BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048115
Article Type:	Protocol
Date Submitted by the Author:	23-Dec-2020
Complete List of Authors:	Yao, Li-Qun; Charles Darwin University, College of Nursing and Midwifery; Charles Darwin University Tan, Jing-Yu (Benjamin); Charles Darwin University, College of Nursing and Midwifery Brisbane Centre Turner, Catherine; Charles Darwin University, College of Nursing and Midwifery Wang, Tao ; Charles Darwin University, College of Nursing and Midwifery Brisbane Centre
Keywords:	Breast tumours < ONCOLOGY, COMPLEMENTARY MEDICINE, Clinical trials < THERAPEUTICS

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Title Page

Feasibility and preliminary effects of tai chi for fatigue-sleep disturbance-depression symptom cluster in breast cancer patients: Protocol of a preliminary randomized controlled trial

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Abstract

Introduction The fatigue-sleep disturbance-depression symptom cluster (FSDSC) is one of the most common and debilitating side effects in breast cancer (BC) patients throughout their treatment trajectory. Tai chi has been supported as a promising non-pharmacological intervention for the individual symptom management of cancer-related fatigue, sleep disturbance, and depression. However, relevant evidence of using tai chi for FSDSC management in BC patients has been lacking.

Methods This study will be a two-arm, single-blinded pilot randomized controlled trial (RCT) involving an 8-week intervention and a 4-week follow-up. Seventy-two BC patients experiencing the FSDSC will be recruited from two tertiary medical centres in China. The participants will be randomized to either a tai chi group (n=36) or a control group (n=36). The participants in the tai chi group will receive an 8-week tai chi intervention in addition to standard care, while the participants in the control group will receive standard care only consisting of a booklet on the self-management of cancer symptoms. The primary outcomes will include a series of feasibility assessments of the study protocol in relation to the study's methodological procedures, including subject recruitment and follow-up process, completion of study questionnaires, and the feasibility, acceptability, and safety of the intervention. The secondary outcomes will be the clinical outcomes regarding the effects of tai chi on the FSDSC and quality of life, which will be measured by the Brief Fatigue Inventory (BFI), the Pittsburgh Sleep Quality Index (PSQI), the Hospital Anxiety and Depression Scale (HADS), and the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaires.

Ethics and dissemination Ethics approval was obtained from the relevant sites (H19094, KY2019133, 201932). The findings of the study will be published in peer-reviewed scientific journals and at conferences.

Trail registration: ClinicalTrials.gov, identifier NCT04190342. Registered on 3 December 2019.

Keywords: Breast cancer; Fatigue; Sleep disturbance; Depression; Symptom cluster; Tai chi

Strengths and limitations of this study

- This will be the first clinical trial to explore the feasibility and preliminary effects of tai chi on FSDSC management in BC patients.
- This study will use an evidence-based tai chi intervention protocol in the intervention group which has been presented in a methodological paper.
- The study design of the pilot study will be guided by the Medical Research Council Framework for Developing and Evaluating Complex Interventions.
- This study will use comprehensive outcome measurements, including a series of feasibility outcomes, which will support the refinement of a clinically feasible tai chi intervention protocol for the future full-scale RCTs.
- There are limited study sites which may not provide a completely representative sample of BC patients who are experiencing the FSDSC.

Introduction

Breast cancer (BC) is regarded as the most common cancer among women worldwide [1]. Although the number of BC survivors is increasing with improved cancer treatment, the substantial negative effects associated with cancer and cancer treatments remain a significant problem for survivors. BC patients following the treatment of surgery, radiation therapy, antihormonal therapy, and/or chemotherapy can experience significant side effects, including fatigue, sleep disturbance, and depression [2]. These frequently reported, troublesome symptoms usually occur concurrently in BC patients as a symptom cluster [3, 4]. According to Dodd et al. [5], "a symptom cluster consists of three or more symptoms that are related to each other and that occur together" (p. 468). The fatigue-sleep disturbance-depression symptom cluster (FSDSC) is one of the most frequent symptom clusters among BC patients, which can negatively impact patients' physical and psychosocial functioning status and quality of life (QoL), including more severe cancer-related symptoms, lower treatment compliance, poorer emotional conditions, worse financial hardship, and even shorter survival time [6-8].

To date, no specific medications are available for the management of cancer symptom clusters. Reviewing the previous evidence, various non-pharmacological approaches have been used as a combination treatment with medication for the comprehensive management of cancer-related symptoms [9-10]. However, most of the widely employed non-pharmacological approaches, such as acupuncture [11], hypnotherapy [12], guided imagery [13], massage [14], and electrical stimulation [15], require intensive professional skills training, supervised practise, and specific equipment, all of which can be significantly time- and energy-consuming and can considerably increase the consumption of healthcare resources and costs. Moreover, due to fatigue intolerance, cancer patients are usually reluctant to participate in energy-consuming non-pharmacological interventions such as intensive exercise [16]. Thus, an energy-saving and cost-effective non-pharmacological approach is much more appropriate for FSDSC management in cancer patients.

Traditional Chinese exercise (TCE) is an appropriate and effective option for FSDSC management in BC patients given its mild-to-moderate intensity and low cost. Tai chi, a very popular TCE, consists of several slow, simple, and repetitive body movements along with deep breathing, and it is easy to master [17]. Additionally, there has been increasing evidence of its positive effects in targeting the management of individual symptoms such as fatigue, sleep disturbance, and depression [18-20]. However, no clinical research has ever been performed using tai chi exercise for symptom cluster management, especially the FSDSC in BC patients. The current study therefore proposes to assess the feasibility and the preliminary effects of using an evidence-based tai chi intervention for managing the FSDSC in BC patients through a pilot randomized controlled trial (RCT).

Methods and materials

Study design

The study's design will be a two-parallel-arm, single-blinded (assessor) pilot RCT. The participants will be randomly allocated into two groups: a tai chi intervention group and a control group, with an allocation ratio of 1:1. The study period will be 12 weeks, which will

involve an 8-week tai chi intervention and a 4-week follow-up for the intervention group. A CONSORT flowchart of the study is presented in **Figure 1**. The schedule of trial enrolment, intervention data collection, and assessments are presented in **Table 1**. This protocol will be reported in accordance with the SPIRIT Checklist.

Study setting

This study will be implemented in two tertiary medical centres in Mainland China, including the Affiliated Hospital of Putian University (Fujian) and the Affiliated Hospital of Southwest Medical University (Sichuan).

Sample size calculation

Thirty or more participants per group is usually recommended as sufficient for a pilot study to examine intervention feasibility [21] and to estimate a between-group effect for a subsequent power analysis that can be used in the main study's sample size estimation [22]. Given that the primary purpose of this study will be to explore the feasibility and acceptability of the study's methodological procedures, intervention protocol, and questionnaires, 30 participants per group is therefore an appropriate sample size in this study. Taking into account a conservative anticipation of a 20% dropout rate, the final sample size will therefore be 36 in each group, with a total of 72 participants [23].

Inclusion and exclusion criteria

Eligible participants will be recruited using the following inclusion criteria:

(1) adult female patients aged over 18 years;
(2) diagnosed with stage I, II, or IIIa BC (non-metastatic BC);
(3) have experienced at least a moderate level of fatigue, sleep disturbance, and depression, with a score of greater than 3 on a 10-point scale, from "0 (no symptom)" to "10 (worst symptom)" for each symptom in the past one month;
(4) have completed breast cancer surgery for over one month;
(5) have recently commenced adjuvant chemotherapy;
(6) able to speak and understand Mandarin Chinese; and
(7) willing and able to give written informed consent for study participation.

Potential participants will be excluded using the following exclusion criteria:

(1) presently taking medications for the treatment of fatigue, sleep disturbance, or depression, such as antidepressant medications, psychostimulants, or hypnotics;
(2) extremely weak or have cognitive impairment and/or severe mental illness;
(3) have participated in a tai chi program during the previous six months;
(4) have practised other TCE for over 30 minutes, three times per week, during the previous three months; and
(5) have scheduled other elective surgery within the trial period.

Recruitment

A research team will be formed before the commencement of the trial. Three investigators, including the doctoral investigator and two clinical nurses, will be primarily responsible for

the subject recruitment and tai chi training. Two research assistants will conduct data collection and telephone follow-ups. To ensure the quality of data collection, the two research assistants will be trained on questionnaire data collection skills, including understanding the questionnaire items and standardizing their conversations with the participants. The academic supervisors of the doctoral investigator will monitor the entire study procedure on an ongoing basis through regular monthly meetings.

Among the hospitalized patients in the Breast Cancer Unit, potential participants will be recruited directly by the doctoral investigator and the two clinical nurses. Some potential participants who attend the breast cancer clinic for regular follow-ups will be referred by physicians and clinic nurses to the doctoral investigator and the two clinical nurses. A participant information sheet, including the research aim, the procedures, and the contact details of the study investigators, will be given to potential participants and will be explained by the doctoral investigator and the two clinical nurses. Potential participants who express interest in participating in the study will be screened for eligibility with reference to the inclusion and exclusion criteria by the doctoral investigator and the two clinical nurses. After their agreement to participate, the participants will be required to provide their written informed consent. The participants will be informed that they can withdraw from the study at any moment without any consequences.

Randomization and allocation concealment

One set of randomization sequences will be generated via an online randomizer (https://www.randomizer.org/) based on the estimated sample size. To ensure allocation concealment, the randomization sequences will be generated and retained by a statistician who will not be involved in any other parts of this study. After the participants' completion of the baseline assessment, the two clinical nurses will telephone the statistician to determine which group the patient should be assigned. The participants will be randomly assigned to either the tai chi intervention group or the control group.

Blinding

Due to the visible nature of the tai chi intervention, the blinding of the study investigators and the participants will be impossible. Thus, blinding will only be applied to the outcome assessors (i.e., the two research assistants) in this pilot RCT to avoid potential detection bias during data collection. The two research assistants will be responsible for data collection and telephone follow-ups, and they will not be involved in the subject recruitment process.

Tai chi intervention group

In addition to the standard care provided to both the control group and the intervention group, the participants in the intervention group will additionally receive instruction on easy 8 form tai chi movements. The development and validation of the evidence-based tai chi intervention protocol are detailed in a methodological paper [24]. The intervention regime will last 60 minutes per session, two sessions per week, for eight weeks, which is based on existing research evidence, theories, practice standards/guidelines, and experts' consensus [24]. To ensure that the patients have fully mastered the tai chi skills, before the commencement of the

intervention, the participants will receive at least three 60-minute training sessions until they can perform the movements correctly and smoothly, along with a home learning package in an audio-visual format (i.e., a recorded video). The training will be conducted and led by either the doctoral investigator or the two clinical nurses, and attendance will be recorded. All the participants will be asked to perform the tai chi movements in front of the trainers (i.e., return demonstration) to make sure that they are correctly performing each movement of the tai chi exercise. In addition, the participants will be tested by the trainers during the last training session to ensure that they have correctly performed the tai chi movements (a "return demonstration").

