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Effect of Mind-body Exercise (Tai Chi) for Patients with Early Dementia: Protocol for a Randomized Controlled Study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-019940
Article Type:	Protocol
Date Submitted by the Author:	05-Oct-2017
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Keywords:	Dementia < NEUROLOGY, Tai Chi, cognitive function

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Manuscripts

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3 **Effect of Mind-body Exercise (Tai Chi) for Patients with Early**
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6 **Dementia: Protocol for a Randomized Controlled Study**
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8
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43
44 **Key words:** dementia, Tai Chi, cognitive function
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47 **Word count:** 1942
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ABSTRACT

Introduction

At present, there is no cure for most types of dementia. Many studies suggest that Tai Chi exercise is a safe and appropriate mind-body exercise for old people and efficiently slows down age-related cognitive decline. This trial is undertaken to create a set of Tai Chi exercise specially designed for people with cognitive impairments by a multidisciplinary team. We will also evaluate its effects on cognitive function, behavior/mood, fall risk and activities of daily living of patients with early dementia.

Methods and analysis

A set of Tai Chi program named "Cognition Protecting Tai Chi" (CPT) was developed by a research team comprised of geriatricians, neurologists, rehabilitation specialists, sports medicine experts, and Chinese medicine experts. Then a randomized controlled study will be conducted. Ninety patients with early dementia will be recruited and randomly divided into intervention group and control group. The intervention group will take this CPT three times a week for 20 minutes under guidance of the professional therapist. The control group will receive routine treatments. The study will last for 10 months. All participants will undergo a battery of neuropsychological and functional evaluations, including Mini-Mental State Examination, Montreal Cognitive Assessment, The World Health

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3 Organization—University of California Los Angeles Auditory Verbal
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5 Learning test, Geriatric Depression Scale, Neuropsychological Inventory,
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7 Barthel Index, at baseline, 5 and 10 months. Fall incidence will also be
8
9 recorded. Primary outcomes are changes of above psychometric
10
11 assessments of the participants, and secondary outcome is fall incidence.
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15 **Ethics and dissemination** This study was approved by the ethical review
16
17 committee of the Beijing Geriatric Hospital (protocol number: 2015-021).
18
19 Informed consents will be got from all participants or their guardians.
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21 Findings of this study will be published in peer-reviewed journals,
22
23 academic conferences, and other healthcare settings where appropriate.
24
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26 27 28 **Trial registration number**

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30 ChiCTR-INR-16009872 (<http://www.chictr.org.cn>)
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33 34 35 **Strengths and limitations of this study**

36
37 ► This is the first study to create a Tai Chi program which is specifically
38
39 designed for patients with cognitive impairments by a multidisciplinary
40
41 professional team.
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45 ► We also design a randomized controlled trial to evaluate its effects.
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47 This will add evidence to nonpharmacological therapy for dementia.
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51 ► An open-label study design may result in bias though is difficult to
52
53 make the Tai Chi intervention blind.
54
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INTRODUCTION

Demented patients can show various clinical symptoms, with memory loss as the most common initial problem. Later on, complaints of inattention, miscalculation, unreasoning and disorientation become more and more evident¹. Besides cognitive disorders, mental and behavioral disturbances, such as depression, anxiety and aggressiveness may happen. As disease going on, these syndromes progressively interfere with vital activities of daily living and resulting in independence. At present, there is no cure for most types of dementia. Current pharmacologic interventions that used to rescue cognitive function, such as acetylcholinesterase inhibitors and memantine, have limited efficacy and their adverse effects are not uncommon²⁻⁵. Meanwhile, typical and atypical antipsychotics for dementia have the same or even severe shortcomings.

According to neuroplasticity theory, the repetition of stimulate-reflect training helps demented patients with preservation and restoration of brain functions, even when their brains have been damaged to some extent⁶. Therefore, there is a considerable focus on investigation of non-pharmacological approach associated with enhancing cognition. Many studies suggest that mind-body exercise efficiently prevent and slow down age-related cognitive decline, and benefit the prognosis of dementia⁷⁻¹⁰.

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4 Tai Chi, one of Chinese traditional martial art, is an aerobic
5
6 mind-body exercise with mild-to-moderate intensity and is safe for the
7
8 elderly. It requires focus of concentration as well as shifting balance of
9
10 the body in accordance with soft limb movements. Its gentle and
11
12 smooth movements are coupled with steady breathing. In the theory of
13
14 traditional Chinese medicine, qi and blood can both be mobilized and
15
16 coordinated when practicing Tai Chi, this unique exercise. Excitability of
17
18 the central nervous system is also improved while some parts of the
19
20 brain areas being in working state and other parts being inhibited. Thus,
21
22 most brain neurons can have enough relaxation, including those are
23
24 getting atrophy. In this kind of alternate tension with relaxation,
25
26 function of cerebral cortex is improved and progress of cognitive decline
27
28 may get delayed. As strength and flexibility of the body both increase,
29
30 fewer falls happen, as well as other complications.

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32
33 Tai Chi has been recommended as a preferred kind of exercise for
34
35 fall prevention in the elderly by the American Geriatrics Society, because
36
37 it improves not only muscular strength, co-ordination and balance, but
38
39 also is an enjoyable activity with the potential for long-term insisting¹¹.
40
41 In a randomized trial carried out in non-demented Chinese elders, 40
42
43 weeks of Tai Chi exercise was proved to increase brain volume and
44
45 improve cognition better than intervention of social interaction¹².
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47 Evidences have also shown that Tai Chi is an appropriate exercise for
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3 individuals with dementia in its early stage, which helps improving
4 quality of life, brain function and even inducing reconstruction of
5 neurons. It has the potential to serve as an alternative therapeutic
6 approach for dementia persons¹³⁻¹⁵. Other studies reported that physical
7 exercise like Tai Chi improved mood and alleviated psychiatric problems
8 in early or middle stages of dementia and also significantly reduced
9 caregiver distresses¹⁶. Sticky Hands Tai Chi, a special Tai Chi training
10 technique practiced with a partner, promoted a comfortably intimate
11 interaction between the two persons and improved exercise adherence
12 and mood in demented older people¹³.

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China mainland is the origin of Tai Chi exercise and it has the
biggest number of demented older people¹⁷. However, almost all the
available evidence was conducted by foreign investigators. Moreover,
though there have been various programs of Tai Chi exercise, none of
them is designed for people with cognitive impairments. Our objective is
to develop an appropriate Tai Chi program specifically for patients with
mild dementia, which is called "Cognition Protecting Tai Chi" (CPT), and
to evaluate its protective effects on cognitive function, behavior/mood,
fall risk and activities of daily living. If results are positive, it will have
potential to be recommended as a routine cost-effective exercise
intervention for this population.

METHODS

Settings: This study is conducted at Center for Cognitive Disorders of Beijing Geriatrics Hospital (BGH). This hospital is a tertiary hospital with 900 inpatient beds located in Haidian District of Beijing City. The Center for Cognitive Disorders of BGH is a department serving for the elderly with cognitive impairments, which is also the Guidance Center for Cognitive Rehabilitation of the Haidian District.

Study design

There are two steps in this study design (Figure 1).

Firstly, a Tai Chi exercise program was specifically designed for cognitively impaired patients by a research team comprised of geriatricians, neurologists, rehabilitation specialists, sports medicine experts, and Chinese medicine experts. We deleted those unsafe and complex actions in traditional 8 style Tai Chi programs and added actions which were thought more beneficial to cognitive functions based on theories of traditional Chinese medicine science. This set of Tai Chi exercise was named "Cognition Protecting Tai Chi" (CPT). It has mainly 8 styles of actions, and each action can be divided into three motions. Then, CPT was performed in 5 patients with mild dementia who were invited to do the pre-experiment for 4 weeks. We modified those Tai Chi actions further where necessary according to their compliance and feedback till the final version was done.

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There are mainly 8 styles of actions in the final version of CPT except routine Starting Posture and Closing Form, which includes Raising Both Hands, Forearm Rollings on Both Sides, Brush Knee and Twist Step on Both sides, Grasp the Bird's Tail-Left Side and then Right Side, Cloud Hands, Single Whip, Work at Shuttles on Both Side, and Raising Left and then Right Hands (Figure 2).

Secondly, we will conduct a randomized controlled trial in participants who have mild dementia.

Recruitments of participants

Participants will be recruited from long-term care facilities near Beijing Geriatric Hospital, including Wenquan senior apartment, Lengquan senior apartment, and Hexihui senior apartment. Residents who meet the inclusion criteria will be recruited and written consent forms will be signed by all participants or their guardians.

Inclusion criteria

Patients aged no less than 60 years and in early stage of dementia (diagnosis based on The Diagnostic and Statistical Manual of Mental Disorders, 4th edition) with a Clinical Dementia Rating score of less than 2 are enrolled in this study.

