Baduanjin mind-body exercise for cancer-related fatigue in cancer participants receiving adjuvant chemotherapy: a randomised control feasibility trial

Short Title: Baduanjin mind-body exercise for cancer-related fatigue

Sponsor
Chinese Medicine Centre (a collaboration between Western Sydney University and Beijing University of Chinese Medicine), Western Sydney University.

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LIST OF COMMON ABBREVIATIONS

AE	Adverse Event
Ahpra	Australian health practitioner regulation agency
BFI	Brief Fatigue Inventory
BDJ	Baduanjin (mind-body exercise)
CEQ	Credibility and Expectancy Questionnaire
CMBA	Chinese Medicine Board Australia
CMC	Chinese Medicine Centre
CRF	Cancer-related Fatigue
CTN	Clinical Trial Notification
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
NCCN	National Comprehensive Cancer Network
PIS	Particpant Information Sheet
PROMIS-29v2.0	Participant-Reported Outcomes Measurement Information System (PROMIS-29) v2.0
RCT	Randomised clinical trial
RDMP	Research Data Management Plan
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SWSLHD	South Western Sydney Local Health District
WSU	Western Sydney University

1. SUMMARY

Study Title	Baduanjin mind-body exercise for cancer-related fatigue in cancer participants receiving adjuvant chemotherapy: a randomised control feasibility trial
Aims/Objectives	*Primary* The feasibility and acceptability of remotely delivered Baduanjin mind-body exercise (the study protocol) via recruitment, retention, and adherence rates. *Secondary* A reduction in the severity of cancer-related fatigue symptoms measured by the Brief Fatigue Inventory (BFI). The improvement in health domains relating to physical function, fatigue, pain interference, depressive symptoms, anxiety, ability to participate in social roles and activities, and sleep disturbance measured by PROMIS–29 Profile v2.0 and the number and severity of adverse events (AEs). Participant's ratings of the intervention before and after using a modified Credibility and Expectancy Questionnaire. Reporting participation frequency via the Baduanjin Mind-Body Exercise Logbook.
Study design	Pilot randomised wait-list controlled feasibility trial
Planned sample size	40 (n = 20 per group)
Inclusion criteria	(1) 18 years of age or older; (2) receiving adjuvant chemotherapy or completed adjuvant chemotherapy; (3) medical history of cancer diagnosis; (4) suffering from moderate Cancer Related Fatigue (CRF) as assessed by the simple fatigue scale (from the BFI); (5) have a computer / device that is Wi-Fi or hotspot connected and be able to use smart phones, email and Zoom conferencing app; (6) be aware of one's disease diagnosis; and (7) understand the intervention process and able to communicate and provide informed consent in English.
Study procedures	Eligible participants will be identified and referred by their treating oncologist, a health care team member or self-referral from advertising. The participants will be randomly assigned in a 1:1 ratio to the Baduanjin mind-body exercise or wait-list control groups respectively. Intervention group data will be collected at baseline (week 0), at 4 weeks, 8 weeks and one-week follow-up (week 9). Waitlist control group data will be collected at recruitment (week 0) and at week 4, week 8 and week 9 (follow-up).
Analysis considerations	*Sample size calculation*: For a pilot study, a sample size of n = 29 is necessary to have a 95% confidence of detecting an event which has a true probability of $\pi = 0.10$. As the participants will be randomised into two groups with a 1:1 allocation ratio, and to overcome the probable potential 15% attrition of participants during the study period, while ensuring availability of sufficient participants, a sample size of n=40 will be recruited in this study. *Analysis plan*: Analyses of the endpoints will follow the 'intention to treat' and 'per-protocol' approaches. Demographics and data will be descriptively summarised at

	baseline using sample means and proportions with corresponding 95% confidence intervals. The primary or secondary outcomes will be addressed using a mixed linear model over time.
Study duration	10 weeks. This includes 1 week for baseline measures (week 0), 8 weeks of intervention (or waitlist control) (week 1-8), and 1 week follow-up (week 9).

2. BACKGROUND AND RATIONALE

Cancer-related fatigue (CRF) is a commonly reported cancer or cancer-related treatment side effect [1]. The National Comprehensive Cancer Network (NCCN) defines CRF as 'a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment' [2]. While most severe in the first 6 months following a cancer diagnosis or treatment, CRF can persist for years [3] and remain present throughout the disease trajectory. CRF is notable for being resistant to relief by rest or sleep and the fatigue is disproportional to recent activity, affecting a person's everyday functioning and quality of life [1, 2].

Most of the population living with a cancer diagnosis report CRF. The NCCN (2016) guidelines reported 80% of participants surveyed (n=1569) experienced CRF following chemotherapy and/or radiotherapy [2], while conservative estimates report this figure as 60-96% of the population [4]. Fatigue is perceived as the most distressing cancer or cancer treatment related symptom experienced. Unlike nausea or vomiting, which is generally manageable with anti-emetics, healthcare practitioners find fatigue challenging to manage [2, 5, 6]. Additionally, advances in treating cancer and improving survivorship rates means more people are living with a disability-related fatigue issue [2]. Consequently, CRF is a significant area of research to support and improve quality of life outcomes for people diagnosed with cancer, and especially given the persistence of CRF into the post-cancer treatment period.

Current treatment options have tended towards recommending exercise-based activities over pharmaceutical interventions. NCCN Clinical Practice Guidelines in Oncology for Cancer-Related Fatigue note the benefits of physical exercise in reducing CRF [2]. A meta-analysis of 26 qualified RCT studies additionally concluded aerobic exercise effective for managing CRF in cancer patients who had completed adjuvant therapy [7]. Cochrane reviews report aerobic exercise reduced CRF both during and after treatment, specifically in people with solid tumours [8, 9]. The benefits of exercise may alleviate both the cognitive and physiological effects of fatigue [10, 11].

Exercise and psychological treatments were reported as better than available pharmaceutical treatments in reducing CRF, both during cancer treatment and in the cancer post-treatment stages [11]. A meta-analysis of non-pharmaceutical cognitive, manual, and mind-body therapies (including tai chi and yoga) reported mild to moderate

effects on alleviating CRF [12]. It was concluded that patients can choose from among different effective types of exercise and non-pharmaceutical interventions to reduce CRF.

