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Effect of customized Health Qigong exercise on freezing of gait and falls in Parkinson's disease: protocol for a single blind randomized controlled trial

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Manuscripts

1 **Effect of customized Health Qigong exercise on freezing of gait**
2 **and falls in Parkinson's disease: protocol for a single blind**
3 **randomized controlled trial**

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19

21 **ABSTRACT**

22 **Introduction** Parkinson's disease (PD) patients with freezing of gait (FOG) demonstrate
23 a sudden inability to step forward or continue walking, resulting in falls or fall-related
24 injury and independent activity loss. Many studies have shown that Health Qigong
25 exercise is a safe, effective mind-body exercise to improve gait function and decrease fall
26 risk. However, studies of the efficacy of customized Health Qigong on PD are rare. Our
27 study will select twelve forms of Health Qigong exercise and investigate the effect of
28 tailor-made Health Qigong exercise on gait function and fall reduction in PD patients.

29 **Methods and analysis** We propose a single-blind randomized control trial, recruiting 90
30 PD patients with FOG. They will randomly assigned to a Health Qigong exercise group,
31 balance exercise group, and a control group by a computer-generated random-sequence
32 table. The Health Qigong group will engage in customized Qigong exercise three times
33 per week for one hour each session. The balance exercise group will focus on static and
34 dynamic balance exercise. The control group will receive health education. The duration
35 of this trial will be 12 weeks. All the participants will be assessed at baseline, 12 weeks
36 (end of intervention), and 3 months follow-up. The primary outcomes will assess the gait
37 parameter and occurrence of FOG. The secondary outcomes will assess the postural
38 instability and walking disability, falls and fearing of fall, quality of life.

39 **Ethics and dissemination** This study has been approve by the ethics committee of
40 Shanghai University of Sport. All the participants or their guardians signed informed
41 consent prior to the study. The findings of the study will be submitted to peer-reviewed
42 journals or academic conferences.

43 **Trial registration** China Clinical Trial Registry, ID: ChiCTR1800016570. Registered on
44 6 June 2018.

45 **Keywords** Freezing of gait, Falls, Randomized control trial, Health Qigong, Parkinson's

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4 46 disease

5
6 47 **Strengths and limitations of this study**

7
8 48 1.The customized Health Qigong exercise for gait improvement is targeted the mild
9
10 49 to moderate Parkinson's disease by the research team of multidisciplinary
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12 50 professionals. In addition, it suits for Parkinson's disease patient to practice for a long
13
14 51 time because of easy movement to practice as well as without site restriction.

15
16 52 2.The randomized controlled trial design reduces the factors of bias.

17
18 53 3.It is difficult to achieve a blinded intervention for this study because exercise as an
19
20 54 intervention is open to the participants.

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22 55

57 INTRODUCTION

58 Freezing of gait (FOG) is a paroxysmal syndrome in Parkinson's disease, and is
59 characterized by sudden and brief episodes of an inability to produce effective forward
60 progression. Freezing of gait occurs in the late stage of Parkinson's disease, which leads
61 to increased risk of falls and loss of independent activities.[1] Although not all patients
62 with PD develop FOG, between 21% and 27% of PD report FOG experience in early
63 stages. However, the number of patients experiencing FOG increases up to 80% in all
64 advanced PD patients.[2-4] Patients with FOG perform shuffling with small steps,
65 tremble in place without forward movement, or experience total akinesia.[5] Patients
66 often have difficulty in turning, transferring, walking across an obstacle, and have a
67 sudden inability to start or continue walking, while their upper body continues its original
68 trajectory. A freezing episode usually lasts 1–2 s, although some episodes exceed 30 s
69 and a patient will fail to generate any steps long enough to provide useful ambulation.[6,
70 7]

71 With progression of the disease, patients with severe FOG have postural instability
72 and gait dysfunction, causing difficulty in managing activities of daily life and frequently
73 fall. The complex pathophysiology of the FOG remains poorly understood but is thought
74 to be relative to degeneration of nigral-striatal dopaminergic neurons,[8] specifically an
75 inhibitory striatal output nuclei projecting to the motor thalamus and brainstem locomotor
76 regions.[5, 9] The prominent characteristics of frozen gait present a prolonged step
77 initiation duration as a potential hallmark of impending freezing. This gait dysfunction
78 can increase the risk of falling as it is often unexpected. Thus, intervention programs in
79 the form of gait training may reduce the risk of falls in these patients.

80 Currently, wide application of multidisciplinary approaches combined with
81 pharmacological and surgical treatment manage FOG. Current studies have verified the

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4 82 effectiveness of non-pharmacological treatment for improving abnormal gait, including
5
6 83 physiotherapy, physical exercise and occupational therapy. While advances have been
7
8 84 made in holistic rehabilitation,[10] PD is an incurable and degenerative disease that
9
10 85 affects functional activities and quality of life. An easily executed and low-cost
11
12 86 therapeutic technique is necessary for PD patients to live independently. Previous studies
13
14 87 have shown some inexpensive exercises without equipment, such as Tai Chi, dance, and
15
16 88 yoga, demonstrating benefits in improving motor symptoms for PD patients.[11]

17
18 89 Traditional Chinese medicine is a unique therapeutic intervention applicable for
19
20 90 disease prevention, treatment, or rehabilitation in chronic disease. Health Qigong exercise
21
22 91 is one type of traditional Chinese exercise which incorporates meditative movements,
23
24 92 breathing patterns, and mental regulation. The exercises are performed in a slow, relaxed
25
26 93 manner which promote a sense of relaxation, improves balance and posture, and enhances
27
28 94 physiological function of internal organs in an energy-efficient and comprehensive
29
30 95 way.[12, 13] Most importantly, practicing Health Qigong is low cost and easy to learn,
31
32 96 without equipment or site restrictions. Therefore, Health Qigong exercise has great
33
34 97 therapeutic potential in chronic disease.

35
36 98 A growing number of studies have shown that Health Qigong exercise can improve
37
38 99 muscle strength and balance in older adults. A systematic review and meta-analysis
39
40 100 provided evidence that elderly people who practice Health Qigong exercise have
41
42 101 enhanced equilibrium function and reduced fall risk.[14] Practicing Health Qigong
43
44 102 requires slow movement, body control in space, and shifting body weight in different
45
46 103 directions; thus, transfer of body posture can be beneficial to improving sense of balance
47
48 104 and prevent falls.[12] In addition, Health Qigong exercise produces significant
49
50 105 improvements in gait speed, stride length, and leg movement ability in PD patients.[15,
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52 106 16]

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54 107 Health Qigong consists of nine categories of exercise, including Baduanjin, Liuzijue,
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4 108 Daoyin,12-step Dao Yin Health Preservation Exercise, Yijinjing, and Wuqinxi. Each
5
6 109 exercise has its own characteristics and efficacy for a variety of diseases. Few studies
7
8 110 have clarified the effect of combining different categories of Health Qigong on gait
9
10 111 function and fall risk. Moreover, some studies concentrated on the efficacy of combined
11
12 112 Tai Chi with Qigong,[13, 17] or one type of Qigong therapeutic effect on Parkinson's
13
14 113 disease.

15
16 114 These two traditional Chinese exercises have similar theories and principles, but
17
18 115 different movement patterns and treatment effects on disease. Qigong emphasizes the
19
20 116 flow of qi harmony in the body and improves health via mind-body exercise, combined
21
22 117 with coordinated rhythmic movements and regulated breathing.[18] Tai Chi is a martial
23
24 118 art that highlights the maintenance of mental and body balance while neutralizing a
25
26 119 rival's attack; the prominent motion is diagonal and requires slow movement in all planes
27
28 120 via a constantly altering range.[19] They have differences in action routine, level of
29
30 121 difficulty, and scale of activities. Therefore, we will select forms from nine categories to
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32 122 tailor Health Qigong exercise for PD patients to generate positive benefits for gait
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34 123 function.

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36 124 The aim of this trial protocol is to explore a combination of different forms of Health
37
38 125 Qigong and determine any improvement in freezing of gait and prevention of falls in
39
40 126 patients with Parkinson's disease. We hypothesize that combining different forms of
41
42 127 Health Qigong customized to the patient may ameliorate freezing of gait and thus lower
43
44 128 the risk of falls in PD patients.

47 48 129 **METHODS**

49 50 51 130 **Study design**

52
53 131 The study design is a prospective, single-blind randomized controlled trial.
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132 **Design and procedures**

133 We will recruit participants from Shanghai, China by means of the neurology department
134 of the local hospital and TV programs during the same recruitment period. To reduce the
135 potential expectation bias and confirm eligibility, a research assistant will make telephone
136 contact with those referred by a neurologist and follow up with interested participants.
137 Participants will be informed that the study will be conducted in three different groups,
138 and will be randomly assigned to one group. The experimental group will perform Health
139 Qigong exercise under instructor guidance, the balance exercise group will perform static
140 and dynamic postural control training, and the control group will receive health education.
141 The total intervention period will be 12 weeks, simultaneous for all patients. The primary
142 and secondary outcomes will be assessed at baseline (pre-intervention), 12 weeks (end of
143 intervention) and 3 months follow-up (see figure 1). Potential eligible participants who
144 satisfy initial inclusion criteria will arrange a 2 hour to visit our research laboratory and
145 register their personal information. The trial protocol has been approved by the ethics
146 committee of Shanghai University of Sports. All participants who meet the inclusion and
147 exclusion criteria will sign informed consent prior to the study. The protocol is registered
148 as a China Clinical Trial (ID: ChiCTR1800016570).

149 **Participants**

150 Inclusion criteria

151 1) PD patients were diagnosed according to the clinical diagnostic criteria of UK; 2) age
152 between 40 and 80 years old; 3) Hoehn & Yahr scale 1–3; 4) item three of the Freezing of
153 Gait Questionnaire (FOGQ) scored ≤ 5 ; 5) Mini–Mental State Examination (MMSE)
154 score >24 ; 6) ability to walk independently; and 7) have had a fall over the past year.

155 Exclusion criteria

156 1) Participation in Qigong exercise during the last year; 2) other diseases that could

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4 157 interfere with conduct of the study protocol such as cardiopulmonary disease, liver and
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6 158 kidney disease, musculoskeletal dysfunction, or cancer; 3) severe cognitive, visual or
7
8 159 auditory impairment; 4) unstable medication; 5) deep brain stimulation.
9

10 160 **Sample size calculation**

11
12 161 The power calculation is based on a pilot study of PD patients with similar characteristics
13
14 162 to those of the patients in this trial, we estimated the effect size at least 35%, statistical
15
16 163 sample size of 80% and alpha level of 0.05 calculated by G*Power 3.1.9.2 software
17
18 164 (Franz Faul, Universitat Kiel, Germany). Considering a 10% attrition rate, the total
19
20 165 sample size would be 90 participants, with 30 participants in each group.
21
22
23 166

24 25 167 **Randomization and blinding**

26
27 168 The study design will utilize a single blinded randomized controlled trial. Two trained
28
29 169 assessors will be blinded to group allocation and will not participate in the intervention.
30
31 170 Using computer generated random number sequencing (STATA 12.0, StataCorp LP,
32
33 171 Texas, USA) in a ratio of 1:1:1, a random number will be put in a sealed envelope, and
34
35 172 participants will be allocated randomly to a Qigong group, balance exercise group, or
36
37 173 control group by extracting the envelope. Participants will reassessed for baseline
38
39 174 measures on another day. This study is difficult to achieve the blinded to participants
40
41 175 because exercise as an intervention is open to the participants.
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45 46 47 177 **Intervention**

48
49 178 Health Qigong exercise group

50
51 179 The Health Qigong group will perform the exercise interventions in the sports science
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53 180 laboratory of Shanghai University of Sports. The Qigong protocol consist of
54
55 181 twelve-forms of exercise, respectively selected movements from the Health Qigong
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4 182 exercise guidelines organized and compiled by the China Qigong Management Center.
5
6 183 The selection of movements will emphasize dynamic postural control and body weight
7
8 184 shift stepping with lateral-medial and anterior-posterior, body symmetry pulling to
9
10 185 upper-down and left-right, hand and eye coordination movement. The twelve forms of
11
12 186 exercise are as follows:[20]

- 13
14 187 P *Form one*: Xu Exercise (Liu Zi Jue)
15
16 188 P *Form two*: CHUI Exercise (Liu Zi Jue)
17
18 189 P *Form three*: Raising the Tiger's Paws (Wu Qin Xi: Tiger Exercise)
19
20 190 P *Form four*: Holding the Hands High with Palms Up to Regulate the Internal Organs
21
22 191 (Ba Duan Jin)
23
24 192 P *Form five*: Drawing a Bow (Mawangdui Daoyin Exercises)
25
26 193 P *Form six*: Posing as an Archer Shooting Both Left-and Right-Handed (Ba Duan Jin)
27
28 194 P *Form seven*: Pulling Nine Cows by Their Tails (Yi Jin Jing)
29
30 195 P *Form eight*: Rub Backbone (Da Wu)
31
32 196 P *Form nine*: Swaying Like a Bear (Wu Qin Xi: Bear exercise)
33
34 197 P *Form ten*: Picking Fruit (Wu Qin Xi: Money exercise)
35
36 198 P *Form eleven*: Golden Rooster Heralds the Dawn (12-Step Dao Yin Health
37
38 199 Preservation Exercise)
39
40 200 P *Form twelve*: Flying Like a Bird (Wu Qin Xi: Bird Exercise)

41
42 201 Two instructors certified by the Chinese Health Qigong Association will instruct
43
44 202 Qigong exercise. The beginning stage (i.e. the first 2 weeks) will emphasize learning the
45
46 203 movement via practicing single forms with repetitions, while the later stages will
47
48 204 concentrate on movement consistency and integrity of form. The instructors will correct
49
50 205 the movements and participants will repeat the exercises in subsequent session to
51
52 206 consolidate learning. A complete set of exercises will be performed in about 20 minutes.
53
54 207 Participants will perform each exercise twice and rest with intervals of 5 minutes. Natural
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4 208 breathing will be integrated into the Qigong movement routine. Each participant will
5
6 209 receive Qigong exercise for 3 sessions per week for 12 consecutive weeks. Each session
7
8 210 will consist of 10-minute warm-up, 40-minute Health Qigong exercise, and 10-minute
9
10 211 cool-down. The heart rate of all the participants will be monitored by Polar-team² (Polar
11
12 212 Electro, Finland) during training.

13 14 15 213 Balance exercise group

16
17 214 All balance exercises will be guided by two trained instructors. The participants in the
18
19 215 balance exercise group will follow their regular medication scheme and perform balance
20
21 216 exercise in their medication stage. They will engage in a 12-week intervention, with 3
22
23 217 sessions per week. Each training session will start with a 10 minute warm-up consist of
24
25 218 breathing exercise, slow walking, and range-of-motion exercises. The 40-minute balance
26
27 219 exercise includes a short resting time, and the training program consists of the following:
28
29 220 1) static balance exercise: standing on unstable surfaces to maintain postural control and
30
31 221 progress to weight Shifting; 2) dynamic balance: postural control in standing position
32
33 222 while adding upper limb and trunk movement; 3) balance strategy exercise: focus on hip
34
35 223 strategy under maintain ankle strategy and stepping strategy under interference in
36
37 224 different directions; 4) adaptation of varying base of support, standing in narrow space
38
39 225 and uneven surface;^[21] and 5) walk integrated balance training: walk a straight line,
40
41 226 walk on soft blanket, and side walk. The end of training will include a 10-minute
42
43 227 cool-down session of limb ROM movements, sustained stretching, and relaxing.

44 45 46 228 Control group

47
48 229 The control group will be instructed to maintain their formal lifestyle and not to engage in
49
50 230 any other form of intensive training. They will receive health education every 4 weeks
51
52 231 over the 12-week intervention period. The health education will involve information for
53
54 232 Parkinson's disease related treatments and prevention such as modality of exercise,

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4 233 regimen, preventing falls, and nutrition. Participants will receive a brochure of health
5
6 234 education and will have follow-up by telephone twice per month.

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8 235 All participants will maintain diaries to record their exercise and fall events every
9
10 236 day throughout the trial, including both in the laboratory and at home. The participants in
11
12 237 the Health Qigong exercise group and balance exercise group will perform the exercise at
13
14 238 “on” stage in the morning.