Exclusion criteria

Patients who have severe visual and auditory impairments, serious physical disease in important organs (such as heart, lung, kidney, liver

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3 and so on), movement disorders, and are unable to accept assessments
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5 or interventions which are required in this study for any reasons.
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8 **Randomization**

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10 Participants enrolled will be randomly divided into intervention group or
11
12 control group at a ratio of 1:1. A computer-generated list will be used to
13
14 do the randomization by a study assist who has no idea of the
15
16 subsequent allotment.
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19 **Intervention**

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21 The intervention group will perform Tai Chi exercise three times a week
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23 for 20 minutes under the guidance of the professional therapists. The
24
25 control group will receive routine treatments. The study will last for 10
26
27 months.
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30 **Assessment**

31
32 The Chinese version of Mini Mental State Examination (MMSE)¹⁸ is a
33
34 30-point questionnaire that is used to measure cognitive impairment. It
35
36 examines functions of attention and calculation, recall, language, ability
37
38 to follow simple commands and orientation.
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42 The Montreal Cognitive Assessment (MoCA) Beijing version
43
44 (www.mocatest.org) is another 30-point test for assessing cognitive
45
46 function. It includes items of short-term memory recall, visuospatial
47
48 abilities, multiple aspects of executive functions, attention,
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50 concentration and working memory, language and orientation to time
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3 and place. More difficult and multiple tasks make it more sensitive to
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6 mild cognitive changes than MMSE.
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8 The World Health Organization–University of California Los Angeles
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10 Auditory Verbal Learning test (WHO-UCLA-AVL)¹⁹ is a tool to assess
11
12 immediate recall and delayed recall with 15 words independent in
13
14 meaning. Immediate recall is performed by asking subject to remember
15
16 and recall those 15 words just after each auditory learning, and this
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18 learning-recall process is repeated for three times. An average
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20 performance is recorded. Delayed recall is performed by asking subject
21
22 to recall those 15 words in 30-45 minutes after the immediate recall
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24 being done.
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30 The Geriatric Depression Scale (GDS)²⁰ is a 30-item self-report
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32 assessment used to identify depression in the elderly, of which questions
33
34 are answered "yes" or "no." It is simple enough to be used when testing
35
36 older individuals with mild or moderate cognitive impairment.
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39
40 The Neuropsychiatric Inventory (NPI)²¹ assesses common psychiatric and
41
42 behavioral symptoms in dementia. Its items include hallucinations,
43
44 delusions, agitation/aggression, dysphoria/depression, anxiety,
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46 irritability, disinhibition, euphoria, apathy, aberrant motor behavior,
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48 sleep and night-time behavior disturbance, appetite and eating disorders.
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51 The NPI is administered by the clinician to the caregiver who has detailed
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53 knowledge of the patient's performance. Besides, the caregiver is also
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3 asked to rate their own distress associated with daily care of the patient.
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6 The Barthel Index (BI)²² is an ordinal scale used to measure performance
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8 in activities of daily living (ADL). The ten variables describing ADL and
9
10 mobility addressed in the Barthel scale are presence or absence of fecal
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12 incontinence, presence or absence of urinary incontinence, help needed
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14 with grooming, help needed with toilet use, help needed with feeding,
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16 help needed with transfers (e.g. from chair to bed), help needed with
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18 walking, help needed with dressing, help needed with climbing stairs
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20 and help needed with bathing.
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25 All participants will undergo above assessments at 0 (baseline), 5
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27 and 10 months. Fall incidence will also be recorded.
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30 **Outcomes**

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32 The primary outcome is score of such psychometric tools and the
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34 secondary outcome is fall incidence.
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37 **Sample size**

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39 The sample size was calculated based on the results of pre-experiment of
40
41 this study. Using a type I error of 0.05 and a power of 80%, a sample size
42
43 of 40 per groups is enough for both primary outcomes and secondary
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45 outcome. Considering a 10% dropout rate may happen, a total number
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47 of 90 participants will be recruited.
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51 **Quality control and quality assurance**

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3 specialists. All data will be monitored and reviewed by the PI or
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5 co-investigators. Training will be provided to all researchers. Consistency
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7 coefficients in scoring assessment scales between researchers should be
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9 no less than 0.85. Data entry of all the case report forms will be verified
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11 by a second person of the study team.
12
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14 15 **Statistical method**

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17 All analyses will be performed using SPSS version 16.0. Comparisons of
18
19 score variations of psychometric assessments over time between two
20
21 groups will be conducted using repeated measurement of variance
22
23 analysis. Difference of fall incidences between groups will be analyzed
24
25 using Chi-square test.
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32 33 **CONCLUSION**

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35 In this protocol, we describe a “Cognition Protecting Tai Chi” (CPT)
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37 exercise developed by our research team including geriatricians,
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39 neurologists, rehabilitation specialists, sports medicine experts, and
40
41 Chinese medicine experts. Moreover, a randomized controlled trial will
42
43 be conducted to evaluate the effect of this CPT on patients with
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45 dementia in early stage.
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49 50 **Contributors**

51
52 Jihui Lyu conceived the idea and supervised this study and is the
53
54 guarantor. Jihui Lyu, Xiangjiang Rong, Xueli Chen, Fangling Li, Wenjie Li
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3 and Lian Wei were involved in the design. Wenjie Li, Yanna Huang and
4
5 Xiangjiang Rong prepared draft manuscript and Jihui Lyu revised the
6
7 manuscript. Wenjie Li, Mo Li and Xiangjiang Rong carried out the
8
9 statistical calculation. All authors approved submission of this
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11 manuscript.
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13
14

15 **Funding**

16
17 This work is supported by Beijing Clinical Characteristics Project of
18
19 Beijing Municipal Science and Technology Commission (Project number
20
21 Z151100004015023)
22
23
24

25 **Competing interests**

26
27 None declared.
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30 **Ethical approval:** This study was approved by the ethical review
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32 committee of the Beijing Geriatric Hospital (Beijing, China).
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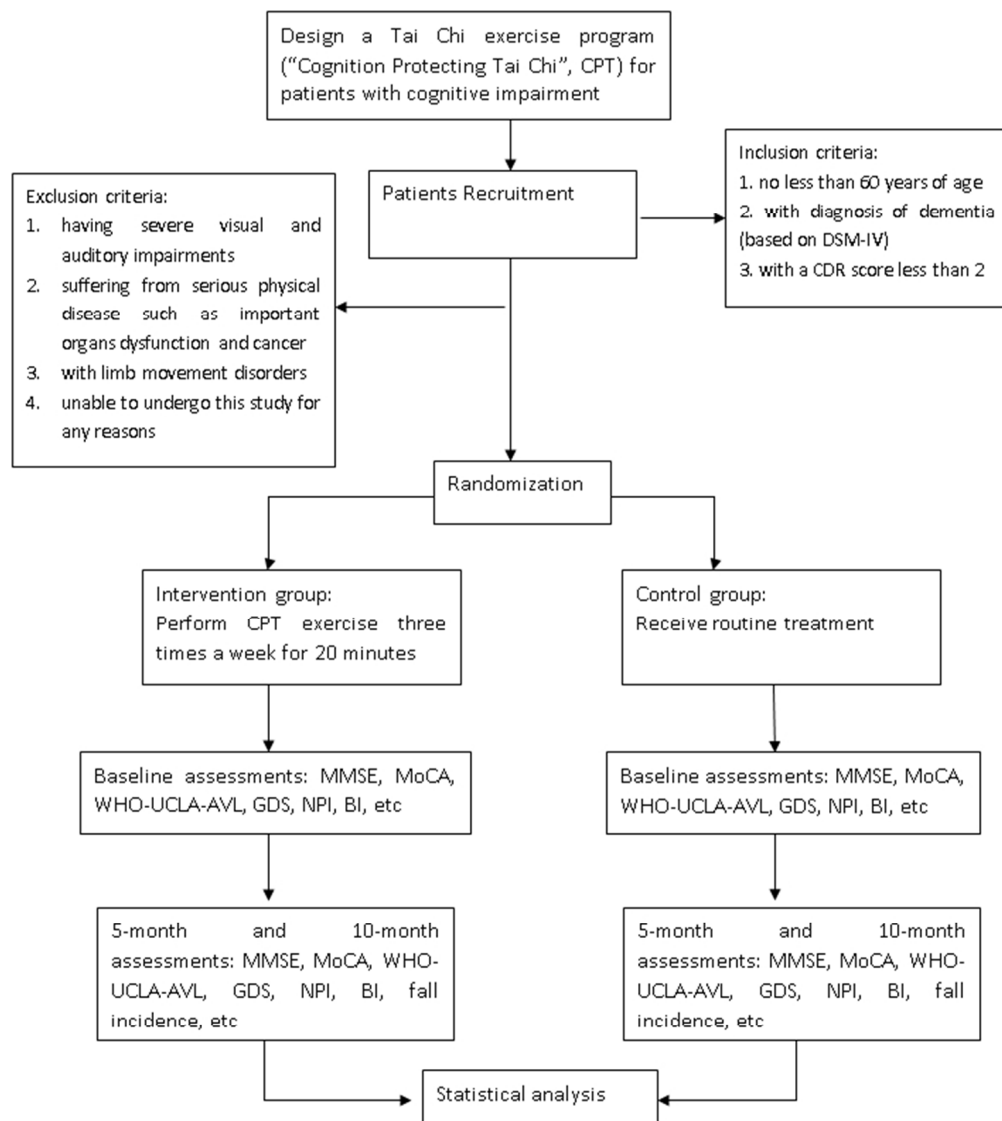


Figure 1. The study flow

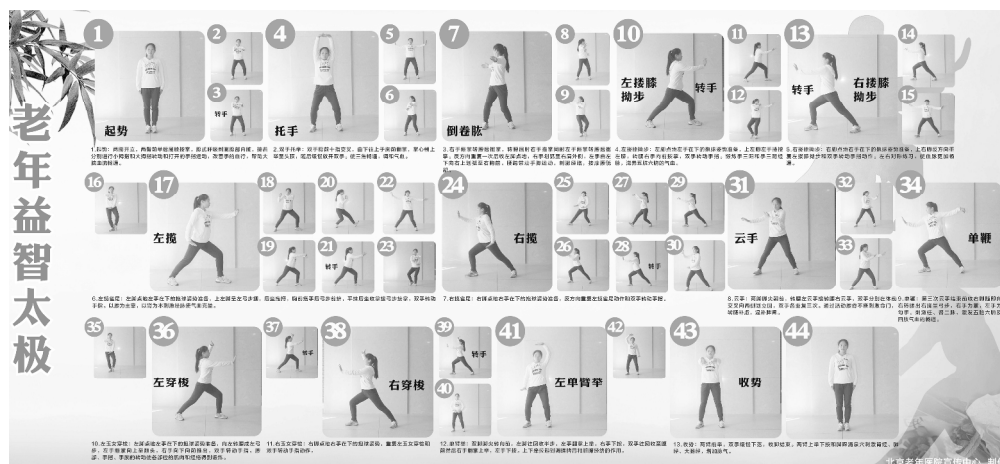


Figure 2. Main actions of Cognitive Protection Tai Chi (CPT)