Easy 8 form tai chi is comprised of the following components: a 10-minute warm-up, 25 to 30 minutes of easy tai chi practising, and a 10-minute cool-down. During each session, the participants will also have a 10-minute break to rest and interact socially. Details of the tai chi protocol are presented in a methodological paper [24]. A specially designed exercise log will be provided to the participants to record information related to their tai chi practice each time, such as duration and frequency of practising tai chi, as well as any potential adverse reactions related to tai chi, such as dizziness, knee pain, musculoskeletal aches and pains, etc. The exercise logs will be returned to the research assistants on the date of the participants' treatment or follow-up appointment at the hospital. To enhance the participants' adherence to the tai chi intervention, the research assistants will conduct follow-ups every week using WeChat (the most popular social media platform in China) or phone calls to remind them to practise their tai chi and to collect information on any potential adverse reactions related to the tai chi intervention.

Control group

The participants allocated to the control group will receive a standard care package, which will be a booklet on the self-management of cancer symptoms. This booklet will offer basic knowledge and management strategies regarding FSDSC management in BC patients during or after chemotherapy treatment. All the information listed in this booklet will be comprehensively adapted from relevant national guidelines developed by professional associations in cancer care and government health department websites, including the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (the NCCN Guidelines) [25] and the Department of Health – Government of Western Australia [26]. Research evidence in published peer-reviewed articles will also be cited as supporting information for the booklet's development [2, 27-29]. Additionally, the participants will be asked to refrain from practising any exercises related to TCE during the study, with reminders at all assessment time points. On completion of the pilot RCT, the participants in the control group will have an opportunity to receive the tai chi training from the study team.

Outcome measurements and follow-up

The outcome measurements for this pilot RCT will include three categories, namely, baseline assessments, feasibility and acceptability outcomes, and clinical outcomes. The feasibility and acceptability outcomes will be the primary outcomes, while the clinical outcomes will be the

secondary outcomes. All the outcomes and follow-ups will be conducted by the two research assistants.

Demographic and clinical characteristics of the participants

A self-designed demographic and clinical data form will be employed to collect the participants' socio-demographic data (e.g., age, education background, employment status, marital status, and household income) and medical history (e.g., date of diagnosis, the current stage of BC, and date and type of treatment) at baseline (T1).

Primary outcomes: Feasibility and acceptability

(1) The feasibility assessment of subject recruitment and follow-up process will include: **(a)** the time that was taken to recruit the planned sample size of participants; **(b)** referral rate – the number of referrals made by clinicians in different departments and hospitals divided by all referrals; **(c)** recruitment rate – the number of subjects who enrolled in the study divided by all subjects eligible for enrolment; **(d)** retention rate – the number of subjects who completed the study divided by all subjects who enrolled in the study; **(e)** dropout rate – the number of subjects who dropped out after randomization divided by all subjects who enrolled in the study; and **(f)** feedback from the dropout subjects to identify their reasons for dropping out. The feasibility of recruitment and follow-up process outcomes will be collected at baseline (T1) and immediately after the intervention (T2).

(2) The feasibility assessment of the outcome measures will include the percentage of missing values for each item of the scales used – the Brief Fatigue Inventory (BFI), the Pittsburgh Sleep Quality Index (PSQI), the Hospital Anxiety and Depression Scale (HADS), and the Functional Assessment of Cancer Therapy-Breast (FACT-B) – at baseline (T1), immediately after the intervention (T2), and four weeks after completion of the intervention (T3).

(3) The feasibility and acceptability of the intervention will include: **(a)** adherence rates – the number of tai chi sessions practised divided by the total number of sessions required; **(b)** the participants' feedback on and satisfaction with the intervention using a self-designed feedback form; and **(c)** records of potential adverse events associated with tai chi, which will be obtained from the exercise log. The feasibility and acceptability of the intervention will be assessed immediately after the intervention (T2).

Secondary outcomes: Fatigue, sleep disturbance, depression, and QoL

The fatigue, sleep disturbance, depression, and QoL of the BC patients as the secondary outcomes will be measured at T1, T2, and T3 using the BFI, the PSQI, the HADS, and the FACT-B.

(1) Fatigue: The participants' severity of fatigue and cancer-related fatigue in daily functioning will be assessed using the BFI. The BFI has nine items, with higher scores corresponding to more severe fatigue [30, 31]. The Chinese version of the BFI has excellent internal consistency reliability (Cronbach's alpha from 0.90 to 0.92), as well as construct validity and convergent validity [32].

(2) Sleep disturbance: The participants' sleep quality and disturbance will be assessed using the PSQI. This questionnaire has seven domains: sleep latency, habitual sleep efficiency, subjective sleep quality, sleep duration, use of sleeping medication, sleep disturbance, and daytime dysfunction [33]. The Chinese version of the PSQI has been demonstrated to be a reliable and valid scale, and it has been widely utilized among cancer patients [34].

(3) Depression: The HADS will be used to assess the participants' depression. The cut-off scores have been classified and labelled as 0 to 7 for "normal", 8 to 10 for "mild", 11 to 15 for "moderate", and ≥16 for "severe" [35]. As a reliable and valid tool for measuring depression, the HADS has been widely utilized among Chinese cancer patients, with well-documented psychometric properties [36].

(4) Quality of life: The FACT-B will be 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 [37].

Data management

The doctoral investigator and one of the research assistants will enter all the collected data into a computer with a double data entry approach. To ensure that there are no discrepancies or coding errors after running descriptive and inferential statistics, data cleaning will be conducted before data analysis [38]. First, the datasets will be checked against the paper recordings of raw data to ensure that the data coding is correct. Then, double-checking will be undertaken by the other research assistant to ensure accuracy. All electronic data will be retained in a compressed folder using password-protected access systems, and all hard copies of the materials will be retained in a cabinet at the study sites. Storage and disposal of research data hard copies will strictly follow the regulations and policies of the lead investigator's institution and the study sites, including the Charles Darwin University Research Data Management Guide.

Data analysis

Statistical analyses will be conducted using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). The intention-to-treat (ITT) principle and the last observation carried forward (LOCF) method will be utilized for the management of missing data. Effect sizes (ES) of between-group comparisons will be estimated using Cohen's d [39]. The chi-squared test or Fisher's exact test will be used to examine the comparisons between the control and intervention groups for categorical variables (e.g., education background, referral rate, retention rate, etc.). An independent t-test or the Mann-Whitney U test will be utilized for the continuous variables (e.g., age, household income, etc.). The Generalized Estimating Equation (GEE) model will be performed for repeated multivariate analysis between the two study groups for the scores and domain scores of the BFI, the PSQI, the HADS, and the FACT-B. The significance level to identify statistical differences will be $p<0.05$.

Patient and public involvement

No patient involved in the study design or any other part of this protocol.

Ethics and dissemination

This study was registered at ClinicalTrials.gov (identifier NCT04190342) before its commencement. The study has been approved by the Human Research Ethics Committee at Charles Darwin University (H19094), the Clinical Trial Ethics Committee at the Affiliated Hospital of Southwest Medical University (KY2019133), and the Clinical Trial Ethics Committee at the Affiliated Hospital of Putian University (201932). The abstract of this study has been submitted to Sigma's 32nd International Nursing Research Congress for presentation in 2021. The results of the study will be published in peer-reviewed scientific journals.

Discussion

As one of the most common symptom clusters in BC patients, the FSDSC can significantly deteriorate patients' QoL and daily functioning [40,41]. An increasing number of studies have demonstrated that tai chi has beneficial effects on symptom management in cancer patients; however, almost all the studies focused on individual symptoms only, such as fatigue, sleep disturbance, and depression [42-44]. No study has ever been performed to investigate the role of tai chi in managing symptom clusters in the BC population. This highlights a great need to explore the effects of tai chi on the FSDSC in BC patients. Given that the patients will have already experienced fatigue upon enrolment in this pilot RCT, lengthy and complicated tai chi movements will be avoided. Easy 8 form tai chi, a traditional Chinese mind-body exercise with only eight simple movements, is an appropriate intervention for FSDSC management as it is easy to learn, is less energy-consuming, and requires no specific equipment [45,46].

This study has some strengths. According to the Medical Research Council Framework for Developing and Evaluating Complex Interventions, the feasibility and acceptability of a proposed intervention and research methodological procedures should be fully examined prior to performing the full-scale study [47]. In this current pilot RCT, the feasibility and acceptability of an easy 8 form tai chi intervention program will be assessed comprehensively using a series of feasibility outcomes, including subject recruitment, intervention delivery, and outcome assessments. A comprehensive assessment will promote the refinement of the intervention protocol for the future main study. Furthermore, different from some current non-pharmacological studies, the tai chi intervention protocol used in the current pilot RCT will be evidence-based and rigorously developed based on systematic review evidence and recommendations [48-56]; TCE principles, theories [57, 58], and practice standards [46, 59]; the characteristics of cancer-related symptoms; and the consensus of an expert panel. In addition, an FSDSC self-management education booklet will be designed and provided to the participants in both the intervention and control groups. The information listed in this booklet will be comprehensively adapted from relevant national guidelines, professional bodies, and research evidence in published peer-reviewed articles. The self-management education booklet will be used as an enhanced care component to improve the patients' knowledge and relevant coping strategies for FSDSC management. Finally, a safety assessment of the tai chi protocol for cancer patients will be set as one of the feasibility outcomes, which has rarely been measured in existing tai chi interventional studies. Although tai chi is a non-invasive intervention that is generally regarded as a relatively safe approach, the exercise program

might still contribute to some minor adverse events such as a lumbar sprain, musculoskeletal aches and pains, dizziness, knee pain, etc. [60]. Therefore, any potential adverse events related to practising tai chi will be monitored and reported in the exercise log.

This study also has some limitations. Given the limited study sites, the study sample in this study may not offer a completely representative sample of BC patients who are experiencing the FSDSC. Due to the visible nature of the tai chi intervention, the blinding of the participants and the tai chi instructor cannot be performed in this study, which might increase the risk of detection bias during the study's implementation, although the outcome assessors will be blinded to the intervention allocation. The lack of long-term follow-up to assess the ongoing effects of tai chi might be another limitation, but this can be considered in the future full-scale RCT as one of the main study outcomes.

