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Effect of a family-involvement aerobic combined resistance exercise on cancer-related fatigue in patients with Breast Cancer during postoperative chemotherapy: study protocol for a quasi-randomized controlled trial

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3 **Effect of a family-involvement aerobic combined resistance exercise on cancer-related**
4 **fatigue in patients with Breast Cancer during postoperative chemotherapy:**
5 **study protocol for a quasi-randomized controlled trial**
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9 Chuhan Huang,¹ Yingjie Cai,^{1,2} Yufei Guo,¹ Jingjing Jia,¹ Tieying Shi,¹
10

11 **ABSTRACT**

12 **Introduction**

13
14 Cancer-related fatigue (CRF) is one of the most common and debilitating side effects in
15 patients with breast cancer (BC) throughout postoperative chemotherapy. Family-involvement
16 aerobic combined resistance exercise has been supported as a promising non-pharmacological
17 intervention for the individual symptom relief of cancer-related fatigue, muscle strength, exercise
18 completion, family intimacy and adaptability, and quality of life. However, relevant evidence of
19 using family-involvement aerobic combined resistance exercise for CRF management in patients
20 with BC is lacking report.
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23 **Methods and analysis**

24
25 This study is a quasi-randomized controlled trial involving an 8-week intervention. Seventy
26 patients with BC is recruited from a tertiary medical center in China. The participants from the
27 first oncology department is assigned to the family-involvement aerobic combined resistance
28 exercise group (n=35), while the participants from the second oncology department is assigned to
29 the control group with standard exercise guidance(n=35). The primary outcome is evaluated by
30 the Piper Fatigue Scale-Revised (R-PFS). The secondary outcomes include muscle strength,
31 exercise completion, family intimacy and adaptability, and quality of life, which are evaluated by
32 the stand-up and sit-down chair test, the grip test, the exercise completion rate, the Family
33 Adaptability and Cohesion Scale, Second Edition - Chinese Version (FACES II -CV) and the
34 Functional Assessment of Cancer Therapy - Breast (FACT-B). Analysis of covariance is adopted
35 for comparisons between groups and paired t-test is used for before exercise and after-exercise
36 comparisons within a group.
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39 **Key Words** breast cancer; cancer-related fatigue; postoperative chemotherapy; family-
40 involvement; aerobic combined resistance exercise
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43 **Ethics and dissemination**

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45 Ethics approval is obtained from relevant site (PJ-KS-KY-2021-288). The findings of this
46 study is published in a peer-reviewed scientific journal.
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49 **Trail registration number**

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51 ChiCTR2200055793
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54 **Strengths and limitations of this study**
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- In this intervention, each participant can choose the type of aerobic exercise they prefer.
- This study will provide exercise instruction videos to increase patients' exercising motivation. An exercise booklet is designed and provided to the participants in both intervention and control groups.
- Given the limited study sites, the sample in this study may only reflect the characteristics of this location .
- Due to the visible nature of the exercise intervention, the blinding of the participants and the investigators cannot be performed in this study which is not a rigorous randomized controlled trial, which might increase the risk of detection bias during the study's implementation.
- The study lacks a long-term follow-up to assess the ongoing effects of family-involvement exercise might be another limitation.

INTRODUCTION

According to the latest data in 2020, the number of new BC patients reached 2.26 million and the number of deaths is 680,000. BC officially replaced lung cancer as the largest cancer worldwide, ranking first in female cancer deaths^[1]. In China, there are about 368,000 new cases of BC in 2018, and about 416,000 new cases of BC in 2020^[2], showing an increasing trend year by year^[3]. The number of cancer survivors has increased, and the 5-year survival rate of BC patients has reached 90%, this has been attributed to the progress made in the realm of screening, diagnosis and therapeutic strategies engaged in breast cancer management^[4].

As a common adjuvant therapy after BC surgery, chemotherapy can improve the survival rate and prolong the survival time of BC patients^[5,6]. However, patients with low immunity during postoperative chemotherapy are prone to various discomforts, which increase their physical and mental burden and reduce their quality of life. Cancer-related fatigue (CRF) is one of the most common symptoms^[7]. According to research reports^[8], 80% to 90% of cancer patients will experience cancer-related fatigue during treatment and last for a long time. Cancer-related fatigue not only increases the risk of accidental falls in BC patients but also reduces their tolerance to chemotherapy drugs and increases the incidence of adverse reactions such as nausea and vomiting^[9]. In addition, compared with other symptoms such as pain and depression caused by cancer, cancer-related fatigue has a great negative impact on patients' social barriers and social re-employment^[10]. Studies have shown that cancer-related fatigue in patients is positively related to muscle strength^[11] and health-related quality of life^[12]. Therefore, it is necessary to improve cancer-related fatigue in BC patients to promote their return to society and improve their quality of life.

Studies have shown that increasing physical activity in BC patients can improve cancer-related fatigue^[13]. Physical activity refers to any physical movement that results in energy

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3 expenditure caused by skeletal muscle contraction^[14], including exercise training such as aerobic
4 exercise, resistance exercise, balance exercise, and flexibility exercise. Among them, aerobic
5 exercise and resistance exercise, as the most common exercise training methods in physical
6 activity, have been proved to be safe and effective^[15]. Studies have found that aerobic exercise
7 combined with resistance exercise has the best effect in improving cancer-related fatigue^[16].
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10 Although the benefits of aerobic combined resistance exercise for cancer-related fatigue
11 have been proven, BC patients do not exercise well. Good external support is one of the
12 important factors for patients to adhere to exercise^[17]. As an important part of external support
13 for patients, family members are the main bearers of daily activities and disease care during
14 hospitalization and after discharge^[18]. And studies have shown that, compared with unsupervised
15 exercise training, supervised exercise training with the participation of family members can
16 better ensure the continuous and regular development of exercise, thereby maintaining and
17 improving exercise effects^[19, 20]. In addition, increasing disease-related communication between
18 family members and patients can effectively increase patients' confidence in treatment, improve
19 the intimacy and adaptability between patients and their families, and thus improve patients'
20 family functions^[21]. Therefore, how to play the active support role of family members in the
21 process of exercise training in BC patients, and then enhance the benefits of exercise in
22 improving cancer-related fatigue in patients is one of the urgent problems to be solved.
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29 The current study, therefore, proposes to assess the feasibility and the preliminary effects of
30 using a family-involvement exercise protocol for alleviating the CRF in patients with BC
31 through a quasi-randomized Controlled Trial(Q-RCT).
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35 **METHODS AND MATERIALS**

36 **Participant Recruitment and Eligibility Criteria**

37 Patients with postoperative chemotherapy of BC in a Grade A tertiary hospital in Dalian are
38 selected for this study.
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41 The inclusion criteria for patients are: (1) pathological diagnosis of BC; (2) with first
42 postoperative chemotherapy for BC; (3) aged 18 to 65; (4) able to cooperate actively; (5)
43 informed consent to participate in this study voluntarily, and (6) with family members during the
44 intervention for 2 months. The exclusion criteria are: (1) with other serious diseases, such as
45 cardiovascular disease, other cancers, etc.; (2) with exercise contraindications, such as asthma,
46 severe anemia, disc herniation or other diseases; (3) with mental illness, previous mental illness
47 or family medical history.
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50 Each patient corresponds to one family member, the inclusion criteria for family members
51 are: (1) aged above 18, with primary school education or above, and good communication skills;
52 (2) spouse, parents, or children of immediate family; (3) the main caregivers determined by the
53 patient and family members who take care of patients above 2 months; (4) voluntary
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3 participation in the investigator. The exclusion criteria are: (1) with remuneration; (2) with a
4 previous history of mental illness.
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6 **Sample size**

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8 According to the previous study^[22], cancer-related fatigue score is expected to decrease by
9 0.6 points. According to the two-sided sample size test formula, a two-sided test with
10 alpha=0.05, and 80% power, this gives a total sample of 30. To account for a 15% attrition rate,
11 the required sample is 70.
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14 **Study Design**

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16 To avoid contamination among the research subjects, this study adopts a lottery method to
17 randomly divide the hospital's first and second oncology departments into a control group and an
18 intervention group, and select 35 patients in each ward who meet the requirements after
19 screening by the inclusion and exclusion criteria.
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22 The intervention group consist of a sports rehabilitator, a senior clinical nursing specialist, a
23 head nurse, three responsible nurses, and a nursing graduate student. The sports rehabilitator
24 participates in the formulation of the exercise program. The nursing specialist participate in the
25 guidance of the experimental program. The head nurse and three nurses are responsible for
26 quality control, finding problems in the implementation of the program, and making
27 rectifications. While the graduate student is responsible for the intervention of patients and their
28 families, as well as data collection and collation. Group members jointly develop an exercise
29 instruction manual (including exercise forms, exercise methods, exercise precautions, etc.), and
30 record an exercise instruction video.
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33 The researcher explains the purpose and implementation process of the study to the subjects
34 when they are admitted to the hospital for the first chemotherapy (T0). After their agreement to
35 participate, the participants will be required to provide their written informed consent. The
36 participants will be informed that they can withdraw from the study at any moment without any
37 consequences. After obtaining the informed consent of the subjects, the researcher conducts the
38 stand-up and sit-down chair test and the grip test to patients and issues general information
39 questionnaires, R-PFS, FACES II -CV, and FACT-B. The intervention study begins after the
40 patients (and their families) have completed their first assessment.
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43 According to the patient's exercise duration and admission chemotherapy time, the patients
44 are tested with the stand-up and sit-down chair test and the grip test at the time of the second
45 admission chemotherapy (T1) and the fourth admission chemotherapy (T2). The exercise
46 completion rate of the two groups is evaluated, and the researcher issues general information
47 questionnaires, R-PFS, FACES II -CV, and FACT-B to evaluate the effect of exercise
48 intervention. In the process of distributing the questionnaire, if patients could not understand the
49 questionnaire items, the researcher explained it. A Consolidated Standards of Reporting Trials
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flow chart of the study is presented in [figure 1](#). The schedule of trial enrolment, intervention data collection, and assessments are presented in [table 1](#).

Table1 The schedule of trial enrolment, interventions and assessments			
Study period	Beginning of intervention	Interxention period	End of intervention
	(week 0)	(week 4)	(week 8)
Inclusion/exclusion criteria	x		
Informed consent	x		
Demograghic characteristics	x		
Randomisation and allocation	x		
R-PFS	x	x	x
The stand-up and sit-down chair test	x	x	x
The grip test	x	x	x
The exercise completion rate		x	x
FACES II -CV	x	x	x
FACT-B	x	x	x

Table1 The schedule of trial enrolment, interventions, and assesments. CRF, cancer-related fatigue; FACES II -CV, the Family Adaptability and Cohesion Scale, Second Edition - Chinese Version; FACT-B, the Functional Assessment of Cancer Therapy - Breast

Control group

When patients are admitted to the hospital for the first chemotherapy, the researcher gives exercise instruction to them, guides patients exercise training through the manual and video, and informs exercise time, form, method, intensity as well as precautions. The patients are followed up monthly to understand their exercise status, and the researcher asks patients why they don't persist in exercising to help them solve their problems, and to encourage them to persist in exercise training.

Intervention group

Based on the control group, the exercise training intervention with family members is presented in [Table 2](#):

Guide family members	Evaluate the patients' life and social environment through family members, and explain to family members the importance of family members accompanying the patient to exercise.
	Distribute exercise manuals to family members and play exercise instruction videos.