3256x1493mm (72 x 72 DPI)



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

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

1				
2	Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9
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4	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Not applicable
5		11b	If relevant, description of the similarity of interventions	Not applicable
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9	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12
10		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12
11				
12	Results			
13	Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Not applicable for a protocol
14		13b	For each group, losses and exclusions after randomisation, together with reasons	Not applicable
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18	Recruitment	14a	Dates defining the periods of recruitment and follow-up	Not applicable
19		14b	Why the trial ended or was stopped	Not applicable
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23	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Not applicable
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26	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Not applicable
27				
28	Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Not applicable
29		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
30				
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32	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
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34	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Not applicable
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40	Discussion			
41	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Not applicable
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			<u>applicable</u>
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Not applicable
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Not applicable
Other information			
Registration	23	Registration number and name of trial registry	<u>3</u>
Protocol	24	Where the full trial protocol can be accessed, if available	<u>This is a protocol</u>
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	<u>13</u>

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

BMJ Open

The Efficacy of Practicing Tai Chi for Older People with Mild Dementia: Protocol for a Pilot Randomized Controlled Study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-019940.R1
Article Type:	Protocol
Date Submitted by the Author:	08-Mar-2018
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Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Neurology, Rehabilitation medicine
Keywords:	Tai Chi, cognitive function, Dementia < NEUROLOGY

SCHOLARONE™
Manuscripts

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3 **The Efficacy of Practicing Tai Chi for Older People with Mild**
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6 **Dementia: Protocol for a Pilot Randomized Controlled Study**
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9 Jihui Lyu^{1,2†*}, Wenjie Li^{1†}, Xiangjiang Rong^{3†}, Lian Wei⁴, Nayan Huang^{1,2},
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54 **Key words:** dementia, Tai Chi, cognitive function
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Word count: 2932

For peer review only

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ABSTRACT

Introduction

Many studies suggest that Tai Chi exercise is a safe and appropriate mind-body exercise for older people and effectively slows down age-related cognitive decline. A set of bespoke Tai Chi exercise named “Cognition Protecting Tai Chi” (CPT) has been created for older people with cognitive impairments by the research team of geriatricians, neurologists, rehabilitation specialists, experts of sports medicine, and experienced practitioners of traditional Chinese medicine. This trial is designed to evaluate its effects on cognitive function, behavior/moods, risk of falls and activities of daily living of the participants with mild dementia.

Methods and analysis

A randomized controlled study will be conducted. Eighty participants with mild dementia will be recruited and randomly allocated to an intervention group and a control group. The intervention group will practice the CPT three times a week for 20 minutes each time under the guidance of professional therapists. The control group will continue receiving their routine treatments. The duration of this study will be 10 months. All participants will be assessed with a battery of neuropsychological and functional evaluations, which include Mini-Mental State Examination, Montreal Cognitive Assessment, the

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3 World Health Organization–University of California Los Angeles Auditory
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5 Verbal Learning test (WHO-UCLA-AVLT), Trail Making Test (TMT),
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8 Geriatric Depression Scale, Neuropsychological Inventory and Barthel
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10 Index, at the baseline, five and ten months during the study period. Fall
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12 incident will also be recorded. The primary outcome will be the
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14 WHO-UCLA-AVLT delayed recall score. The secondary outcome will be
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16 the TMT score.
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20 **Ethics and dissemination**

21
22 This study has been approved by the ethical review committee of the
23
24 Beijing Geriatric Hospital (protocol number: 2015-021). Informed
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26 consent will be obtained from all participants or their guardians. The
27
28 authors intend to submit the findings of the study to peer-reviewed
29
30 journals or academic conferences to be published.
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35 **Trial registration number**

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37 ChiCTR-INR-16009872 (<http://www.chictr.org.cn>)
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Strengths and limitations of this study

- ▶ The bespoke CPT is specially designed for older people with mild dementia by the research team of multidisciplinary professionals. The team consist of geriatricians, neurologists, rehabilitation specialists, experts of sports medicine, and experienced practitioners of traditional Chinese medicine.
- ▶ The randomized controlled trial design minimizes the risk of selection bias.
- ▶ As the sample size is calculated based on the primary outcome, this pilot study may fail to demonstrate statistical differences of secondary outcomes.
- ▶ An open-label study design is often viewed as leaning towards bias, however it is not feasible to achieve a blinded intervention for this study. Therefore special measures for randomization and data collection process will be incorporated into the study to reduce bias.

INTRODUCTION

There are various clinical symptoms of people with dementia, which usually start with cognitive impairments, such as memory loss, and then complaints of inattention, miscalculation, lack of logical reasoning and disorientation¹. Besides cognitive impairments, people with dementia may also experience some changes psychologically and physically. There might be changes in personality, mood swings, ability to communicate and behaviors. It is often observed that patients with dementia feel anxious, depressed and may become verbally and physically aggressive. As the disease progresses, these symptoms gradually affect their ability in maintaining their activities of daily living, which leads to loss of independence. Current pharmacologic interventions used to maintain cognitive function, such as acetylcholinesterase inhibitors and memantine, have limited efficacy, and there are usually side effects²⁻⁵. Meanwhile, typical and atypical antipsychotics for dementia have the same or even severe side effects.

According to neuroplasticity theory, the repetition of stimulate-reflect training can help patients with dementia in preservation and restoration of brain functions, even when the brain has pathological damage to some extent⁶. There has been a considerable focus on the non-pharmacological approach to enhancing cognition. Many studies suggest that mind-body exercise can efficiently prevent the onset of

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3 dementia by delaying age-related cognitive decline, and benefit the
4
5 prognosis of dementia⁷⁻¹⁰.
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8 As one of traditional Chinese martial arts, Tai Chi is an aerobic
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10 mind-body exercise with mild-to-moderate physical movements that are
11
12 safe for older people¹¹. Tai Chi requires mind concentration and shifting
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14 the balance of body in accordance with gentle and smooth movements
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16 and steady breathing. In the theory of traditional Chinese medicine, Qi
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18 (Qi is one of the fixed technical terms in traditional Chinese medicine,
19
20 referring to behavioral patterns seen to occur through the spatial
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22 extension of a physical medium, which is both activity and active
23
24 substance) and blood are the two most fundamental materials to
25
26 maintain human life activities. Qi and blood can both be mobilized
27
28 coordinately when practicing Tai Chi, which helps maintain the balance
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30 of Yin and Yang (the two opposite properties of all natural things in
31
32 traditional Chinese medicine) and improves harmony of human body¹².
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34 As the nature of Tai Chi exercise strengthens the muscles of lower limbs
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36 of the body, it helps improve stability and minimize the risk of falls¹¹. Tai
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38 Chi is a recommended exercise for fall prevention in older people by the
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40 American Geriatrics Society, because it not only improves muscular
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42 strength, co-ordination and balance, but also is an enjoyable activity
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44 with a potential as a long-term exercise regime¹³. A randomized trial in
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46 older Chinese people without dementia carried out by Mortimer, et al in
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4 2012 suggest that Tai Chi increases brain volume and improves cognitive
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6 function more effectively than the intervention of social interaction¹⁴.
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8 Evidence has also shown that Tai Chi is an appropriate exercise for
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10 individuals with dementia in early stages, which helps improve quality of
11
12 life, brain function inducing reconstruction of neurons, and Tai Chi could
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14 become an emerging alternative therapy for people with dementia¹⁵⁻¹⁷.
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17 Other studies reported that physical exercise like Tai Chi improved mood
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19 and alleviated psychiatric problems in early or middle stages of dementia
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21 and also significantly reduced caregiver distresses¹⁸. For example, Sticky
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23 Hands Tai Chi, a special Tai Chi training technique practiced with a
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25 partner, promoted a comforting intimate interaction between the two
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27 persons and improved exercise adherence and mood in older people
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29 with dementia¹⁵.
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35 China has the largest number of older people with dementia¹⁹ and Tai
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37 Chi is originated from China. Tai Chi experts in China have developed
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39 various programs of Tai Chi, but none is especially designed for older
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41 people with cognitive impairments. Therefore, a set of Tai Chi program
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43 named "Cognition Protecting Tai Chi" (CPT) has been designed by the
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45 research team of multidisciplinary professionals in the first stage of this
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47 study. The second stage of this study is to test the effectiveness of the
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49 CPT program in improving cognitive function, and to evaluate its effects
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51 and impacts on psychological behavior, mood swings, risk of falls and
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3 ability in maintaining activities of daily living for people with mild
4 dementia with comparison to usual care. If results are positive, it would
5 demonstrate the potential to become a routine cost-effective exercise
6 for older people with mild dementia.
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15 **METHODS**

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18 **Settings:** This study is designed at Center for Cognitive Disorders of
19 Beijing Geriatric Hospital (BGH). The Case Report Forms will be kept and
20 research data will be analyzed by BGH. This hospital is a tertiary hospital
21 which is the highest rank in China's hospital system in terms of capacity
22 of beds and research capability. BGH has 900 inpatient beds and is
23 located in Haidian District of Beijing. The Center for Cognitive Disorders
24 of BGH is a department serving older people with cognitive impairments.
25 It is also the Guidance Center for Cognitive Rehabilitation of Haidian
26 District. The recruitment, assessment, intervention, and follow-ups of
27 participants will be conducted at three long-term care facilities near BGH
28 at where the participants reside.
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45 **Patient and Public Involvement**