This study will utilize a rigorously designed RCT to assess the feasibility and preliminary effects of an evidence-based tai chi intervention program for managing the FSDSC in BC patients. Findings from this study will provide a significant knowledge and evidence base for cancer symptom management. The convenience of the tai chi intervention for the self-management of the FSDSC may provide BC patients, healthcare professionals, and policymakers with further guidance in FSDSC management in the long run. Furthermore, the results of this trial will contribute to a future multi-centre large-scale main RCT to further conclude the research evidence on the effects and safety of tai chi for FSDSC management in BC patients. Specially, the results regarding the primary outcomes will provide evidence on the feasibility issues of the tai chi intervention protocol and the methodological procedures of the RCT. The results regarding the effect size estimations of the outcome parameters in this pilot RCT will also be utilized for sample size estimation in the future main RCT.

Conclusion

The research design and methodological procedures of the proposed assessor-blinded pilot RCT aim to assess the feasibility and preliminary effects of using an evidence-based tai chi intervention to manage the FSDSC in BC patients. The results of this pilot study will provide research evidence in terms of the feasibility and acceptability of using the evidence-based tai chi intervention for FSDSC management in BC patients, as well as contribute to the refinement of the tai chi intervention protocol, which will be utilized in a future multi-centre large-scale RCT to determine the definite effects of tai chi on the FSDSC in BC patients.

Trial status

The study began in May 2020. Recruitment is ongoing. The study is expected to be completed in May 2021.

Funding

This study was supported by the Australian Government Research Training Program (RTP) scholarship.

Conflict of interest

The authors declare that there is no conflict of interest in terms of the publication of this paper.

Authors' contribution

Yao LQ: study conception and design, trial organization, administration and coordination, quality assurance, and manuscript drafting and revision; **Tan JY**: study conception and design, study procedure supervision, and manuscript revision; **Turner C**: study conception and design, study procedure supervision, and manuscript revision; **Wang T**: study design, study procedure supervision, and manuscript revision.

Table 1. The schedule of trial enrolment, interventions, and assessments

	Study Period				
	Before Enrolment (0 weeks)	**Intervention Period (1-8 weeks)**	**End of Intervention (8 weeks)**	**Follow-up Period (9-12 weeks)**	**End of Follow-up (12 weeks)**
Inclusion/exclusion criteria	×				
Informed consent	×				
Demographic characteristics	×				
Randomization and allocation	×				
Feasibility of recruitment and follow-up process	×		×	×	×
Feasibility assessment of the outcome measures	×		×		×
Feasibility and acceptability of the intervention		×			
BFI	×		×		×
HADS	×		×		×
PSQI	×		×		×
FACT-B	×		×		×
Safety measurement		×			

Figure 1. A CONSORT flowchart of the study

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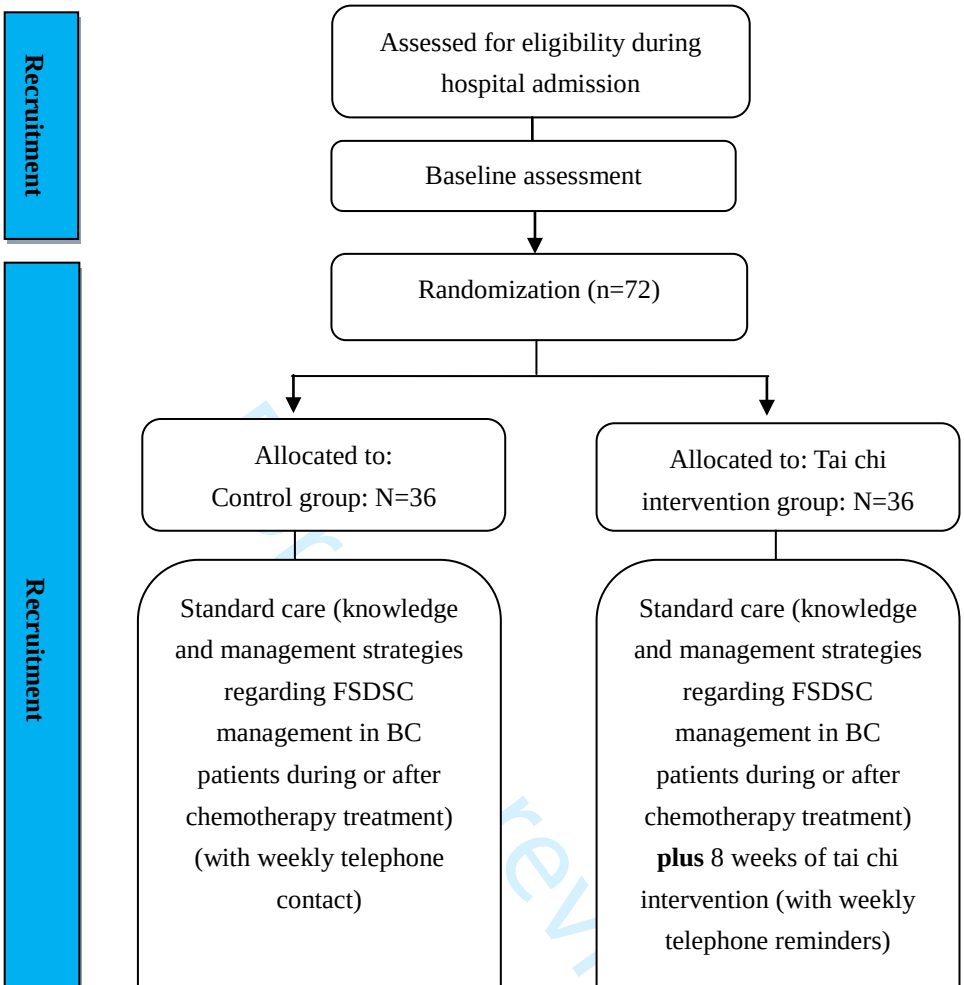

Figure 1. A CONSORT flowchart of the study

BMJ Open

Feasibility and potential effects of tai chi for the fatigue-sleep disturbance-depression symptom cluster in breast cancer patients: Protocol of a preliminary randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048115.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Jul-2021
Complete List of Authors:	Yao, Li-Qun; Charles Darwin University, College of Nursing and Midwifery Brisbane Centre Tan, Jing-Yu (Benjamin); Charles Darwin University, College of Nursing and Midwifery Brisbane Centre Turner, Catherine; Charles Darwin University, College of Nursing and Midwifery Brisbane centre Wang, Tao ; Charles Darwin University, College of Nursing and Midwifery Brisbane Centre
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Nursing, Oncology
Keywords:	Breast tumours < ONCOLOGY, COMPLEMENTARY MEDICINE, Clinical trials < THERAPEUTICS

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Title Page

Feasibility and potential effects of tai chi for the fatigue-sleep disturbance-depression symptom cluster in breast cancer patients: Protocol of a preliminary randomized controlled trial

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Abstract

Introduction The fatigue-sleep disturbance-depression symptom cluster (FSDSC) is one of the most common and debilitating side effects in breast cancer (BC) patients throughout their treatment trajectory. Tai chi has been supported as a promising non-pharmacological intervention for the individual symptom relief of cancer-related fatigue, sleep disturbance, and depression. However, relevant evidence of using tai chi for FSDSC management in BC patients has been lacking.

Methods This study will be a two-arm, single-blinded pilot randomized controlled trial (RCT) involving an 8-week intervention and a 4-week follow-up. Seventy-two BC patients experiencing the FSDSC will be recruited from two tertiary medical centres in China. The participants will be randomized to either a tai chi group (n=36) or a control group (n=36). The participants in the tai chi group will receive an 8-week tai chi intervention in addition to standard care, while the participants in the control group will receive standard care only consisting of a booklet on the self-management of cancer symptoms. The primary outcomes will include a series of feasibility assessments of the study protocol in relation to the study's methodological procedures, including subject recruitment and follow-up process, completion of study questionnaires, and the feasibility, acceptability, and safety of the intervention. The secondary outcomes will be the clinical outcomes regarding the effects of tai chi on the FSDSC and quality of life, which will be evaluated by the Brief Fatigue Inventory (BFI), the Pittsburgh Sleep Quality Index (PSQI), the Hospital Anxiety and Depression Scale (HADS), and the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaires.

Ethics and dissemination Ethics approval was obtained from relevant sites (H19094, KY2019133, 201932). The findings of the study will be published in peer-reviewed scientific journals and at conferences.

Trail registration: ClinicalTrials.gov, identifier NCT04190342. Registered on 3 December 2019.

Keywords: Breast cancer; Fatigue; Sleep disturbance; Depression; Symptom cluster; Tai chi

Strengths and limitations of this study

- This will be the first clinical study to explore the feasibility and preliminary effects of tai chi on FSDSC management in BC patients.
- This study will use an evidence-based tai chi protocol in the intervention group which was comprehensively developed based on best available research evidence, guidelines, theories, and practice standards.
- The design of the pilot study will be guided by the Medical Research Council Framework for Developing and Evaluating Complex Interventions.
- This study will use comprehensive outcome measurements, including a series of feasibility outcomes, which will support the refinement of a clinically feasible tai chi protocol for a future full-scale RCT.
- The sample size of this trial is relatively small and is not power based, which will

contribute to only a preliminary analysis of the effects of tai chi on the FSDSC.

Introduction

Breast cancer (BC) is regarded as the most common cancer among women worldwide [1]. Although the number of BC survivors is increasing with improved cancer treatment, the substantial negative effects associated with cancer and cancer treatments remain a significant problem for survivors. Following the treatment of surgery, radiation therapy, antihormonal therapy, and/or chemotherapy, BC patients can experience significant side effects, including fatigue, sleep disturbance, and depression [2]. These frequently reported, troublesome symptoms usually occur concurrently in BC patients as a symptom cluster [3, 4]. According to Dodd et al. [5], a symptom cluster "consists of three or more symptoms that are related to each other and that occur together" (p. 468). The fatigue-sleep disturbance-depression symptom cluster (FSDSC) is one of the most frequent symptom clusters among BC patients, which can negatively impact patients' physical and psychosocial functioning status and quality of life (QoL), including more severe cancer-related symptoms, lower treatment compliance, poorer emotional conditions, worse financial hardship, and even shorter survival time [6-8].