One such physical exercise intervention is Baduanjin mind-body exercise, which is a practice akin to Tai chi (Tai ji) originating from China. Well-known within Chinese Medicine's health care practice scope, Baduanjin mind-body exercise is the most widely used mind-body exercise in China [4]. In Australia, Baduanjin mind-body exercise is frequently prescribed to patients by Ahpra Chinese Medicine Board Australia (CMBA) registered health care practitioners to assist with health maintenance or support patients' health recovery and maintenance, and physical mobility.

Baduanjin mind-body exercise involves a set of gentle aerobic exercises involving mental focus with controlled breathing while performing a sequenced set of coordinated physical movements [4, 13, 15]. According to the American Sports Medicine Association and the American Centres for Disease Control and Prevention, Baduanjin mind-body exercise is a low-intensity exercise. The metabolic equivalent of Baduanjin mind-body exercise is < 3.0 and the maximum heart rate is 54% [14]. As a low-intensity exercise, Baduanjin mind-body exercise can build muscles, boost perceived energy levels, and improve the participant's body functioning. It can also mediate the stress response and alleviate anxiety, inducing a perceived sense of relaxation and calm, and is associated with reduction in the progression of serum-related anxiety markers [16]. Overall, Baduanjin mind-body exercise training has been shown to reduce fatigue, increase maximum oxygen uptake and muscle strength, improve sleep quality and overall quality of life, without causing significant adverse events [4, 13, 17-20].

A systematic review presented that Baduanjin mind-body exercise is beneficial for quality of life, sleep, general life balance, and physical parameters (hand grip strength, flexibility, blood pressure, and heart rate) among healthy individuals [11, 12] and participants with a variety of diseases [21-23]. Two clinical studies showed that Baduanjin mind-body exercise significantly reduced fatigue and improved perceptions of quality of life of colorectal cancer participants undergoing chemotherapy and breast cancer survivors who completed chemotherapy [4, 5].

Despite evidence showing benefits to survivability and quality of life, people living with a cancer diagnosis face additional barriers to participating and adhering to prescribed exercise interventions [24]. Barriers extend across several domains that include physical (muscle weakness, pain, fatigue), psychological (self-conscious about appearance, procrastination), environmental (weather, lack of equipment) and social (lack of company)

[24, 25]. Distinctly, Baduanjin mind-body exercise whilst providing exercise-like benefits [4], provides a low impact and low intensity intervention that combined with regulated breathing and mindfulness practices can assist patients who cannot otherwise participate in standardised exercise interventions. Baduanjin mind-body exercise may therefore be an appropriate form of exercise in lieu of other prescribed exercises for patients who have difficulty performing aerobic and/or strength training exercises.

However, further study is required to investigate the receptiveness of Baduanjin mind-body exercise for CRF in an Australian-based cancer-care context and population. Additionally, while useful for CRF, these studies were conducted through face-to-face instruction, which is not always suitable for people who find travelling difficult when fatigued, who are living in rural or remote locations or who are in isolation due to risk of acquiring a secondary infection. Consequently, the study additionally proposes a remote delivery model for the intervention.

3. STUDY AIMS/OBJECTIVES

The primary study aim is to assess the feasibility and acceptability of a randomised controlled trial of a remotely delivered program of Baduanjin mind-body exercise with participants diagnosed with any type and stage of cancer and receiving or who have received chemotherapy, and who have identified as having CRF. Remote delivery refers to providing the program over the internet and using the video conferencing software Zoom.

The secondary objectives are to determine the effectiveness and safety of the remotely delivered Baduanjin mind-body exercise program for CRF, with consideration to the design of a larger scale clinical trial. The long-term goal is to contribute to the evidence base of interventions for CRF and improve the quality-of-life outcomes for people living with CRF.

4. PARTICIPATING SITES

The Baduanjin mind-body exercise program will be mainly conducted online. However, supportive sessions (face-to-face) are available for participants in need at Liverpool Hospital, South Western Sydney Local Health District (SWSLHD) and Western Sydney University (WSU) campus. Study protocols, including the eligibility screening, participant communication, data collection and Baduanjin mind-body exercise program intervention

have been designed to be delivered remotely online using Zoom conferencing technology.

5. STUDY DESIGN

5.1 Study Type

A pilot randomised controlled feasibility study.

5.2 Expected Study Duration

The study duration is 10 weeks for participants in both the intervention group and waitlist control group. Potential participant interest might fluctuate from week-to-week depending on advertising exposure and oncologist referrals. Therefore, recruitment into the study will be staggered as people make their interest known to the research team and when they clear the study inclusion criteria. The trial period is from the date of ethics approval until December 2024 .

5.3 Data Source and Population

Participant's meeting study eligibility criteria will have their information collected using a study-specific Case Report Form. The form categories include demographic information (such as age, gender, ethnicity, language spoken at home), living arrangements, education and occupational status, and cancer type and treatment. (Refer to the Case Report Form).

The population are people diagnosed with any type and stage of cancer and receiving or who have received chemotherapy prior to study recruitment, and who have identified as having CRF.

To our knowledge, this will be the first study evaluating the feasibility and effects of Baduanjin mind-body exercise on cancer-related fatigue using a remote delivery method. Group sizes of 12 [26] and 15-20 per group are reported to give reasonable bias-corrected estimation of medium effect sizes in repeat-measure designed studies, as is being proposed for the current pilot [27]. For this pilot study, a sample size of n = 29 is necessary to have a 95% confidence of detecting an event which has a true probability of $\pi = 0.10$. To overcome the probable potential 15% participant attrition rate during the study [27] and to ensure availability of sufficient participants, a sample size of n=40 participants will be recruited in this study. Therefore, there will be 20 participants in the Baduanjin exercise, and another 20 participants in the control group. This number is sufficient to maximise

chances of identifying problems or feasibility issues that might arise with the intervention in preparation for a larger study [27].