	Instruct family members to master the exercise time, method, exercise standard posture, exercise precautions, and precautions for the use of elastic bands and dumbbells for BC patients.	
Supervise family members	Issue supervision diaries to family members ¹ .	Remind and supervise family members to fill in the supervision diary through WeChat or phone every month.
		When the patient is readmitted to the hospital, he is required to carry the supervision diary to check the record in the diary.
	Supervise family members via WeChat.	Establish a special WeChat group for family members, send exercise-related health knowledge to the WeChat group every week, and regularly remind family members to urge patients to exercise.
		Encourage family members to ask questions actively in the WeChat group and provide timely feedback on the supervision situation and feelings, to answer relevant questions for family members in the process of guiding and supervising patients.
	Appropriate praise and rewards are given to the family members who first complete the monitoring goals every week, forming a competition mechanism and stimulating interest.	
Follow up with family members	Make phone calls or face-to-face follow-up with family member monthly, ask them the questions they encountered during the care of the patients and answer them.	
	Ask the patient about the training situation. If patients cannot insist on exercise training, further inquire and analyze the reasons why patients cannot insist, and help the family to solve the problem.	
Family members accompany patients	Participate in the whole process of the patients' exercise and provide the patients with full emotional support. Before exercising, choose the way of aerobic exercise together with the patients according to the patient's preference and play music for patients to relax while they exercise.	
Family members supervise patients	Give exercise guidance to the patient. Guide the patients in the correct exercise method by playing the video. When the patients make an error or non-standard movement during the exercise, correct it in time.	
	Supervise the patient exercising. Take photos or videos while the	

	patients are moving to record the patients' movement. Keep a supervision diary after each patient's exercise and upload exercise photos or videos in the WeChat group to ensure the effect of family supervision.
Family members encourage patients	Encourage and support the patients and enhance their confidence; encourage the patients to tell themselves about the difficulties encountered during exercise, and tell them that they will overcome it together.

¹The first part of the supervision diary is basic information, including initials of family members, initials of patients, the relationship between family members and patients, height, weight, initials of the doctor in charge, date of chemotherapy, etc. This part is filled out by the researcher and distributed to the family members. The second part includes the exercise date, time, location, exercise duration, frequency and number of groups, the patient's exercise status, and whether he or she participated in the exercise guidance and supervision throughout the exercise.

Table 2 The exercise training intervention with family members

Aerobic combined resistance exercise

The exercise training lasts for 8 weeks, and the patients can select the most comfortable period of the week according to the patients' situation every week. Each training time is scheduled for half an hour after a meal, and avoid training on an empty stomach or a full meal. Each workout includes aerobic and resistance exercises which both are progressive. It is allowed 5 minutes of rest between aerobic and resistance exercise. Aerobic exercise is accomplished by cycling, treadmill, or brisk walking on the ground, depending on the patients' preference: twice a week for 15 to 20 minutes in week 1-4; three times a week for 25 to 35 minutes in week 5-8. Resistance exercise used 0.45kg dumbbells or a mineral water bottle filled with 500ml of water and a 1.8cm brown elastic band named TheraBand and provided by the researchers as the main exercise tools, including four resistance exercise movements (hip abduction, seated knee raising, raise before standing, standing lateral raise): twice a week in week 1-4, two sets of each exercise, each set of 8-12 times; three times a week in week 5-8, three sets of each exercise, each set of 8-12 times, with plenty of rest between sets^[23-26].

Hip abduction: When preparing, the body is in a standing position, the ankle of one foot is covered with the elastic band, the other foot is on the elastic band, the opposite hand holds the seat, and the supporting foot firmly grasps the ground to keep the trunk stable; at the beginning The buttocks exert force and pull the elastic band to the side until the angle between the practice leg and the supporting foot is about 30 degrees, and pause for about one second, then slowly restore, alternating with the left and right feet.

Seated knee raising: When preparing, sit in a sitting position with a straight back, hold the seat with both hands, keep the upper torso upright, step on one end of the elastic band with one foot, and put the ankle of one foot on the elastic band to bear the weight; lift the knee at the beginning To the maximum angle of joint activity, and pause for about one second, then slowly lower, alternating left and right.

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Raise before standing: Stand with feet parallel, head straight and look straight ahead, hold dumbbells at both sides of the body with both hands, raise arms in front of the body, pause for about one second, and then slowly restore. Inhale during the horizontal lift, exhale when returning to the original position.

Standing lateral raise: Stand with feet parallel, head straight, look straight ahead, hold dumbbells on both sides of the body, raise arms by the side, bend the elbows slightly, focus on the shoulders, and focus on the shoulders. When the arm is raised to a horizontal position, pause for about one second, slowly lower it, and restore the arm to the initial position. Inhale during the horizontal lift, exhale when returning to the original position.

The intensity of aerobic exercise should be moderate, that is, the Borg subjective fatigue scale score should reach 13-14 points (feeling a little hard); the intensity of resistance exercise should be tolerated by the patient. If there is obvious fatigue and muscle pain during or after training, the intensity of physical activity should be appropriately reduced. If patients have severe pain, discomfort and other symptoms occur, they should immediately stop the activity and be admitted to the hospital for re-examination^[27,28].

During the exercise, pay attention to observe the patients' reaction and adjust the elastic band or exercise speed and intensity in time; pay attention to the patients' exercise force should not be too large to avoid stretching the wound or the place where the catheter is placed; pay attention to the patient's movement at any time, if the patients are dizzy, discomfort and other adverse events occur, they should be promptly instructed to stop exercising and visit the hospital if necessary.

Outcome measurements

The outcome measurements for this pilot will include two categories, namely, baseline assessments and clinical outcomes.

Demographic and clinical characteristics of the participants

A self-designed demographic and clinical data form is employed to collect the participants' sociodemographic data (eg, age, education background, employment status, marital status, and household income), the participants' medical history (eg, date of diagnosis, the current stage of BC and date and type of treatment) and family members' sociodemographic data at baseline (T0).

Primary outcomes: cancer-related fatigue

The Piper Fatigue Scale-Revised (R-PFS)^[29]: The R-PFS is adopted to assess the participants' subjective fatigue. This self-administered questionnaire contains 22 items whose scores range from 0 to 10 and includes four domains of subjective fatigue. The R-PFS is available in a simplified Chinese version^[30], with high reliability and validity and has high reliability in the BC population.

Secondary outcomes: muscle power, exercise completion, family intimacy and adaptability and QOL

The muscle strength exercise completion, family intimacy and adaptability, and QoL of the patients with BC as the secondary outcomes are measured at T0, T1, and T2 using the stand-up and sit-down chair test, the grip test, the exercise completion rate, the FACES II -CV and the FACT-B.

1. The stand-up and sit-down chair test (number of times standing up from the chair within 30 s)^[31]: This test is used to evaluate the leg strength of the subject. The procedure of testing: 1) Put an upright chair (or a folding chair) against the wall (for the sake of safety). 2) The subject sits in the middle of the chair with the right foot and the left foot apart equal to the shoulders, and one foot may be put slightly front and the other slightly back. Both arms are crossed around the waist and close to the chest. 3) During the test, the subject should completely stand up and then completely sit down. 4) Record the number of times that the subject stands up from and sits down in the chair within 30 s. 5) For safety purposes or when necessary, the subject may use her arms for assistance.

2. The grip test^[28]: This test is used to evaluate the arm strength of the subject. Use domestic CAMRY (model EH101) electronic grip strength meter, this grip strength meter is in kg/lb, the maximum range is 90kg/198lb, and the division value is 0.1kg/0.2lb. The subjects are in a standing position, with their hands hanging down naturally, their feet are flush with both shoulders, and the hands are not close to the body.

3. Exercise completion rate: This test is used to assess the performance of the two groups of exercise. The exercise completion rate in this study = the number of subjects in the intervention group who completed 18 or more training sessions (over 90% of the total training volume) ÷ the total number of people in the intervention group × 100%.

4. The Family Adaptability and Cohesion Scale, Second Edition - Chinese Version (FACES II -CV)^[32]: The FACES II -CV is adopted to assess the participants' family intimacy and adaptability. A higher score demonstrates higher intimacy and adaptability. The FACES II -CV is available in a simplified Chinese version, with high reliability and validity.

5. The Functional Assessment of Cancer Therapy - Breast (FACT-B)^[33]: The FACT-B is adopted to assess the participants' QoL. A higher score demonstrates better QoL. The FACT-B is available in a simplified Chinese version, with adequate psychometric properties reported among patients with BC.

Data analysis

The study results underwent statistical analysis with SPSS software version 25.0. Analysis of covariance is adopted for comparisons between groups and paired t-test is used for before exercise and after-exercise comparisons within a group, whereas $p < 0.05$ represents there is a significant difference between the test results.

Data management

After data collection is complete, all paper data is converted to electronic data. All data is independently recorded by two researchers using Excel. The software automatically checks inconsistent or problematic data based on the inspection results and generates a data problem table. After all, data have been confirmed, reconciled, and stored in an electronic database, participants' identifying information (eg, real name) will not appear in the relevant reports of the trial to protect their privacy. Only researchers directly involved in the analysis of this study have access to the final trial dataset, which contains only coded data.

Data sharing statement

Technical appendix, statistical codes and dataset will be available at any time by contacting the corresponding author.

Patient and public involvement

Patients and/or public were not involved in designing this study.

Ethics and dissemination

Ethical approval is granted by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University (PJ-KS-KY-2021-288) and is retrospectively registered in the Chinese Clinical Trial Registry (registration number: ChiCTR2200055793). Only the participants who signed the informed consent document are included in the study.

DISCUSSION

As one of the most common symptom clusters in patients with BC, the CRF can significantly deteriorate patients' QoL and daily functioning^[34]. An increasing number of studies have demonstrated that aerobic combined resistance exercise has beneficial effects on symptom management in patients with cancer^[35]; however, due to the time and intensity of exercise and individual differences, the effect of each study varies. Kajal Gokal^[36] conducted a home-based walking intervention based on self-management in 25 BC patients receiving chemotherapy. The results showed that self-management exercise intervention can improve patients' fatigue symptoms and improve their physical activity level. However, some patients are difficult to adhere to exercise training, causing the patients to stop exercising. Kyeong^[37] conducted a 12-week randomized controlled trial on 356 BC patients. The results showed that aerobic combined resistance exercise can improve patients' fatigue symptoms, muscle strength, and quality of life, but because some patients cannot persist in exercise, the advantages of exercise over traditional exercise programs are not obvious. Existing studies have confirmed that family-involvement exercise interventions have many benefits in stroke^[38], coronary heart disease^[39], lung cancer^[40], and other patients, while there are few reports on the effect of family-involvement exercise interventions on BC patients in China. This highlights a great need to explore the effects of family-involvement exercise on the CRF in patients with BC.

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3 The principal strength (and novel aspect) of this study resides in the fact that in the
4 intervention, each participant chooses the type of aerobic exercise they prefer. And the study
5 provides exercise instruction videos to increase patients' exercising motivation. In addition, we
6 aim to provide new evidence on the cost-effectiveness of this kind of intervention (to our
7 knowledge, virtually no evidence has previously been reported in this regard). Moreover, an
8 exercise booklet is designed and provided to the participants in both the intervention and control
9 groups. The information listed in this booklet is comprehensively adapted from relevant national
10 guidelines, professional bodies, and research evidence in published peer-reviewed articles.

11
12 This study also has some limitations. Given the limited study sites, the study sample in this
13 study may not offer a completely representative sample of patients with BC. Due to the visible
14 nature of the exercise intervention, the blinding of the participants and the investigators cannot
15 be performed in this study, which might increase the risk of detection bias during the study's
16 implementation. The lack of long-term follow-up to assess the ongoing effects of family-
17 involvement exercise might be another limitation, but this can be considered in the future full-
18 scale trial as one of the main study outcomes. Furthermore, this study is not a rigorous
19 randomized controlled trial, and a future multicentre large-scale main RCT should be conducted
20 in the future to further summarize the research evidence on the effects of family-involvement
21 exercise on the management of patients with CPF.

22
23 This study will use a quasi-randomized controlled trial to assess the feasibility and
24 preliminary effects of a family-involvement exercise program for alleviating the CRF in patients
25 with BC under postoperative chemotherapy. The convenience of the family-involvement
26 exercise for the management of the CRF may provide patients with BC, healthcare professionals,
27 and policy-makers with further guidance in CRF management in the long run.

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42
43 **Contributorship statement** Chuhan Huang conceived and designed the study, and Tieying Shi
44 oversaw the research team and research process. Yingjie Cai and Chuhan Huang were the main
45 implementers of the study and drafted the manuscript. Jingjing Jia wrote the ethics review
46 confirmation. Yufei Guo participated in the design of the study and assisted in drafting the
47 manuscript. All authors have read and agree to the final version of the manuscript.

48
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51
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53
54 **Patient consent for publication** Not required.

