to receive inpatient rehabilitation after first-line therapy (35). Therefore,
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42 18 of about a third of patients that survive for more than eight years up to 70% will suffer long-
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44 19 term sequelae of cancer treatment, including reduced HRQoL and CRF (36). A home-based
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46 20 personalized standardized care intervention program beginning already during chemotherapy
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48 21 and continued post-treatment will enable the majority of patients to participate and further
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50 22 empower them to achieve long-term adherence to recommended exercise and nutrition
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52 23 behavior.
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3 1 Thus following this pilot study, it will be important to conduct a multicenter RCT to 1) provide
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5 2 evidence of the effectiveness of a personalized combined exercise and nutrition intervention
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7 3 during adjuvant and maintenance chemotherapy compared to standard care to improve
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9 4 HRQoL and reduce CRF in ovarian cancer patients and 2) to establish an exercise and nutrition
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11 5 program ready for implementation into routine clinical practice for ovarian cancer patients.
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18 7 **Data Statement**

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21 8 Data cannot be made publicly available for legal reasons. Due to data privacy rules and
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23 9 according to German law (§ 75 SGB X) access to the data is granted only to responsible
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25 10 scientific personnel at UKE, Hamburg, Germany within the framework of the respective
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27 11 research project. It is not permitted to give third parties access to the data without a proposal
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29 12 approved by the principal investigator.
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37 14 **Authors Statement**

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40 15 TM, JvG, SP, KHS, BS, BCZ, and JCC contributed to study conception and design. TM, MHB,
41
42 16 JvG, and ZS contributed to data and sample collection. JCC obtained funding for the pilot
43
44 17 project. TM, MHB and JCC drafted the first version of the manuscript. MHB is responsible for
45
46 18 data management of pilot study. HB performed the sample size calculations and supervised
47
48 19 randomization process. All authors revised the protocol critically for important intellectual
49
50 20 content and read and approved the final version of the protocol.
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3 **1 Conflict of interest**
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6 2 The authors declare no conflict of interest.
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11 **4 Funding**
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16
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18
19
20 7 funding and there are no commercial interests.
21
22

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27
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31

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34 12 for providing them with the validated German version of the MEDAS questionnaire.
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41 14 **Figure 1:** Flow diagram of participant recruitment and randomization
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44 15 **Figure 2:** Descriptive results of in-person assessments at baseline (T0), mid-chemotherapy
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46 16 (T1), after completion of chemotherapy (T2) and one year follow-up (T3) by group assignment
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50 17 **Figure 3:** Descriptive results (continued) of in-person assessments at baseline (T0), mid-
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52 18 chemotherapy (T1), after completion of chemotherapy (T2) and one year follow-up (T3) by
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54 19 group assignment
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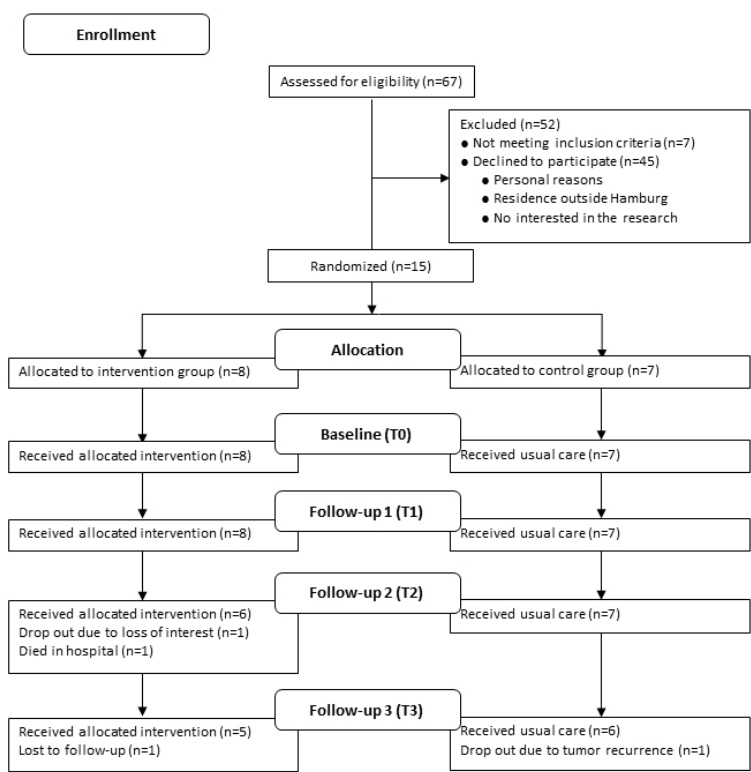