15 16 17 239 **Outcome measures**

18
19 240 All measures will be performed at baseline, 12 weeks (end of intervention), and 3 months
20
21 241 following the completion of the intervention. The measures will be conducted by two
22
23 242 trained assessors and videotaped by a third assessor. All assessors will be blinded to the
24
25 243 participant’s group allocation and time of assessment.

26 27 28 244 **Participants characteristics**

29
30 245 Demographic and health characteristics of participants will be collected at baseline
31
32 246 to describe the sample, compare conditions, and investigate characteristics associated
33
34 247 with outcomes. It will include age, gender, education, age at onset and disease duration,
35
36 248 health status, use of medication, resting blood pressure, body mass (kg/m^2), and height
37
38 249 (cm). Blood pressure will be measured with the use of an automated device (Omron
39
40 250 HealthCare). Body mass and height will be assessed with digital scales (Weighing scale
41
42 251 & Meter)(see table 1).

253 **Table 1** Demographic and clinical characteristics of the study participants*

	Health Qigong (N=)	Balance (N=)	Control (N=)
Age—yr			
Gender—(male% : female%)			
Body-mass index ^a —kg/m ²			
Height—cm			
Hoehn and Yahr stage—no. (%)			
1-1.5			
2-2.5			
M□			
Age of onset—yr			
Duration of disease—yr			
Antiparkinsonian medications taken—no.			
Levodopa or carbidopa			
Pramipexole or ropinirole			
Other			
Self-reported health status ^b —no. (%)			
Poor or fair			
Good			
Very good or excellent			
Falls in previous 6 months—no.			

254 * Mean values (standard deviation). The chi-square test is used for categorical variables,
255 and one-way analysis of variance for continuous variables.

256 ^a The body-mass index is the weight in kilograms divided by the square of the height in
257 meters

258 ^b Self-reported health status, included cardiovascular disease, lung disease, osteoporosis,
259 arthritis, liver and kidney disease, low back pain, and cancer; the number of conditions
260 per participant ranged from 0 to 9.

261

262 Primary outcome assessment

263 Gait parameters were analyzed by a 10-camera Vicon Motion Analysis System (Vicon
264 MX-13, Oxford Metrics, Oxford, UK) at 200 Hz, and reaction force at 1000 Hz will be
265 recorded using force plates (models 9286AA, Kistler Instruments Corp., Winterthur,
266 Switzerland), with Vicon Nexus 1.5.2 and Polygon 3.5.1 analysis software to process
267 kinematic and kinetic parameters. According to the plug-in gait marker set, the
268 trajectories of 45 reflective markers (14 mm in diameter) will be captured at different
269 landmarks of the participants.[22, 23]

270 Freezing of Gait Questionnaire (FOG-Q) will measure the occurrence of FOG
271 during the daily activity. It is constituted of three parts, part I (item 1, score is 0 or 1)
272 detects the presence of FOG and distinguishes if patients are freezers or non-freezers if
273 they have a FOG experience during the past month. Part II (items 2–6, score range 0 to 9)
274 assesses the severity of FOG according to its duration and frequency in its common
275 appearance. Item 2 was added to rate the overall frequency of FOG regardless of
276 environment. Part III (items 7–9, score range from 0 to 9) assesses the influence of FOG
277 on daily life, and the total score ranges from 0 to 28; higher scores reflects more severe
278 FOG.[24]

279 Participants will asked to write the exercise diary to record their falls event. Data on
280 fall will collected from the first day of intervention to the end of follow-up.

281 Secondary outcome assessment

282 Functional Gait Assessment (FGA) is a measure of walking balance ability in older adults
283 and Parkinson's disease, which has shown good reliability and validity in the clinic. It
284 includes walking forward, backward, with eyes closed, stepping over obstacles, changing
285 gait speeds, with different head turns, and with a narrow base of support. The FGA

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4 286 includes 10 total items, with each item scored 0 to 3. A higher total score reflects better
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6 287 balance and walking ability, with a maximum score of 30.[25, 26]

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8 288 Postural instability and gait disability will be evaluated by the Unified Parkinson's
9
10 289 Disease Rating Scale (UPDRS) Part III evaluation. It consists of rigidity measures, gait,
11
12 290 tremor, hand/arm and leg movements (bradykinesia), speech, and facial expressions. The
13
14 291 modified Hoehn and Yahr scale was also used to evaluate disease severity.[27]

15
16 292 Falls and fear of fall were measured with the 14-item Modified Falls Efficacy Scale
17
18 293 (MFES) questionnaire, which reflects self-perceived confidence to engage in activities of
19
20 294 daily living without falling. Each item was scored on a 10-point scale, with a minimum
21
22 295 score of 0 indicating no confidence and a maximum score of 10 indicating full confidence
23
24 296 (high falls efficacy) in performing the tasks without falling. The average score across all
25
26 297 14 items will be taken, with higher scores indicating greater falls efficacy.[28, 29]

27
28 298 The quality of life will be assessed using the 39-item Parkinson's Disease
29
30 299 Questionnaire (PDQ39). It is composed of 39 items grouped in eight domains: mobility,
31
32 300 activities of daily living, emotional well-being, stigma, social support, cognition,
33
34 301 communication, and bodily discomfort. Each item ranges from 0 (never) to 4 (always). A
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36 302 summary index of eight domain scores ranges from 0 to 100, with higher scores
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38 303 representing worse health related quality of life (HRQoL).[30, 31]

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40 304 The data collected are depicted in table 2.
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305 **Table 2** Changes over time within and between control and experimental groups

Group	Baseline*	12-weeks*	Follow-up*	Mean difference at 12-weeks**	Mean difference at Follow-up**	<i>F(P Value) Time Effect</i>	<i>F(P Value) Group Effect</i>	<i>F(P Value) Interaction Effect</i>
Primary Outcome								
Stride length (cm)								
Health Qigong								
Balance								
Control								
Gait velocity (cm/sec)								
Health Qigong								
Balance								
Control								
NFOG								
Health Qigong								
Balance								
Control								
Total falls,								

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no.								
Health Qigong								
Balance								
Control								
Secondary Outcome								
FGA								
Health Qigong								
Balance								
Control								
Health Qigong								
Part-III								
Balance								
Control								
MFES								
Health Qigong								
Balance								
Control								
PDQ-39								
Health Qigong								

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Balance								
Control								

306 *Mean values (standard deviation).

307 **Mean difference (standard error).

308 Abbreviations: FGA, functional gait assessment; MDS-UPDRS Part-III, movement disorder society unified Parkinson’s disease rating
309 scale, motor subscale; MEFS, falls and fear of fall; PDQ-39, Parkinson’s disease questionnaire.

310

311

312

For peer review only

313 **Patient and Public involvement**

314 Participants have not been involved in the study recruitment. The authors conceived the
315 initial research questions and outcome measures, and modified according to the telephone
316 interview with patients and their guardians by a research assistant. In order to assure the
317 safety and feasibility of the intervention, we invited six patients with mild to moderate
318 Parkinson's disease to learn and practice customized Health Qigong exercise before
319 designing the RCT. The Health Qigong movements were revised base on the exercise
320 performance and feedback provided by the participants. The burden of the intervention
321 will assessed by patients and their advisors before signing informed consent. The findings
322 of the study will be disseminated to the participants and their guardians.

324 **Statistical Analysis**

325 The statistical analysis will be performed using SPSS 22.0 software (Company city state).
326 Baseline values of demographic differences in Qigong group and control group will be
327 examined using Chi-squared tests. The analyses will be performed on an
328 intention-to-treat based on original group assignment. The primary outcome and
329 secondary outcome over time (i.e., baseline, 12 weeks, after 3 months follow-up) will be
330 analyzed by mixed design repeated-measures analyses of variance (RM-ANOVA) for
331 between- and within-group differences. Bonferroni's post hoc test will be applied to
332 compare results where main effects are significant. Data will be expressed as the mean
333 and standard deviation, and significance will be set at $p < 0.05$.

334 **DISCUSSION**

335 Medical treatment integrated with exercise therapy are still indispensable methods to
336 manage the motor dysfunction for PD patients. Freezing of gait is common in PD patients
337 which contributes to a protective postural response impairment and increases the risk of

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4 338 falls. Nevertheless, this balance instability can be improved by extra training.[32] Qigong
5
6 339 exercise can increase range of motion of joints, such as the shoulder, sacroiliac, and knee
7
8 340 joints, and thus improve trunk flexibility and physical coordination.[33, 34]
9

10 341 Patients with Parkinson's disease exhibit difficulty in transitions from static to
11
12 342 dynamic states. Transition activity is a vital component of physical activities, especially
13
14 343 gait initiation, turning, and gait termination. Due to the deficiency in postural control,
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16 344 patients generate excessive trunk movement causing sway beyond the limits of stability
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18 345 and thus leading to falls.[35] Wuqingxi is a type of Qigong exercise that imitates the
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20 346 posture of five animals: the tiger, bear, crane, monkey, and deer. The bear swaying
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22 347 movement refers to changes in the center of gravity of the body, strength of the waist
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24 348 muscles and the sequence of the force-release transfer to lower limb muscles. Bear sway
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26 349 contributes to the ability to control the lower limbs and prevents unnecessary injuries in
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28 350 daily life. The monkey exercise requires practitioner to imitate a monkey climbing a tree
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30 351 to pick fruit, and involves stepping backward and forward while simultaneously
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32 352 extending the arm to pick fruit, and thus integrates eye-hand coordination.[36, 37] The
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34 353 Baduanjin movement "Posing as an Archer Shooting Both Left-and-Right-Handed" is
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36 354 akin to drawing the bow in a horse stance, with the chest puffed out and stretching of the
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38 355 shoulders back. This improves the tightness of muscles and joints and restores limb
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40 356 proprioception, strengthens the muscles and adjusts the breathing to promote a body that
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42 357 is more flexible, spiritual, and physically in harmony.[38] Xu Zi Jue and Chui Zi Jue can
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44 358 regulate breathing movements by diaphragmatic breathing and pursed lip breathing to
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46 359 expand lung capacity. These exercises have shown to improve walking endurance.[39, 40]
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48 360 Therefore, combining specific targeted Health Qigong movements based on the patient's
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50 361 specific gait dysfunction in PD can help regain walking ability and independent activities
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52 362 for mild to moderate PD patients.
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54 363 Furthermore, Health Qigong is characterized by slow movement incorporated with
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4 364 moderated breathing, as well as keeping the mind in a state of calm relaxation. The
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6 365 intensity of Health Qigong is around 1.5 to 2.6 metabolic equivalents (METs) and the
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8 366 average induced maximum heart rate ranges from 43% to 49% of the predicted
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10 367 maximum.[41] Thus, Health Qigong is a low-intensity physical exercise which has lower
11
12 368 risk of muscle strain and overfatigue and is suitable for PD patients as a long-term
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14 369 physical exercise program.

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16 370 For a variety of features of gait pattern, whatever muscle stiffness or abnormal
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18 371 postural control, we may consider the global or specific efficacy of Health Qigong on gait
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20 372 function in PD.[42] We expect that a 12-week customized Health Qigong exercise can
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22 373 improve muscle stiffness, postural stability, and joint flexibility in PD patients. This
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24 374 could enhance balance function and locomotion during walking. However, gait
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26 375 deficiency in PD patients is a complex syndrome and is associated with neural control
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28 376 regulated by different areas of the brain, particularly the prefrontal lobe and related
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30 377 circuits.[43] In future studies, we will explore the mechanism of the different forms of
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32 378 Qigong on brain activities, combining imaging with functional magnetic resonance
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34 379 imaging (fMRI) or functional near-infrared spectroscopy (fNIRS),[44] to determine if the
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36 380 Health Qigong exercise is beneficial to restore brain function or prevent brain
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38 381 degeneration. We still consider that environmental changes influence gait performance,
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40 382 and therefore tailor-made Qigong movements are necessary to PD patient adapt to
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42 383 various contexts. We hope this trial will demonstrate that the tailored Health Qigong
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44 384 exercise possesses positive effects on recovery of gait function and prevention of falls for
45
46 385 mild and moderate PD patients. This will provide a supplemental therapy that can be
47
48 386 applied to improve physical dysfunction, improve quality of life, and increase longevity.

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52
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54
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4 390 program.

5
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7
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9
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11
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13
14 395 design of the trial, and to drafting the manuscript. Guiping Xiao and Kuncheng Jie
15
16 396 participated in trail registration, communication, and monitoring. Yan Jiang and Tian
17
18 397 Wang carried out the statistical calculation. All authors participated in revision of the
19
20 398 manuscript and approved the final version.

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23 399 **Patient consent** Obtained.

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26 400 **Ethics approval** This work was approved by the ethics committee of science research of
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28 401 Shanghai University of Sport(protocol number: 2018031).

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30 402 **Provenance and peer review** Not commissioned;externally peer reviewed
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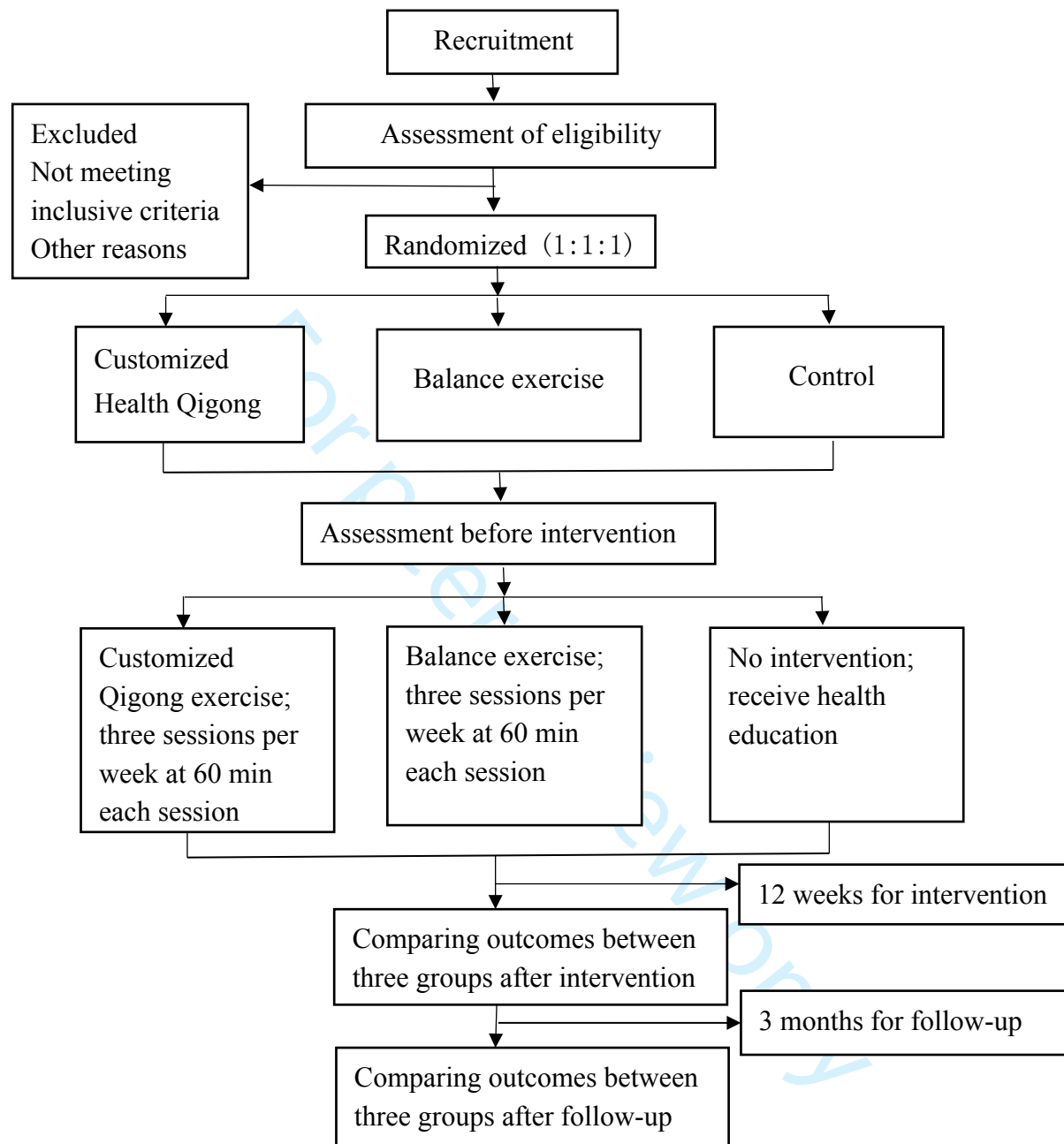
516 **Figure Legend**

517 **Figure 1** Flow diagram of study design.