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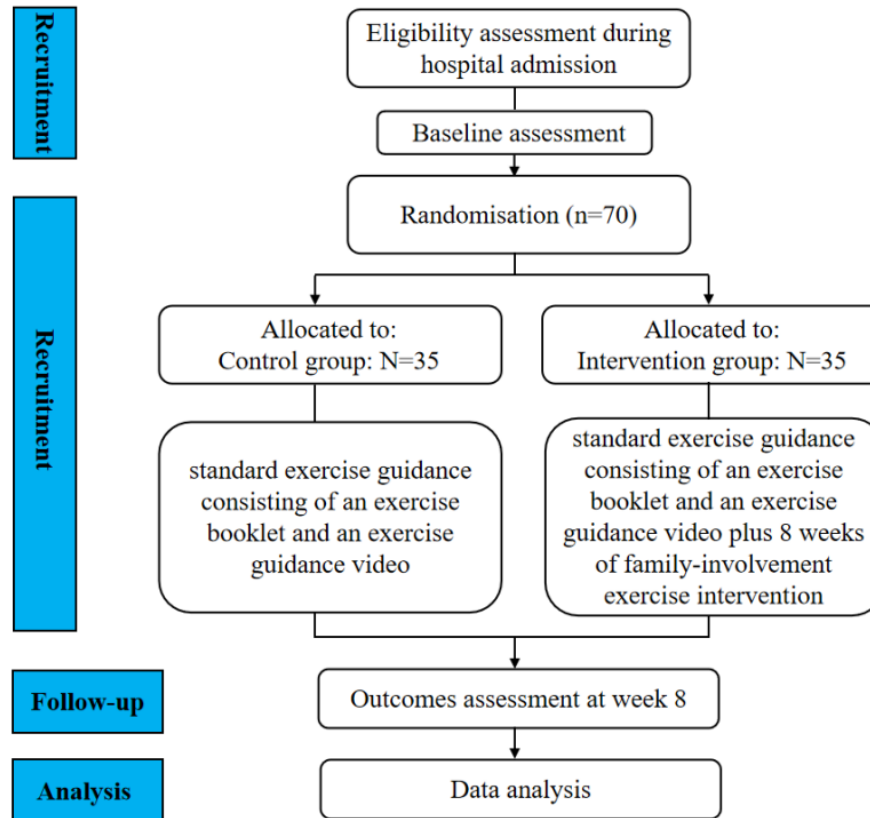
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39 Figure 1 A Consolidated Standards of Reporting Trials flow chart of the study
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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	No.1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	No.1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	No.1-2
	2b	Specific objectives or hypotheses	No.2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	No.4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	No.4
Participants	4a	Eligibility criteria for participants	No.3
	4b	Settings and locations where the data were collected	No.3-4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	No.6-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	No.9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not
Sample size	7a	How sample size was determined	No.4
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Not
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	No.4
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	No.4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	No.4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Not

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

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

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Effect of a family-involvement aerobic combined resistance exercise on cancer-related fatigue in patients with Breast Cancer during postoperative chemotherapy: study protocol for a quasi-randomized controlled trial

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Effect of a family-involvement aerobic combined resistance exercise on cancer-related fatigue in patients with Breast Cancer during postoperative chemotherapy: study protocol for a quasi-randomized controlled trial

Chuhan Huang,¹ Yingjie Cai,¹ Yufei Guo,¹ Jingjing Jia,¹ Tieying Shi,¹

ABSTRACT

Introduction

Cancer-related fatigue (CRF) is one of the most common and debilitating side effects in patients with breast cancer (BC) throughout postoperative chemotherapy. Family-involvement aerobic combined resistance exercise has been supported as a promising non-pharmacological intervention for the individual symptom relief of cancer-related fatigue, muscle strength, exercise completion, family intimacy and adaptability, and quality of life. However, relevant evidence of using family-involvement aerobic combined resistance exercise for CRF management in patients with BC is lacking report.

Methods and analysis

This study is a quasi-randomized controlled trial involving an 8-week intervention. Seventy patients with BC is recruited from a tertiary medical center in China. The participants from the first oncology department is assigned to the family-involvement aerobic combined resistance exercise group (n=35), while the participants from the second oncology department is assigned to the control group with standard exercise guidance(n=35). The primary outcome is evaluated by the Piper Fatigue Scale-Revised (R-PFS). The secondary outcomes include muscle strength, exercise completion, family intimacy and adaptability, and quality of life, which are evaluated by the stand-up and sit-down chair test, the grip test, the exercise completion rate, the Family Adaptability and Cohesion Scale, Second Edition - Chinese Version (FACES II -CV) and the Functional Assessment of Cancer Therapy - Breast (FACT-B). Analysis of covariance is adopted for comparisons between groups and paired t-test is used for before exercise and after-exercise comparisons within a group.

Key Words breast cancer; cancer-related fatigue; postoperative chemotherapy; family-involvement; aerobic combined resistance exercise

Ethics and dissemination

Ethics approval is obtained from relevant site (PJ-KS-KY-2021-288). The findings of this study is published in a peer-reviewed scientific journal.

Trail registration number

ChiCTR2200055793

Strengths and limitations of this study

- 1 ● In this intervention, each participant can choose the type of aerobic exercise they prefer.
- 2 ● This study will provide exercise instruction videos to increase patients' exercising
3 motivation. An exercise booklet is designed and provided to the participants in both
4 intervention and control groups.
- 5 ● Given the limited study sites, the sample in this study may only reflect the characteristics of
6 this location .
- 7 ● Due to the visible nature of the exercise intervention, the blinding of the participants and the
8 investigators cannot be performed in this study which is not a rigorous randomized
9 controlled trial, which might increase the risk of detection bias during the study's
10 implementation.
- 11 ● The study lacks a long-term follow-up to assess the ongoing effects of family-involvement
12 exercise might be another limitation.

14 INTRODUCTION

15 According to the latest data in 2020, the number of new BC patients reached 2.26 million
16 and the number of deaths is 680,000. BC officially replaced lung cancer as the largest cancer
17 worldwide, ranking first in female cancer deaths^[1]. In China, there are about 368,000 new cases
18 of BC in 2018, and about 416,000 new cases of BC in 2020^[2], showing an increasing trend year
19 by year^[3]. And at present, breast cancer patients in China tend to be younger^[4]. The number of
20 cancer survivors has increased, and the 5-year survival rate of BC patients has reached 90%, this
21 has been attributed to the progress made in the realm of screening, diagnosis and therapeutic
22 strategies engaged in breast cancer management^[5].

23 As a common adjuvant therapy after BC surgery, chemotherapy can improve the survival
24 rate and prolong the survival time of BC patients^[6,7]. However, patients with low immunity
25 during postoperative chemotherapy are prone to various discomforts, which increase their
26 physical and mental burden and reduce their quality of life. Cancer-related fatigue (CRF) is one
27 of the most common symptoms^[8]. According to research reports^[9], 80% to 90% of cancer
28 patients will experience cancer-related fatigue during treatment and last for a long time. Cancer-
29 related fatigue not only increases the risk of accidental falls in BC patients but also reduces their
30 tolerance to chemotherapy drugs and increases the incidence of adverse reactions such as nausea
31 and vomiting^[10]. In addition, compared with other symptoms such as pain and depression caused
32 by cancer, cancer-related fatigue has a great negative impact on patients' social barriers and
33 social re-employment^[11]. Studies have shown that cancer-related fatigue in patients is positively
34 related to muscle strength^[12] and health-related quality of life^[13]. Therefore, it is necessary to
35 improve cancer-related fatigue in BC patients to promote their return to society and improve
36 their quality of life.

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2
3 1 Studies have shown that increasing physical activity in BC patients can improve cancer-
4 2 related fatigue^[14]. Physical activity refers to any physical movement that results in energy
5 3 expenditure caused by skeletal muscle contraction^[15], including exercise training such as aerobic
6 4 exercise, resistance exercise, balance exercise, and flexibility exercise. Adult breast cancer
7 5 patients aged 18-65 should engage in regular physical activity at the time and intensity
8 6 recommended by the guidelines^[16]. Aerobic exercise and resistance exercise, as the most
9 7 common exercise training methods in physical activity, have been proved to be safe and
10 8 effective^[17]. Studies have found that aerobic exercise combined with resistance exercise has the
11 9 best effect in improving cancer-related fatigue^[18].

12 10 Although the benefits of aerobic combined resistance exercise for cancer-related fatigue
13 11 have been proven, BC patients do not exercise well. Good external support is one of the
14 12 important factors for patients to adhere to exercise^[19]. As an important part of external support
15 13 for patients, family members are the main bearers of daily activities and disease care during
16 14 hospitalization and after discharge^[20]. And studies have shown that, compared with unsupervised
17 15 exercise training, supervised exercise training with the participation of family members can
18 16 better ensure the continuous and regular development of exercise, thereby maintaining and
19 17 improving exercise effects^[21, 22]. In addition, increasing disease-related communication between
20 18 family members and patients can effectively increase patients' confidence in treatment, improve
21 19 the intimacy and adaptability between patients and their families, and thus improve patients'
22 20 family functions^[23]. Therefore, how to play the active support role of family members in the
23 21 process of exercise training in BC patients, and then enhance the benefits of exercise in
24 22 improving cancer-related fatigue in patients is one of the urgent problems to be solved.

25 23 The current study, therefore, proposes to assess the feasibility and the preliminary effects of
26 24 using a family-involvement exercise protocol for alleviating the CRF in patients with BC
27 25 through a quasi-randomized Controlled Trial(Q-RCT).

26 27 **METHODS AND MATERIALS**

27 28 **Participant Recruitment and Eligibility Criteria**

28 29 Patients with postoperative chemotherapy of BC in a Grade A tertiary hospital in Dalian are
29 30 selected for this study.

30 31 The inclusion criteria for patients are: (1) pathological diagnosis of BC; (2) with first
31 32 postoperative chemotherapy for BC; (3) aged 18 to 65; (4) able to cooperate actively; (5)
32 33 informed consent to participate in this study voluntarily, and (6) with family members during the
33 34 intervention for 2 months. The exclusion criteria are: (1) with other serious diseases, such as
34 35 cardiovascular disease, other cancers, etc.; (2) with exercise contraindications, such as asthma,
35 36 severe anemia, disc herniation or other diseases; (3) with mental illness, previous mental illness
36 37 or family medical history.

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4 1 Each patient corresponds to one family member, the inclusion criteria for family members
5 2 are: (1) aged above 18, with primary school education or above, and good communication skills;
6 3 (2) spouse, parents, or children of immediate family; (3) the main caregivers determined by the
7 4 patient and family members who take care of patients above 2 months; (4) voluntary
8 5 participation in the investigator. The exclusion criteria are: (1) with remuneration; (2) with a
9 6 previous history of mental illness.
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13 8 **Sample size**

14 9 According to the previous study^[24], cancer-related fatigue score is expected to decrease by
15 10 0.6 points. According to the two-sided sample size test formula, a two-sided test with
16 11 $\alpha=0.05$, and 80% power, this gives a total sample of 30. To account for a 15% attrition rate,
17 12 the required sample is 70.
18 13

22 14 **Study Design**

23 15 To avoid contamination among the research subjects, this study adopts a lottery method to
24 16 randomly divide the hospital's first and second oncology departments into a control group and an
25 17 intervention group, and select 35 patients in each ward who meet the requirements after
26 18 screening by the inclusion and exclusion criteria.

29 19 The intervention group consist of a sports rehabilitator, a senior clinical nursing specialist, a
30 20 head nurse, three responsible nurses, and a nursing graduate student. The sports rehabilitator
31 21 participates in the formulation of the exercise program. The nursing specialist participate in the
32 22 guidance of the experimental program. The head nurse and three nurses are responsible for
33 23 quality control, finding problems in the implementation of the program, and making
34 24 rectifications. While the graduate student is responsible for the intervention of patients and their
35 25 families, as well as data collection and collation. Group members jointly develop an exercise
36 26 instruction manual (including exercise forms, exercise methods, exercise precautions, etc.), and
37 27 record an exercise instruction video.