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47 Information leaflets of the study will be available at the three long-term
48 care facilities. The leaflets explain in full detail the aims and objectives of
49 the study, selection criteria and the processes that the study will be
50 adhering to. The research team will provide an individual face to face
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4 consultation to all applicants or their guardian to answer any questions
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6 they may have. The applicants can then discuss this with their family if
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8 they wish and make a decision to opt in or opt out the study prior to
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10 signing the consent form. The findings of this study will be made
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12 available to the participants and their guardians.
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14

15 **Study design**

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18 There are two stages in this study design (Figure 1).
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20
21 The first stage is the development of the CPT program by the research
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23 team. The CPT program was specifically designed for cognitively
24
25 impaired patients by a research team of geriatricians, neurologists,
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27 rehabilitation specialists, experts of sports medicine, and experienced
28
29 practitioners of traditional Chinese medicine in 2016. The team has
30
31 modified the traditional Chinese Tai Chi to suit people with mild
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33 dementia. Any unsafe and complex actions in the traditional eight style
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35 Tai Chi program was removed, and some movements which were
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37 thought to be more beneficial for cognitive functions were added based
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39 on theories of traditional Chinese medical science. For example, the
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41 researchers removed the posture of standing on one foot and added
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43 some movements of rotating wrists and fingers in consideration of the
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45 suitability and safety aspects of the program for people with dementia.
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52 The CPT program contains eight styles of Tai Chi movements and each
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54 movement can be divided into three different maneuvers. Between
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4 January 2017 and May 2017, the CPT has been piloted with five patients
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6 with mild dementia who were invited to learn and practice the CPT
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8 program for four weeks. The CPT has been further modified where
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10 necessary based on the comments and the feedback provided by the
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12 participants before the completion of final version of the CPT.
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16 In addition to routine Starting Posture and Closing Form, there are
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18 eight styles of Tai Chi movements in the CPT, including Raising Both
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20 Hands, Forearm Rolling on Both Sides, Brush Knee and Twist Step on
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22 Both sides, Grasp the Bird's Tail-Left Side and then Right Side,
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24 Cloud Hands, Single Whip, Work at Shuttles on Both Sides, and Raising
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26 Left and then Right Hand (Figure 2).
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30 The second stage is a randomized controlled trial which will be
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32 conducted to test the effectiveness of the CPT program.
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35 **Recruitment of participants**

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37 Participants will be recruited from long-term care facilities near BGH.
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39 These facilities are Wenquan nursing home, Lengquan nursing home,
40
41 and Hexihui nursing home. There are altogether more than one
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43 thousand older residents living in these nursing homes, thus sufficient
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45 samples can be provided. Residents who meet the inclusion criteria will
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47 be recruited. Written consent forms will be signed by all participants or
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49 their guardians.
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54 **Inclusion criteria**

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3 Residents aged 60 years or older with mild dementia (diagnosis is based
4 on The Diagnostic and Statistical Manual of Mental Disorders, 4th
5 edition), who have a Clinical Dementia Rating score less than 2 will be
6 enrolled into this study.
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13 **Exclusion criteria**

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15 Residents who have severe visual or auditory impairment, serious
16 medical conditions in major organs (such as heart, lung, kidney, liver and
17 so on), illnesses affecting mobility, or are unable to accept assessments
18 or interventions which are required in this study for any reasons.
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25 **Randomization and allocation sequence**

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27 Participants will be enrolled by dementia specialists. The
28 randomization will be carried out by an independent research assistant
29 who will not be involved in the enrollment, assessment, or intervention
30 of the participants. Random number sequences will be generated using
31 SAS software. Sealed envelopes with the serial number outside and
32 group number inside will be produced and kept in a locked drawer which
33 will be inaccessible to all the researchers. The envelopes will be opened
34 sequentially by the independent research assistant after baseline
35 assessments and participants will be assigned to two groups (i.e. one
36 intervention group and one control group) at a ratio of 1:1 according to
37 the group number printed inside the envelopes. Outcome evaluators and
38 data analysts will be blinded to the group assignment.
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Intervention

This study is designed as a 10 month-randomized controlled trial. In addition to their routine treatment and usual care for ADL, the intervention group will perform the CPT exercise three times a week for 20 minutes each time under the guidance of the professional therapists at where the participants reside. The intervention will be practiced in groups with one therapist to five to eight participants. The control group will only receive routine treatments and usual care for ADL. The intervention to the participant should be discontinued if any complication that could affect the outcomes of the CPT occurs. The participants will be encouraged to complete follow-ups. The participants and their representatives have access to the research team anytime if they need to discuss any issues or concerns during the study period. The participants will be explained that they can discontinue with the intervention at any time during the period of the study. Demographic information of participants who withdraw from the study after randomization and the reasons for their withdrawal will be collected.

Assessment

The trial will utilize the most commonly used tools (see below) that have been carefully selected to assess the efficacy of CPT. The Chinese version of Mini Mental State Examination (MMSE)²⁰ is a 30-point questionnaire which is used to measure cognitive impairments. It examines functions

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4 of attention, calculation, recall, language, ability to follow simple
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6 commands and orientation.
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8 The Montreal Cognitive Assessment (MoCA) Beijing version
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10 (www.mocatest.org) is also a 30-point test for assessing cognitive
11
12 function. MoCA includes cognitive domains for short-term memory recall,
13
14 visuospatial abilities, multiple aspects of executive functions, attention,
15
16 concentration and working memory, language and orientation to time
17
18 and place. Because there are more difficult and multiple tasks in MoCA,
19
20 MoCA is more sensitive to detect mild cognitive changes than MMSE
21
22 does²¹.
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28 The World Health Organization–University of California Los Angeles
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30 Auditory Verbal Learning test (WHO-UCLA-AVL)²² is a tool to assess
31
32 immediate recall and delayed recall with 15 words independent in
33
34 meaning. Immediate recall is performed by asking the participants to
35
36 remember and recall those 15 words just after each auditory learning,
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38 and this learning-recall process is repeated for three times to generate
39
40 an average performance score. An average performance is recorded.
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45 Delayed recall is performed by asking the participants to recall those 15
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47 words 30-45 minutes after the immediate recall has been completed.
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50 The study utilizes the method of the Trail Making Test (TMT) which is a
51
52 neuropsychological test of visual attention and task switching. It can
53
54 provide information on visual search speed, scanning, speed of
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3 processing, mental flexibility, as well as executive functioning. A Chinese
4 version of Shape TMT was used in this study. This Shape TMT shows
5 numbers from 1 to 25 twice, once in a circle and once in a square. The
6 participants are asked to connect them in sequential order alternately
7 between circles and squares (circle 1, square 1, circle 2, square 2, etc.)²³.
8
9 This Shape TMT has been proved to be a sensitive test of visual search
10 and sequencing²⁴.
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20 The Geriatric Depression Scale (GDS)²⁵ is a 30-item self-report
21 assessment used to identify depression in the elderly, of which questions
22 are answered in a "yes" or "no" format. It is appropriate to test older
23 individuals with mild or moderate cognitive impairment using GDS.
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30 The Neuropsychiatric Inventory (NPI)²⁶ assesses common psychiatric
31 and behavioral symptoms in dementia. Its items include hallucinations,
32 delusions, agitation/aggression, dysphoria/depression, anxiety,
33 irritability, disinhibition, euphoria, apathy, aberrant motor behavior,
34 sleep and night-time behavior disturbance, appetite and eating disorders.
35 Information can be obtained from caregivers who have in-depth
36 knowledge of the patients' performance. The caregivers will also be
37 asked to rate their own distress level associated with daily care and
38 support provided by them to the patients.
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52 The Barthel Index (BI)²⁷ is an ordinal scale used to measure
53 performance in ADL. The ten variables describing ADL and mobility
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3 addressed in the Barthel scale are: presence or absence of fecal
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5 incontinence, urinary incontinence, grooming, toileting, feeding,
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7 transferring (e.g. from chair to bed), walking, dressing, climbing stairs
8
9 and bathing. The scoring is based on information provided by the
10
11 participant's informant, who can be his/her family members or
12
13 caregivers.
14
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16

17
18 All participants will undergo all above assessments at 0 (baseline), five
19
20 and ten months within the current study period. Fall incident will also be
21
22 recorded. Fall will be defined as the experience of a sudden, involuntary,
23
24 unintentional change of position, down on the ground or on a lower
25
26 plane. When assessing a definite fall, the team will try to get an
27
28 eyewitness account or records of security cameras (all the areas of the
29
30 nursing homes where participants live will be monitored by 24-hour
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32 security cameras).
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37 38 **Outcomes**

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40 The psychometric tools used in this study will be analyzed to assess the
41
42 efficacy of the CPT. The primary outcome is the WHO-UCLA-AVLT delayed
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44 recall score. The secondary outcome is the score of the TMT. The fall
45
46 incident will be analyzed to assess the safety of this Tai Chi program.
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48 Complaints of medical symptoms related to the intervention will be
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50 documented and treated when necessary, including fatigue, pain,
51
52 dizziness, and so on.
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Sample size

The sample size was calculated by Power Analysis and Sample Size Calculation Statistical Software V13.0 based on the results of pre-experiment of this study. Using a type I error of 0.05 and a power of 80%, a mean difference of 2 points is expected between two groups after 10 months. The results show a sample size of 34 per groups is adequate for testing the primary outcome (WHO-UCLA-AVLT delayed recall score). Considering a 15% dropout rate, a total number of 80 participants will be recruited.

Quality control and quality assurance

At least three dementia specialists will work together to examine the participants and provide diagnosis for each participant. All data will be monitored and reviewed by the PI or research coordinators. Training will be provided to all researchers. Consistency coefficients in scoring assessment scales between researchers should be no less than 0.85. Data entry will be verified by a second researcher in the team. To protect participants' confidentiality, only supervisors, researchers of this study and the ethics committee will be authorized to have access to the personal information and medical records of the participants.