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For peer review only





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

Section/item	Item No	Description
Administrative information		
Title(P1)	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration(P2)	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding(P17)	4	Sources and types of financial, material, and other support
Roles and responsibilities (P17-18)	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	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
	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)
Introduction		
Background and rationale(P3)	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
	6b	Explanation for choice of comparators
Objectives(P4)	7	Specific objectives or hypotheses

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Trial design(P9) 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)

Methods: Participants, interventions, and outcomes

Study setting(P9) 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

Eligibility criteria(P8-9) 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

Interventions (P9-12) 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

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)

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

Outcomes (P12-14) 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

Participant timeline(Figure1) 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)

Sample size(P9) 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

Recruitment(P8) 15 Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

1			
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation(P9)		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions
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10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13	(P9)		assigned
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16	(P8)		and who will assign participants to interventions
17			
18	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
19	(masking)		participants, care providers, outcome assessors, data analysts), and
20	(P12)		how
21			
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23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial
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Methods: Data collection, management, and analysis

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30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods(P14)		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol
36			
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38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44	(P14)		range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol
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47			
48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
49	methods(P14)		Reference to where other details of the statistical analysis plan can be
50			found, if not in the protocol
51			
52			
53		20b	Methods for any additional analyses (eg, subgroup and adjusted
54			analyses)
55			
56		20c	Definition of analysis population relating to protocol non-adherence
57			(eg, as randomised analysis), and any statistical methods to handle
58			missing data (eg, multiple imputation)
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Methods: Monitoring

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24	Data monitoring (n/a)	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Harms (n/a)	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
	Auditing (n/a)	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Research ethics approval (P8)	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
	Protocol amendments (n/a)	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
	Consent or assent (P8)	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
	Confidentiality (see informed consent)	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
	Declaration of interests (n/a)	28	Financial and other competing interests for principal investigators for the overall trial and each study site
	Access to data (n/a)	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
	Ancillary and post-trial care (n/a)	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

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2	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
3	policy		participants, healthcare professionals, the public, and other relevant
4	(n/a)		groups (eg, via publication, reporting in results databases, or other
5			data sharing arrangements), including any publication restrictions
6			
7		31b	Authorship eligibility guidelines and any intended use of professional
8			writers
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10		31c	Plans, if any, for granting public access to the full protocol, participant-
11			level dataset, and statistical code
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Appendices

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16	Informed consent	32	Model consent form and other related documentation given to
17	materials		participants and authorised surrogates
18	(see informed		
19	consent)		
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22	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
23	specimens		specimens for genetic or molecular analysis in the current trial and for
24	(n/a)		future use in ancillary studies, if applicable
25			

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

BMJ Open

Study protocol for a single-blind, randomized controlled trial evaluating clinical effects of an Integrated Qigong exercise intervention on freezing of gait in Parkinson's disease

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-028869.R1
Article Type:	Protocol
Date Submitted by the Author:	03-Apr-2019
Complete List of Authors:	Li, Zhenlan; Shanghai University of Sport, Zhuang, Jie; Shanghai University of Sport Jiang, Yan; Shanghai University of Sport Xiao, Guiping; Shanghai University of Sport Jie, Kuncheng; Shanghai University of Sport Wang, Tian; Shanghai University of Sport Yin, Wenhan; Shanghai University of Sport Zhang, Yu; Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine Wang, Zhen; Shanghai University of Sport
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Geriatric medicine, Sports and exercise medicine, Neurology
Keywords:	gait interruption, exercise, neurodegenerative disease, movement disorder

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Manuscripts

1 **Study protocol for a single-blind, randomized controlled trial**
2 **evaluating clinical effects of an Integrated Qigong exercise**
3 **intervention on freezing of gait in Parkinson's disease**

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20 **Word count:** 5, 922

21

23 **ABSTRACT**

24 **Introduction**

25 Qigong exercise offers a potentially safe, low-cost, and effective mind–body rehabilitative
26 intervention for mitigating the problem of gait interruption among Parkinson’s disease (PD)
27 patients who have frequent freezing of gait (FOG) episodes. However, its clinical effects
28 have not been established. This paper describes the trial protocol of evaluating the clinical
29 efficacy of a newly developed Integrated Qigong in improving gait among PD patients with
30 FOG.

31 **Methods and analysis**

32 A single-blind, randomized, controlled trial comparing Integrated Qigong and balance
33 training, relative to an attention control. Participants will be mild to moderate PD patients
34 who experience FOG and recruited from local communities in the city of Shanghai, China.
35 Participants will be randomly allocated to one of the three arms: Integrated Qigong, a
36 balance exercise intervention, or an attention control group. The total number of
37 participants will be 126, and masked assessments will be administered at baseline, 12
38 weeks (end of intervention), and 12-week follow-up. Both Integrated Qigong and balance
39 training groups receive a group-based exercise intervention that meets three times per week,
40 60 minutes in duration, for 12 weeks. The control group receives a 60-minute group session
41 per week and monthly health education. The primary outcome measures are gait (stride
42 length, gait velocity, stride time variability) and occurrence of FOG. The secondary
43 outcomes are postural instability and walking disability, falls, fearing of falling, and quality
44 of life.

45 **Ethics and dissemination** This study has been approved by the ethics committee
46 of Shanghai University of Sport and registered at China Clinical Trial Registry
47 (ChiCTR1800016570). Participants will sign informed consent prior to the participation
48 of the trial. The findings of the study will be published in peer-reviewed academic journals

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4 49 and disseminated to PD support groups, medical community, and media.

5
6 50 **Trial registration** China Clinical Trial Registry, ID: ChiCTR1800016570. Registered on
7
8 51 6 June 2018.

9
10 52 **Keywords** gait interruption, exercise, neurodegenerative disease, movement disorder

11
12 53 **Strengths and limitations of this study**

- 13
14 54 1. The first study that combines commonly practiced Qigong exercises into a single
15
16 55 rehabilitative intervention aimed at improving gait outcome for PD patients with FOG.
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18 56 2. The findings of the study will inform patients and healthcare providers of an
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20 57 alternative, potentially low-cost and safe, effective, and easily implementable exercise
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22 58 intervention for treating and managing gait interruption in patients with PD.
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24 59 3. The study patients will come from one geographic area that limits the generalizability.
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61 INTRODUCTION

62 Freezing of gait (FOG) is characterized by a sudden and brief episodic absence or marked
63 reduction of forward progression. The syndrome is most common among patients with
64 Parkinson's disease(PD).[1] It is estimated that between 21% and 27% of early stage
65 patients report FOG episode with number increasing up 80% among those in advanced
66 stages.[2-4] Patients with FOG often show difficulty in turning, transferring, walking, and
67 experience and inability to start or continue walking. As the disease progresses, patients
68 with severe FOG develop postural instability and gait dysfunction, causing difficulty in
69 managing activities of daily living and frequent falls and, consequently, impact negatively
70 on quality of life.[5, 6]

71 There are multidisciplinary approaches, including pharmacological and surgical based
72 treatment for managing FOG among people with PD. Current research evidence has shown,
73 however, effectiveness of non-pharmacological and rehabilitation based intervention,
74 including physiotherapy, physical exercise, and occupational therapy, for improving
75 abnormal gait in patients with FOG.[7, 8] Increasing evidence also suggests the
76 effectiveness of various alternative exercise interventions to ameliorate motor symptoms
77 and improve gait. These include low-cost, non-equipment dependent exercises such as Tai
78 Chi, dance, and yoga.[9]

79 In this study, we focus on Health Qigong exercise which is one of traditional Chinese
80 exercises that incorporates meditative movements, breathing patterns, and mental
81 regulation. The exercises are performed in a slow, rhythmic, relaxed manner; features that
82 are conducive to organs.[10,11] Growing evidence supports the health benefits of Health
83 Qigong. A systematic review and meta-analysis indicates that older adults who practice
84 Health Qigong show an improved balance and postural control and reduced fall risk among
85 individuals with PD.[12] Health Qigong has also been shown to improve gait speed, stride
86 length, and leg movement ability.[13,14]

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87 Qigong consists of various types, including Baduanjin, Liuzijue, Daoyin, 12-step Dao
88 Yin Health Preservation Exercise, Yijinjing, and Wuqinxi. Although each of them has its
89 own training characteristics, they nevertheless share some common features. In general,
90 Qigong integrates both static and dynamic exercises with a great emphasis on regulating
91 breath, and exercising intrinsic control and mental intent.[15] Exercise of Qigong is
92 characterized by trunk rotation, bending and extending at waist and movement of limbs
93 both medial-laterally and anterior-posteriorly, all driven by the core of the body.[14,16]
94 Like other techniques such as Tai Ji Quan, Qigong exercise also involves dynamic
95 movements that involves intermittent stepping and turning. As such, exercise involves
96 postural demanding movements such as single leg standing and chirographic and
97 manipulative moving postures.[17,18] Furthermore, Qigong exercise requires regulating
98 breathing by engaging in diaphragmatic to expand lung capacity and control upright
99 posture.[19,20]

100 To date, there has been little effort made to evaluate the therapeutic effect of combing
101 different types of Qigong exercise on gait in individuals with PD. This paper describes the
102 trial protocol of a newly developed Integrated Qigong intervention that combines seven
103 types of commonly exercised Qigong into a single rehabilitation program for mild to
104 moderate PD patients with FOG. Specifically, we aim to determine the therapeutic effect
105 of the Integrated Qigong intervention on gait. We hypothesize that, relative to an attention
106 control group, both Integrated Qigong and a conventional balance training intervention will
107 be clinically more effective in improving the primary outcome of gait.

108

109

110 **METHODS**

111 **Study design**

112 The study design is a prospective, single-blind randomized controlled trial.

113 **Design and procedures**

114 We will recruit participants from Shanghai, China by means of the neurology department
115 of the local hospital and TV programs during the same recruitment period. To reduce
116 potential expectation bias and confirm eligibility, a research assistant will make telephone
117 contact with those referred by a neurologist and follow up with interested participants.
118 Participants will be informed that they will be randomly assigned to three different groups.
119 The integrated Qigong exercise group will engage in training program that combines seven
120 types of commonly exercised Qigong, the balance training group will perform static and
121 dynamic postural control training, the two intervention groups will receive the guidance of
122 instructor, and the control group will receive group session per week and monthly health
123 education. The total intervention period will be 12 weeks, and will occur simultaneously
124 for all participants. The primary and secondary outcomes will be assessed at baseline (pre-
125 intervention), 12 weeks (end of intervention) and 12-week follow-up (see figure 1).
126 Potential eligible participants who satisfy initial inclusion criteria will arrange a two-hour
127 visit at our research laboratory and register their personal information. The trial protocol
128 has been approved by the ethics committee of Shanghai University of Sport. All
129 participants who meet the inclusion and exclusion criteria will sign informed consent prior
130 to the study. The protocol is registered as a China Clinical Trial (ID: ChiCTR1800016570).

131 **Participants**

132 **Inclusion criteria**

133 (1) PD patients were diagnosed according to the clinical diagnostic of UK Brain Bank

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4 134 criteria; (2) age between 40 and 80 years old; (3) Hoehn & Yahr scale of 1–3; (4) item three
5
6 135 of the New Freezing of Gait Questionnaire (NFOGQ) scored ≥ 1 ; (5) Mini–Mental State
7
8 136 Examination (MMSE) score >24 ; (6) ability to walk independently; and (7) have
9
10 137 experienced a fall over the past six months.

11 12 13 138 Exclusion criteria

14
15 139 (1) Participation in Qigong exercise during the last year; (2) other diseases that could
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17 140 interfere with conduct of the study protocol such as cardiopulmonary disease, liver and
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19 141 kidney disease, musculoskeletal dysfunction, or cancer; (3) severe cognitive, visual or
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21 142 auditory impairment; (4) unstable medication; and (5) deep brain stimulation.

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24 25 26 144 **Sample size calculation**

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28 145 A statistical analysis was conducted for sample size estimation using G*power 3.1 (Franz
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30 146 Faul, Universita Kiel, Germany). The study was powered to detect a between-group
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32 147 difference in primary gait outcome measures between Qigong exercise and Balance
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34 148 training groups relative to the attention control groups. Because there was no a priori
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36 149 hypothesis formulated between the two active interventions (Qigong exercise and Balance
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38 150 Training), the study was not powered on these two conditions. Due to the lack of informed
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40 151 preliminary data and empirical evidence on the effects of Qigong exercise, we
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42 152 approximated the effect size in our power calculations using estimated from the published
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44 153 studies that compared Qigong exercise with a control condition on gait (i.e., gait speed,
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46 154 freezing of gait, and mobility).[13,14] In general, these studies, with an intervention length
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48 155 ranging from 10 weeks to 24 weeks, have shown a weak intervention effect, with effect
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50 156 sizes ranging from no effect to small-to-moderate effects. On the basis of these
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52 157 observations , a conservative approach was taken. Specially, we used a small effect size
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54 158 ($\eta^2=0.01$) based on the partial eta squared estimate within the ANOVA framework.[21]

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4 159 Our initial power estimates indicated that, in a mixed-effect repeated measures design with
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6 160 a between-subject factor (Integrated Qigong, Balance training, Control), and a within-
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8 161 subject factor (baseline, 12 weeks) and a correlation of 0.08 on the repeated measures, a
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10 162 sample size of 99 subjects would be required to achieve an 80% power at an 0.05 error rate.
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12 163 To be more conservative, we estimated the sample sizes based on a range of small sizes
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14 164 ($f=0.08, f=0.10, f=0.12$). The sample sizes generated from these calculations were averaged
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16 165 to arrive at a total of 107 subjects. With an anticipated 15% attrition rate, a final enrollment
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18 166 number of 126 (42 in each group) was set for the study to detect a difference in gait
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20 167 outcomes between Integrated Qigong and Balance Training relative to the attention control
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22 168 group.

23 24 25 169 **Randomization and blinding**

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27 170 The study design will utilize a single blinded randomized controlled trial. Two trained
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29 171 assessors will be blinded to group allocation and will not participate in the intervention.
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31 172 We will apply the stratified random sampling method by stage of the disease (H&Y Stage).
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33 173 Using computer generated random number sequencing (STATA 12.0, StataCorp LP, Texas,
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35 174 USA) in a ratio of 1:1:1, a random number will be placed in a sealed envelope, and
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37 175 participants will be allocated randomly to a Qigong group, balance training group, or
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39 176 control group by extracting the random number from the envelope. Participants will be
40
41 177 reassessed for baseline measurements on another day. This study is not amenable to
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43 178 blinding to participants of their designated experimental groups because the interventional
44
45 179 exercises they perform will reveal their group allocation.

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50 51 52 182 **Intervention**

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54 183 The participants in all groups will follow their regular medication scheme during the study
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4 184 period. Both integrated Qigong and balance training groups will receive group-based
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6 185 exercise intervention at the sports science laboratory of Shanghai University of Sport. The
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8 186 group size is 10-15 people in order to provide sufficient instructional attention to each
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10 187 participant, one trained instructor will guide the participants to perform the exercises. The
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12 188 two interventional groups will perform three weekly sessions of 60 minutes per session for
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14 189 12 consecutive weeks. Each session will consist of 10 minutes of warm-up, 40 minutes of
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16 190 core exercises, 5 minutes of break intervals, and 5 minutes of cool-down. The heart rates
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18 191 of the participants will be monitored by Polar-team² (Polar Electro, Finland) during training.
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20 192 Participants in the interventional groups will be required to not perform any additional in-
21
22 193 home exercises throughout the 12 weeks of training.

24 25 194 Integrated Qigong exercise group

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27 195 The Integrated Qigong protocol will consist of twelve-forms of exercise, with selected
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29 196 movements from the Health Qigong exercise guidelines organized and compiled by the
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31 197 China Qigong Management Center. The integrated Qigong exercise will emphasize
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33 198 dynamic postural control and body weight shift stepping with lateral-medial and anterior-
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35 199 posterior movements, body symmetry pulling across up-down and left-right axes, hand-
36
37 200 eye coordination movement. The twelve forms of exercise have been seen previously
38
39 201 documented[22] and can be seen in Figure 2.