42 28 The researcher explains the purpose and implementation process of the study to the subjects
43 29 when they are admitted to the hospital for the first chemotherapy (T0). After their agreement to
44 30 participate, the participants will be required to provide their written informed consent. The
45 31 participants will be informed that they can withdraw from the study at any moment without any
46 32 consequences. After obtaining the informed consent of the subjects, the researcher conducts the
47 33 stand-up and sit-down chair test and the grip test to patients and issues general information
48 34 questionnaires, R-PFS, FACES II-CV, and FACT-B. The intervention study begins after the
49 35 patients (and their families) have completed their first assessment.

54 36 According to previous relevant studies^[25,26], exercise training begins to play a role in
55 37 "improving cancer-related fatigue" during the 8-week exercise intervention process. Therefore,
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1 the patients are tested with the stand-up and sit-down chair test and the grip test at the time of the
 2 fourth (T1) and eighth (T2) weekends of the intervention. The exercise completion rate of the
 3 two groups is evaluated, and the researcher issues general information questionnaires, R-PFS,
 4 FACES II -CV, and FACT-B to evaluate the effect of exercise intervention. In the process of
 5 distributing the questionnaire, if patients could not understand the questionnaire items, the
 6 researcher explained it. A Consolidated Standards of Reporting Trials flow chart of the study is
 7 presented in [figure 1](#). The schedule of trial enrolment, intervention data collection, and
 8 assessments are presented in [table 1](#).

16 **Table1 The schedule of trial enrolment, interventions and assessments**

Study period	Beginning of intervention (week 0)	Interxention period (week 4)	End of intervention (week 8)
Inclusion/exclusion criteria	x		
Informed consent	x		
Demographic characteristics	x		
Randomisation and allocation	x		
R-PFS	x	x	x
The stand-up and sit-down chair test	x	x	x
The grip test	x	x	x
The exercise completion rate		x	x
FACES II -CV	x	x	x
FACT-B	x	x	x

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 11 Table1 The schedule of trial enrolment, interventions, and assesments. R-PFS, the Piper Fatigue Scale-Revised; FACES II -CV,
 12 the Family Adaptability and Cohesion Scale, Second Edition - Chinese Version; FACT-B, the Functional Assessment of Cancer
 13 Therapy - Breast

14 **Control group**

15 When patients are admitted to the hospital for the first chemotherapy, the researcher
 16 provides exercise guidance for them with “aerobic combined resistance exercise”, and guides
 17 patients exercise training through the manual and video, and informs exercise time, form,
 18 method, intensity as well as precautions. The patients are followed up monthly to understand
 19 their exercise status, and the researcher asks patients why they don’t persist in exercising to help
 20 them solve their problems, and to encourage them to persist in exercise training.

21 **Intervention group**

22 Based on the control group, “aerobic combined resistance exercise” with family members is
 23 presented in [Table 2](#):

Guide family members	Evaluate the patients' life and social environment through family members, and explain to family members the importance of family members accompanying the patient to exercise.	
	Distribute exercise manuals to family members and play exercise instruction videos.	
	Instruct family members to master the exercise time, method, exercise standard posture, exercise precautions, and precautions for the use of elastic bands and dumbbells for BC patients.	
Supervise family members	Issue supervision diaries to family members ¹ .	Remind and supervise family members to fill in the supervision diary through WeChat or phone every month.
		When the patient is readmitted to the hospital, he is required to carry the supervision diary to check the record in the diary.
	Supervise family members via WeChat.	Establish a special WeChat group for family members, send exercise-related health knowledge to the WeChat group every week, and regularly remind family members to urge patients to exercise.
		Encourage family members to ask questions actively in the WeChat group and provide timely feedback on the supervision situation and feelings, to answer relevant questions for family members in the process of guiding and supervising patients.
Appropriate praise and rewards are given to the family members who first complete the monitoring goals every week, forming a competition mechanism and stimulating interest.		
Follow up with family members	Make phone calls or face-to-face follow-up with family member monthly, ask them the questions they encountered during the care of the patients and answer them.	
	Ask the patient about the training situation. If patients cannot insist on exercise training, further inquire and analyze the reasons why patients cannot insist, and help the family to solve the problem.	
Family members accompany patients	Participate in the whole process of the patients' exercise and provide the patients with full emotional support. Before exercising, choose the way of aerobic exercise together with the patients according to the patient's preference and play music for patients to relax while they exercise.	

Family members supervise patients	Give exercise guidance to the patient. Guide the patients in the correct exercise method by playing the video. When the patients make an error or non-standard movement during the exercise, correct it in time. Supervise the patient exercising. Take photos or videos while the patients are moving to record the patients' movement. Keep a supervision diary after each patient's exercise and upload exercise photos or videos in the WeChat group to ensure the effect of family supervision.
Family members encourage patients	Encourage and support the patients and enhance their confidence; encourage the patients to tell themselves about the difficulties encountered during exercise, and tell them that they will overcome it together.

¹The first part of the supervision diary is basic information, including initials of family members, initials of patients, the relationship between family members and patients, height, weight, initials of the doctor in charge, date of chemotherapy, etc. This part is filled out by the researcher and distributed to the family members. The second part includes the exercise date, time, location, exercise duration, frequency and number of groups, the patient's exercise status, and whether he or she participated in the exercise guidance and supervision throughout the exercise.

Table 2 The exercise training intervention with family members

Aerobic combined resistance exercise

The exercise training lasts for 8 weeks, and the patients can select the most comfortable period of the week according to the patients' situation every week. Each training time is scheduled for half an hour after a meal, and avoid training on an empty stomach or a full meal. Each workout includes aerobic and resistance exercises which both are progressive. It is allowed 5 minutes of rest between aerobic and resistance exercise. Aerobic exercise is accomplished by cycling, treadmill, or brisk walking on the ground, depending on the patients' preference: twice a week for 15 to 20 minutes in week 1-4; three times a week for 25 to 35 minutes in week 5-8. Resistance exercise used 0.45kg dumbbells or a mineral water bottle filled with 500ml of water and a 1.8cm brown elastic band named TheraBand and provided by the researchers as the main exercise tools, including four resistance exercise movements (hip abduction, seated knee raising, raise before standing, standing lateral raise): twice a week in week 1-4, two sets of each exercise, each set of 8-12 times; three times a week in week 5-8, three sets of each exercise, each set of 8-12 times, with plenty of rest between sets^[27-30].

Hip abduction: When preparing, the body is in a standing position, the ankle of one foot is covered with the elastic band, the other foot is on the elastic band, the opposite hand holds the seat, and the supporting foot firmly grasps the ground to keep the trunk stable; at the beginning The buttocks exert force and pull the elastic band to the side until the angle between the practice leg and the supporting foot is about 30 degrees, and pause for about one second, then slowly restore, alternating with the left and right feet.

1
2
3 1 Seated knee raising: When preparing, sit in a sitting position with a straight back, hold the
4 2 seat with both hands, keep the upper torso upright, step on one end of the elastic band with one
5 3 foot, and put the ankle of one foot on the elastic band to bear the weight; lift the knee at the
6 4 beginning To the maximum angle of joint activity, and pause for about one second, then slowly
7 5 lower, alternating left and right.

8 6 Raise before standing: Stand with feet parallel, head straight and look straight ahead, hold
9 7 dumbbells at both sides of the body with both hands, raise arms in front of the body, pause for
10 8 about one second, and then slowly restore. Inhale during the horizontal lift, exhale when
11 9 returning to the original position.

12 10 Standing lateral raise: Stand with feet parallel, head straight, look straight ahead, hold
13 11 dumbbells on both sides of the body, raise arms by the side, bend the elbows slightly, focus on
14 12 the shoulders, and focus on the shoulders. When the arm is raised to a horizontal position, pause
15 13 for about one second, slowly lower it, and restore the arm to the initial position. Inhale during the
16 14 horizontal lift, exhale when returning to the original position.

17 15 The intensity of aerobic exercise should be moderate, that is, the Borg subjective fatigue
18 16 scale score should reach 13-14 points (feeling a little hard); the intensity of resistance exercise
19 17 should be tolerated by the patient. If there is obvious fatigue and muscle pain during or after
20 18 training, the intensity of physical activity should be appropriately reduced. If patients have
21 19 severe pain, discomfort and other symptoms occur, they should immediately stop the activity and
22 20 be admitted to the hospital for re-examination^[31,32].

23 21 During the exercise, pay attention to observe the patients' reaction and adjust the elastic
24 22 band or exercise speed and intensity in time; pay attention to the patients' exercise force should
25 23 not be too large to avoid stretching the wound or the place where the catheter is placed; pay
26 24 attention to the patient's movement at any time, if the patients are dizzy, discomfort and other
27 25 adverse events occur, they should be promptly instructed to stop exercising and visit the hospital
28 26 if necessary.

29 27 **Outcome measurements**

30 28 The outcome measurements for this pilot will include two categories, namely, baseline
31 29 assessments and clinical outcomes.

32 30 **Demographic and clinical characteristics of the participants**

33 31 A self-designed demographic and clinical data form is employed to collect the participants'
34 32 sociodemographic data (eg, age, education background, employment status, marital status, and
35 33 household income), the participants' medical history (eg, date of diagnosis, the current stage of
36 34 BC and date and type of treatment) and family members' sociodemographic data at baseline (T0).

37 35 **Primary outcomes: cancer-related fatigue**

38 36 The Piper Fatigue Scale-Revised (R-PFS)^[33]: The R-PFS is adopted to assess the
39 37 participants' subjective fatigue. This self-administered questionnaire contains 22 items whose

1 scores range from 0 to 10 and includes four domains of subjective fatigue. The R-PFS is
2 available in a simplified Chinese version^[34], with high reliability and validity and has high
3 reliability in the BC population.

4 **Secondary outcomes: muscle power, exercise completion, family intimacy and adaptability** 5 **and QOL**

6 The muscle strength exercise completion, family intimacy and adaptability, and QoL of the
7 patients with BC as the secondary outcomes are measured at T0, T1, and T2 using the stand-up
8 and sit-down chair test, the grip test, the exercise completion rate, the FACES II -CV and the
9 FACT-B.

10 1. The stand-up and sit-down chair test (number of times standing up from the chair within
11 30 s)^[35]: This test is used to evaluate the leg strength of the subject. The procedure of testing: 1)
12 Put an upright chair (or a folding chair) against the wall (for the sake of safety). 2) The subjects
13 sit in the middle of the chair with the right foot and the left foot apart equal to the shoulders, and
14 one foot may be put slightly front and the other slightly back. Both arms are crossed around the
15 waist and close to the chest. 3) During the test, the subjects should completely stand up and then
16 completely sit down. 4) Record the number of times that the subjects stand up from and sit down
17 in the chair within 30 s. 5) For safety purposes or when necessary, the subject may use her arms
18 for assistance.

19 2. The grip test^[32]: This test is used to evaluate the arm strength of the subject. Use
20 domestic CAMRY (model EH101) electronic grip strength meter, this grip strength meter is in
21 kg/lb, the maximum range is 90kg/198lb, and the division value is 0.1kg/0.2lb. The subjects are
22 in a standing position, with their hands hanging down naturally, their feet are flush with both
23 shoulders, and the hands are not close to the body.

24 3. Exercise completion rate: This test is used to assess the performance of the two groups of
25 exercise. The exercise completion rate in this study = the number of subjects in the intervention
26 group who completed 18 or more training sessions (over 90% of the total training volume) ÷ the
27 total number of people in the intervention group × 100%.

28 4. The Family Adaptability and Cohesion Scale, Second Edition - Chinese Version
29 (FACES II -CV)^[36]: The FACES II -CV is adopted to assess the subjects' family intimacy and
30 adaptability. A higher score demonstrates higher intimacy and adaptability. The FACES II -CV is
31 available in a simplified Chinese version, with high reliability and validity.

32 5. The Functional Assessment of Cancer Therapy - Breast (FACT-B)^[37]: The FACT-B is
33 adopted to assess the subjects' QoL. A higher score demonstrates better QoL. The FACT-B is
34 available in a simplified Chinese version, with adequate psychometric properties reported among
35 patients with BC.

36 **Data analysis**

1 The study results underwent statistical analysis with SPSS software version 25.0. Analysis
2 of covariance is adopted for comparisons between groups and paired t-test is used for before
3 exercise and after-exercise comparisons within a group, whereas $p < 0.05$ represents there is a
4 significant difference between the test results.