Figure 1: Flow diagram of participant recruitment and randomization
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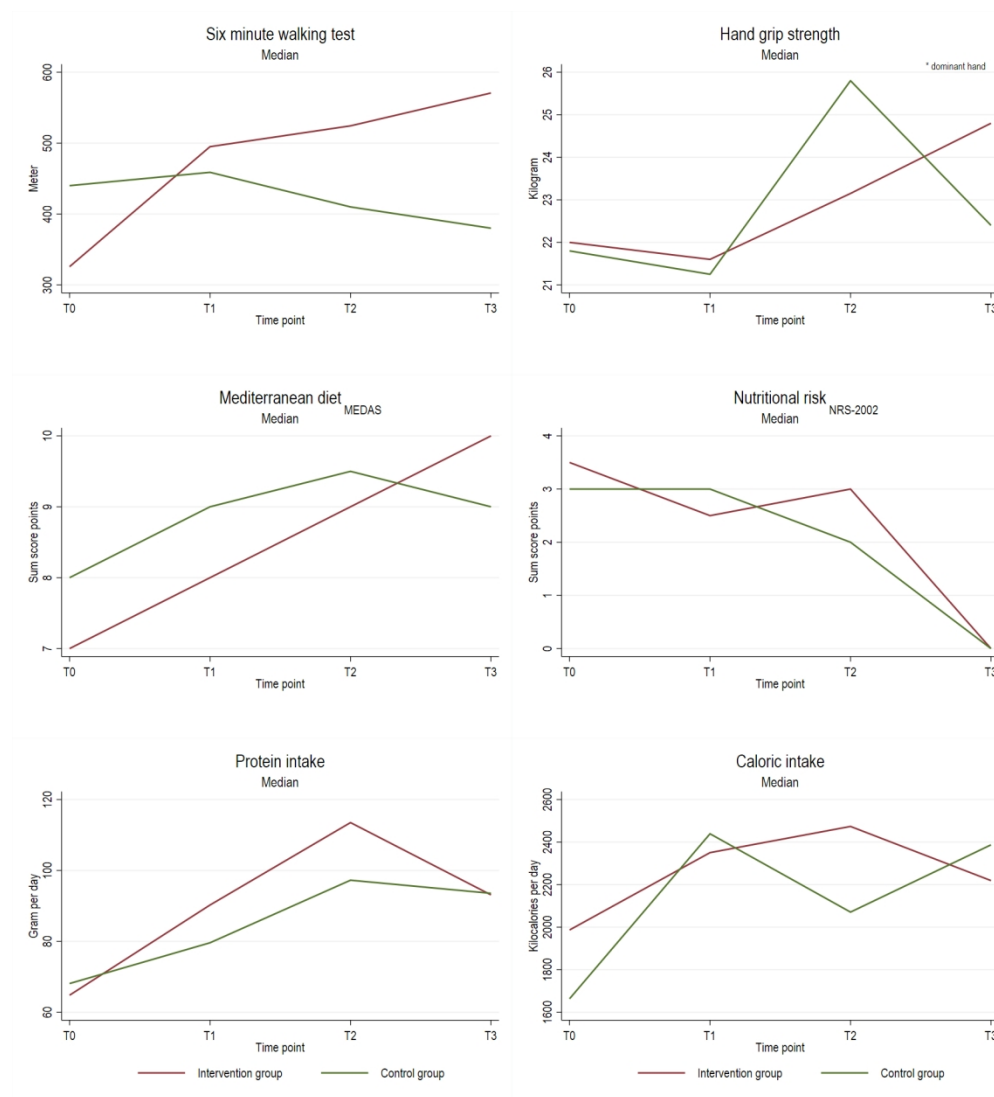