5.4 Recruitment and Screening

Interested participants will be referred by their treating oncologist at Cancer Therapy Centre, Liverpool Hospital, other health practitioners or self-referral after seeing advertising for the study.

Resources required for the recruitment phase of the study include advertising materials (flyers and online advertisement). Only HREC approved participant recruitment material will be used during this study.

Advertising information will be placed on the noticeboards at Liverpool Hospital (SWSLHD) and the Western Sydney University campus. Online advertisement might be placed at the Wellness Centre, Liverpool Hospital and Western Sydney University website and via its Facebook and other social media pages to raise awareness of the study.

Potentially eligible study participants are screened from all people who have expressed an interest, and who have contacted a member of the research team or have given permission to their oncologist to be contacted by a member of the research team. The research team member will contact interested people over the phone to check their eligibility with the study inclusion/exclusion criteria using the Screening Checklist Form. Potentially eligible participants will then complete one question on a Brief Fatigue Inventory (BFI) score (simple fatigue scale) rating their CRF on a scale of 0 to 10 (0 = no fatigue; 10 = worst fatigue imaginable). If the screening process determines that fatigue is at a moderate level (4-6), they are eligible for study enrolment.

Participants who meet the inclusion criteria will be randomly assigned in a 1:1 ratio to the Baduanjin mind-body exercise group or the control group respectively.

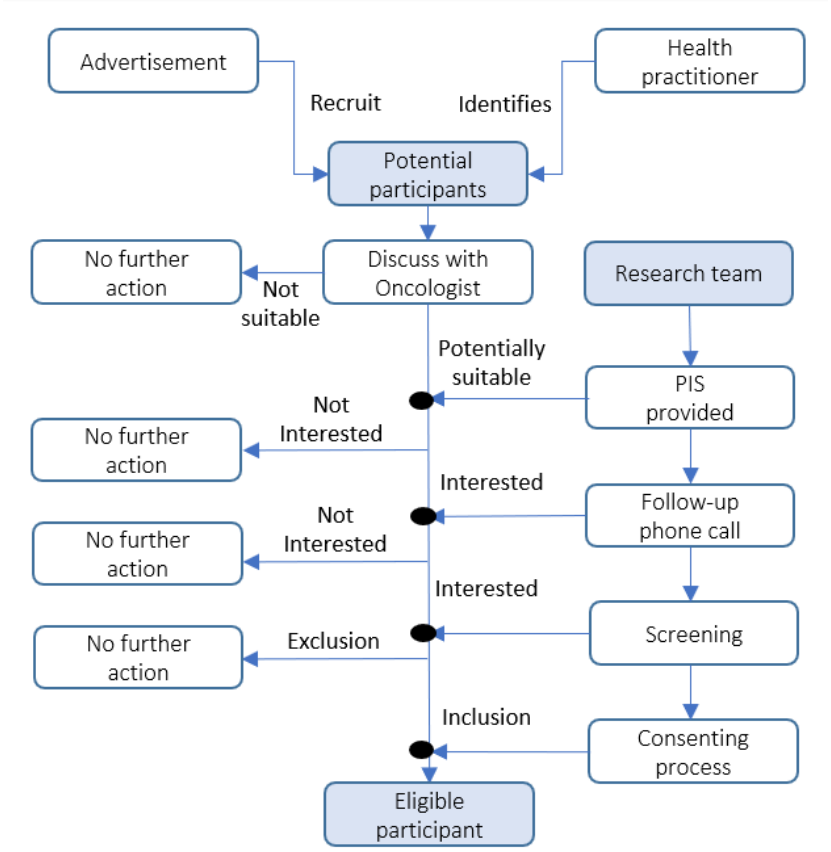

Figure 1: Recruitment and screening flow chart

5.5 Inclusion Criteria

The inclusion criteria are: (1) 18 years of age or older; (2) receiving adjuvant chemotherapy or completed adjuvant chemotherapy; (3) medical history of cancer diagnosis; (4) suffering from moderate CRF (rating of 4 to 6) as assessed by the BFI simple fatigue scale; (5) have a computer / device that is Wi-Fi or hotspot connected and be able to use smart phones, email, phone camera, (such as Facetime on iPhone), and Zoom conferencing app; (6) be aware of one's cancer diagnosis; and (7) understand the intervention process and able to communicate and provide informed consent in English.

5.6 Exclusion Criteria

The exclusion criteria are: (1) uncontrolled cardiopulmonary disease, angina, uncontrolled hypertension or uncontrolled postural hypotension; (2) uncontrolled nerve, muscle, or joint disease or injury affecting coordinated movement; (3) psychiatric illness or serious cognitive impairment and communication or language barriers that effect informed

consent; (4) postoperative heart, cerebral vessel, or other serious complications; (5) those not fully recovered from breast surgery, axillary surgery, transabdominal rectus abdominus muscle reconstructive surgery or any other surgery that would preclude full participation in the programme, (6) if an individual is otherwise not approved by their oncologist as being potentially eligible; (7) enrolled in other investigational studies which would impact cancer-related fatigue; and (8) a recent history (within previous 3 months) of regularly participating in Baduanjin mind-body exercise.

5.7 Consent Process

Once eligibility is determined, and for those people interested in further information, a research team member will email a copy of the Participant Information Sheet (PIS) and Consent Form for review. Eligible participants can take the study information and discuss further with their General Practitioner, other medical staff, family and/or other support persons.

If requested, a follow-up phone call will be arranged one week later (or sooner on request) to check if the eligible participant is still interested in participating in the study. For those who indicate an interest, the phone call will provide an opportunity to ask further questions or seek clarification of information in the PIS with a member of the research team, and that they have a clear understanding of the research and its requirements. Eligible participants are to confirm a cancer diagnosis and treatment to a member of the research team member. For those still wishing to participate at this time, written consent will be discussed and organised to be collected from the participant via email and/or post. This will happen prior to randomisation, and before any study procedures commence.

Participants will voluntarily confirm their willingness to participate in the study, after being informed (in writing via the PIS and review copy of the consent form, and verbally, with a member of the research team reading from the consent form) of all aspects of the study that are relevant to their decision to participate.