To date, no specific medications are available for the management of cancer symptom clusters. Reviewing the previous evidence, various non-pharmacological approaches have been used as a combination treatment with medication for the comprehensive management of cancer-related symptoms [9-10]. However, most of the widely employed non-pharmacological approaches, such as acupuncture [11], hypnotherapy [12], guided imagery [13], massage [14], and electrical stimulation [15], require intensive professional skills training, supervised practise, and specific equipment, all of which can be significantly time- and energy-consuming and can considerably increase the consumption of healthcare resources and costs. Moreover, due to fatigue intolerance, cancer patients are usually reluctant to participate in energy-consuming non-pharmacological interventions such as intensive exercise [16]. Thus, an energy-saving and cost-effective non-pharmacological approach would be more appropriate for FSDSC management in cancer patients.

Traditional Chinese exercise (TCE) could be an appropriate and effective option for FSDSC relief in BC patients given its low cost and mild-to-moderate intensity. Tai chi, a very popular TCE, consists of several slow, simple, and repetitive body movements along with deep breathing, and it is easy to master [17]. There has been increasing evidence of its positive effects in targeting the management of individual symptoms such as fatigue, sleep disturbance, and depression [18-20]. However, no clinical research has ever been performed using tai chi exercise for symptom cluster management, especially the FSDSC in BC patients. The current study therefore proposes to assess the feasibility and the preliminary effects of using an evidence-based tai chi protocol for alleviating the FSDSC in BC patients through a pilot randomized controlled trial (RCT).

Methods and materials

Study design

The study's design will be a two-parallel-arm, single-blinded (assessor) pilot RCT. The

participants will be randomly allocated into two groups: a tai chi intervention group and a control group, with an allocation ratio of 1:1. The study period will be 12 weeks, which will involve an 8-week tai chi intervention and a 4-week follow-up for the intervention group. A CONSORT flowchart of the study is presented in **Figure 1**. The schedule of trial enrolment, intervention data collection, and assessments are presented in **Table 1**. This protocol was reported in accordance with the SPIRIT Checklist.

Study setting

This study will be implemented in two tertiary medical centres in Mainland China, including the Affiliated Hospital of Putian University (Fujian) and the Affiliated Hospital of Southwest Medical University (Sichuan).

Sample size calculation

Thirty or more participants per group is usually recommended as sufficient for a pilot study to examine intervention feasibility [21] and to estimate a between-group effect for a subsequent power analysis that can be used in the main study's sample size estimation [22]. Given that the primary purpose of this study will be exploring the feasibility and acceptability of the study's methodological procedures, intervention protocol, and questionnaires, 30 participants per group was therefore determined to be an appropriate sample size. Taking into account a conservative anticipation of a 20% dropout rate, the final sample size will therefore be 36 in each group, with a total of 72 participants [23].

Inclusion and exclusion criteria

Eligible participants will be recruited using the following inclusion criteria:

(1) adult female patients aged over 18 years;
(2) diagnosed with stage I, II, or IIIa BC (non-metastatic BC);
(3) have experienced at least a moderate level of fatigue, sleep disturbance, and depression, with a score of greater than 3 (which means a score of "4" and above) on a 10-point scale, from "0 (no symptom)" to "10 (worst symptom)" for each symptom in the past one month;
(4) have completed breast cancer surgery for over one month;
(5) have recently (within the past two months) commenced adjuvant chemotherapy;
(6) able to speak and understand Mandarin Chinese; and
(7) willing and able to give written informed consent for study participation.

Potential participants will be excluded using the following exclusion criteria:

(1) presently taking medications for the treatment of fatigue, sleep disturbance, or depression, such as antidepressant medications, psychostimulants, or hypnotics;
(2) extremely weak (unable to do physical activities due to advanced stages of chronic illnesses) or have cognitive impairment and/or severe mental illness;
(3) have participated in a tai chi program during the previous six months;
(4) have practised other TCE for over 30 minutes, three times per week, during the previous three months; and
(5) have scheduled other elective surgery within the trial period.

Recruitment

A research team will be formed before the commencement of the trial. Three investigators, including the doctoral investigator and two clinical nurses, will be primarily responsible for the subject recruitment and tai chi training. The investigators will receive intensive training from a qualified tai chi instructor to ensure a standardized tai chi practice. Prior to the tai chi intervention, the tai chi instructor will examine the accuracy of the movements among the three researchers, and the accuracy rate should be 100%. Two research assistants will conduct data collection and telephone follow-ups. To ensure the quality of data collection, the two research assistants will be trained on questionnaire data collection skills, including understanding the questionnaire items and standardizing their conversations with the participants. The academic supervisors of the doctoral investigator will monitor the entire study procedure on an ongoing basis through regular monthly meetings.

Among the hospitalized patients in the Breast Cancer Unit, potential participants will be recruited directly by the doctoral investigator and the two clinical nurses. Some potential participants who attend a breast cancer clinic for regular follow-ups will be referred by physicians and clinic nurses to the doctoral investigator and the two clinical nurses. A participant information sheet, including the research aim, the procedures, and the contact details of the study investigators, will be given to potential participants and will be explained by the doctoral investigator and the two clinical nurses. Potential participants who express interest in participating in the study will be screened for eligibility with reference to the inclusion and exclusion criteria by the doctoral investigator and the two clinical nurses. After their agreement to participate, the participants will be required to provide their written informed consent. The participants will be informed that they can withdraw from the study at any moment without any consequences.

Randomization and allocation concealment

The pilot trial will be randomized and controlled in a 1:1 allocation ratio. One set of randomization sequences will be generated via an online randomizer (https://www.randomizer.org/) based on the estimated sample size. To ensure allocation concealment, the randomization sequences will be generated by a statistician who will not be involved in any other parts of this study. Specifically, the statistician will use the online randomizer to generate the randomization sequences, which will include 36 even and 36 odd numbers. The randomization sequences will be accessed by the statistician only. Once an eligible participant consents to participate in the study and completes the baseline assessment, the two clinical nurses will telephone the statistician to determine which group the patient should be assigned to according to the pre-defined random numbers. The participants will be randomly assigned to either the tai chi intervention group or the control group.

Blinding

Due to the visible nature of the tai chi intervention, blinding of the study investigators and the participants will be impossible. Thus, blinding will only be applied to the outcome assessors (i.e., the two research assistants) in this pilot RCT to avoid potential detection bias during data collection. The two research assistants will be responsible for data collection and

telephone follow-ups, and they will not be involved in the subject recruitment process.

Tai chi intervention group

In addition to the standard care provided to both the intervention group and the control group, the participants in the intervention group will additionally receive instruction on easy 8 form tai chi movements. The development and validation of the evidence-based tai chi protocol are detailed in a methodological paper [24]. The intervention regime will last 60 minutes per session, two sessions per week, for eight weeks, which is based on current research evidence, practice standards/guidelines, theories, and experts' consensus [24]. To ensure that the participants have fully mastered the tai chi skills, before the commencement of the intervention, they will receive at least three 60-minute training sessions until they can perform the movements correctly and smoothly, along with a home learning package in an audio-visual format (i.e., a recorded video). The training will be conducted and led by either the doctoral investigator or the two clinical nurses, and attendance will be recorded. All the participants will be asked to perform the tai chi movements in front of the trainers (i.e., return demonstration) to make sure that they are correctly performing each movement of the tai chi exercise. In addition, the participants will be tested by the trainers during the last training session to ensure that they have correctly performed the tai chi movements (via return demonstration).

The intervention sessions will be 60 minutes and will be comprised of the following components: a 10-minute warm-up, 25 to 30 minutes of easy 8 form tai chi practising, and a 10-minute cool-down. During each session, the participants will also have a 10-minute break to rest. The tai chi intervention protocol was adapted in clinical practice to develop a personalized intervention that will be tailored to the participants' convenience and preference regarding the time and venue of the intervention. Details of the tai chi protocol are presented in a methodological paper [24]. A specially designed exercise log will be provided to the participants to record information related to their tai chi practice immediately after tai chi practising each time, such as duration and frequency of practising tai chi, as well as any potential adverse reactions related to tai chi, such as dizziness, knee pain, musculoskeletal aches and pains, etc. The exercise logs will be returned to the research assistants on the date of the participants' treatment or follow-up appointment at the hospital. To enhance the participants' adherence to the tai chi intervention, the research assistants will conduct telephone follow-ups every week to remind them to practise their tai chi and to collect information on any potential adverse reactions related to the tai chi intervention.

Control group

The participants allocated to the control group will receive a standard care package, which will be a booklet on the self-management of cancer symptoms. This booklet will offer basic knowledge and management strategies regarding FSDSC management in BC patients during or after chemotherapy treatment. All the information listed in this booklet will be comprehensively adapted from relevant national guidelines developed by professional associations in cancer care and government health department websites, including the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (the NCCN Guidelines) [25] and the Department of Health – Government of Western

Australia [26]. Research evidence in published peer-reviewed articles will also be cited as supporting information for the booklet's development [2, 27-29]. Additionally, the participants will be asked to refrain from practising any exercises related to TCE during the study, with reminders at all assessment time points. On completion of the pilot RCT, the participants in the control group will have an opportunity to receive the tai chi training from the study team.

Outcome measurements and follow-up

The outcome measurements for this pilot RCT will include three categories, namely, baseline assessments, feasibility and acceptability outcomes, and clinical outcomes. The feasibility and acceptability outcomes will be the primary outcomes, while the clinical outcomes will be the secondary outcomes. All the outcomes and follow-ups will be conducted by the two research assistants.

Demographic and clinical characteristics of the participants

A self-designed demographic and clinical data form will be employed to collect the participants' socio-demographic data (e.g., age, education background, employment status, marital status, and household income) and medical history (e.g., date of diagnosis, the current stage of BC, and date and type of treatment) at baseline (T1).

Primary outcomes: Feasibility and acceptability

(1) The feasibility assessment of subject recruitment and the follow-up process will include: **(a)** the time that was taken to recruit the planned sample size of participants; **(b)** referral rate – the number of referrals made by clinicians in different departments and hospitals divided by all referrals; **(c)** recruitment rate – the number of subjects who enrolled in the study divided by all subjects eligible for enrolment; **(d)** retention rate – the number of subjects who completed the study divided by all subjects who enrolled in the study; **(e)** dropout rate – the number of subjects who dropped out after randomization divided by all subjects who enrolled in the study; and **(f)** feedback from the dropout subjects to identify their reasons for dropping out. The feasibility of recruitment and follow-up process outcomes will be collected at baseline (T1) and immediately after the intervention (T2).