Statistical method

All analyses will be carried out using SPSS version 16.0. The variations of scores of psychometric assessments over time between two groups will

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4 be examined using repeated measurement of variance analysis. The
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6 association between intervention and incidence of falls will be analyzed
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8 using Chi-Square test.
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10 11 12 13 **CONCLUSION**

14
15 This protocol outlined the objectives of the study and explained the CPT
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17 exercise developed by the research team including geriatricians,
18
19 neurologists, rehabilitation specialists, experts of sports medicine, and
20
21 experienced practitioners of in traditional Chinese medicine. The study is
22
23 designed as a randomized controlled trial in order to evaluate the effects
24
25 of this especially designed CPT on the participants with mild dementia.
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27
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29

30 31 **Contributors**

32
33 Jihui Lyu conceived the idea and supervised this study and is the
34
35 guarantor. Jihui Lyu, Xiangjiang Rong, Xueli Chen, Fangling Li, Wenjie Li
36
37 and Lian Wei were involved in the design. Wenjie Li, Nayan Huang and
38
39 Xiangjiang Rong prepared draft manuscript. Jihui Lyu, Mei Champ, and
40
41 Qian Xiong revised the manuscript. Wenjie Li, Mo Li and Xiangjiang Rong
42
43 carried out the statistical calculation. All authors approved submission of
44
45 this manuscript.
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50 51 **Acknowledgements**

52
53 We thank Kai Hao (a staff of Publicity and Education Centre of BGH) for
54
55 helping us to improve the images of this article. We thank all the
56
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3 participants and their advisors for their cooperation.
4

5
6 **Funding**
7

8 This work is supported by Beijing Clinical Characteristics Project of
9
10 Beijing Municipal Science and Technology Commission (Project number
11
12 Z151100004015023)
13
14

15
16 **Competing interests**
17

18 None declared.
19

20 **Ethical approval:** This study was approved by the ethical review
21
22 committee of the Beijing Geriatric Hospital (Beijing, China).
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Md State Med J 1965;14:61-5.

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4 **Figure legends:**
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6 **Figure 1 Trail Flow Chart.**
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8 **Figure 2 Main movements of the “Cognition Protecting Tai Chi” (CPT).**
9

10 A1-3: Raising Both Hands
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12 B1-3: Forearm Rolling on Both Sides
13

14 C1-3: Brush Knee and Twist Step on Both sides
15

16 D1-3: Grasp the Bird's Tail-Left Side and then Right Side, Cloud Hands
17

18 E1-3: Cloud Hands
19

20 F1-3: Single Whip
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22 G1-3: Work at Shuttles on Both Sides
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24 H1-3: Raising Left and then Right Hand
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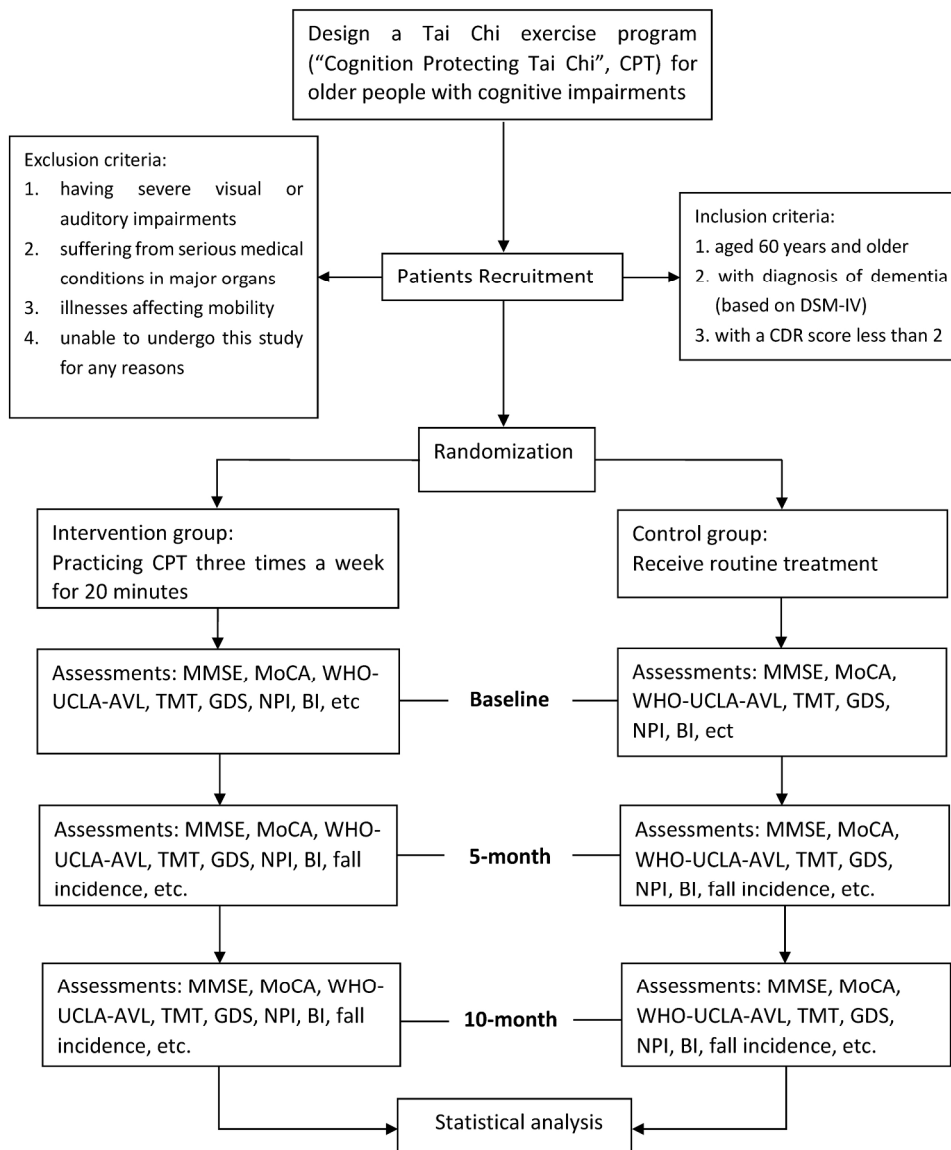


Figure 1 Trail Flow Chart.

221x266mm (300 x 300 DPI)



Figure 2 Main movements of the "Cognition Protecting Tai Chi" (CPT).

A1-3: Raising Both Hands

B1-3: Forearm Rolling on Both Sides

C1-3: Brush Knee and Twist Step on Both sides

D1-3: Grasp the Bird's Tail-Left Side and then Right Side, Cloud Hands

E1-3: Cloud Hands

F1-3: Single Whip

G1-3: Work at Shuttles on Both Sides

H1-3: Raising Left and then Right Hand

292x223mm (300 x 300 DPI)





 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	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18
	5b	Name and contact information for the trial sponsor	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	NA
	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)	NA

Introduction

1				
2				
3	Background	6a	Description of research question and justification for undertaking the trial, including summary of relevant	6-8
4	and rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	9
7	Objectives	7	Specific objectives or hypotheses	8, 9
8				
9	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	10, 11
10			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	
11				
12				
13	Methods: Participants, interventions, and outcomes			
14				
15	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be	9
16			collected. Reference to where list of study sites can be obtained	
17				
18	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals	11, 12
19			who will perform the interventions (eg, surgeons, psychotherapists)	
20				
21	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	13
22			administered	
23				
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	13
25			change in response to harms, participant request, or improving/worsening disease)	
26				
27		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg,	13
28			drug tablet return, laboratory tests)	
29				
30		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
31				
32	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	16
33			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
34			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy	
35			and harm outcomes is strongly recommended	
36				
37	Participant	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	Figure 1. Trail
38	timeline		participants. A schematic diagram is highly recommended (see Figure)	flow chart
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3	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	17
4				
5	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
6				
7				
8	Methods: Assignment of interventions (for controlled trials)			
9				
10	Allocation:			
11				
12	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	12
13				
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17	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	12
18				
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21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
28				
29				
30				
31	Methods: Data collection, management, and analysis			
32				
33	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	13-16
34				
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38		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	13
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3	Data	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	17
4	management		(eg, double data entry; range checks for data values). Reference to where details of data management	
5			procedures can be found, if not in the protocol	
6				
7	Statistical	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the	17, 18
8	methods		statistical analysis plan can be found, if not in the protocol	
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
11				
12		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any	NA
13			statistical methods to handle missing data (eg, multiple imputation)	
14				
15	Methods: Monitoring			
16				
17	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of	NA
18			whether it is independent from the sponsor and competing interests; and reference to where further details	
19			about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
20				
21		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim	NA
22			results and make the final decision to terminate the trial	
23				
24	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events	16
25			and other unintended effects of trial interventions or trial conduct	
26				
27	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from	NA
28			investigators and the sponsor	
29				
30				
31	Ethics and dissemination			
32				
33	Research ethics	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	4, 19
34	approval			
35				
36	Protocol	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes,	NA
37	amendments		analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals,	
38			regulators)	
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3	Consent or	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how	4
4	assent		(see Item 32)	
5				
6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary	NA
7			studies, if applicable	
8				
9	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in	17
10			order to protect confidentiality before, during, and after the trial	
11				
12	Declaration of	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
13	interests			
14				
15	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit	NA
16			such access for investigators	
17				
18	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial	NA
19	post-trial care		participation	
20				
21	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the	4
22	policy		public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing	
23			arrangements), including any publication restrictions	
24				
25		31b	Authorship eligibility guidelines and any intended use of professional writers	NA
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
28				
29	Appendices			
30				
31	Informed	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
32	consent			
33	materials			
34				
35	Biological	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	NA
36	specimens		analysis in the current trial and for future use in ancillary studies, if applicable	
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2 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
3 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
4 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.
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BMJ Open

The Efficacy of Practicing Tai Chi for Older People with Mild Dementia: Protocol for a Randomized Controlled Study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-019940.R2
Article Type:	Protocol
Date Submitted by the Author:	06-Apr-2018
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Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Neurology, Rehabilitation medicine
Keywords:	Tai Chi, cognitive function, Dementia < NEUROLOGY

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Manuscripts

The Efficacy of Practicing Tai Chi for Older People with Mild Dementia: Protocol for a Randomized Controlled Study

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Key words: dementia, Tai Chi, cognitive function

Word count: 3033

For peer review only

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ABSTRACT

Introduction

Many studies suggest that Tai Chi exercise is a safe and appropriate mind-body exercise for older people and effectively slows down age-related cognitive decline. A set of bespoke Tai Chi exercise named “Cognition Protecting Tai Chi” (CPT) has been created for older people with cognitive impairments by the research team of geriatricians, neurologists, rehabilitation specialists, experts of sports medicine, and experienced practitioners of traditional Chinese medicine. This trial is designed to evaluate its effects on cognitive function, behavior/moods, risk of falls and activities of daily living of the participants with mild dementia.