40
41 202 During initial 2-3 weeks, training will mainly emphasize learning and practicing two
42
43 203 or three forms through multiple repetitions along with review of previously learned
44
45 204 movements. The practice in each session concentrate on upper and lower limbs in place,
46
47 205 trunk rotation, as well as stepping in different directions (i.e., forward, backward,
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49 206 sideways, diagonal). Participants will be requested to perform personalized movement
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51 207 requirements based on functional level. The range of motion of each movement will be
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53 208 reduced for participates with rigidity. The pace of movement will be decreased for

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4 209 participate with bradykinesia. For participants with freezing, they will be instructed to
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6 210 perform transferring and stepping while maintaining postural stability. The intensity,
7
8 211 difficulty of movement, time, and frequency will be adjusted to demands of each
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10 212 participant. The later weeks concentrate on improving balance, locomotion, and action
11
12 213 consistency, participants will practice each movement with six repetitions, and natural
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14 214 breathing will be incorporated into the movement routine. Participants will be guided to
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16 215 perform the entire range of movement in which they felt safe.
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217 Balance training group

218 Each training session will start with a 10 minute warm-up consist of breathing exercise,
219 slow walking, and range-of-motion exercises. The 40-minute balance training will
220 include a short resting time, and the training program will consist of the following: 1) static
221 balance training: standing on unstable surfaces to maintain postural control and
222 progression to weight shifting; 2) dynamic balance training: postural control in standing
223 position while adding upper limb and trunk movements; 3) balance strategy exercise:
224 focus on hip strategy while maintaining ankle strategy and stepping strategy under
225 interference in different directions; 4) adaptation of varying base of support, and standing
226 in a narrow space and on uneven surface;[23] and 5) walk integrated balance training: walk
227 in a straight line, walk on a soft blanket, and sideways. The training will progress from
228 simple to complex, static to dynamic, low to high the center of gravity, wide to narrow the
229 base of support, and will continue to raise challenges in regard to flexibility, stability and
230 range of movement. The end of training will include a 5-minute cool-down session of limb
231 ROM movements, sustained stretching, and relaxing.

232 Control group

233 The control group will be instructed to maintain their formal lifestyle and not to engage in

234 any other form of intensive training. The participant in control group will join one 60-min
235 group session per week, which will consist of a 30-min lecture, 20-min discussion, and will
236 be followed by a 10-min question and answer session. Participants in control group will
237 receive health education every four weeks over the 12-week interventional period. The
238 health education will involve information for PD-related treatments and prevention such as
239 modalities of exercise, regimens, fall prevention, and nutrition. Participants will receive a
240 brochure of health education and will have follow-up by telephone twice per month, which
241 will involve discussion of physical activity, progression of disease, health status, and
242 psychological status.

243 All participants will maintain diaries to record their exercise and fall events every day
244 throughout the trial, including both in the laboratory and at home. The participants in the
245 Health Qigong exercise group and balance training group will perform the exercises at the
246 “on” stage in the morning.

247 **Outcome measures**

248 All measurements will be performed at baseline, 12 weeks (end of intervention), and 12
249 weeks following the completion of the intervention. The measurements will be conducted
250 by two trained assessors and will be videotaped by a third assessor. All assessors will be
251 blinded to the participant’s group allocation and time of assessment.

252 **Participants characteristics**

253 Demographic and health characteristics of participants will be collected at baseline to
254 describe the sample, compare conditions, and investigate characteristics associated with
255 outcomes. These characteristics will include age, gender, education, age at disease onset,
256 disease duration, health status, use of medication, resting blood pressure, body mass
257 (kg/m^2), height (cm), family situation and physical performance. Blood pressure will be
258 measured with the use of an automated device (Omron HealthCare). Body mass and height

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4 259 will be assessed with digital scales (Weighing scale & Meter) Physical performance will
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6 260 be measured by the scores from self-reported habitual physical activity scale. (See Table
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263 **Table 1** Demographic and clinical characteristics of the study participants*

	Integrated Qigong (N=)	Balance Training (N=)	Control (N=)
Age—yr			
Gender—(male% : female%)			
Body-mass index ^a —kg/m ²			
Height—cm			
Hoehn and Yahr stage—no. (%)			
1-1.5			
2-2.5			
≥3			
Age of onset—yr			
Duration of disease—yr			
Antiparkinsonian medications taken—no.			
Levodopa or carbidopa			
Pramipexole or ropinirole			
Other			
Self-reported health status ^b —no. (%)			
Poor or fair			
Good			
Very good or excellent			
Family situation-no. (%)			
Living along			
Living with husband/wife			
Living with husband/wife and children			
Score for Self-reported habitual physical activity ^c			
Falls in previous 6 months—no.			

264 * Mean values (standard deviation). The chi-square test is used for categorical variables,
265 and one-way analysis of variance for continuous variables.

266 ^a The body-mass index is the weight in kilograms divided by the square of the height in
267 meters

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4 268 ^b Self-reported health status, included cardiovascular disease, lung disease, osteoporosis,
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6 269 arthritis, liver and kidney disease, low back pain, and cancer; the number of conditions per
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8 270 participant ranged from 0 to 9.

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10 271 ^c This is measured by the Physical Activity Scale for the Elderly,[24] with higher scores
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12 272 indicating higher levels of habitual physical activity
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4 273 **Primary outcome assessment**

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6 274 Gait will be analyzed using a 7-m-long instrumented computerized walkway (GAIRite,
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8 275 CIR, System Inc., Franklin, NJ), and will include gait velocity, stride length, and stride
9
10 276 time variability. Gait velocity is crucial parameter for walking coordination and can be
11
12 277 used as basic factor for the assessment of normal and pathological gait. [25] Gait
13
14 278 variability is a valuable indicator of whole-gait performance and can reflect gait disorder.
15
16 279 Stride length and stride time variability are sensitive measures that related to fall risk in
17
18 280 older people. [26, 27]

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20
21 281 New freezing of gait questionnaire (NFOG-Q) is a reliable tool to detect and assess
22
23 282 the influence and severity of FOG. It consists of the following three parts: (1) part I (item
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25 283 1, score is 0 or 1) detects the presence of FOG and distinguishes if patients are freezers or
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27 284 non-freezers if they have had a FOG experience during the past month; (2) part II (items
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29 285 2–6, score range from 0-9) assesses the severity of FOG according to its duration and
30
31 286 frequency and its common appearance. Item 2 was added to rate the overall frequency of
32
33 287 FOG regardless of the environment; (3) part III (items 7–9, score range from 0-9) assesses
34
35 288 the influence of FOG on daily life, and the total score ranges from 0-28; higher scores
36
37 289 reflects more severe FOG.[28]

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40 290 **Secondary outcome assessment**

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42 291 Functional Gait Assessment (FGA) is a measure of walking balance ability in older adults
43
44 292 and individuals with PD and has shown good reliability and validity in the clinic. FGA
45
46 293 includes under following conditions: forward, backward, with eyes closed, stepping over
47
48 294 obstacles, changing gait speeds, with different head turns, and with a narrow base of
49
50 295 support. The FGA includes 10 total items, with each item scored from 0-3. A higher total
51
52 296 score reflects better balance and walking ability, with a maximum score of 30. [29, 30]

53
54 297 Postural instability and gait disability will be evaluated by the Unified Parkinson's

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4 298 Disease Rating Scale (UPDRS) Part III evaluation. It consists of rigidity measures, gait,
5
6 299 tremor, hand/arm and leg movements (bradykinesia), speech, and facial expressions. The
7
8 300 modified Hoehn and Yahr scale has also been used to evaluate disease severity.[31]

9
10 301 Falls frequency will be reported at the baseline test, during the 12-week training
11
12 302 period, and at 12-week of follow-up. A blind assessor will record fall event based on the
13
14 303 following definition of falling: “a person unintentionally coming to rest on the ground or
15
16 304 other lower level, not occurring as a result of a major intrinsic overwhelming
17
18 305 hazard.”[32] The following approaches will be used to ascertain the fall event: (1)
19
20 306 monthly collection of fall diary, (2) monthly phone interview, and (3) self-report from
21
22 307 each assessment.

23
24 308 Falls and fear of falling will measured with the 14-item Modified Falls Efficacy Scale
25
26 309 (MFES) questionnaire, which reflects self-perceived confidence to engage in activities of
27
28 310 daily living without falling. Each item is scored on a 10-point scale, with a minimum score
29
30 311 of 0 indicating no confidence and a maximum score of 10 indicating full confidence (high
31
32 312 falls efficacy) in performing the tasks without falling. The average score across all 14 items
33
34 313 will be taken, with higher scores indicating greater falls efficacy.[33, 34]

35
36 314 The quality of life will be assessed using the 39-item Parkinson’s Disease
37
38 315 Questionnaire (PDQ39). It is composed of 39 items grouped in eight domains: mobility,
39
40 316 activities of daily living, emotional well-being, stigma, social support, cognition,
41
42 317 communication, and bodily discomfort. Each item ranges from 0 (never) to 4 (always). A
43
44 318 summary index of eight domain scores ranges from 0 to 100, with higher scores
45
46 319 representing worse health related quality of life (HRQoL).[35, 36]

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48 320 The data collected are depicted in Table 2.
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321 **Table 2** Changes over time within and between control and experimental groups

Group	Baseline*	12-weeks*	Follow-up*	Mean difference at 12-weeks**	Mean difference at Follow-up**	F(P Value) Time Effect	F(P Value) Group Effect	F(P Value) Interaction Effect
Primary Outcome								
Stride length (cm)								
Integrated Qigong								
Balance training								
Control								
Gait velocity (cm/sec)								
Integrated Qigong								
Balance training								
Control								
Stride time Vability(CV)								
Integrated Qigong								

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Balance training								
Control								
NFOG								
Integrated Qigong								
Balance training								
Control								
Secondary Outcome								
FGA								
Integrated Qigong								
Balance training								
Control								
MDS-UPDRS Part-III								
Integrated Qigong								
Balance training								
Control								
Total falls,								

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no.								
Integrated Qigong								
Balance training								
Control								
MFES								
Integrated Qigong								
Balance training								
Control								
PDQ-39								
Integrated Qigong								
Balance training								
Control								

322 *Mean values (standard deviation).

323 **Mean difference (standard error).

324 Abbreviations: CV, coefficient variation; NFOG, new freezing of gait questionnaire; FGA, functional gait assessment; MDS-UPDRS

325 Part-III, movement disorder society unified Parkinson’s disease rating scale, motor subscale; MEFS, falls and fear of fall; PDQ-39, the

326 39-item Parkinson’s disease questionnaire.

327 **Patient and Public involvement**

328 Participants will not been involved in the study recruitment. The authors conceived the
329 initial research questions and outcome measures, and modified according to the telephone
330 interview with patients and their guardians by a research assistant. In order to assure the
331 safety and feasibility of the intervention, we invited six patients with mild to moderate
332 Parkinson's disease to learn and practice Integrated Qigong exercise before designing the
333 RCT. The Integrated Qigong movements were revised based on the exercise performance
334 and feedback provided by the participants. The burden of the intervention will assessed
335 by patients and their advisors through face-to-face interview before signing informed
336 consent. The findings of the study will be disseminated to the participants and their
337 guardians.

338

339 **Statistical Analysis**

340 The statistical analysis will be performed using SPSS 22.0 software(IBM Corp, Armonk,
341 New York). Baseline values of demographic differences in intervention groups and control
342 group will be examined using Chi-squared tests. The primary outcome and secondary
343 outcome over time (i.e., baseline, 12 weeks, after 12-week follow-up) will be analyzed by
344 mixed design repeated-measures analyses of variance (RM-ANOVA) for between- and
345 within-group differences. Bonferroni's post hoc test will be applied to compare results
346 where main effects are significant. Data will be expressed as the mean and standard
347 deviation or standard error, and significance will be set at $p < 0.05$. An intention-to-treat
348 analysis will be adopted to deal with missing data, including all participants in the analysis
349 based on the initial group allocation.

350 **DISCUSSION**

351 Medical treatment integrated with exercise therapy is still an indispensable method to

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4 352 manage the motor dysfunction for PD. FOG is common in people with PD which
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6 353 contributes to a protective postural response impairment and increases the risk of falls.
7
8 354 Nevertheless, this balance instability can be improved by extra training.[37] Qigong
9
10 355 exercise synthesizes training in balance, flexibility, neuromuscular coordination, and
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12 356 cognition, it consists of body consciousness, attention, imagination, multiple activities and
13
14 357 goal-oriented training which may benefit to the improvement of improve gait and postural
15
16 358 control, beyond conventional single-mode exercise.[38]

17
18 359 Patients with PD exhibit difficulty in transitions from static to dynamic states.
19
20 360 Transitional activity is a vital component of physical activities, especially gait initiation,
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22 361 turning, and gait termination. Due to the deficiency in postural control, patients generate
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24 362 excessive trunk movement that causes swaying beyond the limits of stability and, thus,
25
26 363 lead to falling. [39] Qigong practice requires the center of gravity moves and changes
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28 364 accompany with the movement of the upper limb, slow movement, body control in space,
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30 365 and shifting body weight in different directions. Thus, Qigong practice can be beneficial
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32 366 to improve the ability to focus on the base of support and postural stability. Moreover,
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34 367 Qigong exercise can enhance core muscle to stress weight-bearing joints and to increase
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36 368 proprioception input of trunk and lower limb joint. Most Qigong movements involve
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38 369 closed-chain exercise of the lower limbs, and contribute to rectifying deficiencies of heel
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40 370 stride and knee extension on gait cycle. [14, 38] In addition, the meditative movement in
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42 371 Qigong exercise can relieve psychological load and consumption, which may benefit for
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44 372 practitioner to reduce muscle tension, and alleviate effect of freezing on stepping
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46 373 forward. [40]

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48 374 Furthermore, Qigong is characterized by slow movement incorporated with
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50 375 moderated breathing, as well as keeping the mind in a state of calm relaxation. The
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52 376 intensity of Qigong is around 1.5 to 2.6 metabolic equivalents (METs) and the average
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54 377 induced maximum heart rate ranges from 43% to 49% of the predicted maximum.[13]

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4 378 Thus, Qigong is a low-intensity physical exercise that has lower risk of muscle strain and
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6 379 overfatigue and is suitable for individuals with PD as a long-term physical exercise
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8 380 program.

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10 381 For a variety of features of gait pattern, whatever muscle stiffness or abnormal
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12 382 postural control, we may consider the global or specific efficacy of Qigong on gait function
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14 383 in PD.[41] We expect that a 12-week Integrated Qigong exercise can create positive
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16 384 therapeutic effects on PD patients with FOG. However, gait deficiency in individuals with
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18 385 PD is a complex syndrome and is associated with neural control regulated by different areas
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20 386 of the brain, particularly the prefrontal lobe and related circuits.[42] In future studies, we
21
22 387 might focus on the mechanism of the different forms of Qigong on the relationship between
23
24 388 brain activities and FOG, and explore whether Qigong exercise is conducive to restoring
25
26 389 brain function and/or preventing brain degeneration. We hope that this trial will
27
28 390 demonstrate that the Integrated Qigong exercise promote the recovery of gait function and
29
30 391 prevention of falls for people with mild and moderate PD. The results of this study may
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32 392 furnish evidence to support the beneficial effects of Qigong exercise on improvement of
33
34 393 walking ability and reduction of fall risk in people with PD. The findings of this study will
35
36 394 provide evidence for a supplemental therapy to manage gait disorder for clinicians and
37
38 395 physical therapist.

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42
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5
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7
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9
10 406 design of the trial, and drafted the manuscript. Guiping Xiao, Kuncheng Jie and Wenhan
11
12 407 Yin participated in trial registration, communication, and monitoring. Yan Jiang and Tian
13
14 408 Wang carried out statistical calculations. Yu Zhang provided medical clearance and
15
16 409 Parkinson's disease stage diagnoses for the participating patients. All authors participated
17
18 410 in revision of the manuscript and approved the final version.

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21 411 **Patient consent** Obtained.

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24 412 **Ethics approval** This work was approved by the ethics committee of science research of
25
26 413 Shanghai University of Sport(protocol number: 2018031).

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527 **Figure Legend**528 **Figure 1** Flow diagram of study design.

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4 **Figure 2** Twelve forms of Integrated Qigong exercise.