(2) The feasibility assessment of the outcome measures will include the percentage of missing values for each item of the scales used – the Brief Fatigue Inventory (BFI), the Pittsburgh Sleep Quality Index (PSQI), the Hospital Anxiety and Depression Scale (HADS), and the Functional Assessment of Cancer Therapy-Breast (FACT-B) – at baseline (T1), immediately after the intervention (T2), and four weeks after completion of the intervention (T3).

(3) The feasibility and acceptability of the intervention will include: **(a)** adherence rates – the number of tai chi sessions practised divided by the total number of sessions required; **(b)** the participants' feedback on and satisfaction with the intervention using a self-designed feedback form; **(c)** records of adverse events associated with tai chi, which will be obtained from the exercise logs; and **(d)** the number of participants who completed the exercise log. The feasibility and acceptability of the intervention will be assessed immediately after the intervention (T2).

Secondary outcomes: Fatigue, sleep disturbance, depression, and QoL

The fatigue, sleep disturbance, depression, and QoL of the BC patients as the secondary outcomes will be measured at T1, T2, and T3 using the BFI, the PSQI, the HADS, and the FACT-B.

(1) Fatigue: The participants' severity of fatigue and cancer-related fatigue in daily functioning will be measured using the BFI. The BFI has nine items, with higher scores corresponding to more severe fatigue [30, 31]. The Chinese version of the BFI has excellent internal consistency reliability (Cronbach's alpha from 0.90 to 0.92), as well as construct validity and convergent validity [32].

(2) Sleep disturbance: The participants' sleep quality and disturbance will be assessed using the PSQI. This questionnaire has seven domains: sleep latency, habitual sleep efficiency, subjective sleep quality, sleep duration, use of sleeping medication, sleep disturbance, and daytime dysfunction [33]. A total score will be calculated from the sum of the seven domains' scores. A higher total score indicates poorer sleep quality. The Chinese version of the PSQI has been demonstrated to be a reliable and valid scale, and it has been widely utilized among cancer patients [34].

(3) Depression: The HADS will be used to assess the participants' depression. The cut-off scores have been classified and labelled as 0 to 7 for "normal", 8 to 10 for "mild", 11 to 15 for "moderate", and ≥16 for "severe" [35]. As a reliable and valid tool for measuring depression, the HADS has been widely utilized among Chinese cancer patients, with well-documented psychometric properties [36].

(4) Quality of life: The FACT-B will be 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 [37].

Data management

The doctoral investigator and one of the research assistants will enter all the collected data into a computer with a double data entry approach. To ensure that there are no discrepancies or coding errors after running descriptive and inferential statistics, data cleaning will be conducted before data analysis [38]. First, the datasets will be checked against the paper recordings of raw data to ensure that the data coding is correct. Then, double-checking will be undertaken by the other research assistant to ensure accuracy. All electronic data will be retained in a compressed folder using password-protected access systems, and all hard copies of the materials will be retained in a cabinet at the study sites. Storage and disposal of research data hard copies will strictly follow the regulations and policies of the lead investigator's institution and the study sites, including the Charles Darwin University Research Data Management Guide.

Data analysis

Statistical analyses will be conducted using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). The intention-to-treat (ITT) principle will be utilized for

the management of missing data. Effect sizes (ES) of between-group comparisons will be estimated using Cohen's *d* [39]. The chi-squared test or Fisher's exact test will be used to examine the comparisons between the control and intervention groups for categorical variables (e.g., education background, referral rate, retention rate, etc.). An independent t-test or the Mann-Whitney U test will be utilized for the continuous variables (e.g., age, household income, etc.). The Generalized Estimating Equation (GEE) model will be performed for repeated multivariate analysis between the two study groups for the total scores and domain scores of the BFI, the PSQI, the HADS, and the FACT-B. The significance level to identify statistical differences will be $p<0.05$.

Patient and public involvement

No patient was involved in the study design or any other part of this protocol.

Ethics and dissemination

This study was registered at ClinicalTrials.gov (identifier NCT04190342) before its commencement. The study has been approved by the Human Research Ethics Committee at Charles Darwin University (H19094), the Clinical Trial Ethics Committee at the Affiliated Hospital of Southwest Medical University (KY2019133), and the Clinical Trial Ethics Committee at the Affiliated Hospital of Putian University (201932). The abstract of this study has been submitted to Sigma's 32nd International Nursing Research Congress for presentation in 2021. The results of the trial will be published in peer-reviewed scientific journals.

Discussion

As one of the most common symptom clusters in BC patients, the FSDSC can significantly deteriorate patients' QoL and daily functioning [40, 41]. An increasing number of studies have demonstrated that tai chi has beneficial effects on symptom management in cancer patients; however, almost all the studies focused on individual symptoms only, such as fatigue, sleep disturbance, or depression [42-44]. No study has ever been performed to investigate the role of tai chi in managing symptom clusters in the BC population. This highlights a great need to explore the effects of tai chi on the FSDSC in BC patients. Given that the patients will have already experienced fatigue upon enrolment in this pilot RCT, lengthy and complicated tai chi movements will be avoided. Easy 8 form tai chi, a traditional Chinese mind-body exercise with only eight simple movements, is an appropriate intervention for FSDSC management as it is easy to learn, is less energy-consuming, and requires no specific equipment [45, 46].

This study has some strengths. According to the Medical Research Council Framework for Developing and Evaluating Complex Interventions, the feasibility and acceptability of a proposed intervention and research methodological procedures should be fully examined prior to performing the full-scale study [47]. In this current pilot RCT, the feasibility and acceptability of an easy 8 form tai chi intervention program will be assessed comprehensively using a series of feasibility outcomes, including subject recruitment, intervention delivery, and outcome assessments. A comprehensive assessment will promote the refinement of the intervention protocol for the future main study. Furthermore, different from some current non-pharmacological studies, the tai chi intervention protocol used in the current pilot RCT

will be evidence-based and rigorously developed based on systematic review evidence and recommendations [48-56]; TCE principles, theories [57, 58], and practice standards [46, 59]; the characteristics of cancer-related symptoms; and the consensus of an expert panel. In addition, an FSDSC self-management education booklet will be designed and provided to the participants in both the intervention and control groups. The information listed in this booklet will be comprehensively adapted from relevant national guidelines, professional bodies, and research evidence in published peer-reviewed articles. The self-management education booklet will be used as an enhanced care component to improve the patients' knowledge and relevant coping strategies for FSDSC management. Finally, a safety assessment of the tai chi protocol for cancer patients will be set as one of the feasibility outcomes, which has rarely been measured in existing tai chi interventional studies. Although tai chi is a non-invasive intervention that is generally regarded as a relatively safe approach, the exercise program might still contribute to some minor adverse events such as a lumbar sprain, musculoskeletal aches and pains, dizziness, knee pain, etc. [60]. Therefore, any potential adverse events related to practising tai chi will be monitored and reported in the exercise log.

This study also has some limitations. Given the limited study sites, the study sample in this study may not offer a completely representative sample of BC patients who are experiencing the FSDSC. Due to the visible nature of the tai chi intervention, the blinding of the participants and the tai chi instructor cannot be performed in this study, which might increase the risk of detection bias during the study's implementation, although the outcome assessors will be blinded to the intervention allocation. The lack of long-term follow-up to assess the ongoing effects of tai chi might be another limitation, but this can be considered in the future full-scale RCT as one of the main study outcomes.

This study will utilize a rigorously designed RCT to assess the feasibility and preliminary effects of an evidence-based tai chi program for alleviating the FSDSC in BC patients. The convenience of the tai chi for the self-management of the FSDSC may provide BC patients, healthcare professionals, and policymakers with further guidance in FSDSC management in the long run. Furthermore, the results of this trial will contribute to a future multi-centre large-scale main RCT to further conclude the research evidence on the effects and safety of tai chi for FSDSC management in BC patients.

Trial status

The study began in May 2020. Data collection and analysis is ongoing.

Funding

This trial was funded by the Australian Government Research Training Program (RTP) scholarship, and the Award/Grant number is not applicable.

Conflict of interest

No conflict of interest regarding the publication of this paper was declared.

Authors' contributions

Yao LQ: study conception and design, trial organization, administration and coordination, quality assurance, and manuscript drafting and revision; **Tan JY**: study conception and design,

study procedure supervision, and manuscript revision; **Turner C**: study conception and design, study procedure supervision, and manuscript revision; **Wang T**: study design, study procedure supervision, and manuscript revision.

Table 1. The schedule of trial enrolment, interventions, and assessments

	Study Period				
	Before Enrolment (0 weeks)	**Intervention Period (1-8 weeks)**	**End of Intervention (8 weeks)**	**Follow-up Period (9-12 weeks)**	**End of Follow-up (12 weeks)**
Inclusion/exclusion criteria	×				
Informed consent	×				
Demographic characteristics	×				
Randomization and allocation	×				
Feasibility of recruitment and follow-up process	×		×	×	×
Feasibility assessment of the outcome measures	×		×		×
Feasibility and acceptability of the intervention		×			
BFI	×		×		×
HADS	×		×		×
PSQI	×		×		×
FACT-B	×		×		×
Safety measurement		×			