5 **Data management**

6 After data collection is complete, all paper data is converted to electronic data. All data is
7 independently recorded by two researchers using Excel. The software automatically checks
8 inconsistent or problematic data based on the inspection results and generates a data problem
9 table. After all, data have been confirmed, reconciled, and stored in an electronic database,
10 participants' identifying information (eg, real name) will not appear in the relevant reports of the
11 trial to protect their privacy. Only researchers directly involved in the analysis of this study have
12 access to the final trial dataset, which contains only coded data.

13 **Data sharing statement**

14 Technical appendix, statistical codes and dataset will be available at any time by contacting
15 the corresponding author.

17 **Patient and public involvement**

18 Patients or the public were not involved in the design, or conduct, or reporting, or
19 dissemination plans of our research.

21 **Ethics and dissemination**

22 Ethical approval is granted by the Ethics Committee of the First Affiliated Hospital of
23 Dalian Medical University (PJ-KS-KY-2021-288) and is retrospectively registered in the
24 Chinese Clinical Trial Registry (registration number: ChiCTR2200055793). Only the
25 participants who signed the informed consent document are included in the study.

26 **DISCUSSION**

27 As one of the most common symptom clusters in patients with BC, the CRF can
28 significantly deteriorate patients' QoL and daily functioning^[38]. An increasing number of studies
29 have demonstrated that aerobic combined resistance exercise has beneficial effects on symptom
30 management in patients with cancer^[39]; however, due to the time and intensity of exercise and
31 individual differences, the effect of each study varies. Kajal Gokal^[40] conducted a home-based
32 walking intervention based on self-management in 25 BC patients receiving chemotherapy. The
33 results showed that self-management exercise intervention can improve patients' fatigue
34 symptoms and improve their physical activity level. However, some patients are difficult to
35 adhere to exercise training, causing the patients to stop exercising. Kyeong^[41] conducted a 12-
36 week randomized controlled trial on 356 BC patients. The results showed that aerobic combined
37 resistance exercise can improve patients' fatigue symptoms, muscle strength, and quality of life,

1 but because some patients cannot persist in exercise, the advantages of exercise over traditional
2 exercise programs are not obvious. Existing studies have confirmed that family-involvement
3 exercise interventions have many benefits in stroke^[42], coronary heart disease^[43], lung cancer^[44],
4 and other patients, while there are few reports on the effect of family-involvement exercise
5 interventions on BC patients in China. This highlights a great need to explore the effects of
6 family-involvement exercise on the CRF in patients with BC.

7 The principal strength (and novel aspect) of this study resides in the fact that in the
8 intervention, each participant chooses the type of aerobic exercise they prefer. And the study
9 provides exercise instruction videos to increase patients' exercising motivation. In addition, we
10 aim to provide new evidence on the cost-effectiveness of this kind of intervention (to our
11 knowledge, virtually no evidence has previously been reported in this regard). Moreover, an
12 exercise booklet is designed and provided to the participants in both the intervention and control
13 groups. The information listed in this booklet is comprehensively adapted from relevant national
14 guidelines, professional bodies, and research evidence in published peer-reviewed articles.

15 This study also has some limitations. Given the limited study sites, the study sample in this
16 study may not offer a completely representative sample of patients with BC. Due to the visible
17 nature of the exercise intervention, the blinding of the participants and the investigators cannot
18 be performed in this study, which might increase the risk of detection bias during the study's
19 implementation. The lack of long-term follow-up to assess the ongoing effects of family-
20 involvement exercise might be another limitation, but this can be considered in the future full-
21 scale trial as one of the main study outcomes. Furthermore, this study is not a rigorous
22 randomized controlled trial, and a future multicentre large-scale main RCT should be conducted
23 in the future to further summarize the research evidence on the effects of family-involvement
24 exercise on the management of patients with CPF.

25 This study will use a quasi-randomized controlled trial to assess the feasibility and
26 preliminary effects of a family-involvement exercise program for alleviating the CRF in patients
27 with BC under postoperative chemotherapy. The convenience of the family-involvement
28 exercise for the management of the CRF may provide patients with BC, healthcare professionals,
29 and policy-makers with further guidance in CRF management in the long run.

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34
35 **Contributorship statement** Chuhan Huang conceived and designed the study, and Tieying Shi
36 oversaw the research team and research process. Yingjie Cai and Chuhan Huang were the main
37 implementers of the study and drafted the manuscript. Jingjing Jia wrote the ethics review

1 confirmation. Yufei Guo participated in the design of the study and assisted in drafting the
2 manuscript. All authors have read and agree to the final version of the manuscript.

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7 **Competing interests** None declared.

8 **Patient consent for publication** Not required.

9 **Provenance and peer review** Not commissioned; externally peer reviewed.

10 **Ethics approval** The study has been approved by the Ethics Committee of the First Affiliated
11 Hospital of Dalian Medical University, China(PJ-KS-KY-2021-288).

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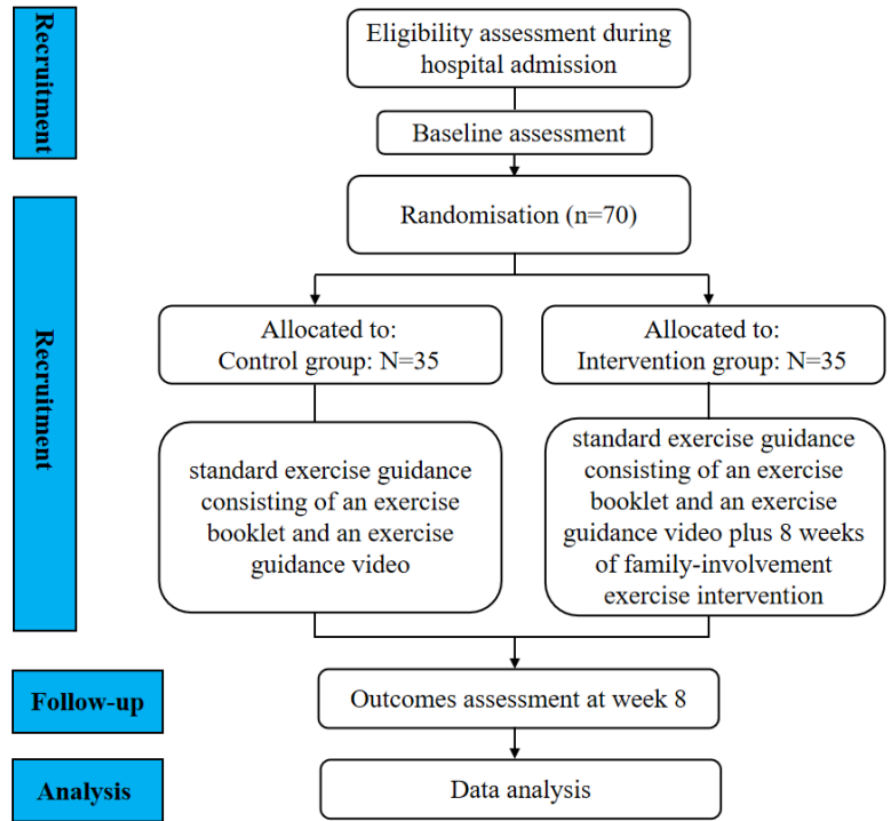
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10 6 Figure 1 A Consolidated Standards of Reporting Trials flow chart of the study
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For peer review only





SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	No.1 No.2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	No.2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	No.13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	No.13
	5b	Name and contact information for the trial sponsor	No.13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	No.13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	No.13
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	No.3-4
	6b	Explanation for choice of comparators	No.3-4
Objectives	7	Specific objectives or hypotheses	No.4

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2	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	No.5-6
3				
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8	Methods: Participants, interventions, and outcomes			
9				
10	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	No.4
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14	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	No.4-5
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19	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	No.6-9
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22		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	
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26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
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31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
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34	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	No.9-11
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42	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1
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47	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	No.5
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51	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	No.4-5
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-	
3	generation		generated random numbers), and list of any factors for stratification.	
4			To reduce predictability of a random sequence, details of any planned	
5			restriction (eg, blocking) should be provided in a separate document	
6			that is unavailable to those who enrol participants or assign	
7			interventions	
8				
9				
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
12	mechanism		describing any steps to conceal the sequence until interventions are	
13			assigned	
14				
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,	No.5
16			and who will assign participants to interventions	
17				
18				
19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	
20	(masking)		participants, care providers, outcome assessors, data analysts), and	
21			how	
22				
23		17b	If blinded, circumstances under which unblinding is permissible, and	
24			procedure for revealing a participant's allocated intervention during	
25			the trial	
26				
27				
28	Methods: Data collection, management, and analysis			
29				
30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other	No.5
31	methods		trial data, including any related processes to promote data quality (eg,	No.9-11
32			duplicate measurements, training of assessors) and a description of	
33			study instruments (eg, questionnaires, laboratory tests) along with	
34			their reliability and validity, if known. Reference to where data	
35			collection forms can be found, if not in the protocol	
36				
37				
38		18b	Plans to promote participant retention and complete follow-up,	No.6
39			including list of any outcome data to be collected for participants who	
40			discontinue or deviate from intervention protocols	
41				
42	Data	19	Plans for data entry, coding, security, and storage, including any	No.11
43	management		related processes to promote data quality (eg, double data entry;	
44			range checks for data values). Reference to where details of data	
45			management procedures can be found, if not in the protocol	
46				
47				
48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.	No.11
49	methods		Reference to where other details of the statistical analysis plan can be	
50			found, if not in the protocol	
51				
52		20b	Methods for any additional analyses (eg, subgroup and adjusted	
53			analyses)	
54				
55		20c	Definition of analysis population relating to protocol non-adherence	
56			(eg, as randomised analysis), and any statistical methods to handle	
57			missing data (eg, multiple imputation)	
58				
59				
60				

1
2 **Methods: Monitoring**

3
4 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role
5 and reporting structure; statement of whether it is independent from
6 the sponsor and competing interests; and reference to where further
7 details about its charter can be found, if not in the protocol.
8 Alternatively, an explanation of why a DMC is not needed
9
10
11 21b Description of any interim analyses and stopping guidelines, including
12 who will have access to these interim results and make the final
13 decision to terminate the trial
14
15 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and
16 spontaneously reported adverse events and other unintended effects
17 of trial interventions or trial conduct
18
19 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and
20 whether the process will be independent from investigators and the
21 sponsor
22
23
24 **Ethics and dissemination**

25
26 Research ethics 24 Plans for seeking research ethics committee/institutional review board No.11
27 approval (REC/IRB) approval
28
29 Protocol 25 Plans for communicating important protocol modifications (eg,
30 amendments (eg, investigators, REC/IRBs, trial participants, trial registries, journals,
31 regulators)
32
33
34
35 Consent or assent 26a Who will obtain informed consent or assent from potential trial No.5
36 participants or authorised surrogates, and how (see Item 32)
37
38 26b Additional consent provisions for collection and use of participant data
39 and biological specimens in ancillary studies, if applicable
40
41 Confidentiality 27 How personal information about potential and enrolled participants will No.13
42 be collected, shared, and maintained in order to protect confidentiality
43 before, during, and after the trial
44
45
46 Declaration of 28 Financial and other competing interests for principal investigators for No.13
47 interests the overall trial and each study site
48
49 Access to data 29 Statement of who will have access to the final trial dataset, and No.13
50 disclosure of contractual agreements that limit such access for
51 investigators
52
53
54 Ancillary and 30 Provisions, if any, for ancillary and post-trial care, and for
55 post-trial care compensation to those who suffer harm from trial participation
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1				
2	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to	No.11
3	policy		participants, healthcare professionals, the public, and other relevant	
4			groups (eg, via publication, reporting in results databases, or other	
5			data sharing arrangements), including any publication restrictions	
6				
7		31b	Authorship eligibility guidelines and any intended use of professional	
8			writers	
9				
10				
11		31c	Plans, if any, for granting public access to the full protocol, participant-	No.11
12			level dataset, and statistical code	
13				
14				

Appendices

15				
16				
17	Informed consent	32	Model consent form and other related documentation given to	
18	materials		participants and authorised surrogates	
19				
20	Biological	33	Plans for collection, laboratory evaluation, and storage of biological	
21	specimens		specimens for genetic or molecular analysis in the current trial and for	
22			future use in ancillary studies, if applicable	
23				

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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Effect of a family-involvement combined aerobic and resistance exercise protocol on cancer-related fatigue in breast cancer patients during postoperative chemotherapy: study protocol for a quasi-randomized controlled trial

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2
3 1 **Effect of a family-involvement combined aerobic and resistance exercise protocol on**
4 2 **cancer-related fatigue in breast cancer patients during postoperative chemotherapy:**
5 3 **study protocol for a quasi-randomized controlled trial**
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8 6

9 5 Chuhan Huang,¹ Yingjie Cai,¹ Yufei Guo,¹ Jingjing Jia,¹ Tieying Shi,¹
10 6

11 7 **ABSTRACT**

12 8 *Introduction:* Cancer-related fatigue (CRF) is one of the most common and debilitating side
13 9 effects experienced by breast cancer (BC) patients during postoperative chemotherapy. Family-
14 10 involvement combined aerobic and resistance exercise has been introduced as a promising non-
15 11 pharmacological intervention for CRF symptom relief and improving patients' muscle strength,
16 12 exercise completion, family intimacy and adaptability, and quality of life. However, evidence for
17 13 the practice of home participation in combined aerobic and resistance exercise for the management
18 14 of CRF in BC patients is lacking.