5 A: Form one: Xu Exercise

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7 B: Form two: Chui Exercise

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9 C: Form three: Raising the Tiger's Paws

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11 D: Form four: Holding the Hands High with Palms Up to Regulate the Internal Organ

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13 E: Form five: Drawing a Bow

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15 F: Form six: Posing as an Archer Shooting Both Left-and Right-Handed

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17 G: Form seven: Pulling Nine Cows by Their Tails

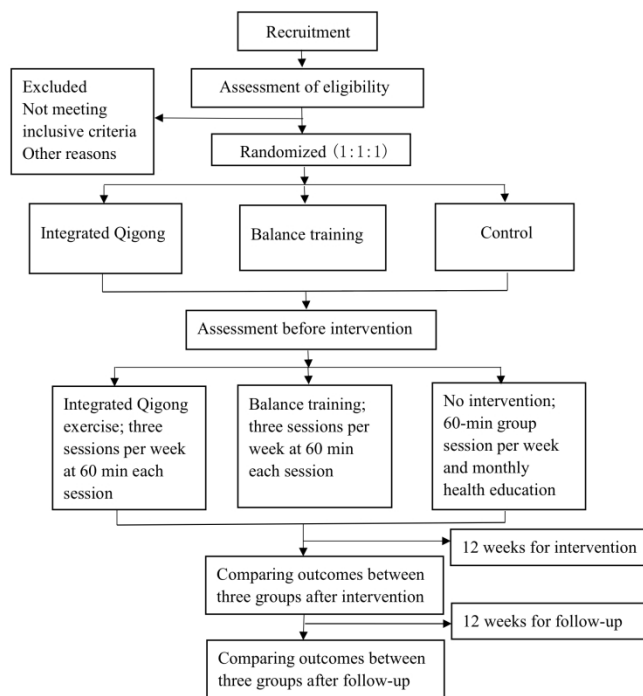
18
19 H: Form eight: Rub Backbone

20
21 I: Form nine: Swaying Like a Bear

22
23 J: Form ten: Picking Fruit

24
25 K: Form eleven: Golden Rooster Heralds the Dawn

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27 L: Form twelve: Flying Like a Bird



45 Flow diagram of study design.

46 209x297mm (300 x 300 DPI)

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Twelve forms of Integrated Qigong exercise.

90x90mm (600 x 600 DPI)



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

Section/item	Item No	Description
Administrative information		
Title(P0)	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration(P2)	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding(P21)	4	Sources and types of financial, material, and other support
Roles and responsibilities (P22)	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	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
	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)
Introduction		
Background and rationale(P3)	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
	6b	Explanation for choice of comparators
Objectives(P3)	7	Specific objectives or hypotheses

1
2 Trial design(P5) 8 Description of trial design including type of trial (eg, parallel group,
3 crossover, factorial, single group), allocation ratio, and framework (eg,
4 superiority, equivalence, noninferiority, exploratory)
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8 **Methods: Participants, interventions, and outcomes**

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10 Study setting(P8) 9 Description of study settings (eg, community clinic, academic hospital)
11 and list of countries where data will be collected. Reference to where
12 list of study sites can be obtained
13

14 Eligibility 10 Inclusion and exclusion criteria for participants. If applicable, eligibility
15 criteria(P6) criteria for study centres and individuals who will perform the
16 interventions (eg, surgeons, psychotherapists)
17

18
19 Interventions 11a Interventions for each group with sufficient detail to allow replication,
20 (P8-10) including how and when they will be administered
21

22 11b Criteria for discontinuing or modifying allocated interventions for a
23 given trial participant (eg, drug dose change in response to harms,
24 participant request, or improving/worsening disease)
25

26 11c Strategies to improve adherence to intervention protocols, and any
27 procedures for monitoring adherence (eg, drug tablet return,
28 laboratory tests)
29

30 11d Relevant concomitant care and interventions that are permitted or
31 prohibited during the trial
32
33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific
35 (P10-15) measurement variable (eg, systolic blood pressure), analysis metric
36 (eg, change from baseline, final value, time to event), method of
37 aggregation (eg, median, proportion), and time point for each
38 outcome. Explanation of the clinical relevance of chosen efficacy and
39 harm outcomes is strongly recommended
40
41

42 Participant 13 Time schedule of enrolment, interventions (including any run-ins and
43 timeline(Figure1) washouts), assessments, and visits for participants. A schematic
44 diagram is highly recommended (see Figure)
45

46 Sample size(P6- 14 Estimated number of participants needed to achieve study objectives
47 7) and how it was determined, including clinical and statistical
48 assumptions supporting any sample size calculations
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51 Recruitment(P5) 15 Strategies for achieving adequate participant enrolment to reach
52 target sample size
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54 **Methods: Assignment of interventions (for controlled trials)**

55 Allocation:
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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation(P7)		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions
8			
9			
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13	(P7)		assigned
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16	(P7)		and who will assign participants to interventions
17			
18	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
19	(masking)		participants, care providers, outcome assessors, data analysts), and
20	(P7)		how
21			
22		17b	If blinded, circumstances under which unblinding is permissible, and
23			procedure for revealing a participant's allocated intervention during
24			the trial
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Methods: Data collection, management, and analysis

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30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods(P10)		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol
36			
37			
38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44	(P19)		range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol
46			
47			
48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
49	methods(P19)		Reference to where other details of the statistical analysis plan can be
50			found, if not in the protocol
51			
52		20b	Methods for any additional analyses (eg, subgroup and adjusted
53			analyses)
54			
55		20c	Definition of analysis population relating to protocol non-adherence
56			(eg, as randomised analysis), and any statistical methods to handle
57			missing data (eg, multiple imputation)
58			
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60			

Methods: Monitoring

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24	Data monitoring (n/a)	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
25 26 27 28 29 30 31 32 33 34	Harms (n/a)	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54	Auditing (n/a)	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Research ethics approval (P5)	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Protocol amendments (n/a)	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Consent or assent (P5)	26a 26b	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Confidentiality (see informed consent)	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Declaration of interests (n/a)	28	Financial and other competing interests for principal investigators for the overall trial and each study site
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Access to data (n/a)	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Ancillary and post-trial care (n/a)	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

1 2 3 4 5 6 7 8 9 10 11 12 13	Dissemination policy (n/a)	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
		31b	Authorship eligibility guidelines and any intended use of professional writers
		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

14 15 16 17 18 19 20 21 22 23 24 25	Informed consent materials (see informed consent)	32	Model consent form and other related documentation given to participants and authorised surrogates
26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Biological specimens (n/a)	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

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

BMJ Open

A study protocol for a single-blind, randomized controlled trial to evaluate clinical effects of an Integrated Qigong exercise intervention on freezing of gait in Parkinson's disease

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Geriatric medicine, Rehabilitation medicine
Keywords:	gait interruption, exercise, neurodegenerative disease, movement disorder

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Manuscripts

1 **A study protocol for a single-blind, randomized controlled trial**
2 **to evaluate clinical effects of an Integrated Qigong exercise**
3 **intervention on freezing of gait in Parkinson's disease**

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20 **Word count:** 6,240

21

23 **ABSTRACT**

24 **Introduction**

25 Qigong exercise offers a potentially safe, low-cost, and effective mind–body rehabilitative
26 intervention for mitigating the problem of gait interruption among Parkinson’s disease (PD)
27 patients who have frequent freezing of gait (FOG) episodes. However, its clinical effects
28 have not been established. This paper describes the trial protocol of evaluating the clinical
29 efficacy of a newly developed Integrated Qigong in improving gait among PD patients with
30 FOG.

31 **Methods and analysis**

32 A single-blind, randomized, controlled trial is designed to compare Integrated Qigong and
33 balance training with an attention control. Participants will be mild to moderate PD patients
34 who experience FOG and are recruited from local communities in Shanghai, China.
35 Participants will be randomly allocated to one of the three groups: Integrated Qigong group,
36 a balance exercise intervention group, or control group. The total number of participants
37 will be 126, and masked assessments will be made at baseline, 12 weeks (end of
38 intervention), and 12-week follow-up. Both Integrated Qigong group and balance training
39 group will receive a group-based exercise intervention that meets three times per week, 60
40 minutes in duration, for 12 weeks. The control group will receive a 60-minute weekly group
41 session and monthly health education. The primary outcome are gait parameters (stride
42 length, gait velocity, stride time variability) and occurrence of FOG. The secondary
43 outcomes are postural instability, walking disability, falling, fear of falling, and quality of
44 life.

45 **Ethics and dissemination** This study has been approved by the ethics committee
46 of Shanghai University of Sport and registered at China Clinical Trial Registry
47 (ChiCTR1800016570). Participants will sign informed consent prior to the participation of
48 the trial. The findings of the study will be published in peer-reviewed academic journals

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4 49 and disseminated to PD support groups, medical community, and media.

5
6 50 **Trial registration** China Clinical Trial Registry, ID: ChiCTR1800016570. Registered on
7
8 51 6 June 2018.

9
10 52 **Keywords** gait interruption, exercise, neurodegenerative disease, movement disorder

11
12 53 **Strengths and limitations of this study**

- 13
14 54 1. The first study that combines commonly practiced Qigong exercises into a single
15
16 55 rehabilitative intervention aims at improving gait outcomes for PD patients with FOG.
17
18 56 2. The findings of the study will inform patients and healthcare providers of an
19
20 57 alternative, potentially low-cost and safe, effective, and easily implementable exercise
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22 58 intervention for treating and managing gait interruption in patients with PD.
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24 59 3. The patients will come from one geographic area which limits the generalizability.
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61 INTRODUCTION

62 Freezing of gait (FOG) is characterized by a sudden and brief episodic absence or marked
63 reduction of forward progression. The syndrome is most common in patients with
64 Parkinson's disease(PD).[1] It is estimated that between 21% and 27% of early stage
65 patients report FOG episode with number increasing up 80% among those in advanced
66 stages.[2-4] Patients with FOG often show difficulty in turning, transferring, walking, and
67 experience and inability to start or continue walking. As the disease progresses, patients
68 with severe FOG develop postural instability and gait dysfunction, causing difficulty in
69 managing daily life and frequent falls, which consequently impact on the quality of life.[5,
70 6]

71 There are multidisciplinary approaches, including pharmacological and surgical based
72 treatment for managing FOG among people with PD. Current research evidence has shown,
73 however, effectiveness of non-pharmacological and rehabilitation based intervention,
74 including physiotherapy, physical exercise, and occupational therapy, for improving
75 abnormal gait in patients with FOG.[7, 8] More researches suggest that various alternative
76 exercise interventions can ameliorate motor symptoms and improve gait. These
77 interventions include low-cost, non-equipment dependent exercises such as Tai Chi, dance,
78 and yoga.[9]

79 In this study, we focus on Health Qigong exercise which is one of traditional Chinese
80 exercises that incorporates meditative movements, breathing patterns, and mental
81 regulation. The exercises are performed in a slow, rhythmic, relaxed manner; features that
82 are conducive to organs.[10,11] Growing evidence supports the health benefits of Health
83 Qigong. A systematic review and meta-analysis indicates that older adults who practice
84 Health Qigong improves balance and postural control and reduces fall risk among
85 individuals with PD.[12] Health Qigong also improves gait speed, stride length, and leg
86 movement ability.[13,14]

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4 87 Qigong consists of various types, including Baduanjin, Liuzijue, Daoyin, 12-step Dao
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6 88 Yin Health Preservation Exercise, Yijinjing, and Wuqinxi. Although each of them has its
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8 89 own training characteristics, they nevertheless share some common features. In general,
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10 90 Qigong integrates both static and dynamic exercises with a great emphasis on regulating
11
12 91 breath, and exercising intrinsic control and mental intent.[15] Exercise of Qigong is
13
14 92 characterized by trunk rotation, bending and extending at waist and movement of limbs
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16 93 both medial-laterally and anterior-posteriorly, all driven by the core of the body.[14,16]
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18 94 Like other techniques such as Tai Ji Quan, Qigong exercise also involves dynamic
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20 95 movements with intermittent stepping and turning. Besides, exercise involves postural
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22 96 demanding movements such as single leg standing and chirographic and manipulative
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24 97 moving postures.[17,18] Furthermore, Qigong exercise requires regulating breathing by
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26 98 engaging in diaphragmatic to expand lung capacity and control upright posture.[19,20]

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28 99 To date, there has been little effort to evaluate the therapeutic effect of combing
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30 100 different types of Qigong exercise on gait in individuals with PD. This paper describes the
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32 101 trial protocol of a newly developed Integrated Qigong intervention that combines seven
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34 102 types of commonly exercised Qigong into a single rehabilitation program for mild to
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36 103 moderate PD patients with FOG. Specifically, we aim to determine the therapeutic effect
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38 104 of the Integrated Qigong intervention on gait. We hypothesize that, compared to control
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40 105 group, both Integrated Qigong and conventional balance training intervention will be
41
42 106 clinically more effective in improving the primary outcomes of gait.

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47 48 49 50 109 **METHODS**

51 52 53 110 **Study design**

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55 111 The study is designed as a prospective, single-blind randomized controlled trial.

112 **Design and procedures**

113 We will recruit participants from Shanghai, China by means of the neurology department
114 of the local hospital and TV programs during the same recruitment period. To reduce
115 potential expectation bias and confirm eligibility, a research assistant will make telephone
116 contact with those referred by a neurologist and follow up with interested participants.
117 Participants will be informed that they will be randomly assigned to three groups. The
118 integrated Qigong exercise group will engage in training program that combines seven
119 types of commonly exercised Qigong. The balance training group will perform static and
120 dynamic postural control training. The two intervention groups will receive the guidance
121 of instructor, and the control group will receive weekly group session and monthly health
122 education. The total intervention period will be 12 weeks, and will occur simultaneously
123 for all participants. The primary and secondary outcomes will be assessed at baseline (pre-
124 intervention), 12 weeks (end of intervention) and 12-week follow-up (see figure 1).
125 Potential eligible participants who satisfy initial inclusion criteria will arrange a two-hour
126 visit at our research laboratory and register their personal information. The trial protocol
127 has been approved by the ethics committee of Shanghai University of Sport. All
128 participants who meet the inclusion and exclusion criteria need to sign informed consent
129 prior to the study. The protocol is registered as a China Clinical Trial (ID:
130 ChiCTR1800016570).

131 **Participants**

132 Inclusion criteria

133 (1) PD patients diagnosed according to the clinical diagnostic of UK Brain Bank criteria;
134 (2) age between 40 and 80 years old; (3) Hoehn & Yahr scale of 1–3; (4) item three of the
135 New Freezing of Gait Questionnaire (NFOGQ) scored ≥ 1 ; (5) Mini-Mental State
136 Examination (MMSE) score >24 ; (6) ability to walk independently.

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4 137 Exclusion criteria

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6 138 (1) Participation in Qigong exercise during the last year; (2) other diseases that could
7
8 139 interfere with conduct of the study protocol such as cardiopulmonary disease, liver and
9
10 140 kidney disease, musculoskeletal dysfunction, or cancer; (3) severe cognitive, visual or
11
12 141 auditory impairment; (4) unstable medication; (5) deep brain stimulation.
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17 143 **Sample size calculation**

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19 144 A statistical analysis was conducted for sample size estimation using G*power 3.1 (Franz
20
21 145 Faul, Universita Kiel, Germany). The study was powered to detect a between-group
22
23 146 difference in primary gait outcome measures between Qigong exercise group and balance
24
25 147 training group relative to the attention control group. Because there was no a priori
26
27 148 hypothesis formulated between the two active interventions (Qigong exercise and balance
28
29 149 training), the study was not powered on these two conditions. Due to the lack of informed
30
31 150 preliminary data and empirical evidence on the effects of Qigong exercise, we
32
33 151 approximated the effect size in our power calculations using estimated from the published
34
35 152 studies that compared Qigong exercise with a control condition on gait (i.e., gait speed,
36
37 153 freezing of gait, and mobility).[13,14] In general, these studies, with an intervention length
38
39 154 ranging from 10 weeks to 24 weeks, have shown a weak intervention effect, with effect
40
41 155 sizes ranging from no effect to small-to-moderate effects. On the basis of these
42
43 156 observations, a conservative approach was taken. Specially, we used a small effect size
44
45 157 ($\eta^2=0.01$) based on the partial eta squared estimate within the ANOVA framework.[21]
46
47 158 Our initial power estimates indicated that, in a mixed-effect repeated measures design with
48
49 159 a between-subject factor (Integrated Qigong, balance training, control), and a within-
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51 160 subject factor (baseline, 12 weeks) and a correlation of 0.08 on the repeated measures, a
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53 161 sample size of 99 subjects would be required to achieve an 80% power at an 0.05 error rate.
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4 162 To be more conservative, we estimated the sample sizes based on a range of small sizes
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6 163 ($f=0.08, f=0.10, f=0.12$). The sample sizes generated from these calculations were averaged
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8 164 to arrive at a total of 107 subjects. With an anticipated 15% attrition rate, a final enrollment
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10 165 number of 126 (42 in each group) was set for the study to detect a difference in gait
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12 166 outcomes between Integrated Qigong and balance training relative to the attention control
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14 167 group.