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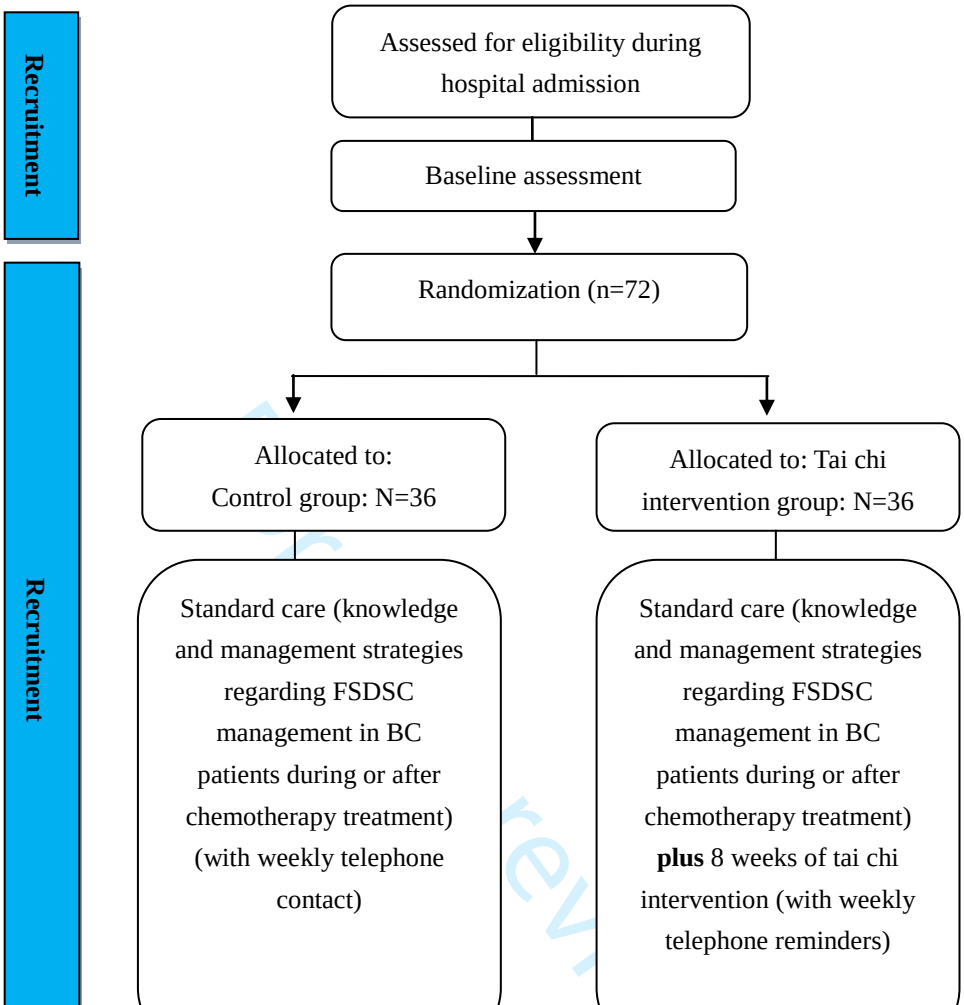

Figure 1. A CONSORT flowchart of the study

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**Page 1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**Page 2**
	2b	All items from the World Health Organization Trial Registration Data Set	**Not applicable**
Protocol version	3	Date and version identifier	**Page 2**
Funding	4	Sources and types of financial, material, and other support	**Page 10**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**Page 11**
	5b	Name and contact information for the trial sponsor	**Page 1**
	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	**Page 11**
	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)	**Page 8**

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	**Page 3**
	6b	Explanation for choice of comparators	**Page 3**
Objectives	7	Specific objectives or hypotheses	**Page 3**
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)	**Page 3-4**
Methods: Participants, interventions, and outcomes			
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	**Page 4**
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)	**Page 4**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**Page 6-7**
	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)	**Not applicable**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**Page 6-7**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**Page 6-7**
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	**Page 7-8**
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)	**Page 12**

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	Page 4
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 4-5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 5
Methods: Data collection, management, and analysis			
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	Page 7-8
	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	Page 8

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	**Page 8**
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	**Page 8-9**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**Page 8-9**
	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)	**Page 8-9**
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	**Page 8**
	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	**Page 8**
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	**Page 7**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**Page 5**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**Page 9**
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)	**Not applicable**

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 4 &5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
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	Page 8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 10
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	Page 8
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	Not applicable
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	Page 9
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*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" license.

BMJ Open

Feasibility and potential effects of tai chi for the fatigue-sleep disturbance-depression symptom cluster in breast cancer patients: Protocol of a preliminary randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048115.R2
Article Type:	Protocol
Date Submitted by the Author:	03-Aug-2021
Complete List of Authors:	Yao, Li-Qun; Charles Darwin University, College of Nursing and Midwifery Brisbane Centre Tan, Jing-Yu (Benjamin); Charles Darwin University, College of Nursing and Midwifery Brisbane Centre Turner, Catherine; Charles Darwin University, College of Nursing and Midwifery Brisbane centre Wang, Tao ; Charles Darwin University, College of Nursing and Midwifery Brisbane Centre
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Nursing, Oncology
Keywords:	Breast tumours < ONCOLOGY, COMPLEMENTARY MEDICINE, Clinical trials < THERAPEUTICS

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Title Page

Feasibility and potential effects of tai chi for the fatigue-sleep disturbance-depression symptom cluster in breast cancer patients: Protocol of a preliminary randomized controlled trial

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Abstract

Introduction The fatigue-sleep disturbance-depression symptom cluster (FSDSC) is one of the most common and debilitating side effects in breast cancer (BC) patients throughout their treatment trajectory. Tai chi has been supported as a promising non-pharmacological intervention for the individual symptom relief of cancer-related fatigue, sleep disturbance, and depression. However, relevant evidence of using tai chi for FSDSC management in BC patients has been lacking.

Methods This study will be a two-arm, single-blinded pilot randomized controlled trial (RCT) involving an 8-week intervention and a 4-week follow-up. Seventy-two BC patients experiencing the FSDSC will be recruited from two tertiary medical centres in China. The participants will be randomized to either a tai chi group (n=36) or a control group (n=36). The participants in the tai chi group will receive an 8-week tai chi intervention in addition to standard care, while the participants in the control group will receive standard care only consisting of a booklet on the self-management of cancer symptoms. The primary outcomes will include a series of feasibility assessments of the study protocol in relation to the study's methodological procedures, including subject recruitment and follow-up process, completion of study questionnaires, and the feasibility, acceptability, and safety of the intervention. The secondary outcomes will be the clinical outcomes regarding the effects of tai chi on the FSDSC and quality of life, which will be evaluated by the Brief Fatigue Inventory (BFI), the Pittsburgh Sleep Quality Index (PSQI), the Hospital Anxiety and Depression Scale (HADS), and the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaires.

Ethics and dissemination Ethics approval was obtained from relevant sites (H19094, KY2019133, 201932). The findings of the study will be published in peer-reviewed scientific journals and at conferences.

Trail registration: ClinicalTrials.gov, identifier NCT04190342. Registered on 3 December 2019.

Keywords: Breast cancer; Fatigue; Sleep disturbance; Depression; Symptom cluster; Tai chi

Strengths and limitations of this study

- This will be the first clinical study to explore the feasibility and preliminary effects of tai chi on FSDSC management in BC patients.
- This study will use an evidence-based tai chi protocol in the intervention group which was comprehensively developed based on best available research evidence, guidelines, theories, and practice standards.
- The design of the pilot study will be guided by the Medical Research Council Framework for Developing and Evaluating Complex Interventions.
- This study will use comprehensive outcome measurements, including a series of feasibility outcomes, which will support the refinement of a clinically feasible tai chi protocol for a future full-scale RCT.
- The sample size of this trial is relatively small and is not power based, which will

contribute to only a preliminary analysis of the effects of tai chi on the FSDSC.

Introduction

Breast cancer (BC) is regarded as the most common cancer among women worldwide [1]. Although the number of BC survivors is increasing with improved cancer treatment, the substantial negative effects associated with cancer and cancer treatments remain a significant problem for survivors. Following the treatment of surgery, radiation therapy, antihormonal therapy, and/or chemotherapy, BC patients can experience significant side effects, including fatigue, sleep disturbance, and depression [2]. These frequently reported, troublesome symptoms usually occur concurrently in BC patients as a symptom cluster [3, 4]. According to Dodd et al. [5], a symptom cluster "consists of three or more symptoms that are related to each other and that occur together" (p. 468). The fatigue-sleep disturbance-depression symptom cluster (FSDSC) is one of the most frequent symptom clusters among BC patients, which can negatively impact patients' physical and psychosocial functioning status and quality of life (QoL), including more severe cancer-related symptoms, lower treatment compliance, poorer emotional conditions, worse financial hardship, and even shorter survival time [6-8].

To date, no specific medications are available for the management of cancer symptom clusters. Reviewing the previous evidence, various non-pharmacological approaches have been used as a combination treatment with medication for the comprehensive management of cancer-related symptoms [9-10]. However, most of the widely employed non-pharmacological approaches, such as acupuncture [11], hypnotherapy [12], guided imagery [13], massage [14], and electrical stimulation [15], require intensive professional skills training, supervised practise, and specific equipment, all of which can be significantly time- and energy-consuming and can considerably increase the consumption of healthcare resources and costs. Moreover, due to fatigue intolerance, cancer patients are usually reluctant to participate in energy-consuming non-pharmacological interventions such as intensive exercise [16]. Thus, an energy-saving and cost-effective non-pharmacological approach would be more appropriate for FSDSC management in cancer patients.

Traditional Chinese exercise (TCE) could be an appropriate and effective option for FSDSC relief in BC patients given its low cost and mild-to-moderate intensity. Tai chi, a very popular TCE, consists of several slow, simple, and repetitive body movements along with deep breathing, and it is easy to master [17]. There has been increasing evidence of its positive effects in targeting the management of individual symptoms such as fatigue, sleep disturbance, and depression [18-20]. However, no clinical research has ever been performed using tai chi exercise for symptom cluster management, especially the FSDSC in BC patients. The current study therefore proposes to assess the feasibility and the preliminary effects of using an evidence-based tai chi protocol for alleviating the FSDSC in BC patients through a pilot randomized controlled trial (RCT).

Methods and materials

Study design

The study's design will be a two-parallel-arm, single-blinded (assessor) pilot RCT. The

participants will be randomly allocated into two groups: a tai chi intervention group and a control group, with an allocation ratio of 1:1. The study period will be 12 weeks, which will involve an 8-week tai chi intervention and a 4-week follow-up for the intervention group. A CONSORT flowchart of the study is presented in **Figure 1**. The schedule of trial enrolment, intervention data collection, and assessments are presented in **Table 1**. This protocol was reported in accordance with the SPIRIT Checklist.

Study setting

This study will be implemented in two tertiary medical centres in Mainland China, including the Affiliated Hospital of Putian University (Fujian) and the Affiliated Hospital of Southwest Medical University (Sichuan).

Sample size calculation

Thirty or more participants per group is usually recommended as sufficient for a pilot study to examine intervention feasibility [21] and to estimate a between-group effect for a subsequent power analysis that can be used in the main study's sample size estimation [22]. Given that the primary purpose of this study will be exploring the feasibility and acceptability of the study's methodological procedures, intervention protocol, and questionnaires, 30 participants per group was therefore determined to be an appropriate sample size. Taking into account a conservative anticipation of a 20% dropout rate, the final sample size will therefore be 36 in each group, with a total of 72 participants [23].

Inclusion and exclusion criteria

Eligible participants will be recruited using the following inclusion criteria:

(1) adult female patients aged over 18 years;
(2) diagnosed with stage I, II, or IIIa BC (non-metastatic BC);
(3) have experienced at least a moderate level of fatigue, sleep disturbance, and depression, with a score of greater than 3 (which means a score of "4" and above) on a 10-point scale, from "0 (no symptom)" to "10 (worst symptom)" for each symptom in the past one month;
(4) have completed breast cancer surgery for over one month;
(5) have recently (within the past two months) commenced adjuvant chemotherapy;
(6) able to speak and understand Mandarin Chinese; and
(7) willing and able to give written informed consent for study participation.