Methods and analysis

A randomized controlled study will be conducted. Eighty participants with mild dementia will be recruited and randomly allocated to an intervention group and a control group. The intervention group will practice the CPT three times a week for 20 minutes each time under the guidance of professional therapists. The control group will continue receiving their routine treatments. The duration of this study will be 10 months. All participants will be assessed with a battery of neuropsychological and functional evaluations, which include Mini-Mental State Examination, Montreal Cognitive Assessment, the

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3 World Health Organization–University of California Los Angeles Auditory
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5 Verbal Learning test (WHO-UCLA-AVLT), Trail Making Test (TMT),
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8 Geriatric Depression Scale, Neuropsychological Inventory and Barthel
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10 Index, at the baseline, five and ten months during the study period. Fall
11
12 incident will also be recorded. The primary outcome will be the
13
14 WHO-UCLA-AVLT delayed recall score. The secondary outcome will be
15
16 the TMT score.
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20 **Ethics and dissemination**

21
22 This study has been approved by the ethical review committee of the
23
24 Beijing Geriatric Hospital (protocol number: 2015-021). Informed
25
26 consent will be obtained from all participants or their guardians. The
27
28 authors intend to submit the findings of the study to peer-reviewed
29
30 journals or academic conferences to be published.
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35 **Trial registration number**

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37 ChiCTR-INR-16009872 (<http://www.chictr.org.cn>)
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Strengths and limitations of this study

- ▶ The bespoke CPT is specially designed for older people with mild dementia by the research team of multidisciplinary professionals
- ▶ The randomized controlled trial design minimizes the risk of selection bias.
- ▶ As the sample size is calculated based on the primary outcome, this study may fail to demonstrate statistical differences of secondary outcomes.
- ▶ An open-label study design is often viewed as leaning towards bias, however it is not feasible to achieve a blinded intervention for this study.

INTRODUCTION

There are various clinical symptoms of people with dementia, which usually start with cognitive impairments, such as memory loss, and then complaints of inattention, miscalculation, lack of logical reasoning and disorientation¹. Besides cognitive impairments, people with dementia may also experience some changes psychologically and physically. There might be changes in personality, mood swings, ability to communicate and behaviors. It is often observed that patients with dementia feel anxious, depressed and may become verbally and physically aggressive. As the disease progresses, these symptoms gradually affect their ability in maintaining their activities of daily living, which leads to loss of independence. Current pharmacologic interventions used to maintain cognitive function, such as acetylcholinesterase inhibitors and memantine, have limited efficacy, and there are usually side effects²⁻⁵. Meanwhile, typical and atypical antipsychotics for dementia have the same or even severe side effects.

According to neuroplasticity theory, the repetition of stimulate-reflect training can help patients with dementia in preservation and restoration of brain functions, even when the brain has pathological damage to some extent⁶. There has been a considerable focus on the non-pharmacological approach to enhancing cognition. Many studies suggest that mind-body exercise can efficiently prevent the onset of

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3 dementia by delaying age-related cognitive decline, and benefit the
4
5 prognosis of dementia⁷⁻¹⁰.
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8 As one of traditional Chinese martial arts, Tai Chi is an aerobic
9
10 mind-body exercise with mild-to-moderate physical movements that are
11
12 safe for older people¹¹. Tai Chi requires mind concentration and shifting
13
14 the balance of body in accordance with gentle and smooth movements
15
16 and steady breathing. In the theory of traditional Chinese medicine, Qi
17
18 (Qi is one of the fixed technical terms in traditional Chinese medicine,
19
20 referring to behavioral patterns seen to occur through the spatial
21
22 extension of a physical medium, which is both activity and active
23
24 substance) and blood are the two most fundamental materials to
25
26 maintain human life activities. Qi and blood can both be mobilized
27
28 coordinately when practicing Tai Chi, which helps maintain the balance
29
30 of Yin and Yang (the two opposite properties of all natural things in
31
32 traditional Chinese medicine) and improves harmony of human body¹².
33
34 As the nature of Tai Chi exercise strengthens the muscles of lower limbs
35
36 of the body, it helps improve stability and minimize the risk of falls¹¹. Tai
37
38 Chi is a recommended exercise for fall prevention in older people by the
39
40 American Geriatrics Society, because it not only improves muscular
41
42 strength, co-ordination and balance, but also is an enjoyable activity
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44 with a potential as a long-term exercise regime¹³. A randomized trial in
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46 older Chinese people without dementia carried out by Mortimer, et al in
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4 2012 suggest that Tai Chi increases brain volume and improves cognitive
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6 function more effectively than the intervention of social interaction¹⁴.
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8 Evidence has also shown that Tai Chi is an appropriate exercise for
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10 individuals with dementia in early stages, which helps improve quality of
11
12 life, brain function inducing reconstruction of neurons, and Tai Chi could
13
14 become an emerging alternative therapy for people with dementia¹⁵⁻¹⁷.
15
16 Other studies reported that physical exercise like Tai Chi improved mood
17
18 and alleviated psychiatric problems in early or middle stages of dementia
19
20 and also significantly reduced caregiver distresses¹⁸. For example, Sticky
21
22 Hands Tai Chi, a special Tai Chi training technique practiced with a
23
24 partner, promoted a comforting intimate interaction between the two
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26 persons and improved exercise adherence and mood in older people
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28 with dementia¹⁵.
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35 China has the largest number of older people with dementia¹⁹ and Tai
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37 Chi is originated from China. Tai Chi experts in China have developed
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39 various programs of Tai Chi, but none is especially designed for older
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41 people with cognitive impairments. Therefore, a set of Tai Chi program
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43 named "Cognition Protecting Tai Chi" (CPT) has been designed by the
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45 research team of multidisciplinary professionals in the first stage of this
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47 study. The second stage of this study is to test the effectiveness of the
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49 CPT program in improving cognitive function, and to evaluate its effects
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51 and impacts on psychological behavior, mood swings, risk of falls and
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3 ability in maintaining activities of daily living for people with mild
4 dementia with comparison to usual care. If results are positive, it would
5 demonstrate the potential to become a routine cost-effective exercise
6 for older people with mild dementia.
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15 **METHODS**

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18 **Settings:** This study is designed at Center for Cognitive Disorders of
19 Beijing Geriatric Hospital (BGH). The Case Report Forms will be kept and
20 research data will be analyzed by BGH. This hospital is a tertiary hospital
21 which is the highest rank in China's hospital system in terms of capacity
22 of beds and research capability. BGH has 900 inpatient beds and is
23 located in Haidian District of Beijing. The Center for Cognitive Disorders
24 of BGH is a department serving older people with cognitive impairments.
25 It is also the Guidance Center for Cognitive Rehabilitation of Haidian
26 District. The recruitment, assessment, intervention, and follow-ups of
27 participants will be conducted at three long-term care facilities near BGH
28 at where the participants reside.
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44 **Study design**

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47 There are two stages in this study design (Figure 1).
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50 The first stage is the development of the CPT program by the research
51 team. The CPT program was specifically designed for cognitively
52 impaired patients by a research team of geriatricians, neurologists,
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4 rehabilitation specialists, experts of sports medicine, and experienced
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6 practitioners of traditional Chinese medicine in 2016. The team has
7
8 modified the traditional Chinese Tai Chi to suit people with mild
9
10 dementia. Any unsafe and complex actions in the traditional eight style
11
12 Tai Chi program was removed, and some movements which were
13
14 thought to be more beneficial for cognitive functions were added based
15
16 on theories of traditional Chinese medical science. For example, the
17
18 researchers removed the posture of standing on one foot and added
19
20 some movements of rotating wrists and fingers in consideration of the
21
22 suitability and safety aspects of the program for people with dementia.
23
24 The CPT program contains eight styles of Tai Chi movements and each
25
26 movement can be divided into three different maneuvers. Between
27
28 January 2017 and May 2017, the CPT has been performed in five patients
29
30 with mild dementia who were invited to learn and practice the CPT
31
32 program for four weeks. The CPT has been further modified where
33
34 necessary based on the comments and the feedback provided by the
35
36 participants before the completion of final version of the CPT.
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45 In addition to routine Starting Posture and Closing Form, there are
46
47 eight styles of Tai Chi movements in the CPT, including Raising Both
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49 Hands, Forearm Rolling on Both Sides, Brush Knee and Twist Step on
50
51 Both sides, Grasp the Bird's Tail-Left Side and then Right Side,
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53 Cloud Hands, Single Whip, Work at Shuttles on Both Sides, and Raising
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4 Left and then Right Hand (Figure 2).
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6 The second stage is a randomized controlled trial which will be
7
8 conducted to test the effectiveness of the CPT program.
9