168 **Randomization and blinding**

169 The study design will utilize a single blinded randomized controlled trial. Two trained
170 assessors will be blinded to group allocation and will not participate in the intervention.
171 We will apply the stratified random sampling method by stage of the disease (H&Y Stage).
172 Using computer generated random number sequencing (STATA 12.0, StataCorp LP, Texas,
173 USA) in a ratio of 1:1:1, a random number will be placed in a sealed envelope, and
174 participants will be allocated randomly to Integrated Qigong group, balance training group,
175 or control group by extracting the random number from the envelope. Participants will be
176 reassessed for baseline measurements on another day. This study is not amenable to
177 blinding to participants of their designated experimental groups because the interventional
178 exercises they perform will reveal their group allocation.

179

180

181 **Intervention**

182 The participants in all groups will follow their regular medication scheme during the study
183 period. Both Integrated Qigong group and balance training group will receive group-based
184 exercise intervention at the sports science laboratory of Shanghai University of Sport. The
185 group size is 10 to 15 people in order to provide sufficient instructional attention to each
186 participant. Two trained instructors will guide the participants to perform the exercises of

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4 187 their own group. The two interventional groups will perform three weekly sessions of 60
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6 188 minutes per session for 12 consecutive weeks. Each session will consist of 10 minutes of
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8 189 warm-up, 40 minutes of core exercises, 5 minutes of break intervals, and 5 minutes of cool-
9
10 190 down. The heart rates of the participants will be monitored by Polar-team² (Polar Electro,
11
12 191 Finland) during training in order to progressively control the intensity. Participants in the
13
14 192 interventional groups will be required to not perform any additional in-home exercises
15
16 193 throughout the 12 weeks of training.

194 Integrated Qigong exercise group

195 The Integrated Qigong protocol will consist of twelve-forms of exercise, with selected
196 movements from the Health Qigong exercise guidelines organized and compiled by the
197 China Qigong Management Center. The Integrated Qigong exercise will emphasize
198 dynamic postural control and body weight shift stepping with lateral-medial and anterior-
199 posterior movements, body symmetry pulling across up-down and left-right axes, hand-
200 eye coordination movement. The twelve forms of exercise have been previously
201 documented [22] and can be seen in Figure 2.

202 During the initial 2to 3 weeks, training will mainly emphasize learning and
203 practicing two or three forms through multiple repetitions along with review of
204 previously learned movements. The practice in each session concentrate on upper and
205 lower limbs in place, trunk rotation, as well as stepping in different directions (i.e.,
206 forward, backward, sideways, diagonal). Participants will be requested to perform
207 personalized movement requirements based on functional level. The range of motion of
208 each movement will be reduced for participants with rigidity. The pace of movement will
209 be decreased for participants with bradykinesia. For participants experiencing FOG
210 episode during training, they will be instructed to perform transferring and stepping while
211 maintaining postural stability. The intensity, difficulty of movement, time, and frequency

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4 212 will be adjusted to the demands of each participant. The later weeks will concentrate on
5
6 213 improving balance, locomotion, and action consistency. Participants will practice each
7
8 214 movement with six repetitions, and natural breathing will be incorporated into the
9
10 215 movement routine. Participants will be guided to perform the entire range of movement
11
12 216 in which they feel safe.

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16 17 218 Balance training group

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19 219 Each training session will start with a 10 minutes warm-up consisting of breathing exercise,
20
21 220 slow walking, and range-of-motion exercises. The 40-minute balance training will include
22
23 221 a short resting time, and the training program will consist of the following: 1) static balance
24
25 222 training: standing on unstable surfaces to maintain postural control and progression to
26
27 223 weight shifting; 2) dynamic balance training: postural control in standing position while
28
29 224 adding upper limb and trunk movements; 3) balance strategy exercise: focus on hip
30
31 225 strategy while maintaining ankle strategy and stepping strategy under interference in
32
33 226 different directions; 4) adaptation of varying base of support, and standing in a narrow
34
35 227 space and on uneven surface; [23] and 5) walk integrated balance training: walk in a straight
36
37 228 line, walk on a soft blanket, and sideways. The training will progress from simple to
38
39 229 complex, static to dynamic, low to high center of gravity, wide to narrow the base of
40
41 230 support, and will continue to raise challenges in regard to flexibility, stability and range of
42
43 231 movement. The end of training will include a 5-minute cool-down session of limb ROM
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45 232 movements, sustained stretching, and relaxing.

47 48 233 Control group

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50 234 The control group will be instructed to maintain their formal lifestyle and not to engage in
51
52 235 any other form of intensive training. The participants in the control group will join one 60-
53
54 236 min group session per week, which will consist of a 30-min lecture, 20-min discussion, and

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4 237 will be followed by a 10-min question and answer session. Participants in the control group
5
6 238 will receive health education every four weeks over the 12-week interventional period. The
7
8 239 health education will involve information for PD-related treatments and prevention such as
9
10 240 modalities of exercise, regimens, fall prevention, and nutrition. Participants will receive a
11
12 241 brochure of health education and will have follow-up by telephone twice per month, which
13
14 242 will involve discussion of physical activity, progression of disease, health status, and
15
16 243 psychological status.

17
18 244 All participants will maintain diaries to record their exercise and fall events every day
19
20 245 throughout the trial, including both in the laboratory and at home. The participants in the
21
22 246 Integrated Qigong exercise group and balance training group will perform the exercises at
23
24 247 the “on” stage in the morning.

27 248 **Outcome measures**

28
29 249 All measurements will be performed at baseline, 12 weeks (end of intervention), and 12
30
31 250 weeks following the completion of the intervention. The measurements will be conducted
32
33 251 by two trained assessors and will be videotaped by a third assessor. All assessors will be
34
35 252 blinded to the participant’s group allocation and time of assessment.

38 253 **Participants characteristics**

39
40 254 Demographic and health characteristics of participants will be collected at baseline to
41
42 255 describe the sample, compare conditions, and investigate characteristics associated with
43
44 256 outcomes. These characteristics will include age, gender, education, age at disease onset,
45
46 257 disease duration, cognition ability, health status, medication dose, resting blood pressure,
47
48 258 body mass (kg/m^2), height (cm), family situation and physical performance. Blood pressure
49
50 259 will be measured with the use of an automated device (Omron HealthCare). Body mass
51
52 260 and height will be assessed with digital scales (Weighing scale & Meter) Physical
53
54 261 performance will be measured by the scores from self-reported habitual physical activity

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4 262 scale. (See Table 1)
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264 **Table 1** Demographic and clinical characteristics of the study participants*

	Integrated Qigong (N=)	Balance Training (N=)	Control (N=)
Age—yr			
Gender—(male% : female%)			
Body-mass index ^a —kg/m ²			
Height—cm			
Hoehn and Yahr stage—no. (%)			
1-1.5			
2-2.5			
≥3			
Age of onset—yr			
Duration of disease—yr			
Score of MoCA(/30) ^b			
Antiparkinsonian medications taken—no.			
Levodopa or carbidopa			
Pramipexole or ropinirole			
Other			
Self-reported health status ^c —no. (%)			
Poor or fair			
Good			
Very good or excellent			
Family situation-no. (%)			
Living along			
Living with husband/wife			
Living with husband/wife and children			
Score for Self-reported habitual physical activity ^d			
Falls in previous 6 months—no.			

265 * Mean values (standard deviation). The chi-square test is used for categorical variables,
 266 and one-way analysis of variance for continuous variables.

267 ^a The body-mass index is the weight in kilograms divided by the square of the height in

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4 268 meters.

5
6 269 ^b MoCA, Montreal Cognitive Assessment.

7
8 270 ^c Self-reported health status, included cardiovascular disease, lung disease, osteoporosis,
9
10 271 arthritis, liver and kidney disease, low back pain, and cancer; the number of conditions per
11
12 272 participant ranged from 0 to 9.

13
14 273 ^d This is measured by the Physical Activity Scale for the Elderly, [24] with higher scores
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16 274 indicating higher levels of habitual physical activity.
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4 **275 Primary outcome assessment**

5
6 276 Gait will be analyzed using a 7-m-long instrumented computerized walkway (GAIRite,
7
8 277 CIR, System Inc., Franklin, NJ), and will include gait velocity, stride length, and stride
9
10 278 time variability. Gait velocity is crucial parameter for walking coordination and can be
11
12 279 used as basic factor for the assessment of normal and pathological gait. [25] Gait
13
14 280 variability is a valuable indicator of whole-gait performance and can reflect gait
15
16 281 disorders. Stride length and stride time variability are sensitive measures that relate to fall
17
18 282 risk in older people. [26, 27]

19
20 283 New freezing of gait questionnaire (NFOG-Q) is a reliable tool to detect and assess
21
22 284 the influence and severity of FOG. It consists of the following three parts: (1) part I (item
23
24 285 1, score is 0 or 1) detects the presence of FOG and distinguishes if patients are freezers or
25
26 286 non-freezers if they have had a FOG experience during the past month; (2) part II (items
27
28 287 2–6, score range from 0-9) assesses the severity of FOG according to its duration and
29
30 288 frequency and its common appearance. Item 2 was added to rate the overall frequency of
31
32 289 FOG regardless of the environment; (3) part III (items 7–9, score range from 0-9) assesses
33
34 290 the influence of FOG on daily life, and the total score ranges from 0-28; higher scores
35
36 291 reflect more severe FOG.[28]

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39
40 **292 Secondary outcome assessment**

41
42 293 Functional Gait Assessment (FGA) is a measure of walking balance ability in older adults
43
44 294 and individuals with PD and has shown good reliability and validity in the clinic. FGA
45
46 295 includes under following conditions: forward, backward, with eyes closed, stepping over
47
48 296 obstacles, changing gait speeds, with different head turns, and a narrow base of support.
49
50 297 The FGA includes 10 total items, with each item scored from 0-3. A higher total score
51
52 298 reflects better balance and walking ability, with a maximum score of 30. [29, 30]

53
54 299 Postural instability and gait disability will be evaluated by the Unified Parkinson's

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4 300 Disease Rating Scale (UPDRS) Part III evaluation. It consists of rigidity measures, gait,
5
6 301 tremor, hand/arm and leg movements (bradykinesia), speech, and facial expressions. The
7
8 302 modified Hoehn and Yahr scale has also been used to evaluate disease severity.[31]

9
10 303 The balance performance will be measured by Mini-Balance Evaluation Systems Test
11
12 304 (Mini-BESTest), consisting of 14 items from 4 different balance control systems:
13
14 305 anticipatory postural adjustments, reactive postural control, sensory orientation, and
15
16 306 dynamic gait. Each item is evaluated on a 3-point scale from 0 to 2 and the total score
17
18 307 ranges from 0 to 28, with a higher score indicating better balance performance.[32,33]

19
20 308 Falling frequency will be reported at the baseline test, during the 12-week training
21
22 309 period, and at a 12-week follow-up. A blind assessor will record fall event based on the
23
24 310 following definition of falling: “a person unintentionally coming to rest on the ground or
25
26 311 other lower level, not occurring as a result of a major intrinsic overwhelming
27
28 312 hazard.”[34] The following approaches will be used to ascertain the fall event: (1)
29
30 313 monthly collection of fall diary, (2) monthly phone interview, and (3) self-report from
31
32 314 each assessment.

33
34 315 Falls and fear of falling will be measured with the 14-item Modified Falls Efficacy Scale
35
36 316 (MFES) questionnaire, which reflects self-perceived confidence to engage in activities of
37
38 317 daily living without falling. Each item is scored on a 10-point scale, with a minimum score
39
40 318 of 0 indicating no confidence and a maximum score of 10 indicating full confidence (high
41
42 319 falls efficacy) in performing the tasks without falling. The average score across all 14 items
43
44 320 will be taken, with higher scores indicating greater falls efficacy.[35,36]

45
46 321 The quality of life will be assessed using the 39-item Parkinson’s Disease
47
48 322 Questionnaire (PDQ39). It is composed of 39 items grouped in eight domains: mobility,
49
50 323 activities of daily living, emotional well-being, stigma, social support, cognition,
51
52 324 communication, and bodily discomfort. Each item ranges from 0 (never) to 4 (always). A
53
54 325 summary index of eight domain scores ranges from 0 to 100, with higher scores

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326 representing worse health related quality of life (HRQoL).[37,38]

327 The data collected are depicted in Table 2.

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328 **Table 2** Changes over time within and between control and experimental groups

Group	Baseline*	12-weeks*	Follow-up*	Mean difference at 12-weeks**	Mean difference at Follow-up**	<i>F(P Value)</i> Time Effect	<i>F(P Value)</i> Group Effect	<i>F(P Value)</i> Interaction Effect
Primary Outcome								
Stride length (cm)								
Integrated Qigong								
Balance training								
Control								
Gait velocity (cm/sec)								
Integrated Qigong								
Balance training								
Control								
Stride time Variability (CV)								
Integrated Qigong								
Balance training								
Control								
NFOG								
Integrated Qigong								
Balance training								
Control								
Secondary								

1								
2								
3								
4	Outcome							
5	FGA							
6	Integrated							
7	Qigong							
8	Balance							
9	training							
10	Control							
11								
12								
13	MDS-							
14	UPDRS							
15	Part-III							
16								
17	Integrated							
18	Qigong							
19	Balance							
20	training							
21	Control							
22								
23								
24	Mini-							
25	BESTest							
26								
27	Integrated							
28	Qigong							
29	Balance							
30	training							
31	Control							
32								
33								
34	Total falls,							
35	no.							
36								
37	Integrated							
38	Qigong							
39	Balance							
40	training							
41	Control							
42								
43								
44	MFES							
45	Integrated							
46	Qigong							
47	Balance							
48	training							
49	Control							
50								
51								
52	PDQ-39							
53	Integrated							
54	Qigong							
55								
56								
57								
58								
59								
60								

Balance training								
Control								

329 *Mean values (standard deviation).

330 **Mean difference (standard error).

331 Abbreviations: CV, coefficient variation; NFOG, new freezing of gait questionnaire; FGA,
 332 functional gait assessment; MDS-UPDRS Part-III, movement disorder society unified
 333 Parkinson's disease rating scale, motor subscale; Mini-BESTest, Mini-Balance Evaluation
 334 Systems Test; MEFS, falls and fear of fall; PDQ-39, the 39-item Parkinson's disease
 335 questionnaire.

336 **Patient and Public involvement**

337 Participants will not been involved in the study recruitment. The authors conceived the
 338 initial research questions and outcome measures, and modified according to the telephone
 339 interviews with patients and their guardians by a research assistant. In order to assure the
 340 safety and feasibility of the intervention, we invited six patients with mild to moderate
 341 PD to learn and practice Integrated Qigong exercise before designing the RCT. Integrated
 342 Qigong movements were revised based on the exercise performance and feedback
 343 provided by the participants. The burden of the intervention will assessed by patients and
 344 their advisors through face-to-face interviews before signing informed consent. The
 345 findings of the study will be disseminated to the participants and their guardians.

346

347 **Statistical Analysis**

348 The statistical analysis will be performed using SPSS 22.0 software (IBM Corp,
 349 Armonk, New York). Baseline values of demographic differences in interventional
 350 groups and the control group will be examined using Chi-squared tests. The primary
 351 outcomes and secondary outcomes over time (i.e., baseline, 12 weeks, after 12-week

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4 352 follow-up) will be analyzed by mixed design repeated-measures analyses of variance
5
6 353 (RM-ANOVA) for between- and within-group differences. Bonferroni's post hoc test will
7
8 354 be applied to compare results where main effects are significant. Data will be expressed
9
10 355 as the mean and standard deviation or standard error, and significance will be set at $p <$
11
12 356 0.05. An intention-to-treat analysis will be adopted to deal with missing data, including
13
14 357 all participants in the analysis based on the initial group allocation. A linear mixed model
15
16 358 approach (a direct likelihood estimation method) will be applied to analyze all continuous
17
18 359 as value is missing at random. All analysis will include H&Y and MoCA as covariates, as
19
20 360 these variables may differ significantly between groups.