The participants are informed that they are free to withdraw from the study at any time, at their own discretion, without obligation to provide a reason. They are informed that a decision to withdraw will not jeopardise or affect their current and future routine treatment and health care, nor affect their relationship with those treating them or their relationship with Liverpool Hospital, SWSLHD, WSU or my medical attendants. The research assistant will retain the original signed consent form and/or a copy or photo of the completed consent form and the associated email if it was returned electronically.

If a participant does decide to withdraw, there is a *Revocation of Consent Form* to complete. The original will be retained and/or a copy or photo of the completed *Revocation of Consent Form* and the associated email if it was returned electronically.

5.8 Study Procedures

The participant will be enrolled into the study after the informed consent process has been completed and the participant has met all *inclusion* criteria and none of the exclusion criteria. The participant will receive a randomised study enrolment identification number, and this will be documented in the participant's Case Report Form and on other study documents.

Baduanjin mind-body exercise intervention group
Please note: Baduanjin mind-body exercise program is in addition to a participant's standard care. There are no changes to a participant's usual care practices.

Participants commencing the exercise program will have a meeting with a research team member (in week 0), who will organise delivery of the information pack and resources in advance of the participant commencing their Baduanjin mind-body exercise in Week 1. An introductive session (30-minute) is held for participants individually, which is comprised of an introduction to the Baduanjin mind-body exercise program, guidelines for performing the exercise movements, and illustrations of all movements. The participant is provided with a study resource including Baduanjin mind-body exercise online demonstration video link, a picture-based Instruction Handbook displaying the movements, and an Exercise Logbook to record the completion of the daily exercise routine. The picture-based Instruction Handbook and Exercise Logbook are sent to the participant late by email (only mailing hard copies as required). The picture-based Instruction Handbook is produced by the research team, the demonstration video is accessible via a YouTube link (https://youtu.be/F5OtK935Y8w). This is an information session, no instruction on how to perform the exercise is given until one week after, that is, the participants are required not to commence their Baduanjin mind-body exercise.

After receiving the study information pack and resources, a Baduanjin mind-body exercise instructor (who is a member of the research team) will organise a Zoom meeting to meet with each participant to explain and demonstrate the eight movements and natural breathing methods that comprise the Baduanjin mind-body exercise program.

Using the Zoom App, participants will be invited to watch the Baduanjin mind-body exercise demonstration videos which explains how to perform the exercise movements where the instructor will explain and demonstrate the eight movements and natural breathing methods with the participants. This is done before commencing the first exercise session in the program.

In addition to self-guided practice, the participants will be asked to join in a coached Zoom exercise program with an instructor, either in the morning or afternoon or both sessions at their own choice throughout the intervention period (8 weeks). Participants will be requested to practice Baduanjin mind-body exercise at least 2 sessions per day, 6 days per week with each session lasting about 15 mins for 8 weeks. Missed sessions will not be considered as a protocol deviation.

The Baduanjin mind-body exercise sessions via Zoom are instructed by members of the research team who have at least two years' experience in the practice of Baduanjin mind-body exercise. If participants miss out on any Zoom sessions, they can watch the demonstration video as a reference. Participants will be asked to record their daily Baduanjin mind-body exercise schedule in the Exercise Logbook. Recording this in the Exercise Logbook will take approximately 2 minutes each session. This will happen twice daily, 6 times per week for 8 weeks. Weekly telephone calls will be performed by a research assistant to see how the participants are progressing and engaging with the Baduanjin mind-body exercise program. The weekly phone calls will also discuss any unexpected side effects or adverse events that might be related to the exercise.

Finally, participants are asked to complete two (2) questionnaires at baseline (week 0) as part of the study intake process, and again at the end of week 4 and week 8 of the exercise program. These questionnaires are the brief fatigue inventory (BFI) and the PROMIS-29v2.0. The BFI measures fatigue. The PROMIS-29v2.0 is a patient reported outcome measure used by health services in NSW. Together, these will take 5-10 minutes to complete online and can be accessed using secure links that will be emailed to participants.

There is also the *Credibility and Expectancy Questionnaire* (CEQ) which has four questions and takes one minute to complete. Two questions are completed before entry into the study (week 0), and two at the completion of the Baduanjin mind-body exercise program (week 9).

One week after completing the Baduanjin mind-body exercise program (in week 9), a study team member will contact participants by phone for a final time. This is to check on the participant and see if there have any reports or adverse experiences. Participants will also be asked to complete for the final time the BFI and the PROMIS-29v2.0, along with the final two questions from the CEQ.

The timeline below illustrates the weeks required to meet via phone call or video call from the start of the trial through to completion of the trial.