19 15 *Methods and analysis:* We present a protocol for a quasi-randomized controlled trial
20 16 involving an 8-week intervention. Seventy BC patients will be recruited from a tertiary care center
21 17 in China. Participants from the first oncology department will be assigned to the family-
22 18 involvement combined aerobic and resistance exercise group (n=28), while participants from the
23 19 second oncology department will be assigned to the control group that will receive standard
24 20 exercise guidance (n=28). The primary outcome will be the Piper Fatigue Scale-Revised (R-PFS)
25 21 score. The secondary outcomes will include muscle strength, exercise completion, family intimacy
26 22 and adaptability, and quality of life, which will be evaluated by the stand-up and sit-down chair
27 23 test, grip test, exercise completion rate, Family Adaptability and Cohesion Scale, Second Edition
28 24 - Chinese Version (FACES II -CV), and Functional Assessment of Cancer Therapy - Breast
29 25 (FACT-B) scale. Analysis of covariance will be applied for comparisons between groups, and
30 26 paired t-tests will be used for comparison of data before and after exercise within a group.

31 27
32 28 **Key Words:** breast cancer; cancer-related fatigue; postoperative chemotherapy; family-
33 29 involvement; combined aerobic and resistance exercise
34 30

35 31 **Ethics and dissemination:** This study has been approved by the Ethics Committee of the First
36 32 Affiliated Hospital of Dalian Medical University (PJ-KS-KY-2021-288). The results of this study
37 33 will be published via peer-reviewed publications and presentations at conferences.
38 34

39 35 **Trail registration number:** ChiCTR2200055793
40 36

41 37 **Strengths and limitations of this study**
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- 1 ● This will be the first clinical study to explore the preliminary effects of a family-involvement
2 combined aerobic and resistance exercise protocol on cancer-related fatigue in breast cancer
3 patients during postoperative chemotherapy.
- 4 ● The family members of the intervention group will record activities in a supervision diary and
5 check in a WeChat group throughout the intervention to illustrate the role of the family
6 members in the intervention process.
- 7 ● The main limitation of this study will be the small sample size.
- 8 ● The findings of this study may only reflect the characteristics of patients in this location given
9 the limited study sites.
- 10 ● Another potential limitation is that study protocol lacks a long-term follow-up to assess the
11 ongoing effects of family-involvement exercise.

13 INTRODUCTION

14 According to the latest data published for 2020, the number of newly diagnosed cases of
15 breast cancer (BC) in that year reached 2.26 million worldwide and the number of deaths due to
16 BC was 680,000. BC has officially replaced lung cancer as the most common cancer worldwide
17 and ranks first among females as the cause of cancer-related deaths^[1]. In China, approximately
18 368,000 new BC cases were diagnosed in 2018, and approximately 416,000 new cases of BC were
19 diagnosed in 2020^[2], showing an increasing trend year by year^[3]. At present, BC patients in China
20 tend to be younger than those in other populations^[4]. Overall, the number of BC survivors has
21 increased, as the 5-year survival rate of BC patients has reached 90%. This has been attributed to
22 the progress made in screening, diagnosis and therapeutic strategies applied in BC management^[5].

23 As a common adjuvant therapy after BC surgery, chemotherapy can improve the survival rate
24 and prolong the survival time of BC patients^[6,7]. However, patients with low immunity during
25 postoperative chemotherapy are prone to various discomforts, which increase their physical and
26 mental burden and reduce their quality of life. Cancer-related fatigue (CRF) is one of the most
27 common symptoms experienced by BC patients during postoperative chemotherapy^[8]. According
28 to previous research^[9], 80%–90% of cancer patients will experience CRF during treatment, and
29 this condition will persist for a long time. Research has also shown that CRF not only increases
30 the risk of accidental falls in BC patients but also reduces their tolerance to chemotherapy drugs
31 and increases the incidence of adverse reactions such as nausea and vomiting^[10]. In addition,
32 compared with other symptoms such as pain and depression caused by cancer, CRF has a major
33 negative impact on patients' social interactions and re-employment^[11]. Studies have shown that
34 CRF in patients is significantly related to muscle strength^[12] and health-related quality of life^[13].
35 Therefore, it is necessary to improve CRF in BC patients to promote their return to society and
36 improve their quality of life.

1 Increased physical activity in BC patients has been shown to improve CRF^[14]. Physical
2 activity refers to any physical movement that results in energy expenditure caused by skeletal
3 muscle contraction^[15], including exercise training such as aerobic exercise, resistance exercise,
4 balance exercise, and flexibility exercise. Adult BC patients aged 18–65 years are recommended
5 to engage in regular physical activity at the intensity and for the duration specified by current
6 guidelines^[16]. Aerobic exercise and resistance exercise, as the most common exercise training
7 methods in physical activity, have been proven to be safe and effective^[17]. Studies have found that
8 aerobic exercise combined with resistance exercise has the best effect on improving CRF^[18].

9 Although the benefits of combined aerobic and resistance exercise for CRF have been proven,
10 many BC patients do not exercise well. Good external support is one of the important factors for
11 patients' adherence to exercise^[19]. As an important part of external support for patients, family
12 members are the main facilitators of daily activities and disease care during hospitalization and
13 after discharge^[20]. Studies have shown that, compared with unsupervised exercise training,
14 supervised exercise training with the participation of family members can better ensure the
15 continuous and regular development of exercise, thereby maintaining and improving exercise
16 effects^[21, 22]. In addition, increasing disease-related communication between family members and
17 patients can effectively increase patients' confidence in treatment, improve the intimacy and
18 adaptability between patients and their family members, and thereby, improve patients' family
19 functioning^[23]. Therefore, there is an urgent need for a method to promote the active support role
20 of family members in the process of exercise training for BC patients, which will then enhance the
21 benefits of exercise in improving CRF in these patients.

22 The current study, therefore, proposes to assess the preliminary effects of a family-
23 involvement exercise protocol on alleviating CRF in BC patients through a quasi-randomized
24 controlled trial (Q-RCT).

26 METHODS AND MATERIALS

27 Participant Recruitment and Eligibility Criteria

28 Patients receiving postoperative chemotherapy for BC in a Grade A tertiary hospital in Dalian
29 will be selected for this study.

30 The inclusion criteria will be: (1) pathological diagnosis of BC; (2) receiving first course of
31 postoperative chemotherapy for BC; (3) age 18–65 years; (4) able to cooperate actively; (5)
32 voluntary provision of informed consent to participate in this study; and (6) residing with family
33 members during the intervention for 2 months. The exclusion criteria will be: (1) any other serious
34 disease, such as cardiovascular disease, other type of cancer, etc.; (2) exercise contraindications,
35 such as asthma, severe anemia, disc herniation or other diseases; and (3) mental illness, previous
36 mental illness, or family history of mental illness.

1
2
3 1 One family member will be included for each BC patients, and the inclusion criteria for family
4 2 members will be: (1) age >18 years, with primary school education or above, and good
5 3 communication skills; (2) spouse, parent, or child of the BC patient (immediate family member);
6 4 (3) main caregiver as determined by the BC patient and family members for at least 2 months; and
7 5 (4) voluntary participation in the study. The exclusion criteria will be: (1) payment of remuneration
8 6 for care of the BC patient; and (2) a previous history of mental illness.
9 7

13 8 **Sample size**

14 9 According to a previous study^[24], the score for CRF is expected to decrease by 2.29 points.
15 10 According to the two-sided sample size test formula, a two-sided test with $\alpha=0.05$ and 90%
16 11 power will require a total sample of 23 patients in each of the two groups. To account for a 20%
17 12 attrition rate, the required sample size is 56.
18 13

22 14 **Study Design**

23 15 To avoid contamination among the research participants, this study will adopt a lottery
24 16 method to randomly divide the hospital's first and second oncology departments into a control
25 17 group and intervention group and then select 28 patients from each ward who meet the
26 18 requirements after screening by the inclusion and exclusion criteria.

29 19 The intervention team will consist of a sports rehabilitator, a senior clinical nursing specialist,
30 20 a head nurse, three responsible nurses, and a nursing graduate student. The sports rehabilitator will
31 21 participate in the formulation of the exercise program. The nursing specialist will participate in the
32 22 guidance of the experimental program. The head nurse and three nurses will be responsible for
33 23 quality control, identifying problems in the implementation of the program, and making
34 24 rectifications. The graduate student will be responsible for explaining the intervention to the BC
35 25 patients and their families as well as data collection and collation. Group members will jointly
36 26 develop an exercise instruction manual (including exercise form, methods, precautions, etc.) and
37 27 record an instructional video for the exercise protocol.

42 28 The researcher will explain the purpose and implementation process of the study to the BC
43 29 patients when they are admitted to the hospital for their first chemotherapy treatment (T0). After
44 30 their agreement to participate, participants will be asked to provide written informed consent. The
45 31 participants will be informed that they can withdraw from the study at any time without any
46 32 consequences. After obtaining informed consent from the patients, the researcher will conduct the
47 33 stand-up and sit-down chair test and grip test with patients and issue general information
48 34 questionnaires along with the R-PFS, FACES II -CV, and FACT-B. The intervention study will
49 35 begin after the patients (and their family members) have completed their first assessment.
50 36

54 36 According to previous relevant studies^[25,26], exercise training begins to play a role in
55 37 improving CRF during the 8-week exercise intervention process. Therefore, the patients will be
56 38

1 tested with the stand-up and sit-down chair test and the grip test at the time of the fourth (T1) and
 2 eighth (T2) weekends of the intervention. The exercise completion rates in the two groups will be
 3 evaluated at these time points, and the researcher will again issue the general information
 4 questionnaires, R-PFS, FACES II -CV, and FACT-B to evaluate the effects of the exercise
 5 intervention. In the process of distributing the questionnaires, if patients are unable to understand
 6 the questionnaire items, the researcher will explain the items. A Consolidated Standards of
 7 Reporting Trials flow chart for the study is presented in Figure 1. The schedule for trial enrolment,
 8 intervention, and assessment is presented in Table 1.
 9

Table 1 Schedule of trial enrolment, intervention and assessment

Study period	Beginning of intervention	Intervention period	End of intervention
	(week 0)	(week 4)	(week 8)
Inclusion/exclusion criteria	×		
Informed consent	×		
Demographic characteristics	×		
Randomization and allocation	×		
R-PFS	×	×	×
Stand-up and sit-down chair test	×	×	×
Grip test	×	×	×
Exercise completion rate		×	×
FACES II -CV	×	×	×
FACT-B	×	×	×

10
 11 Abbreviations: R-PFS, Piper Fatigue Scale-Revised; FACES II -CV, Family Adaptability and Cohesion Scale, Second Edition -
 12 Chinese Version; FACT-B, Functional Assessment of Cancer Therapy – Breast

13 **Control group**

14
 15 When patients are admitted to the hospital for their first chemotherapy treatment, the
 16 researcher will provide exercise guidance for “combined aerobic and resistance exercise” and
 17 guide patients through the manual and video for exercise training, informing them of the
 18 recommended exercise time, form, method, intensity and precautions. The patients will be
 19 followed up monthly to learn their exercise status, and if patients have not persisted in following
 20 the recommendations, the researcher will ask patients why in order to help solve their problems
 21 and to encourage them to persist in exercise training.