Potential participants will be excluded using the following exclusion criteria:

(1) presently taking medications for the treatment of fatigue, sleep disturbance, or depression, such as antidepressant medications, psychostimulants, or hypnotics;
(2) extremely weak (unable to do physical activities due to advanced stages of chronic illnesses) or have cognitive impairment and/or severe mental illness;
(3) have participated in a tai chi program during the previous six months;
(4) have practised other TCE for over 30 minutes, three times per week, during the previous three months; and
(5) have scheduled other elective surgery within the trial period.

Recruitment

A research team will be formed before the commencement of the trial. Three investigators, including the doctoral investigator and two clinical nurses, will be primarily responsible for the subject recruitment and tai chi training. The investigators will receive intensive training from a qualified tai chi instructor to ensure a standardized tai chi practice. Prior to the tai chi intervention, the tai chi instructor will examine the accuracy of the movements among the three researchers, and the accuracy rate should be 100%. Two research assistants will conduct data collection and telephone follow-ups. To ensure the quality of data collection, the two research assistants will be trained on questionnaire data collection skills, including understanding the questionnaire items and standardizing their conversations with the participants. The academic supervisors of the doctoral investigator will monitor the entire study procedure on an ongoing basis through regular monthly meetings.

Among the hospitalized patients in the Breast Cancer Unit, potential participants will be recruited directly by the doctoral investigator and the two clinical nurses. Some potential participants who attend a breast cancer clinic for regular follow-ups will be referred by physicians and clinic nurses to the doctoral investigator and the two clinical nurses. A participant information sheet, including the research aim, the procedures, and the contact details of the study investigators, will be given to potential participants and will be explained by the doctoral investigator and the two clinical nurses. Potential participants who express interest in participating in the study will be screened for eligibility with reference to the inclusion and exclusion criteria by the doctoral investigator and the two clinical nurses. After their agreement to participate, the participants will be required to provide their written informed consent. The participants will be informed that they can withdraw from the study at any moment without any consequences.

Randomization and allocation concealment

The pilot trial will be randomized and controlled in a 1:1 allocation ratio. One set of randomization sequences will be generated via an online randomizer (https://www.randomizer.org/) based on the estimated sample size. To ensure allocation concealment, the randomization sequences will be generated by a statistician who will not be involved in any other parts of this study. Specifically, the statistician will use the online randomizer to generate the randomization sequences, which will include 36 even and 36 odd numbers. The randomization sequences will be accessed by the statistician only. Once an eligible participant consents to participate in the study and completes the baseline assessment, the two clinical nurses will telephone the statistician to determine which group the patient should be assigned to according to the pre-defined random numbers. The participants will be randomly assigned to either the tai chi intervention group or the control group.

Blinding

Due to the visible nature of the tai chi intervention, blinding of the study investigators and the participants will be impossible. Thus, blinding will only be applied to the outcome assessors (i.e., the two research assistants) in this pilot RCT to avoid potential detection bias during data collection. The two research assistants will be responsible for data collection and

telephone follow-ups, and they will not be involved in the subject recruitment process.

Tai chi intervention group

In addition to the standard care provided to both the intervention group and the control group, the participants in the intervention group will additionally receive instruction on easy 8 form tai chi movements. The development and validation of the evidence-based tai chi protocol are detailed in a methodological paper [24]. The intervention regime will last 60 minutes per session, two sessions per week, for eight weeks, which is based on current research evidence, practice standards/guidelines, theories, and experts' consensus [24]. To ensure that the participants have fully mastered the tai chi skills, before the commencement of the intervention, they will receive at least three 60-minute training sessions until they can perform the movements correctly and smoothly, along with a home learning package in an audio-visual format (i.e., a recorded video). The training will be conducted and led by either the doctoral investigator or the two clinical nurses, and attendance will be recorded. All the participants will be asked to perform the tai chi movements in front of the trainers (i.e., return demonstration) to make sure that they are correctly performing each movement of the tai chi exercise. In addition, the participants will be tested by the trainers during the last training session to ensure that they have correctly performed the tai chi movements (via return demonstration).

The intervention sessions will be 60 minutes and will be comprised of the following components: a 10-minute warm-up, 25 to 30 minutes of easy 8 form tai chi practising, and a 10-minute cool-down. During each session, the participants will also have a 10-minute break to rest. The tai chi intervention protocol was adapted in clinical practice to develop a personalized intervention that will be tailored to the participants' convenience and preference regarding the time and venue of the intervention. Details of the tai chi protocol are presented in a methodological paper [24]. A specially designed exercise log will be provided to the participants to record information related to their tai chi practice immediately after tai chi practising each time, such as duration and frequency of practising tai chi, as well as any potential adverse reactions related to tai chi, such as dizziness, knee pain, musculoskeletal aches and pains, etc. The exercise logs will be returned to the research assistants on the date of the participants' treatment or follow-up appointment at the hospital. To enhance the participants' adherence to the tai chi intervention, the research assistants will conduct telephone follow-ups every week to remind them to practise their tai chi and to collect information on any potential adverse reactions related to the tai chi intervention.

Control group

The participants allocated to the control group will receive a standard care package, which will be a booklet on the self-management of cancer symptoms. This booklet will offer basic knowledge and management strategies regarding FSDSC management in BC patients during or after chemotherapy treatment. All the information listed in this booklet will be comprehensively adapted from relevant national guidelines developed by professional associations in cancer care and government health department websites, including the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (the NCCN Guidelines) [25] and the Department of Health – Government of Western

Australia [26]. Research evidence in published peer-reviewed articles will also be cited as supporting information for the booklet's development [2, 27-29]. Additionally, the participants will be asked to refrain from practising any exercises related to TCE during the study, with reminders at all assessment time points. On completion of the pilot RCT, the participants in the control group will have an opportunity to receive the tai chi training from the study team.

Outcome measurements and follow-up

The outcome measurements for this pilot RCT will include three categories, namely, baseline assessments, feasibility and acceptability outcomes, and clinical outcomes. The feasibility and acceptability outcomes will be the primary outcomes, while the clinical outcomes will be the secondary outcomes. All the outcomes and follow-ups will be conducted by the two research assistants.

Demographic and clinical characteristics of the participants

A self-designed demographic and clinical data form will be employed to collect the participants' socio-demographic data (e.g., age, education background, employment status, marital status, and household income) and medical history (e.g., date of diagnosis, the current stage of BC, and date and type of treatment) at baseline (T1).

Primary outcomes: Feasibility and acceptability

(1) The feasibility assessment of subject recruitment and the follow-up process will include: **(a)** the time that was taken to recruit the planned sample size of participants; **(b)** referral rate – the number of referrals made by clinicians in different departments and hospitals divided by all referrals; **(c)** recruitment rate – the number of subjects who enrolled in the study divided by all subjects eligible for enrolment; **(d)** retention rate – the number of subjects who completed the study divided by all subjects who enrolled in the study; **(e)** dropout rate – the number of subjects who dropped out after randomization divided by all subjects who enrolled in the study; and **(f)** feedback from the dropout subjects to identify their reasons for dropping out. The feasibility of recruitment and follow-up process outcomes will be collected from baseline (T1) to the completion of the intervention (T2).

(2) The feasibility assessment of the outcome measures will include the percentage of missing values for each item of the scales used – the Brief Fatigue Inventory (BFI), the Pittsburgh Sleep Quality Index (PSQI), the Hospital Anxiety and Depression Scale (HADS), and the Functional Assessment of Cancer Therapy-Breast (FACT-B) – at baseline (T1), immediately after the intervention (T2), and four weeks after completion of the intervention (T3).

(3) The feasibility and acceptability of the intervention will include: **(a)** adherence rates – the number of tai chi sessions practised divided by the total number of sessions required; **(b)** the participants' feedback on and satisfaction with the intervention using a self-designed feedback form; **(c)** records of adverse events associated with tai chi, which will be obtained from the exercise logs; and **(d)** the number of participants who completed the exercise log. The feasibility and acceptability of the intervention will be assessed immediately after the intervention (T2).

Secondary outcomes: Fatigue, sleep disturbance, depression, and QoL

The fatigue, sleep disturbance, depression, and QoL of the BC patients as the secondary outcomes will be measured at T1, T2, and T3 using the BFI, the PSQI, the HADS, and the FACT-B.

(1) Fatigue: The participants' severity of fatigue and cancer-related fatigue in daily functioning will be measured using the BFI. The BFI has nine items, with higher scores corresponding to more severe fatigue [30, 31]. The Chinese version of the BFI has excellent internal consistency reliability (Cronbach's alpha from 0.90 to 0.92), as well as construct validity and convergent validity [32].

(2) Sleep disturbance: The participants' sleep quality and disturbance will be assessed using the PSQI. This questionnaire has seven domains: sleep latency, habitual sleep efficiency, subjective sleep quality, sleep duration, use of sleeping medication, sleep disturbance, and daytime dysfunction [33]. A total score will be calculated from the sum of the seven domains' scores. A higher total score indicates poorer sleep quality. The Chinese version of the PSQI has been demonstrated to be a reliable and valid scale, and it has been widely utilized among cancer patients [34].

(3) Depression: The HADS will be used to assess the participants' depression. The cut-off scores have been classified and labelled as 0 to 7 for "normal", 8 to 10 for "mild", 11 to 15 for "moderate", and ≥16 for "severe" [35]. As a reliable and valid tool for measuring depression, the HADS has been widely utilized among Chinese cancer patients, with well-documented psychometric properties [36].

(4) Quality of life: The FACT-B will be 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 [37].

Data management

The doctoral investigator and one of the research assistants will enter all the collected data into a computer with a double data entry approach. To ensure that there are no discrepancies or coding errors after running descriptive and inferential statistics, data cleaning will be conducted before data analysis [38]. First, the datasets will be checked against the paper recordings of raw data to ensure that the data coding is correct. Then, double-checking will be undertaken by the other research assistant to ensure accuracy. All electronic data will be retained in a compressed folder using password-protected access systems, and all hard copies of the materials will be retained in a cabinet at the study sites. Storage and disposal of research data hard copies will strictly follow the regulations and policies of the lead investigator's institution and the study sites, including the Charles Darwin University Research Data Management Guide.