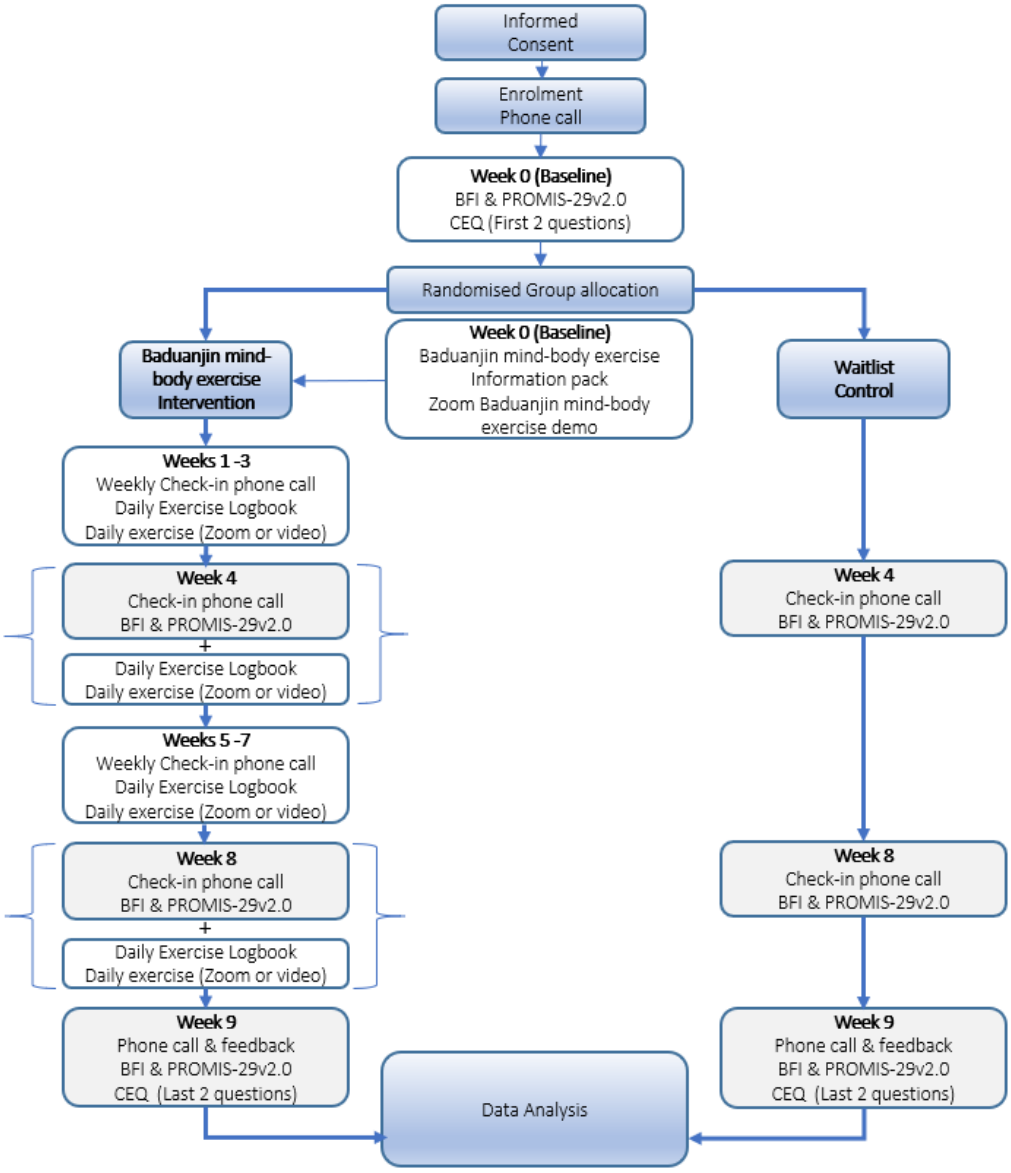

Figure 2: Intervention group and control group study flow

Baduanjin mind-body exercise includes three phases: warm-up, exercise, and cool-down which together, consist of the intervention in this study.

During the warm-up and cool-down phases, the participants will perform deep breathing and stretching exercises to improve range of motion in their joints and flexibility and reduce possible muscle and joint soreness.

During the exercise phase, the participants will perform eight sets of movements led by the Baduanjin mind-body exercise video and/or instructor via Zoom. Each set of movements are classically described and shown with an image approximating the completed movement in the *Baduanjin Mind-Body Exercise Instruction Handbook*. All movements require a mindful mental focus to coordinate sequenced body movements with breathing.

Wait list control group

From week 0 to week 9 (10 weeks in total), participants will receive their usual care/medications and undergo no Baduanjin mind-body exercise intervention. Participants in the waitlist control group also maintain their lifestyle without modifications to usual daily care routines. Participants will be asked to complete the BFI and the PROMIS-29v2.0 questionnaires to monitor changes in their cancer-related fatigue to compare changes with the intervention group. This will happen upon enrolment into the study (week 0 - baseline), and at week 4, week 8 and again at week 9.

Participants in the waitlist control will be offered entry into the Baduanjin mind-body exercise program at completion of their waitlist control period. Entry will be as a non-study participant which means access to the exercise program but without any further need to complete questionnaires. This is voluntary and no longer as part of the study.

The summary of the total approximate time participants dedicate to the study is noted below:

Intervention group (approx. 28 hours)

- Screening and recruitment phone call: 30 minutes (in week 0)
- Information session (Zoom): 30 minutes (in week 0)
- Baduanjin mind-body exercise routine: approximately 30 minutes per day or 3 hours per week; (24 hours in total spaced across weeks 1 to 8)
- Completion of Exercise Logbook: approximately 10 minutes per week (1 hour and 20 minutes in total, spaced across the 8 weeks of the Baduanjin intervention)
- Telephone weekly check-ins: approx. 5 minutes per week (40 minutes in total)
- Outcome measures: 5-10 minutes each time (in week 0, week 4, week 8, and week 9) (Approximately 20 – 40 minutes in total) and
- Final week telephone call: 5- 10 minutes (in week 9)

Control Group (2 hours)

- Screening and recruitment phone call: 30 minutes (in week 0)
- Telephone weekly check-ins: approx. 5 minutes per week (40 minutes)
- Outcome measures: 5-10 minutes each time (in week 0, week 4, week 8, and week 9) (Approximately 20 – 40 minutes in total)
- Final week telephone call: 5- 10 minutes (in week 9)

5.9 Randomisation

The participant will be randomised after they have met the inclusion criteria and completed the initial round of outcome measures (that is, baseline enrolment). At this time the participant will be randomised to 'Baduanjin mind-body exercise group' or 'waiting list control group' and receive a computer-generated 'Randomisation Number' based on a randomisation service software, the allocation concealment is undertaken by an independent research assistant.

6. ETHICAL CONSIDERATIONS

6.1 Study Procedure Benefits

There are several possible study benefits from the study's procedures.

Firstly, the Baduanjin mind-body exercise program is easy to learn, offered free-of-charge, and an appropriate home-based exercise program. It involves eight integrated active movements coordinated with breathing. The movements are simple, slow, and often reported as relaxing [20]. It is a low intensity activity suitable for participants with chronic illnesses (for example, cancer, Parkinson's disease, osteoarthritis, hypertension, heart failure, and ischemic stroke) [4, 5, 16, 21-23]. There are no special material requirements.