1 Intervention group

2 The family-involvement combined aerobic and resistance protocol to be applied in the
3 intervention group is described in detail in Table 2.

4
5 Table 2 Exercise training intervention with family members

Guidance for family members	Evaluate the patients' life and social environment through family members and explain to family members the importance of family members accompanying the patient during exercise.	
	Distribute exercise manuals to family members and play exercise instructional videos.	
	Instruct family members to master the exercise time, method, standard posture and precautions, as well as precautions for the use of elastic bands and dumbbells for BC patients.	
Supervision of family members	Issue supervision diaries to family members ¹	Instruct and remind family members regarding the completion of the supervision diary through WeChat or phone every month.
		Upon readmission to the hospital, the patient will be required to bring the supervision diary in order for the record in the diary to be checked.
	Supervision of family members via WeChat	Establish a special WeChat group for family members, send exercise-related health knowledge to the WeChat group every week and regularly remind family members to urge patients to exercise.
		Encourage family members to ask questions actively in the WeChat group and provide timely feedback on the supervision situation and their feelings, answering relevant questions from family members in the process of guiding and supervising patients.
Follow-up with family members	Provide appropriate praise and rewards to the family members who complete the monitoring goals every week first, forming a competition mechanism to stimulate interest.	
	Make phone calls or complete face-to-face follow-up with family member monthly, asking them about questions they encountered during the care of the patients and answering those questions.	
Ask the patient about the training situation. If patients' exercise completion are poor, further inquire about why and analyze the reasons, helping the family to solve the problem.		
Instructions to family members		

Family members will accompany patients	Participate in the whole process of the patient's exercise protocol and provide the patient with full emotional support. Before exercising, choose the method of aerobic exercise together with the patient according to the patient's preference and play music to help the patient relax while they exercise.
Family members will supervise patients	Give exercise guidance to the patient, informing the patient of the correct exercise method by playing the provided video. When the patient makes an error or non-standard movement during the exercise, provide timely correction.
	Supervise the patient exercising. Take photos or videos while the patient is moving to record the patient's movement. Keep a supervision diary after each exercise session and upload exercise photos or videos in the WeChat group to ensure the effect of family supervision.
Family members will encourage patients	Encourage and support the patient to enhance their confidence; encourage the patient to describe difficulties encountered during exercise, and ensure them that the patient and family member will overcome the difficulty together.

¹The first part of the supervision diary includes basic information, including initials of family members, initials of patients, the relationship between family members and patients, patients' height and weight, initials of the doctor in charge, date of chemotherapy, etc. This part is filled out by the researcher before the diary is distributed to the family members. The second part includes the exercise date, time, location, exercise duration, frequency and number of groups, the patient's exercise status, and whether the family member participated in the exercise guidance and supervision throughout the exercise.

7 Combined aerobic and resistance exercise

8 The designed exercise training intervention will last for 8 weeks, and each patient can select
9 the most comfortable period of the week according to his or her own situation every week. Each
10 training time is scheduled for half an hour after a meal, and participants are instructed to avoid
11 training with an empty or full stomach. Each workout includes aerobic and resistance exercises
12 that are both progressive. A rest period of 5 minutes is allowed between aerobic and resistance
13 exercise. Aerobic exercise is accomplished by cycling, walking on a treadmill, or brisk walking
14 on the ground, depending on the patient's preference, according to the following schedule: twice
15 per week for 15–20 minutes in weeks 1–4 and three times per week for 25–35 minutes in weeks
16 5–8. For resistance exercise, the patients will use 0.45-kg dumbbells or a mineral water bottle filled
17 with 500 ml of water and a 18-cm brown elastic band with the brand name TheraBand. These items
18 will be provided by the researchers as the main exercise tools for four resistance exercise
19 movements: hip abduction, seated knee raising, raise before standing, and standing lateral raise.
20 These exercises are to be completed twice per week in weeks 1–4, with two sets of each exercise
21 and each set consisting of 8–12 repetitions and then three times per week in weeks 5–8, with three
22 sets of each exercise (each set includes 8–12 repetitions), with plenty of rest between sets^[27-30].

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1 Hip abduction: This exercise is done in a standing position, with the elastic band around the
2 ankle of one foot while the other foot is on the elastic band. The opposite hand holds the seat, and
3 the supporting foot is firmly planted on the ground to keep the trunk stable. Initially, the buttocks
4 exert force as the elastic band is stretched outward to the side by raising the leg until the angle
5 between the practice leg and the supporting foot is about 30 degrees. After a pause for about 1
6 second, the leg is slowly lowered to the ground. The exercise is done by alternating the left and
7 right feet between sets.

8 Seated knee raising: This exercise is done in a sitting position with a straight back while
9 holding the seat with both hands, keeping the upper torso upright, stepping on one end of the elastic
10 band with one foot, and pulling the elastic band around the ankle of the other foot. The knee is
11 then lifted to the maximum angle of joint activity and the after a pause for about 1 second, slowly
12 lowered. The exercise is done by alternating the left and right legs between sets.

13 Raise before standing: While standing with feet parallel, head straight and looking straight
14 ahead, the dumbbells are held at both sides of the body by both hands. Both arms are then raised
15 in front of the body, and after a pause for about 1 second, the arms are slowly lowered. Participants
16 are instructed to inhale during the horizontal lift and exhale while returning the arms to their
17 original positions.

18 Standing lateral raise: While standing with feet parallel, head straight and looking straight
19 ahead, the dumbbells are held at both sides of the body by both hands. The arms are raised from
20 the sides, with elbows slightly bent and focus placed on the shoulders. Once the arm is raised to a
21 horizontal position, participants pause for about 1 second before slowly lowering the arms to the
22 initial positions. Participants are instructed to inhale during the horizontal lift and exhale while
23 returning the arms to their original positions.

24 The intensity of aerobic exercise should be moderate; that is, the Borg subjective fatigue scale
25 score should reach 13–14 points (feeling a little hard). The intensity of resistance exercise should
26 be tolerable to the patient. If obvious fatigue and muscle pain occur during or after training, the
27 intensity of physical activity should be appropriately reduced. If patients have severe pain,
28 discomfort and other symptoms, they should immediately stop the activity and be admitted to the
29 hospital for re-examination^[31,32].

30 During the exercise, family members are instructed to pay attention to the patient's reactions
31 and to adjust the elastic band or exercise speed and intensity as needed. They must also ensure the
32 patient is not straining or using too much force during exercise to prevent stretching the wound or
33 the place where the catheter is placed. They should also pay attention to the patient's movement
34 at all times. If the patient experiences dizziness, discomfort or other adverse events, they should
35 be promptly instructed to stop exercising and visit the hospital if necessary.

36 Outcome measurements

1 The outcome measurements for this pilot study will be derived from baseline assessments and
2 clinical outcomes.

3 **Demographic and clinical characteristics of the participants**

4 A self-designed demographic and clinical data form will be employed to collect the
5 participants' sociodemographic data (e.g., age, educational background, employment status,
6 marital status, and household income), the participants' medical history (e.g., date of BC diagnosis,
7 current stage of BC, and date and type of treatment) and family members' sociodemographic data
8 at baseline (T0).

9 **Primary outcome: CRF**

10 Piper Fatigue Scale-Revised (R-PFS)^[33]: The R-PFS will be applied to assess the participants'
11 subjective fatigue. This self-administered questionnaire contains 22 items with scores ranging
12 from 0 to 10 and includes four domains of subjective fatigue. The R-PFS is available in a simplified
13 Chinese version^[34], with high reliability and validity, and has high reliability in the BC population.

14 **Secondary outcomes: muscle power, exercise completion, family intimacy and adaptability, 15 and quality of life**

16 Muscle strength, exercise completion, family intimacy and adaptability, and patient quality
17 of life will be assessed as secondary outcomes at T0, T1, and T2 using the stand-up and sit-down
18 chair test, grip test, exercise completion rate, FACES II -CV and FACT-B.

19 Stand-up and sit-down chair test (number of times standing up from the chair within 30
20 seconds)^[35]: This test will be used to evaluate the leg strength of the participant. The test procedure
21 is as follows: 1) an upright chair (or a folding chair) is placed against a wall (for the sake of safety);
22 2) the participant sit in the middle of the chair with the right and left feet shoulder-width apart, and
23 one foot may be put slightly forward and the other slightly back, while both arms are crossed at
24 the waist and held near the chest; 3) during the test, participants should completely stand up and
25 then completely sit down; 4) the number of times that the participant stands up from and sits down
26 in the chair within 30 seconds is recorded; and 5) for safety purposes or when necessary, the
27 participant may use his or her arms for assistance.

28 Grip test^[32]: This test will be used to evaluate the arm strength of the participants. A CAMRY
29 (model EH101) electronic grip strength meter is used in units of kg/lb. The maximum force is 90
30 kg/198 lb, and the division value is 0.1 kg/0.2 lb. Participants are in a standing position, with their
31 hands hanging down naturally, while their feet are positioned under the shoulders and hands are
32 held away from the body.

33 Exercise completion rate: This test will be used to assess the performance of the two types of
34 exercise. The exercise completion rate in this study will be calculated by dividing the number of
35 participants in the intervention group who completed 18 or more training sessions (more than 90%
36 of the total training volume) by the total number of people in the intervention group and
37 multiplying that value by 100%.

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1 **FACES II -CV**^[36]: The FACES II -CV will be adopted to assess the participants' family
2 intimacy and adaptability. A higher score indicates higher intimacy and adaptability. The
3 FACES II -CV is available in a simplified Chinese version, with high reliability and validity.

4 **FACT-B**^[37]: The FACT-B will be adopted to assess the patients' quality of life. A higher
5 score reflects better quality of life. The FACT-B is available in a simplified Chinese version, with
6 adequate psychometric properties reported among patients with BC.

7 **Data analysis**

8 Statistical analysis of the results will be completed using SPSS software version 25.0.
9 Analysis of covariance will be applied for comparisons between groups, and paired t-tests will be
10 used for comparisons from before to after exercise within a group. Values of $p < 0.05$ will represent
11 that a significant difference has been detected between test results.

12 **Data management**

13 After data collection is complete, all handwritten data will be converted to electronic data.
14 All data will be independently recorded by two researchers in Excel spreadsheets. The software
15 will automatically check for inconsistent or problematic data based on the inspection results and
16 generate a data problem table. After all data have been confirmed, reconciled, and stored in an
17 electronic database, participants' identifying information (e.g., real name) will not appear in the
18 relevant reports of the trial to protect their privacy. Only researchers directly involved in the
19 analysis of this study will have access to the final trial dataset, which will contain only coded data.

20 **Data sharing statement**

21 A technical appendix, statistical codes and dataset will be available at any time upon request
22 to the corresponding author.

23 **Patient and public involvement**

24 Patients or the public were not involved in the design of this study and will not be involved
25 in conducting the research or reporting the results.

26 **Ethics and dissemination**

27 Ethical approval of the proposed study has been granted by the Ethics Committee of the First
28 Affiliated Hospital of Dalian Medical University (PJ-KS-KY-2021-288), and the trial has been
29 registered in the Chinese Clinical Trial Registry (registration number: ChiCTR2200055793). Only
30 participants who provided written informed consent will be included in the study. The results of
31 this study will be published via peer-reviewed publications and presentations at conferences.