10 **Recruitment of participants**

11
12 Participants will be recruited from long-term care facilities near BGH.
13
14 These facilities are Wenquan nursing home, Lengquan nursing home,
15
16 and Hexihui nursing home. There are altogether more than one
17
18 thousand older residents living in these nursing homes, thus sufficient
19
20 samples can be provided. Residents who meet the inclusion criteria will
21
22 be recruited.
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28 **Inclusion criteria**

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30 Residents aged 60 years or older with mild dementia (diagnosis is based
31
32 on The Diagnostic and Statistical Manual of Mental Disorders, 4th
33
34 edition), who have a Clinical Dementia Rating score less than 2 will be
35
36 enrolled into this study.
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40 **Exclusion criteria**

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42 Residents who have severe visual or auditory impairment, serious
43
44 medical conditions in major organs (such as heart, lung, kidney, liver and
45
46 so on), illnesses affecting mobility, or are unable to accept assessments
47
48 or interventions which are required in this study for any reasons.
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52 **Randomization and allocation sequence**

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54 Participants will be enrolled by dementia specialists. The
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3 randomization will be carried out by an independent research assistant
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5 who will not be involved in the enrollment, assessment, or intervention
6
7 of the participants. Random number sequences will be generated using
8
9 SAS software. Sealed envelopes with the serial number outside and
10
11 group number inside will be produced and kept in a locked drawer which
12
13 will be inaccessible to all the researchers. The envelopes will be opened
14
15 sequentially by the independent research assistant after baseline
16
17 assessments and participants will be assigned to two groups (i.e. one
18
19 intervention group and one control group) at a ratio of 1:1 according to
20
21 the group number printed inside the envelopes. Outcome evaluators and
22
23 data analysts will be blinded to the group assignment.
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30 **Intervention**

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32 This study is designed as a 10 month-randomized controlled trial. In
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34 addition to their routine treatment and usual care for ADL, the
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36 intervention group will perform the CPT exercise three times a week for
37
38 20 minutes each time under the guidance of the professional therapists
39
40 at where the participants reside. The intervention will be practiced in
41
42 groups with one therapist to five to eight participants. The control group
43
44 will only receive routine treatments and usual care for ADL. The
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46 intervention to the participant should be discontinued if any
47
48 complication that could affect the outcomes of the CPT occurs. The
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50 participants will be encouraged to complete follow-ups. The participants
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4 and their representatives have access to the research team anytime if
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6 they need to discuss any issues or concerns during the study period. The
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8 participants will be explained that they can discontinue with the
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10 intervention at any time during the period of the study. Demographic
11
12 information of participants who withdraw from the study after
13
14 randomization and the reasons for their withdrawal will be collected.
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17 **Assessment**

18
19 The trial will utilize the most commonly used tools (see below) that have
20
21 been carefully selected to assess the efficacy of CPT. The Chinese version
22
23 of Mini Mental State Examination (MMSE)²⁰ is a 30-point questionnaire
24
25 which is used to measure cognitive impairments. It examines functions
26
27 of attention, calculation, recall, language, ability to follow simple
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29 commands and orientation.
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35 The Montreal Cognitive Assessment (MoCA) Beijing version
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37 (www.mocatest.org) is also a 30-point test for assessing cognitive
38
39 function. MoCA includes cognitive domains for short-term memory recall,
40
41 visuospatial abilities, multiple aspects of executive functions, attention,
42
43 concentration and working memory, language and orientation to time
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45 and place. Because there are more difficult and multiple tasks in MoCA,
46
47 MoCA is more sensitive to detect mild cognitive changes than MMSE
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49 does²¹.
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55 The World Health Organization–University of California Los Angeles
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3 Auditory Verbal Learning test (WHO-UCLA-AVL)²² is a tool to assess
4 immediate recall and delayed recall with 15 words independent in
5 meaning. Immediate recall is performed by asking the participants to
6 remember and recall those 15 words just after each auditory learning,
7 and this learning-recall process is repeated for three times to generate
8 an average performance score. An average performance is recorded.
9
10 Delayed recall is performed by asking the participants to recall those 15
11 words 30-45 minutes after the immediate recall has been completed.
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23 The study utilizes the method of the Trail Making Test (TMT) which is a
24 neuropsychological test of visual attention and task switching. It can
25 provide information on visual search speed, scanning, speed of
26 processing, mental flexibility, as well as executive functioning. A Chinese
27 version of Shape TMT was used in this study. This Shape TMT shows
28 numbers from 1 to 25 twice, once in a circle and once in a square. The
29 participants are asked to connect them in sequential order alternately
30 between circles and squares (circle 1, square 1, circle 2, square 2, etc.)²³.
31
32 This Shape TMT has been proved to be a sensitive test of visual search
33 and sequencing²⁴.
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47 The Geriatric Depression Scale (GDS)²⁵ is a 30-item self-report
48 assessment used to identify depression in the elderly, of which questions
49 are answered in a "yes" or "no" format. It is appropriate to test older
50 individuals with mild or moderate cognitive impairment using GDS.
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3 The Neuropsychiatric Inventory (NPI)²⁶ assesses common psychiatric
4 and behavioral symptoms in dementia. Its items include hallucinations,
5
6 and behavioral symptoms in dementia. Its items include hallucinations,
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8 delusions, agitation/aggression, dysphoria/depression, anxiety,
9
10 irritability, disinhibition, euphoria, apathy, aberrant motor behavior,
11
12 sleep and night-time behavior disturbance, appetite and eating disorders.
13
14 Information can be obtained from caregivers who have in-depth
15
16 knowledge of the patients' performance. The caregivers will also be
17
18 asked to rate their own distress level associated with daily care and
19
20 support provided by them to the patients.
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25 The Barthel Index (BI)²⁷ is an ordinal scale used to measure
26
27 performance in ADL. The ten variables describing ADL and mobility
28
29 addressed in the Barthel scale are: presence or absence of fecal
30
31 incontinence, urinary incontinence, grooming, toileting, feeding,
32
33 transferring (e.g. from chair to bed), walking, dressing, climbing stairs
34
35 and bathing. The scoring is based on information provided by the
36
37 participant's informant, who can be his/her family members or
38
39 caregivers.
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45 All participants will undergo all above assessments at 0 (baseline), five
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47 and ten months within the current study period. Fall incident will also be
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49 recorded. Fall will be defined as the experience of a sudden, involuntary,
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51 unintentional change of position, down on the ground or on a lower
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53 plane. When assessing a definite fall, the team will try to get an
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4 eyewitness account or records of security cameras (all the areas of the
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6 nursing homes where participants live will be monitored by 24-hour
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8 security cameras).
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10 **Outcomes**

11
12 The psychometric tools used in this study will be analyzed to assess the
13
14 efficacy of the CPT. The primary outcome is the WHO-UCLA-AVLT delayed
15
16 recall score. The secondary outcome is the score of the TMT. The fall
17
18 incident will be analyzed to assess the safety of this Tai Chi program.
19
20 Complaints of medical symptoms related to the intervention will be
21
22 documented and treated when necessary, including fatigue, pain,
23
24 dizziness, and so on.
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30 **Sample size**

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32 The sample size was calculated by Power Analysis and Sample Size
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34 Calculation Statistical Software V13.0 based on the results of
35
36 pre-experiment of this study. Using a type I error of 0.05 and a power of
37
38 80%, a mean difference of 2 points is expected between two groups after
39
40 10 months. The results show a sample size of 34 per groups is adequate
41
42 for testing the primary outcome (WHO-UCLA-AVLT delayed recall score).
43
44 Considering a 15% dropout rate, a total number of 80 participants will be
45
46 recruited.
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52 **Quality control and quality assurance**

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54 At least three dementia specialists will work together to examine the
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3 participants and provide diagnosis for each participant. All data will be
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5 monitored and reviewed by the PI or research coordinators. Training will
6
7 be provided to all researchers. Consistency coefficients in scoring
8
9 assessment scales between researchers should be no less than 0.85.
10
11 Data entry will be verified by a second researcher in the team. To protect
12
13 participants' confidentiality, only supervisors, researchers of this study
14
15 and the ethics committee will be authorized to have access to the
16
17 personal information and medical records of the participants.
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22 23 **Statistical method**

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25 All analyses will be carried out using SPSS version 16.0. The variations of
26
27 scores of psychometric assessments over time between two groups will
28
29 be examined using repeated measurement of variance analysis. The
30
31 association between intervention and incidence of falls will be analyzed
32
33 using Chi-Square test.
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36

37 38 **Ethics and dissemination**

39
40 This study has been approved by the ethical review committee of the
41
42 Beijing Geriatric Hospital (protocol number: 2015-021). Information
43
44 leaflets of the study will be available at the three long-term care facilities.
45
46 The leaflets explain in full detail the aims and objectives of the study,
47
48 selection criteria and the processes that the study will be adhering to.
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50 The research team will provide an individual face to face consultation to
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52 all applicants or their guardian to answer any questions they may have.
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3 The applicants can then discuss this with their family if they wish and
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5 make a decision to opt in or opt out the study prior to signing the
6
7 consent form. Informed consent will be obtained from all participants or
8
9 their guardians. The authors intend to submit the findings of the study to
10
11 peer-reviewed journals or academic conferences to be published.
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14

15 **Patient and Public Involvement**

16
17 The original research question and outcome measures were conceived
18
19 by the authors and were modified based on the face to face screening
20
21 interview with patients and their guardians by a research assistant. Five
22
23 patients with mild dementia were invited to learn and practice the CPT
24
25 program prior to designing the RCT. The CPT was modified based on the
26
27 comments and the feedback provided by the participants in order to
28
29 ensure the safety and the applicability of the intervention. Both the
30
31 burden and the potential benefit of the intervention will be assessed by
32
33 patients and their advisors before the consent forms are signed. The
34
35 findings of this study will be made available to the participants and their
36
37 guardians.
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44 **CONCLUSION**