Secondly, the Baduanjin mind-body exercise program has been specially designed to be carried out at home. The exercise program can be undertaken in different locations as the participant chooses, including outdoors. This helps with adherence, is convenient to participants and reduces study burden relating to time and travelling (compared to an on-site study). This means potential participants living in rural and remote locations have an equal opportunity of participating as those living in regional and city locations.

Thirdly, the study employs commonly available communication technologies and services such as Zoom video conferencing, telephone, email, and post, instead of in person site

visits, although the latter is available upon request. This also supports ease of user interaction with program instructors and the research team. There is no cost for the intervention or the use of these technologies to participants; any study related Wi-Fi or telephone usage costs will be covered.

Fourthly, the Exercise Logbook takes 2 minutes a day to complete. This reports frequency and compliance of the Baduanjin mind-body exercise participation and may assist with motivating participants. The outcome measure questionnaires (BFI and PROMIS-29v2.0) are estimated to take less than 10 minutes to complete. Telephone check-ins monitor for study related adverse impacts and provide support to ensure study procedure compliance.

Fifthly, Baduanjin mind-body exercises benefits the unmet needs of patients who may have difficulty performing prescribed aerobic and/or strength training exercises such as walking. By providing exercises that comprise of gentle and slow movements with low impact, Baduanjin mind-body exercises offers an additional option to patients living with cancer-related fatigue.

Finally, remote delivery reduces the incidence of potential community exposure of participants to infections, such as the COVID-19 virus, since it is designed for home-based participation (rather than face-to-face). Remote delivery also maintains social distancing.

Overall, the research project is subject to minimal burden and harm. The Baduanjin mind-body exercise training have been shown to reduce fatigue, increase maximum oxygen uptake and muscle strength, improve sleep quality and quality of life, with few significant Adverse Events (AEs) reported. The significant benefit of translating the project into practice includes no additional clinical costs, no limit in terms of place to practice, it is easy to learn. In addition, participants will be receiving intervention adjuvant to standard treatment.

The research team comprises of experienced Chinese medicine practitioners and other medical health care professionals who are experienced in conducting research and are GCP certified. Hence, there remains an expectation of research team members continuing to abide by professional and ethical codes of conduct and know their responsibilities with the conduct of ethical research.

Participants will be informed that this is a clinical trial (in the PIS and recruitment telephone call) and the study cannot guarantee or promise any benefits from this research (PIS); however, the potential benefits to participants might include decreased fatigue leading to

quality-of-life benefits. Participation may benefit future cancer survivors and research by helping to understand the feasibility, advantages and any problems that may arise when Baduanjin mind-body exercise is used for CRF for people living with cancer or a cancer diagnosis.

6.2 Study Procedure Risks

A systematic review identified 22 of 47 clinical trials (involving a total of 3877 participants) with (AE) reporting protocols, with only 2 trials subsequently reporting AEs potentially caused by Baduanjin mind-body exercise training [28]. There were no reported serious adverse events (SAE).

Baduanjin mind-body exercises may cause mild muscle soreness or stiffness during and after exercise in participant's who are physically unfamiliar with the prescribed movements. Physical mild soreness and stiffness usually ease shortly after the exercise session. However, this program is low in intensity, and has been structured with a warm-up and cool down phase to reduce this potential side effect.

There is the potential that side effects can be more serious [28]. Adverse reactions to professionally administered Baduanjin mind-body exercise have been reported and may include:

- Mild dizziness or drowsiness after treatment (rare).
- Mild chest pain, shortness of breath, cold sweats, nausea, and vomiting (very rare).

The study screening criteria excludes people with a known and uncontrolled health condition that might increase their risk of experiencing a rare or very rare adverse events. If fatigue begins to worsen (BFI is more than 8/10), the participant is advised to seek medical advice and may stop participation in the study's Baduanjin mind-body exercise. The Exercise Logbook also iterates instructions to inform the research team and stop and seek medical advice immediately if they experience any of the warning signs or symptoms noted.

Incorrect interpretation of Baduanjin mind-body exercise instructions might result in physical discomfort if the body movement is incorrectly executed. This potential risk will be minimised by having instructors who are experienced Baduanjin mind-body exercise instructors. Participants are additionally provided with daily Zoom support with instructors who can correct movements through demonstration and provide further clarity of exercise movements. Movements can be cross-referenced to the videos and brochure resources.

The Baduanjin Mind-Body Exercise Instruction Handbook also advises participants to stop exercise and seek medical attention immediately if they experience warning signs such as chest pain, shortness of breath, dizziness, cold sweats, nausea, or vomiting.

Completing the study forms and outcome measures may pose some risk. While many of the questions are general, participants are being asked to reflect upon CRF because of a known cancer diagnosis or cancer-related fatigue that resulted from their cancer treatment. This might cause feelings of distress in some participants. Participants will be advised in the PIS of this and to consider their present health status.

The research takes place over a total of 10 weeks for both the intervention and control groups which may cause some inconvenience with participants time and to their usual established routines. However, for participants in the intervention group, the time for exercising is spaced and is limited to approximately 15 minutes twice a day for six days a week over 8 weeks (24 hours in total), undertaken online over Zoom, and is home-based. This minimises the time impact and inconvenience that would otherwise happen with traveling to a study site away from home. Additionally, the outcome measures are quick to complete. The BFI and PROMIS-29v2.0 together take approximately 10 minutes to complete. These are completed at four time points in the study, which is approximately 40 minutes for each study participant. Additionally, the intervention group participants each complete the Exercise Logbook which takes approximately 10 minutes each week (or 80 minutes in total across the 8 weeks of the intervention).

The study will use the WSU's Zoom subscription (available to Apple, Android devices and IBM) and configured security settings with password setting active to maintain secure links. The video recording feature will be automatically turned off. The Zoom app is free to download and easy to access through a mobile device or computer.

The nature of the study will not expose participants to illegal activity, and economic harm is not anticipated. Participants will have anticipated study-related internet usage costs covered (total of $40). Participation in this study is voluntary and participants can withdraw at any time or stage of the research.