21 22 23 361 **DISCUSSION**

24
25 362 Medical treatment integrated with exercise therapy is still an indispensable method to
26
27 363 manage the motor dysfunction for PD. FOG is common in people with PD which
28
29 364 contributes to a protective postural response impairment and increases the risk of falls.
30
31 365 Nevertheless, this balance instability can be improved by extra training.[39] Qigong
32
33 366 exercise synthesizes training in balance, flexibility, neuromuscular coordination, and
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35 367 cognition, it consists of body consciousness, attention, imagination, multiple activities and
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37 368 goal-oriented training which may benefit the improvement of gait and postural control,
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39 369 beyond conventional single-mode exercise.[40]

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42 370 Patients with PD exhibit difficulty in transitions from static to dynamic states.
43
44 371 Transitional activity is a vital component of physical activities, especially gait initiation,
45
46 372 turning, and gait termination. Due to the deficiency in postural control, patients generate
47
48 373 excessive trunk movement that causes swaying beyond the limits of stability. [41]
49
50 374 Moreover, people with PD often manifest impaired protective postural response and
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52 375 postural adjustment in preparation for stepping, thus, increasing the risk of fall.[42,43]
53
54 376 Qigong practice requires that the center of gravity moves and changes to accompany with

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4 377 the movement of the upper limb, slow movement, body control in space, and shifting
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6 378 body weight in different directions. Hence, Qigong practice can be beneficial to improve
7
8 379 the ability to focus on the base of support and postural stability, as well as enhance core
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10 380 muscle to stress weight-bearing joints and to increase proprioception input of trunk and
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12 381 lower limb joints.

13
14 382 Most Qigong movements involve closed-chain exercise of the lower limbs, and
15
16 383 contribute to rectifying deficiencies of heel stride and knee extension on gait cycle. [14,
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18 384 40] In addition, the meditative movement in Qigong exercise can relieve psychological
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20 385 load and consumption, which may benefit for practitioner to reduce muscle tension, and
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22 386 alleviate effect of freezing on stepping forward. [44] Furthermore, Qigong is
23
24 387 characterized by slow movement incorporated with moderated breathing, as well as
25
26 388 keeping the mind in a state of calm relaxation. The intensity of Qigong is around 1.5 to
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28 389 2.6 metabolic equivalents (METs) and the average induced maximum heart rate ranges
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30 390 from 43% to 49% of the predicted maximum.[13] Therefore, Qigong is a low-intensity
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32 391 physical exercise that has lower risk of muscle strain and overfatigue and is suitable for
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34 392 individuals with PD as a long-term physical exercise program.

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36 393 There are several limitations in this study. First, it is difficult to achieve a blinded
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38 394 intervention for this study because exercise served as an intervention is widely open to
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40 395 the participants. Second, participants are limited to people with mild-to-moderate PD.
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42 396 Therefore, it is unclear whether the results would be valid for people with advanced PD.
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44 397 Third, the study patients will come from the same geographic area which limits the
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46 398 generalizability and so that it is not a multicenter trial.

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48 399 For a variety of features of gait pattern, whatever muscle stiffness or abnormal
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50 400 postural control, we may consider the global or specific efficacy of Qigong on gait function
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52 401 in PD.[45] We expect that a 12-week Integrated Qigong exercise can establish positive
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54 402 therapeutic effects on PD patients with FOG. However, gait deficiency in individuals with

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4 403 PD is a complex syndrome and is associated with neural control regulated by different areas
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6 404 of the brain, particularly the prefrontal lobe and related circuits.[46] In future studies, we
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8 405 might focus on the mechanism of the different forms of Qigong on the relationship between
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10 406 brain activities and FOG, and explore whether Qigong exercise is conducive to restoring
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12 407 brain function and/or preventing brain degeneration. We hope that this trial will
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14 408 demonstrate that the Integrated Qigong exercise promote the recovery of gait function and
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16 409 prevention of falls for people with mild and moderate PD. The results of this study may
17
18 410 furnish evidence to support the beneficial effects of Qigong exercise on improvement of
19
20 411 walking ability and reduction of fall risk in people with PD. The findings of this study will
21
22 412 provide evidence for a supplemental therapy to manage gait disorder for clinicians and
23
24 413 physical therapist.

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28
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30
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34
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38
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40
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42
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50 425 **Contributors** Zhenlan Li, Jie Zhuang and Zheng Wang conceived the conception and
51
52 426 design of the trial, and drafted the manuscript. Guiping Xiao, Kuncheng Jie and Wenhan
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54 427 Yin participated in trial registration, communication, and monitoring. Yan Jiang and Tian

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4 428 Wang carried out statistical calculations. Yu Zhang provided medical clearance and
5
6 429 Parkinson's disease stage diagnoses for the participating patients. All authors participated
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8 430 in revision of the manuscript and approved the final version.
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10 431 **Patient consent** Obtained.
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13 432 **Ethics approval** This work was approved by the ethics committee of science research of
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15 433 Shanghai University of Sport (protocol number: 2018031).
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17 434 **Provenance and peer review** Not commissioned;externally peer reviewed
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12 556 **Figure Legend**

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14 557 **Figure 1** Flow diagram of study design.

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For peer review only

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4 **Figure 2** Twelve forms of Integrated Qigong exercise.

5 A: Form one: Xu Exercise

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7 B: Form two: Chui Exercise

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9 C: Form three: Raising the Tiger's Paws

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11 D: Form four: Holding the Hands High with Palms Up to Regulate the Internal Organ

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13 E: Form five: Drawing a Bow

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15 F: Form six: Posing as an Archer Shooting Both Left-and Right-Handed

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17 G: Form seven: Pulling Nine Cows by Their Tails

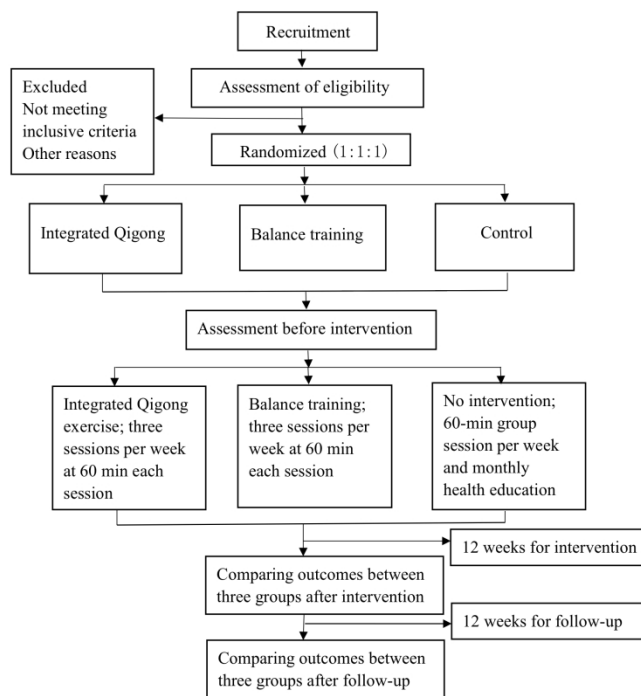
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19 H: Form eight: Rub Backbone

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21 I: Form nine: Swaying Like a Bear

22
23 J: Form ten: Picking Fruit

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25 K: Form eleven: Golden Rooster Heralds the Dawn

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27 L: Form twelve: Flying Like a Bird



Flow diagram of study design.

209x297mm (300 x 300 DPI)

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Twelve forms of Integrated Qigong exercise.

90x90mm (600 x 600 DPI)



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

Section/item	Item No	Description
Administrative information		
Title(P0)	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration(P2)	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding(P21)	4	Sources and types of financial, material, and other support
Roles and responsibilities (P21-22)	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	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
	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)
Introduction		
Background and rationale(P3)	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
	6b	Explanation for choice of comparators
Objectives(P4)	7	Specific objectives or hypotheses

1
2 Trial design(P5) 8 Description of trial design including type of trial (eg, parallel group,
3 crossover, factorial, single group), allocation ratio, and framework (eg,
4 superiority, equivalence, noninferiority, exploratory)
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8 **Methods: Participants, interventions, and outcomes**

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10 Study setting(P7) 9 Description of study settings (eg, community clinic, academic hospital)
11 and list of countries where data will be collected. Reference to where
12 list of study sites can be obtained
13

14 Eligibility 10 Inclusion and exclusion criteria for participants. If applicable, eligibility
15 criteria(P5-6) criteria for study centres and individuals who will perform the
16 interventions (eg, surgeons, psychotherapists)
17

18
19 Interventions 11a Interventions for each group with sufficient detail to allow replication,
20 (P7-10) including how and when they will be administered
21

22 11b Criteria for discontinuing or modifying allocated interventions for a
23 given trial participant (eg, drug dose change in response to harms,
24 participant request, or improving/worsening disease)
25

26 11c Strategies to improve adherence to intervention protocols, and any
27 procedures for monitoring adherence (eg, drug tablet return,
28 laboratory tests)
29

30 11d Relevant concomitant care and interventions that are permitted or
31 prohibited during the trial
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33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific
35 (P10-15) measurement variable (eg, systolic blood pressure), analysis metric
36 (eg, change from baseline, final value, time to event), method of
37 aggregation (eg, median, proportion), and time point for each
38 outcome. Explanation of the clinical relevance of chosen efficacy and
39 harm outcomes is strongly recommended
40
41

42 Participant 13 Time schedule of enrolment, interventions (including any run-ins and
43 timeline(Figure1) washouts), assessments, and visits for participants. A schematic
44 diagram is highly recommended (see Figure)
45

46 Sample size(P6- 14 Estimated number of participants needed to achieve study objectives
47 7) and how it was determined, including clinical and statistical
48 assumptions supporting any sample size calculations
49

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51 Recruitment(P5) 15 Strategies for achieving adequate participant enrolment to reach
52 target sample size
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54 **Methods: Assignment of interventions (for controlled trials)**

55 Allocation:
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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation(P7)		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions
8			
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10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13	(P7)		assigned
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16	(P7)		and who will assign participants to interventions
17			
18	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
19	(masking)		participants, care providers, outcome assessors, data analysts), and
20	(P7)		how
21			
22		17b	If blinded, circumstances under which unblinding is permissible, and
23			procedure for revealing a participant's allocated intervention during
24			the trial
25			
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Methods: Data collection, management, and analysis

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30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods(P10)		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol
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37			
38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44	(P19-20)		range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol
46			
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48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
49	methods(P19-20)		Reference to where other details of the statistical analysis plan can be
50			found, if not in the protocol
51			
52		20b	Methods for any additional analyses (eg, subgroup and adjusted
53			analyses)
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55		20c	Definition of analysis population relating to protocol non-adherence
56			(eg, as randomised analysis), and any statistical methods to handle
57			missing data (eg, multiple imputation)
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Methods: Monitoring

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24	Data monitoring (n/a)	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Harms (n/a)	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
	Auditing (n/a)	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Research ethics approval (P5)	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
	Protocol amendments (n/a)	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
	Consent or assent (P5)	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
	Confidentiality (see informed consent)	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
	Declaration of interests (n/a)	28	Financial and other competing interests for principal investigators for the overall trial and each study site
	Access to data (n/a)	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
	Ancillary and post-trial care (n/a)	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

1 2 3 4 5 6 7 8 9 10 11 12 13	Dissemination policy (n/a)	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
14 15 16 17 18 19 20 21 22 23 24 25	Appendices	31b	Authorship eligibility guidelines and any intended use of professional writers
26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Informed consent materials (see informed consent)	32	Model consent form and other related documentation given to participants and authorised surrogates
	Biological specimens (n/a)	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

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

BMJ Open

A study protocol for a single-blind, randomized controlled trial to evaluate clinical effects of an Integrated Qigong exercise intervention on freezing of gait in Parkinson's disease

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1 **A study protocol for a single-blind, randomized controlled trial**
2 **to evaluate clinical effects of an Integrated Qigong exercise**
3 **intervention on freezing of gait in Parkinson's disease**

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21

23 **ABSTRACT**

24 **Introduction**

25 Qigong exercise offers a potentially safe, low-cost, and effective mind–body rehabilitative
26 intervention for mitigating the problem of gait interruption among Parkinson’s disease (PD)
27 patients who have frequent freezing of gait (FOG) episodes. However, its clinical effects
28 have not been established. This paper describes the trial protocol of evaluating the clinical
29 efficacy of a newly developed Integrated Qigong in improving gait among PD patients with
30 FOG.

31 **Methods and analysis**

32 A single-blind, randomized, controlled trial is designed to compare Integrated Qigong and
33 balance training with an attention control. Participants will be mild to moderate PD patients
34 who experience FOG and are recruited from local communities in Shanghai, China.
35 Participants will be randomly allocated to one of the three groups: Integrated Qigong group,
36 a balance exercise intervention group, or control group. The total number of participants
37 will be 126, and masked assessments will be made at baseline, 12 weeks (end of
38 intervention), and 12-week follow-up. Both Integrated Qigong group and balance training
39 group will receive a group-based exercise intervention that meets three times per week, 60
40 minutes in duration, for 12 weeks. The control group will receive a 60-minute weekly group
41 session and monthly health education. The primary outcome are gait parameters (stride
42 length, gait velocity, stride time variability) and occurrence of FOG. The secondary
43 outcomes are postural instability, walking disability, falling, fear of falling, and quality of
44 life.

45 **Ethics and dissemination** This study has been approved by the ethics committee
46 of Shanghai University of Sport and registered at China Clinical Trial Registry
47 (ChiCTR1800016570). Participants will sign informed consent prior to the participation of
48 the trial. The findings of the study will be published in peer-reviewed academic journals

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4 49 and disseminated to PD support groups, medical community, and media.

5
6 50 **Trial registration** China Clinical Trial Registry, ID: ChiCTR1800016570. Registered on
7
8 51 6 June 2018.

9
10 52 **Keywords** gait interruption, exercise, neurodegenerative disease, movement disorder

11
12 53 **Strengths and limitations of this study**

- 13
14 54 1. The first study that combines commonly practiced Qigong exercises into a single
15
16 55 rehabilitative intervention aims at improving gait outcomes for PD patients with FOG.
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18 56 2. The findings of the study will inform patients and healthcare providers of an
19
20 57 alternative, potentially low-cost and safe, effective, and easily implementable exercise
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22 58 intervention for treating and managing gait interruption in patients with PD.
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24 59 3. The patients will come from one geographic area which limits the generalizability.
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61 INTRODUCTION

62 Freezing of gait (FOG) is characterized by a sudden and brief episodic absence or marked
63 reduction of forward progression. The syndrome is most common in patients with
64 Parkinson's disease(PD).[1] It is estimated that between 21% and 27% of early stage
65 patients report FOG episode with number increasing up 80% among those in advanced
66 stages.[2-4] Patients with FOG often show difficulty in turning, transferring, walking, and
67 experience and inability to start or continue walking. As the disease progresses, patients
68 with severe FOG develop postural instability and gait dysfunction, causing difficulty in
69 managing daily life and frequent falls, which consequently impact on the quality of life.[5,
70 6]

71 There are multidisciplinary approaches, including pharmacological and surgical based
72 treatment for managing FOG among people with PD. Current research evidence has shown,
73 however, effectiveness of non-pharmacological and rehabilitation based intervention,
74 including physiotherapy, physical exercise, and occupational therapy, for improving
75 abnormal gait in patients with FOG.[7, 8] More researches suggest that various alternative
76 exercise interventions can ameliorate motor symptoms and improve gait. These
77 interventions include low-cost, non-equipment dependent exercises such as Tai Chi, dance,
78 and yoga.[9]

79 In this study, we focus on Health Qigong exercise which is one of traditional Chinese
80 exercises that incorporates meditative movements, breathing patterns, and mental
81 regulation. The exercises are performed in a slow, rhythmic, relaxed manner; features that
82 are conducive to organs.[10,11] Growing evidence supports the health benefits of Health
83 Qigong. A systematic review and meta-analysis indicates that older adults who practice
84 Health Qigong improves balance and postural control and reduces fall risk among
85 individuals with PD.[12] Health Qigong also improves gait speed, stride length, and leg
86 movement ability.[13,14]