45
46 This protocol outlined the objectives of the study and explained the CPT
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48 exercise developed by the research team including geriatricians,
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50 neurologists, rehabilitation specialists, experts of sports medicine, and
51
52 experienced practitioners of in traditional Chinese medicine. The study is
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3 designed as a randomized controlled trial in order to evaluate the effects
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5 of this especially designed CPT on the participants with mild dementia.
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7

8 **Contributors**

9
10 Jihui Lyu conceived the idea and supervised this study and is the
11
12 guarantor. Jihui Lyu, Xiangjiang Rong, Xueli Chen, Fangling Li, Wenjie Li
13
14 and Lian Wei were involved in the design. Wenjie Li, Nayan Huang and
15
16 Xiangjiang Rong prepared draft manuscript. Jihui Lyu, Mei Champ, and
17
18 Qian Xiong revised the manuscript. Wenjie Li, Mo Li and Xiangjiang Rong
19
20 carried out the statistical calculation. All authors approved submission of
21
22 this manuscript.
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27 **Acknowledgements**

28
29 We thank Kai Hao (a staff of Publicity and Education Centre of BGH) for
30
31 helping us to improve the images of this article. We thank all the
32
33 participants and their advisors for their cooperation.
34
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36

37 **Funding**

38
39 This work is supported by Beijing Clinical Characteristics Project of
40
41 Beijing Municipal Science and Technology Commission (Project number
42
43 Z151100004015023) and Major Clinical Medicine Development Plan of
44
45 Beijing Municipal Administration of Hospitals (Project number
46
47 ZYXL201834).
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51 **Competing interests**

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55 None declared.
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4 **Figure legends:**
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6 **Figure 1 Trail Flow Chart.**
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8 **Figure 2 Main movements of the “Cognition Protecting Tai Chi” (CPT).**
9

10 A1-3: Raising Both Hands
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12 B1-3: Forearm Rolling on Both Sides
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14 C1-3: Brush Knee and Twist Step on Both sides
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16 D1-3: Grasp the Bird's Tail-Left Side and then Right Side, Cloud Hands
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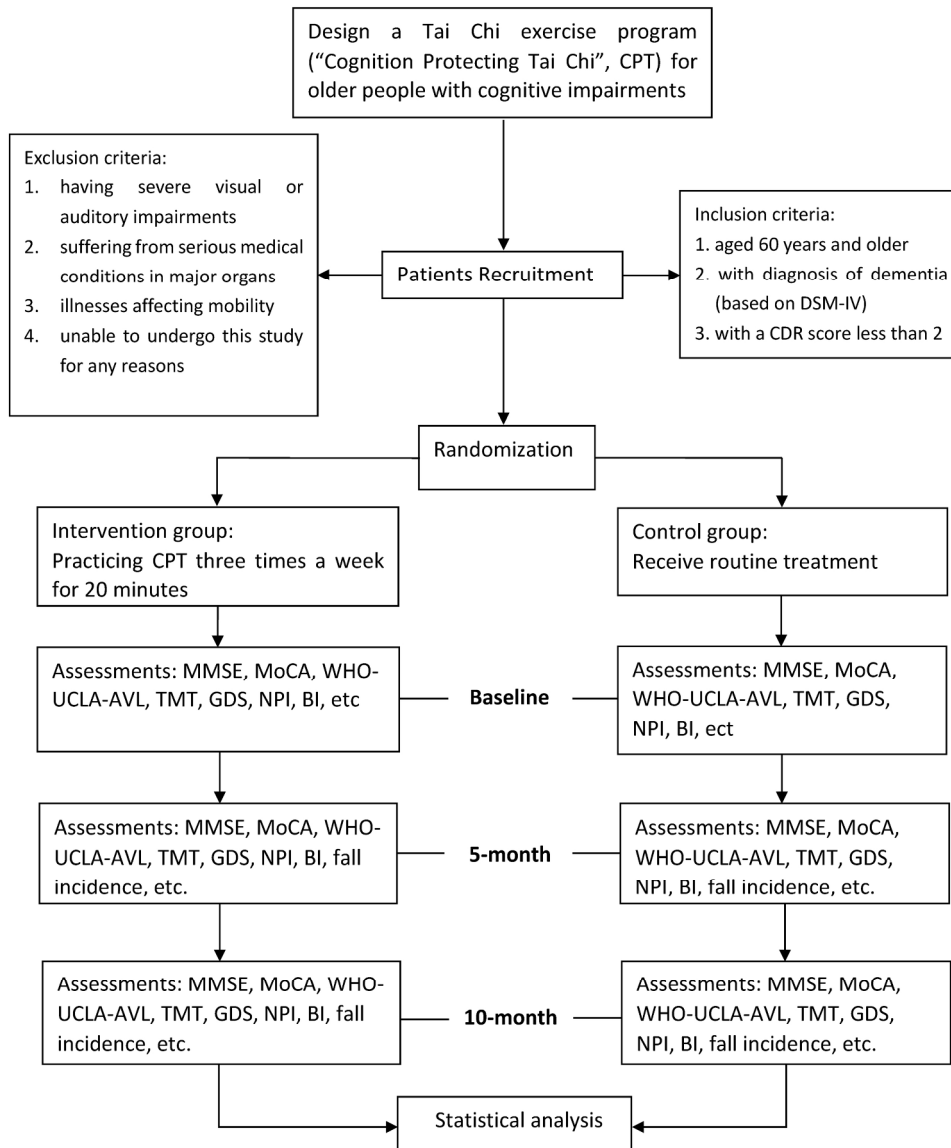
18 E1-3: Cloud Hands
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20 F1-3: Single Whip
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22 G1-3: Work at Shuttles on Both Sides
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24 H1-3: Raising Left and then Right Hand
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221x266mm (300 x 300 DPI)



Figure 2 Main movements of the "Cognition Protecting Tai Chi" (CPT).

A1-3: Raising Both Hands

B1-3: Forearm Rolling on Both Sides

C1-3: Brush Knee and Twist Step on Both sides

D1-3: Grasp the Bird's Tail-Left Side and then Right Side, Cloud Hands

E1-3: Cloud Hands

F1-3: Single Whip

G1-3: Work at Shuttles on Both Sides

H1-3: Raising Left and then Right Hand

292x223mm (300 x 300 DPI)





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	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	19
	5b	Name and contact information for the trial sponsor	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	NA
	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)	NA

Introduction

1				
2				
3	Background	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	6-9
4	and rationale			
5				
6		6b	Explanation for choice of comparators	9
7	Objectives	7	Specific objectives or hypotheses	8, 9
8				
9	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)	9, 10, 11
10				
11				
12				
13	Methods: Participants, interventions, and outcomes			
14				
15	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	9
16				
17				
18	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)	11
19				
20				
21	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12, 13
22				
23				
24		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)	12, 13
25				
26				
27		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12, 13
28				
29				
30		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
31				
32	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	16
33				
34				
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36				
37	Participant	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)	Figure 1. Trail flow chart
38	timeline			
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3 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including 16

4 clinical and statistical assumptions supporting any sample size calculations

5

6 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size 11

7

8 **Methods: Assignment of interventions (for controlled trials)**

9

10 Allocation:

11

12 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any 11, 12

13 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg,

14 blocking) should be provided in a separate document that is unavailable to those who enrol participants or

15 assign interventions

16

17 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, 12

18 concealment sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

19 mechanism

20

21 Implementati 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to 12

22 on interventions

23

24 Blinding 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome 12

25 (masking) assessors, data analysts), and how

26

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's 12

28 allocated intervention during the trial

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31 **Methods: Data collection, management, and analysis**

32

33 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related 13-16

34 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of

35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.

36 Reference to where data collection forms can be found, if not in the protocol

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38 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be 12, 13

39 collected for participants who discontinue or deviate from intervention protocols

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3	Data	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	16, 17
4	management		(eg, double data entry; range checks for data values). Reference to where details of data management	
5			procedures can be found, if not in the protocol	
6				
7	Statistical	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the	17
8	methods		statistical analysis plan can be found, if not in the protocol	
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
11				
12		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any	NA
13			statistical methods to handle missing data (eg, multiple imputation)	
14				
15	Methods: Monitoring			
16				
17	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of	NA
18			whether it is independent from the sponsor and competing interests; and reference to where further details	
19			about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
20				
21		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim	NA
22			results and make the final decision to terminate the trial	
23				
24	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events	17
25			and other unintended effects of trial interventions or trial conduct	
26				
27	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from	NA
28			investigators and the sponsor	
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31	Ethics and dissemination			
32				
33	Research ethics	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	4, 17, 18
34	approval			
35				
36	Protocol	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes,	NA
37	amendments		analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals,	
38			regulators)	
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3	Consent or	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how	4, 17, 18
4	assent		(see Item 32)	
5				
6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary	NA
7			studies, if applicable	
8				
9	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in	17, 18
10			order to protect confidentiality before, during, and after the trial	
11				
12	Declaration of	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
13	interests			
14				
15	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit	NA
16			such access for investigators	
17				
18	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial	NA
19	post-trial care		participation	
20				
21	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the	4, 17, 18
22	policy		public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing	
23			arrangements), including any publication restrictions	
24				
25		31b	Authorship eligibility guidelines and any intended use of professional writers	NA
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
28				
29	Appendices			
30				
31	Informed	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
32	consent			
33	materials			
34				
35	Biological	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	NA
36	specimens		analysis in the current trial and for future use in ancillary studies, if applicable	
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2 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
3 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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For peer review only