Given that there are no viable therapeutic options for CRF, the result of this research may provide a new therapeutic direction for CRF and improve the quality-of-life outcomes for people living with CRF. Hence, the benefit is justifiable considering the potential risks imposed.

6.3 Confidentiality and Privacy

Data collection and management

All study data collected will be recorded in the Case Report Forms and other templates prepared for this study. Socio-demographic information, medical history, any occurrence of adverse events and intervention outcomes during the study will be collected and recorded on paper or in electronic files.

All electronic data will be entered and managed using the Research Electronic Data Capture (REDCap) management system, and/or with Microsoft (MS) Excel spreadsheets and MS Word files with compatible file formats for SPSS (V 24.0; IBM Corp; Armonk, NY, USA).

Each member of the research team has responsibility for the accuracy, authenticity, collection and reporting of all clinical and safety data, or any other data on collection forms and to enter data as it is reported (such as during telephone calls) or as received (returned outcome measures). All completed forms must be signed by the research team member collecting the information or by an authorised team member to attest that the data contained on the study collection forms is true. The Principal Investigator or nominated research team member will audit the records weekly to ensure compliance with the study protocol.

Confidentiality and Privacy

Any information obtained in connection with this study that can identify a participant will remain confidential. Identifying information is also kept separate from other information provided on other study forms. Participants will be randomly allocated a study identification code. Consequently, the participants code will be appended to all data collection forms relating to their participation in this study.

The coding key is held separate from participant's identifiable and de-identified study information and documentation, to assist in maintaining data de-identification. The coding key is locked in a password-protected cloud partition in the WSU's computer systems so it cannot be used to decode participant's information. A hardcopy of the coding key is also be held separately in a locked file in the Chinese Medicine Centre (CMC) (Level 3, School of Health Sciences, Western Sydney University (WSU), Campbelltown Campus) accessible to the study team. Only the members of the research team have access to the

coding key. All other research data and information in electronic form are also stored in a separate password-protected cloud partition on the university's computer systems. The password is only made available to members of the research team.

Zoom

The WSU secure Zoom subscription will have password enabled to ensure the correct people are admitted. The 'waiting room' function will also be active so the Baduanjin mind-body exercise instructor can cross check the details of each participant before entry into the main Zoom room.

6.4 Data Storage and Record Retention

Any hard copy documents (inclusive of source documents) and information will be kept in a locked cabinet at the CMC, (Level 3, School of Health Sciences, WSU, Campbelltown Campus). The CMC offices and file cabinet are only accessible to staff involved in this study. This includes the Principal Investigator and members of the research team. Participant information is not made available in any form to third parties without written permission from the WSU. The information collected from participants will only be used for the purpose of this research project, except disclosed as required by law. (Refer to the Research Data Management Plan - RDMP).

After participants have completed the trial, all paper documents will be retained for 5 years in locked archive storage at the Chinese Medicine Centre in the Western Sydney University (Campbelltown Campus). Electronic data will be archived on the WSU secure computer server with password, restricted access to members of the research team and also retained for 5 years.

7. DATA SAFETY MONITORING BOARD

One of the investigators with medical qualifications will be nominated as study medical representative and another non-investigator will provide an independent review for safety on all adverse events. This person will also monitor for correctness of completion of study documentation in terms of reporting any adverse events and other trial conduct issues that may arise in terms of safety or ethical happenings.

8. CONFLICT OF INTEREST

The investigators declare there is no conflict of interest.

9. FUNDING

The project is supported by funding from the Chinese Medicine Centre, Western Sydney University. The total amount is: $84,702. The funding will cover:

- $ 48.04 (HEW4-2) for research assistant 1 (recruitment, telephone calls and administration) – 8 hours/week x 50 weeks = $19,216
- $51.4 (HEW5-2) for research assistant 2 (Baduanjin instruction) – 20 hours/week x 50 weeks = $51,400
- $62.43 (HEW6-4) for researcher (data analysis and preparing documents) – 10 hours/week x 20 weeks = $12,486
- Participant vouchers for study-related internet costs calculated as a total of $40: 40 participants x $40 (maximum cost $1,600)

10. RESEARCH OUTCOMES

Primary outcome

Feasibility

a). Recruitment rate: number of enquiries and number of enrolments per month of active recruitment; or

b). Percentage conversion to enrolment measured as participants (n) enrolled / the total number of enquiries; and participants (n) enrolled / people (n) potentially eligible.

c). Retention rate: participants (n) completing 8-week intervention (96 sessions) and outcome measures/ participants (n) enrolled.

d). Adherence rate: participants (n) completing at least 80% or 10 out of 12 Baduanjin mind-body exercise days per week / total participants (n) allocated to the intervention group.

Secondary Outcomes (this will be done for calculating power for a larger study)

a) Change (reduction) in the severity of cancer-related fatigue symptoms measured by the *Brief Fatigue Inventory* (BFI).

b) Change (reduction) in any of health domains in physical function, fatigue, pain interference, depressive symptoms, anxiety, ability to participate in social roles and activities, and sleep disturbance measured by *PROMIS–29 Profile v2.0*.

c) The number and severity of reported side effects and / or adverse events.

d) Participant's perceptions of the Baduanjin (mind-body exercise) program before

randomization and after completion of the program as measured by the (modified) *Credibility and Expectancy Questionnaire*.

Outcome Measurements

Brief fatigue inventory (BFI)

The brief fatigue inventory is a validated measure sensitive to assessing patient reported fatigue [29]. It comprises nine items measured on a ten-point scale that assesses the severity of fatigue and its effects on the participant's ability in activities of daily living. A global fatigue score is calculated by averaging the score of the items. The BFI is short and easy to use (approximately 5 minutes to complete).

PROMIS–29 Profile v2.0

The Participant-Reported Outcomes Measurement Information System (PROMIS-29) v2.0 profile assesses pain intensity using a single 0–10 numeric rating item and seven health domains, (physical function, fatigue, pain interference, depressive symptoms, anxiety, ability to participate in social roles and activities, and sleep disturbance), using four items per domain [30]. It assesses health intervention impacts and tracks changes in health overtime [31]. It is a standard outcome reporting tool used in NSW Health.