Figure 2: Descriptive results of in-person assessments at baseline (T0), mid-chemotherapy (T1), after completion of chemotherapy (T2) and one year follow-up (T3) by group assignment

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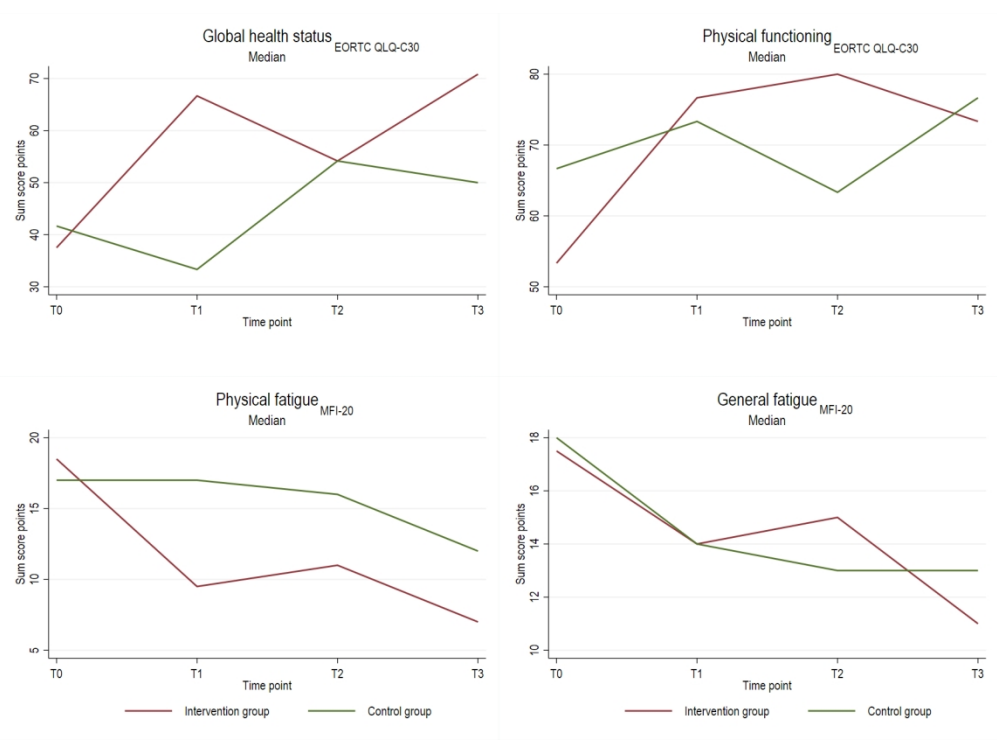


Figure 3: Descriptive results (continued) of in-person assessments at baseline (T0), mid-chemotherapy (T1), after completion of chemotherapy (T2) and one year follow-up (T3) by group assignment

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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

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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.

For peer review only



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

1	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Doesn't apply
2				
3		11b	If relevant, description of the similarity of interventions	Doesn't apply
4	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6-7
5		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6-7
6				
7	Results			
8	Participant flow (a	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and	7-8
9	diagram is strongly		were analysed for the primary outcome	
10	recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	7-8
11	Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
12		14b	Why the trial ended or was stopped	Doesn't apply
13	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9
14	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was	8
15			by original assigned groups	
16	Outcomes and	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its	No inferential
17	estimation		precision (such as 95% confidence interval)	statistics
18				(feasibility)
19		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Doesn't apply
20	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	13-16
21			pre-specified from exploratory	
22	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	No adverse
23				events
24	Discussion			
25	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17
26	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	17 ff
27	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	18-19
28	Other information			
29	Registration	23	Registration number and name of trial registry	3
30	Protocol	24	Where the full trial protocol can be accessed, if available	Published
31				(IJGC)
32	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	21

1 *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
2 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.
3 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.
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