32 **DISCUSSION**

1 As one of the most common symptom clusters in patients with BC, CRF can significantly
2 diminish patients' quality of life and daily functioning^[38]. An increasing number of studies has
3 demonstrated that combined aerobic and resistance exercise has beneficial effects on symptom
4 management in patients with cancer^[39]. However, due to differences in the time and intensity of
5 exercise as well as individual differences, the effect of such exercise has varied among different
6 studies. Gokal et al.^[40] tested a home-based walking intervention based on self-management in 25
7 BC patients receiving chemotherapy and found that this self-management exercise intervention
8 could improve patients' fatigue symptoms as well as their physical activity level. However, some
9 patients had difficulty adhering to exercise training, causing them to stop exercising. Uhm et al.^[41]
10 conducted a 12-week RCT on 356 BC patients, which showed that combined aerobic and
11 resistance exercise improved patients' fatigue symptoms, muscle strength, and quality of life.
12 However, because some patients could not persist in completing the exercise, the advantages of
13 the tested exercise over traditional exercise programs were not obvious. Previous studies have
14 confirmed that family-involvement exercise interventions have many benefits for patients after
15 stroke^[42], coronary heart disease^[43], lung cancer^[44], and other conditions, but there are few reports
16 on the effect of family-involvement exercise interventions in BC patients in China. This highlights
17 a great need to explore the effects of family-involvement exercise on CRF in patients with BC.

18 The principal strength (and novel aspect) of this study resides in the fact that in the
19 intervention, each participant will be able to choose the type of aerobic exercise they prefer. Also,
20 the study will provide exercise instruction videos designed to increase patients' motivation to
21 exercise. In addition, we aim to provide new evidence on the cost-effectiveness of this type of
22 intervention (to our knowledge, virtually no evidence has previously been reported in this regard).
23 Moreover, an exercise booklet will be provided to the participants in both the intervention and
24 control groups. The information presented in this booklet has been comprehensively adapted from
25 relevant national guidelines, professional bodies, and research evidence in published peer-
26 reviewed articles.

27 The proposed study will also have some limitations. Given the limited number of study sites,
28 the study sample may not offer a widely representative sample of patients with BC. Moreover, due
29 to the visible nature of the exercise intervention, blinding of the participants and investigators
30 cannot be performed in this study, which might increase the risk of detection bias during the
31 study's implementation. The lack of long-term follow-up to assess the ongoing effects of family-
32 involvement exercise might be another limitation, but this can be considered in the future full-
33 scale trial as one of the main study outcomes. Furthermore, this study will not be a rigorous RCT
34 but rather a Q-RCT, and a future multi-center, large-scale RCT will need to be conducted to further
35 verify the research evidence for the effects of family-involvement exercise on the management of
36 BC patients with CRF.

1 The proposed Q-RCT will assess the preliminary effects of a family-involvement exercise
2 program for alleviating CRF in BC patients undergoing postoperative chemotherapy. The
3 convenience of the family-involvement exercise for the management of CRF may provide patients,
4 healthcare professionals, and policy-makers with further guidance for CRF management in the
5 long-term.

6 7 **Author affiliations**

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9 China

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11 **Contributorship statement:** Chuhan Huang conceived and designed the study, and Tieying Shi
12 will oversee the research team and research process. Yingjie Cai and Chuhan Huang will be the
13 main implementers of the study and drafted this manuscript. Jingjing Jia wrote the ethics review
14 confirmation. Yufei Guo participated in the design of the study and assisted in drafting this
15 manuscript. All authors have read and agreed to the final version of the manuscript.

16 **Funding:** Preparation of this study protocol was funded by the Dalian Science and Technology
17 Innovation Fund Science and Technology Benefit People Project (Award/Grant No.
18 2022JJ13FG109). The authors have not declared a specific grant that will fund the proposed
19 research from any funding agency in the public, commercial or not-for-profit sectors.

20 **Competing interests:** None declared.

21 **Patient consent for publication:** Not required for present manuscript.

22 **Provenance and peer review:** Not commissioned; externally peer reviewed.

23 **Ethics approval:** The study protocol has been approved by the Ethics Committee of the First
24 Affiliated Hospital of Dalian Medical University, China (PJ-KS-KY-2021-288).

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20 Figure 1 A Consolidated Standards of Reporting Trials flow chart of the study

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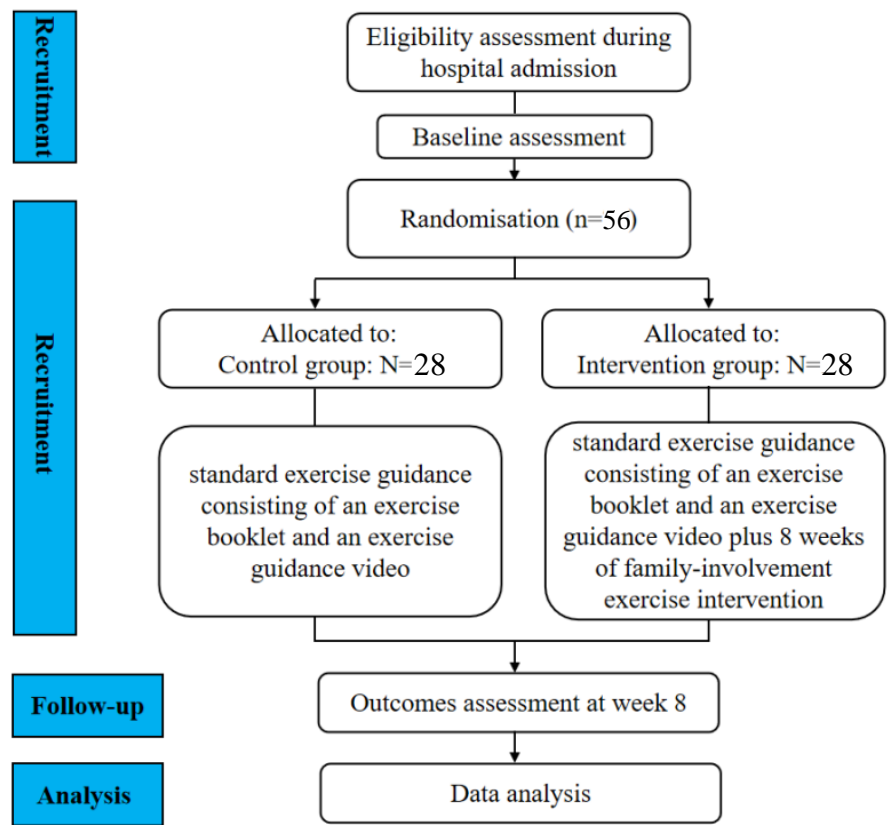
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Effect of a family-involvement combined aerobic and resistance exercise protocol on cancer-related fatigue in breast cancer patients during postoperative chemotherapy: study protocol for a quasi-randomized controlled trial (No.1/No.2)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	ChiCTR2200055793(No.12)
	2b	All items from the World Health Organization Trial Registration Data Set	The trial has been registered in the Chinese Clinical Trial Registry(No.12)
Protocol version	3	Date and version identifier	Date: 2021.10.12 Version 1.0
Funding	4	Sources and types of financial, material, and other support	Preparation of this study protocol was funded by the Dalian Science and Technology Innovation Fund Science and Technology Benefit People Project (Award/Grant No. 2022JJ13FG109). (No.13)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Names: Chuhan Huang Affiliations: The First Affiliated Hospital of Dalian Medical University Roles: The general design of the protocol
	5b	Name and contact information for the trial sponsor	The study has not any trial sponsor.

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2		5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
3			The study has not any trial sponsor.
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12		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
13			It has not yet been identified the Composition of data monitoring committee (DMC) in the study protocol.
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24	Introduction		
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26	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
27			It has been elucidated in the study protocol context.(No.3-4)
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34		6b	Explanation for choice of comparators
35			The researcher will provide exercise guidance for “combined aerobic and resistance exercise”for the control group to verify the effect of family members’ participation (No.6-7)
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40	Objectives	7	Specific objectives or hypotheses
41			The current study, therefore, proposes to assess the preliminary effects of a family-involvement exercise protocol on alleviating CRF in BC patients through a quasi-randomized controlled trial (Q-RCT).(No.4)
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48	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
49			The trial will be a quasi-randomized controlled trial (Q-RCT).(No.4)
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57	Methods: Participants, interventions, and outcomes		
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2	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
3			Patients receiving postoperative chemotherapy for BC in a Grade A tertiary hospital in Dalian will be selected for this study.(No.4)
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8	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
9			It is already described in the part “Participant Recruitment and Eligibility Criteria” of the main document.(No.4-5)
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17	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
18			The text has been described at page 5-10.
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23		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
24			The text has been described at page 9-10.
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31		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
32			The text has been described at page 7.
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38		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
39			Relevant concomitant care and interventions that are not prohibited during the trial.
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42	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
43			The text has been described at page 10.
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2	Participant	13	Time schedule of enrolment,	The text has been described at page 6,
3	timeline		interventions (including any run-ins	figure 1.
4			and washouts), assessments, and	
5			visits for participants. A schematic	
6			diagram is highly recommended (see	
7			Figure)	
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10	Sample size	14	Estimated number of participants	The text has been described at page 5.
11			needed to achieve study objectives	
12			and how it was determined, including	
13			clinical and statistical assumptions	
14			supporting any sample size	
15			calculations	
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18	Recruitment	15	Strategies for achieving adequate	Due to the sufficient sample size in this
19			participant enrolment to reach target	study, the strategies for achieving
20			sample size	adequate participant enrolment to reach
21				target sample size will be not adopted.
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24 **Methods: Assignment of interventions (for controlled trials)**

25 Allocation:

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28	Sequence	16a	Method of generating the allocation	This study used a quasi-randomized
29	generation		sequence (eg, computer-generated	controlled trial without assignment of
30			random numbers), and list of any	sequence generation.
31			factors for stratification. To reduce	
32			predictability of a random sequence,	
33			details of any planned restriction (eg,	
34			blocking) should be provided in a	
35			separate document that is unavailable	
36			to those who enrol participants or	
37			assign interventions	
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41	Allocation	16b	Mechanism of implementing the	This study has not allocation concealment
42	concealment		allocation sequence (eg, central	mechanism.
43	mechanism		telephone; sequentially numbered,	
44			opaque, sealed envelopes),	
45			describing any steps to conceal the	
46			sequence until interventions are	
47			assigned	
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50	Implementation	16c	Who will generate the allocation	The text has been described at page 5.
51			sequence, who will enrol participants,	
52			and who will assign participants to	
53			interventions	
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1 2 3 4 5 6 7 8 9 10 11 12	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	No blinding was set in this study due to the limited study conditions.
13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	No blinding was set in this study due to the limited study conditions.

Methods: Data collection, management, and analysis

15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	The text has been described at page 5, 9-11.
		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	The text has been described at page 11.
	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	The text has been described at page 11.
	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	The text has been described at page 11.
		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	This study has not any methods for any additional analyses.

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20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	It is not involved definition of analysis population relating to protocol non-adherence and any statistical methods to handle missing data.
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Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	It has not yet been identified the Composition of data monitoring committee (DMC) in the study protocol. The research team will monitor and manage the data.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Graduate students in the research group will conduct any interim analyses.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	The text has been described at page 9-10.
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	The process which auditing trial conduct will be independent from investigators.

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	The text has been described at page 11-12.
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	The study protocol has been communicated with the Ethics Committee of the First Affiliated Hospital of Dalian Medical University.

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2	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
3			The text has been described at page 12.
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7		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
8			It is not involved additional consent provisions for collection and use of participant data and biological specimens in ancillary studies.
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11	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
12			This process will be all performed by one investigator.
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20	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
21			The text has been described at page 13.
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24	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
25			The text has been described at page 11.
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30	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
31			It is not involved ancillary and post-trial care.
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36	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
37			The text has been described at page 13.
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47		31b	Authorship eligibility guidelines and any intended use of professional writers
48			The text has been described at page 13.
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52		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
53			The text has been described at page 11.
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Appendices

1				
2	Informed consent	32	Model consent form and other related	Model consent form and other related
3	materials		documentation given to participants	documentation will be given to participants
4			and authorised surrogates	and authorised surrogates.
5				
6	Biological	33	Plans for collection, laboratory	Biological specimens will be not involved
7	specimens		evaluation, and storage of biological	in this study.
8			specimens for genetic or molecular	
9			analysis in the current trial and for	
10			future use in ancillary studies, if	
11			applicable	
12				
13				

14 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
 15 Explanation & Elaboration for important clarification on the items. Amendments to the
 16 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
 17 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)"
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