Data analysis

Statistical analyses will be conducted using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). The intention-to-treat (ITT) principle will be utilized for

the management of missing data. Effect sizes (ES) of between-group comparisons will be estimated using Cohen's *d* [39]. The chi-squared test or Fisher's exact test will be used to examine the comparisons between the control and intervention groups for categorical variables (e.g., education background, referral rate, retention rate, etc.). An independent t-test or the Mann-Whitney U test will be utilized for the continuous variables (e.g., age, household income, etc.). The Generalized Estimating Equation (GEE) model will be performed for repeated multivariate analysis between the two study groups for the total scores and domain scores of the BFI, the PSQI, the HADS, and the FACT-B. The significance level to identify statistical differences will be $p<0.05$.

Patient and public involvement

No patient was involved in the study design or any other part of this protocol.

Ethics and dissemination

This study was registered at ClinicalTrials.gov (identifier NCT04190342) before its commencement. The study has been approved by the Human Research Ethics Committee at Charles Darwin University (H19094), the Clinical Trial Ethics Committee at the Affiliated Hospital of Southwest Medical University (KY2019133), and the Clinical Trial Ethics Committee at the Affiliated Hospital of Putian University (201932). The abstract of this study has been submitted to Sigma's 32nd International Nursing Research Congress for presentation in 2021. The results of the trial will be published in peer-reviewed scientific journals.

Discussion

As one of the most common symptom clusters in BC patients, the FSDSC can significantly deteriorate patients' QoL and daily functioning [40, 41]. An increasing number of studies have demonstrated that tai chi has beneficial effects on symptom management in cancer patients; however, almost all the studies focused on individual symptoms only, such as fatigue, sleep disturbance, or depression [42-44]. No study has ever been performed to investigate the role of tai chi in managing symptom clusters in the BC population. This highlights a great need to explore the effects of tai chi on the FSDSC in BC patients. Given that the patients will have already experienced fatigue upon enrolment in this pilot RCT, lengthy and complicated tai chi movements will be avoided. Easy 8 form tai chi, a traditional Chinese mind-body exercise with only eight simple movements, is an appropriate intervention for FSDSC management as it is easy to learn, is less energy-consuming, and requires no specific equipment [45, 46].

This study has some strengths. According to the Medical Research Council Framework for Developing and Evaluating Complex Interventions, the feasibility and acceptability of a proposed intervention and research methodological procedures should be fully examined prior to performing the full-scale study [47]. In this current pilot RCT, the feasibility and acceptability of an easy 8 form tai chi intervention program will be assessed comprehensively using a series of feasibility outcomes, including subject recruitment, intervention delivery, and outcome assessments. A comprehensive assessment will promote the refinement of the intervention protocol for the future main study. Furthermore, different from some current non-pharmacological studies, the tai chi intervention protocol used in the current pilot RCT

will be evidence-based and rigorously developed based on systematic review evidence and recommendations [48-56]; TCE principles, theories [57, 58], and practice standards [46, 59]; the characteristics of cancer-related symptoms; and the consensus of an expert panel. In addition, an FSDSC self-management education booklet will be designed and provided to the participants in both the intervention and control groups. The information listed in this booklet will be comprehensively adapted from relevant national guidelines, professional bodies, and research evidence in published peer-reviewed articles. The self-management education booklet will be used as an enhanced care component to improve the patients' knowledge and relevant coping strategies for FSDSC management. Finally, a safety assessment of the tai chi protocol for cancer patients will be set as one of the feasibility outcomes, which has rarely been measured in existing tai chi interventional studies. Although tai chi is a non-invasive intervention that is generally regarded as a relatively safe approach, the exercise program might still contribute to some minor adverse events such as a lumbar sprain, musculoskeletal aches and pains, dizziness, knee pain, etc. [60]. Therefore, any potential adverse events related to practising tai chi will be monitored and reported in the exercise log.

This study also has some limitations. Given the limited study sites, the study sample in this study may not offer a completely representative sample of BC patients who are experiencing the FSDSC. Due to the visible nature of the tai chi intervention, the blinding of the participants and the tai chi instructor cannot be performed in this study, which might increase the risk of detection bias during the study's implementation, although the outcome assessors will be blinded to the intervention allocation. The lack of long-term follow-up to assess the ongoing effects of tai chi might be another limitation, but this can be considered in the future full-scale RCT as one of the main study outcomes.

This study will utilize a rigorously designed RCT to assess the feasibility and preliminary effects of an evidence-based tai chi program for alleviating the FSDSC in BC patients. The convenience of the tai chi for the self-management of the FSDSC may provide BC patients, healthcare professionals, and policymakers with further guidance in FSDSC management in the long run. Furthermore, the results of this trial will contribute to a future multi-centre large-scale main RCT to further conclude the research evidence on the effects and safety of tai chi for FSDSC management in BC patients.

Trial status

The study began in May 2020. Data collection and analysis is ongoing.

Funding

This trial was funded by the Australian Government Research Training Program (RTP) scholarship, and the Award/Grant number is not applicable.

Conflict of interest

No conflict of interest regarding the publication of this paper was declared.

Authors' contributions

Yao LQ: study conception and design, trial organization, administration and coordination, quality assurance, and manuscript drafting and revision; **Tan JY**: study conception and design,

study procedure supervision, and manuscript revision; **Turner C**: study conception and design, study procedure supervision, and manuscript revision; **Wang T**: study design, study procedure supervision, and manuscript revision.

Table 1. The schedule of trial enrolment, interventions, and assessments

	Study Period				
	Before Enrolment (0 weeks)	**Intervention Period (1-8 weeks)**	**End of Intervention (8 weeks)**	**Follow-up Period (9-12 weeks)**	**End of Follow-up (12 weeks)**
Inclusion/exclusion criteria	×				
Informed consent	×				
Demographic characteristics	×				
Randomization and allocation	×				
Feasibility of recruitment and follow-up process	×		×	×	×
Feasibility assessment of the outcome measures	×		×		×
Feasibility and acceptability of the intervention		×			
BFI	×		×		×
HADS	×		×		×
PSQI	×		×		×
FACT-B	×		×		×
Safety measurement		×			

Figure 1. CONSORT flowchart of the study

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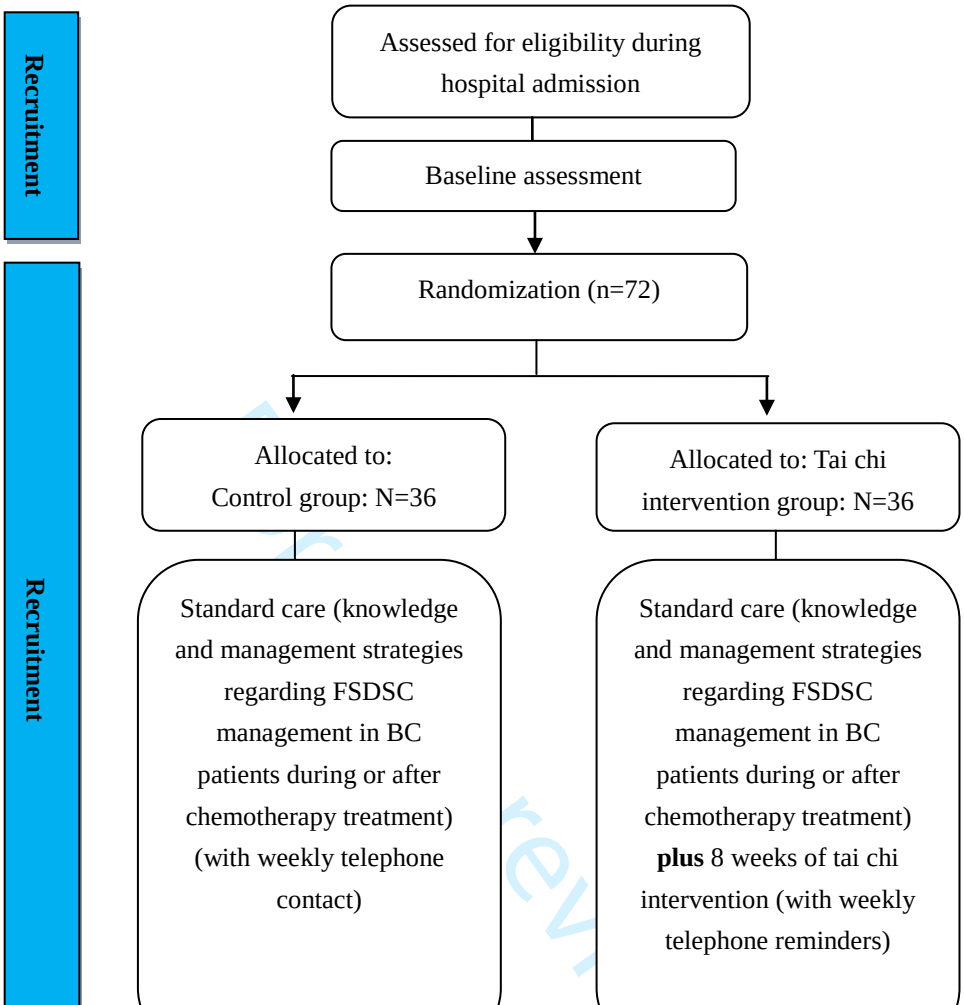

Figure 1. A CONSORT flowchart of the study

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**Page 1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**Page 2**
	2b	All items from the World Health Organization Trial Registration Data Set	**Not applicable**
Protocol version	3	Date and version identifier	**Page 2**
Funding	4	Sources and types of financial, material, and other support	**Page 10**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**Page 11**
	5b	Name and contact information for the trial sponsor	**Page 1**
	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	**Page 11**
	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)	**Page 8**

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	**Page 3**
	6b	Explanation for choice of comparators	**Page 3**
Objectives	7	Specific objectives or hypotheses	**Page 3**
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)	**Page 3-4**
Methods: Participants, interventions, and outcomes			
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	**Page 4**
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)	**Page 4**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**Page 6-7**
	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)	**Not applicable**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**Page 6-7**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**Page 6-7**
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	**Page 7-8**
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)	**Page 12**

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	Page 4
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 4-5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 5
Methods: Data collection, management, and analysis			
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	Page 7-8
	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	Page 8

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	**Page 8**
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	**Page 8-9**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**Page 8-9**
	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)	**Page 8-9**
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	**Page 8**
	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	**Page 8**
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	**Page 7**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**Page 5**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**Page 9**
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)	**Not applicable**

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 4 &5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
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	Page 8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 10
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	Page 8
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	Not applicable
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	Page 9
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*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" license.