Credibility and Expectancy Questionnaire

The *Credibility and Expectancy Questionnaire* has been modified to assess participants perspectives on the credibility of the Baduanjin mind-body exercise program for their fatigue [32]. There are four (4) questions and takes 1 minute to complete. Questions 1 & 2 are completed before randomisation about participants expectations, and questions 3 & 4 after the final Baduanjin mind-body exercise session on the credibility of their experience [33]. Each question is measured on a Likert scale of 1-9 where 9 is the most credible.

Exercise Logbook

Participants in the intervention group will be asked to record their daily Baduanjin mind-body exercise schedule in a logbook for the 8 weeks of their exercise. This takes approximately 2 minutes each day or 10 minutes a week in total. The logbook helps understand any relationship between frequency of exercise and changes in CRF scores. It additionally assists with determining feasibility with adherence rates.

Final Feedback Form (Week 9)

Participants in the intervention group will be contacted by a member of the research team to thank them for their participation and inform them the final feedback form will be the last data collection. The research team member will check the completion of final outcome

measures and ask if participants would like a copy of the study report of findings. The participant will also be asked for further feedback on the participants experiences and future changes to assist with participation and completion of the program.

Adverse Events Reporting and Management

There are weekly telephone calls with a member of the research team to check on participants engagement with the Baduanjin mind-body exercise program and discuss any exercise related expected and unexpected side effects. If present, these are reported using the Adverse Events Form. The Principal Investigator is responsible for assessing any event as meeting the adverse event criteria threshold. Participants can report any side effects of concern daily with the exercise instructors (who are also registered health care practitioners), and these will also be reported in the Adverse Events Form for the Principal Investigator to investigate and decide.

Each intervention group participant will receive an Exercise Logbook for reporting side effects of concern related to the Baduanjin mind-body exercise program. All Serious Adverse Events (SAEs) occurring between consent and the last visit for the study are recorded in detail in the Adverse Events Form by the member of the research team who received the original report, and who also informs the Principal Investigator. All AEs that occur between the first intervention and the last intervention for the study must be recorded in detail. In case of an AE/SAE, the Principal Investigator will initiate contact with appropriate members of the participant's health care team, or as according to their health care judgement given the nature of the AE/SAE. If necessary, participants will be withdrawn from the study. Participants with SAE/AEs present at the last intervention will be followed up until resolution of the event.

The SWSHLD Ethics Committee will be notified of any AE/SEA. Regular meetings will be scheduled by the Principal Investigator to discuss the AE with hospital clinicians. Participants will be provided a 24-hour contact number for any urgent matters or concerns. The severity, expectedness and causal relationship with the intervention will be assessed for every AE reported. The number and severity of AE, as recorded on an Adverse Events Form, will be reported in adherence to the requirements of the National Health and Medical Research Council for Clinical Trials Adverse Event Reporting.

Endpoints

Key feasibility endpoints are recruitment rates, and the participation and completion of the study interventions (from Logbook data) within the stated study periods. For feasibility and contributing to the design of a larger clinical trial, the primary outcome measure endpoint

will also include the effect of Baduanjin mind-body exercise on changes of fatigue as measured by the BFI score at baseline (week 0), at 4 weeks (mid-point), 8 weeks (final week) and 9 weeks (1 week follow-up) [29] (Additional secondary outcome measure endpoints will be the PROMIS-29v2.0 [28] and reported adverse events at baseline (week 0), 4 weeks, 8 weeks and 9 weeks (1 week follow-up) (Appendix 1. & Figure 1.) Participant's credibility and expectation ratings are compared prior to study group randomisation with their credibility scores on completing the Baduanjin mind-body exercise program.

Data analysis

Data are transcribed into an excel spreadsheet and checked for accuracy. Data will be cleaned using frequency counts and logic checks. At the completion of cleaning the final data set will be locked with any further errors addressed as study limitations. Analyses of the endpoints will follow the Intent-to-Treat (all participants as per randomisation) and per-protocol (participants adhering to the protocol). These analyses will include, as appropriate, participant demographic (co-variates) and Baduanjin mind-body exercise participatory frequency data. Participant demographics and data will be summarised at baseline using sample means and proportions with corresponding 95% confidence intervals. We will explore and report confounders in the modelling.

To our knowledge, this will be the first study evaluating the feasibility and effects of Baduanjin mind-body exercise on cancer-related fatigue using a remote delivery method. Data will therefore help calculate an effect size for predicting power in a larger future study. This includes using these data to formulate study hypotheses. As such, data will be transformed to ensure approximate normal distributions.

All data will be entered and managed using the Research Electronic Data Capture (REDCap) management system and all analyses performed using SPSS (V 24.0; IBM Corp; Armonk, NY, USA) or descriptive analyses and data sorting with Microsoft Excel.

Publication

The results of this study will be published and/or presented in journal articles, conference posters, seminars and presentations. We will use de-identified and aggregated data. In any publication and/or presentation, it will be impossible to identify participants.

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12. APPENDICES

1. Study Assessment Time-points

		Week 0 (Baseline)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9 (Follow-up)
PIS and Consent	X										
Information phone call	X										
Screening (inclusion/exclusion)	X										
Consent & Enrolment		X									
Randomisation		X									
Information pack		I									
Baduanjin Zoom		I	I	I	I	I	I	I	I	I	
AE Assessment			I	I	I	I	I	I	I	I	I
Telephone Check-in		I & W	I	I	I	I &W	I	I	I	I & W	I &W
BFI	X	X				X				X	X
PROMIS-29 V2.0		X				X				X	X
CEQ (questions 1,2)		X				X				X	X
CEQ (questions 3, 4)		X									X

X = everyone

I = Baduanjin Intervention group

W = Waitlist control group

Appendix 2. Participant Exercise Handbook and Daily Exercise Logbook

Please see separate files:

Baduanjin_Mind_Body_Exercise_Instruction_Handbook

Baduanjin_Exercise_Logbook