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4 87 Qigong consists of various types, including Baduanjin, Liuzijue, Daoyin, 12-step Dao
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6 88 Yin Health Preservation Exercise, Yijinjing, and Wuqinxi. Although each of them has its
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8 89 own training characteristics, they nevertheless share some common features. In general,
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10 90 Qigong integrates both static and dynamic exercises with a great emphasis on regulating
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12 91 breath, and exercising intrinsic control and mental intent.[15] Exercise of Qigong is
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14 92 characterized by trunk rotation, bending and extending at waist and movement of limbs
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16 93 both medial-laterally and anterior-posteriorly, all driven by the core of the body.[14,16]
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18 94 Like other techniques such as Tai Ji Quan, Qigong exercise also involves dynamic
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20 95 movements with intermittent stepping and turning. Besides, exercise involves postural
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22 96 demanding movements such as single leg standing and chirographic and manipulative
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24 97 moving postures.[17,18] Furthermore, Qigong exercise requires regulating breathing by
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26 98 engaging in diaphragmatic to expand lung capacity and control upright posture.[19,20]
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28 99 To date, there has been little effort to evaluate the therapeutic effect of combing
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30 100 different types of Qigong exercise on gait in individuals with PD. This paper describes the
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32 101 trial protocol of a newly developed Integrated Qigong intervention that combines seven
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34 102 types of commonly exercised Qigong into a single rehabilitation program for mild to
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36 103 moderate PD patients with FOG. Specifically, we aim to determine the therapeutic effect
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38 104 of the Integrated Qigong intervention on gait. We hypothesize that, compared to control
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40 105 group, both Integrated Qigong and conventional balance training intervention will be
41
42 106 clinically more effective in improving the primary outcomes of gait.
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48 108 **METHODS**

51 109 **Study design**

53 110 The study is designed as a prospective, single-blind randomized controlled trial.
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111 **Design and procedures**

112 We will recruit participants from Shanghai, China by means of the neurology department
113 of the local hospital and TV programs during the same recruitment period. To reduce
114 potential expectation bias and confirm eligibility, a research assistant will make telephone
115 contact with those referred by a neurologist and follow up with interested participants.
116 Participants will be informed that they will be randomly assigned to three groups. The
117 integrated Qigong exercise group will engage in training program that combines seven
118 types of commonly exercised Qigong. The balance training group will perform static and
119 dynamic postural control training. The two intervention groups will receive the guidance
120 of instructor, and the control group will receive weekly group session and monthly health
121 education. The total intervention period will be 12 weeks, and will occur simultaneously
122 for all participants. The primary and secondary outcomes will be assessed at baseline (pre-
123 intervention), 12 weeks (end of intervention) and 12-week follow-up (see figure 1).
124 Potential eligible participants who satisfy initial inclusion criteria will arrange a two-hour
125 visit at our research laboratory and register their personal information. The trial protocol
126 has been approved by the ethics committee of Shanghai University of Sport. All
127 participants who meet the inclusion and exclusion criteria need to sign informed consent
128 prior to the study. The protocol is registered as a China Clinical Trial (ID:
129 ChiCTR1800016570).

130 **Participants**

131 Inclusion criteria

132 (1) PD patients diagnosed according to the clinical diagnostic of UK Brain Bank criteria;
133 (2) age between 40 and 80 years old; (3) Hoehn & Yahr scale of 1–3; (4) item three of the
134 New Freezing of Gait Questionnaire (NFOGQ) scored ≥ 1 ; (5) Mini–Mental State
135 Examination (MMSE) score >24 ; (6) ability to walk independently; and (7) have

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4 136 experienced a fall over the past six months.

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7 137 Exclusion criteria

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9 138 (1) Participation in Qigong exercise during the last year; (2) other diseases that could
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11 139 interfere with conduct of the study protocol such as cardiopulmonary disease, liver and
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13 140 kidney disease, musculoskeletal dysfunction, or cancer; (3) severe cognitive, visual or
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15 141 auditory impairment; (4) unstable medication; (5) unstable deep brain stimulation.

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20 143 **Sample size calculation**

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22 144 A statistical analysis was conducted for sample size estimation using G*power 3.1 (Franz
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24 145 Faul, Universita Kiel, Germany). The study was powered to detect a between-group
25
26 146 difference in primary gait outcome measures between Qigong exercise group and balance
27
28 147 training group relative to the attention control group. Because there was no a priori
29
30 148 hypothesis formulated between the two active interventions (Qigong exercise and balance
31
32 149 training), the study was not powered on these two conditions. Due to the lack of informed
33
34 150 preliminary data and empirical evidence on the effects of Qigong exercise, we
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36 151 approximated the effect size in our power calculations using estimated from the published
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38 152 studies that compared Qigong exercise with a control condition on gait (i.e., gait speed,
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40 153 freezing of gait, and mobility).[13,14] In general, these studies, with an intervention length
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42 154 ranging from 10 weeks to 24 weeks, have shown a weak intervention effect, with effect
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44 155 sizes ranging from no effect to small-to-moderate effects. On the basis of these
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46 156 observations, a conservative approach was taken. Specially, we used a small effect size
47
48 157 ($\eta^2=0.01$) based on the partial eta squared estimate within the ANOVA framework.[21]
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50 158 Our initial power estimates indicated that, in a mixed-effect repeated measures design with
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52 159 a between-subject factor (Integrated Qigong, balance training, control), and a within-
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54 160 subject factor (baseline, 12 weeks) and a correlation of 0.08 on the repeated measures, a

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4 161 sample size of 99 subjects would be required to achieve an 80% power at an 0.05 error rate.
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6 162 To be more conservative, we estimated the sample sizes based on a range of small sizes
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8 163 ($f=0.08, f=0.10, f=0.12$). The sample sizes generated from these calculations were averaged
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10 164 to arrive at a total of 107 subjects. With an anticipated 15% attrition rate, a final enrollment
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12 165 number of 126 (42 in each group) was set for the study to detect a difference in gait
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14 166 outcomes between Integrated Qigong and balance training relative to the attention control
15
16 167 group.

168 **Randomization and blinding**

169 The study design will utilize a single blinded randomized controlled trial. Two trained
170 assessors will be blinded to group allocation and will not participate in the intervention.
171 We will apply the stratified random sampling method by stage of the disease (H&Y Stage).
172 Using computer generated random number sequencing (STATA 12.0, StataCorp LP, Texas,
173 USA) in a ratio of 1:1:1, a random number will be placed in a sealed envelope, and
174 participants will be allocated randomly to Integrated Qigong group, balance training group,
175 or control group by extracting the random number from the envelope. Participants will be
176 reassessed for baseline measurements on another day. This study is not amenable to
177 blinding to participants of their designated experimental groups because the interventional
178 exercises they perform will reveal their group allocation.

179

180 **Intervention**

181 The participants in all groups will follow their regular medication scheme during the study
182 period. Both Integrated Qigong group and balance training group will receive group-based
183 exercise intervention at the sports science laboratory of Shanghai University of Sport. The
184 group size is 5 to 7 people in order to provide sufficient instructional attention to each
185 participant. Two trained instructors will guide the participants to perform the exercises of

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4 186 their own group. The two interventional groups will perform three weekly sessions of 60
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6 187 minutes per session for 12 consecutive weeks. Each session will consist of 10 minutes of
7
8 188 warm-up, 40 minutes of core exercises, 5 minutes of break intervals, and 5 minutes of cool-
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10 189 down. The heart rates of the participants will be monitored by Polar-team² (Polar Electro,
11
12 190 Finland) during training in order to progressively control the intensity. Participants in the
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14 191 interventional groups will be required to not perform any additional in-home exercises
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16 192 throughout the 12 weeks of training.

193 Integrated Qigong exercise group

194 The Integrated Qigong protocol will consist of twelve-forms of exercise, with selected
195 movements from the Health Qigong exercise guidelines organized and compiled by the
196 China Qigong Management Center. The Integrated Qigong exercise will emphasize
197 dynamic postural control and body weight shift stepping with lateral-medial and anterior-
198 posterior movements, body symmetry pulling across up-down and left-right axes, hand-
199 eye coordination movement. The twelve forms of exercise have been previously
200 documented [22] and can be seen in Figure 2.

201 During the initial 2 to 3 weeks, training will mainly emphasize learning and
202 practicing two or three forms through multiple repetitions along with review of
203 previously learned movements. The practice in each session concentrate on upper and
204 lower limbs in place, trunk rotation, as well as stepping in different directions (i.e.,
205 forward, backward, sideways, diagonal). Participants will be requested to perform
206 personalized movement requirements based on functional level. The range of motion of
207 each movement will be reduced for participants with rigidity. The pace of movement will
208 be decreased for participants with bradykinesia. For participants experiencing FOG
209 episode during training, they will be instructed to perform transferring and stepping while
210 maintaining postural stability. The intensity, difficulty of movement, time, and frequency
211 will be adjusted to the demands of each participant. The later weeks will concentrate on

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4 212 improving balance, locomotion, and action consistency. Participants will practice each
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6 213 movement with six repetitions, and natural breathing will be incorporated into the
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8 214 movement routine. Participants will be guided to perform the entire range of movement
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10 215 in which they feel safe.

11 12 13 216 Balance training group

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15 217 Each training session will start with a 10 minutes warm-up consisting of breathing exercise,
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17 218 slow walking, and range-of-motion exercises. The 40-minute balance training will include
18
19 219 a short resting time, and the training program will consist of the following: 1) static balance
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21 220 training: standing on unstable surfaces to maintain postural control and progression to
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23 221 weight shifting; 2) dynamic balance training: postural control in standing position while
24
25 222 adding upper limb and trunk movements; 3) balance strategy exercise: focus on hip
26
27 223 strategy while maintaining ankle strategy and stepping strategy under interference in
28
29 224 different directions; 4) adaptation of varying base of support, and standing in a narrow
30
31 225 space and on uneven surface; [23] and 5) walk integrated balance training: walk in a straight
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33 226 line, walk on a soft blanket, and sideways. The training will progress from simple to
34
35 227 complex, static to dynamic, low to high center of gravity, wide to narrow the base of
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37 228 support, and will continue to raise challenges in regard to flexibility, stability and range of
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39 229 movement. The end of training will include a 5-minute cool-down session of limb ROM
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41 230 movements, sustained stretching, and relaxing.

42 43 44 231 Control group

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46 232 The control group will be instructed to maintain their formal lifestyle and not to engage in
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48 233 any other form of intensive training. The participants in the control group will join one 60-
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50 234 min group session per week, which will consist of a 30-min lecture, 20-min discussion, and
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52 235 will be followed by a 10-min question and answer session. Participants in the control group
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54 236 will receive health education every four weeks over the 12-week interventional period. The

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4 237 health education will involve information for PD-related treatments and prevention such as
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6 238 modalities of exercise, regimens, fall prevention, and nutrition. Participants will receive a
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8 239 brochure of health education and will have follow-up by telephone twice per month, which
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10 240 will involve discussion of physical activity, progression of disease, health status, and
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12 241 psychological status.

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14 242 All participants will maintain diaries to record their exercise and fall events every day
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16 243 throughout the trial, including both in the laboratory and at home. The participants in the
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18 244 Integrated Qigong exercise group and balance training group will perform the exercises at
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20 245 the “on” stage in the morning.

21 22 23 246 **Outcome measures**

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25 247 All measurements will be performed at baseline, 12 weeks (end of intervention), and 12
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27 248 weeks following the completion of the intervention. The measurements will be conducted
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29 249 by two trained assessors and will be videotaped by a third assessor. All assessors will be
30
31 250 blinded to the participant’s group allocation and time of assessment.

32 33 34 251 **Participants characteristics**

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36 252 Demographic and health characteristics of participants will be collected at baseline to
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38 253 describe the sample, compare conditions, and investigate characteristics associated with
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40 254 outcomes. These characteristics will include age, gender, education, age at disease onset,
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42 255 disease duration, cognition ability, health status, medication dose, resting blood pressure,
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44 256 body mass (kg/m²), height (cm), family situation and physical performance. Blood pressure
45
46 257 will be measured with the use of an automated device (Omron HealthCare). Body mass
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48 258 and height will be assessed with digital scales (Weighing scale & Meter) Physical
49
50 259 performance will be measured by the scores from self-reported habitual physical activity
51
52 260 scale. (See Table 1)

262 **Table 1** Demographic and clinical characteristics of the study participants*

	Integrated Qigong (N=)	Balance Training (N=)	Control (N=)
Age—yr			
Gender—(male% : female%)			
Body-mass index ^a —kg/m ²			
Height—cm			
Hoehn and Yahr stage—no. (%)			
1-1.5			
2-2.5			
≥3			
Age of onset—yr			
Duration of disease—yr			
Score of MoCA(/30) ^b			
Antiparkinsonian medications taken—no.			
Levodopa or carbidopa			
Pramipexole or ropinirole			
Other			
Self-reported health status ^c —no. (%)			
Poor or fair			
Good			
Very good or excellent			
Family situation-no. (%)			
Living along			
Living with husband/wife			
Living with husband/wife and children			
Score for Self-reported habitual physical activity ^d			
Falls in previous 6 months—no.			

263 * Mean values (standard deviation). The chi-square test is used for categorical variables,
 264 and one-way analysis of variance for continuous variables.

265 ^a The body-mass index is the weight in kilograms divided by the square of the height in

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4 266 meters.

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6 267 ^b MoCA, Montreal Cognitive Assessment.

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8 268 ^c Self-reported health status, included cardiovascular disease, lung disease, osteoporosis,
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10 269 arthritis, liver and kidney disease, low back pain, and cancer; the number of conditions per
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12 270 participant ranged from 0 to 9.

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14 271 ^d This is measured by the Physical Activity Scale for the Elderly, [24] with higher scores
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16 272 indicating higher levels of habitual physical activity.
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273 **Primary outcome assessment**

274 Spatiotemporal kinematic parameters is one approach to characterize FOG, particular the
275 increased cadence, decreased stride before FOG episode.[25] Hence, we will describe
276 spatiotemporal characteristics to better understand the relationship between gait and
277 FOG. Gait parameters will be analyzed using a 7-m-long instrumented computerized
278 walkway (GAIRite, CIR, System Inc., Franklin, NJ), and will include stride length, gait
279 velocity, cadence, and stride time variability. Gait velocity is crucial parameter for
280 walking coordination and can be used as basic factor for the assessment of normal and
281 pathological gait. [26] Gait variability is a valuable indicator of whole-gait performance
282 and can reflect gait disorders. Stride length and stride time variability are sensitive
283 measures that relate to fall risk in older people. [27,28]

284 New freezing of gait questionnaire (NFOG-Q) is a reliable tool to detect freezing
285 behavior and assess effectiveness of intervention. It consists of the following three parts:
286 (1) part I (item 1, score is 0 or 1) detects the presence of FOG and distinguishes if patients
287 are freezers or non-freezers if they have had a FOG experience during the past month; (2)
288 part II (items 2–6, score range from 0-9) assesses the severity of FOG according to its
289 duration and frequency and its common appearance. Item 2 was added to rate the overall
290 frequency of FOG regardless of the environment; (3)part III (items 7–9, score range from
291 0-9) assesses the influence of FOG on daily life, and the total score ranges from 0-28;
292 higher scores reflect more severe FOG.[29]

293 **Secondary outcome assessment**

294 Functional Gait Assessment (FGA) is a measure of walking balance ability in older adults
295 and individuals with PD and has shown good reliability and validity in the clinic. FGA
296 includes under following conditions: forward, backward, with eyes closed, stepping over
297 obstacles, changing gait speeds, with different head turns, and a narrow base of support.

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4 298 The FGA includes 10 total items, with each item scored from 0-3. A higher total score
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6 299 reflects better balance and walking ability, with a maximum score of 30. [30,31]

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8 300 Postural instability and gait disability will be evaluated by the Unified Parkinson's
9
10 301 Disease Rating Scale (UPDRS) Part III evaluation. It consists of rigidity measures, gait,
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12 302 tremor, hand/arm and leg movements (bradykinesia), speech, and facial expressions. The
13
14 303 modified Hoehn and Yahr scale has also been used to evaluate disease severity.[32]

15
16 304 The balance performance will be measured by Mini-Balance Evaluation Systems Test
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18 305 (Mini-BESTest), consisting of 14 items from 4 different balance control systems:
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20 306 anticipatory postural adjustments, reactive postural control, sensory orientation, and
21
22 307 dynamic gait. Each item is evaluated on a 3-point scale from 0 to 2 and the total score
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24 308 ranges from 0 to 28, with a higher score indicating better balance performance.[33, 34]

25
26 309 Falling frequency will be reported at the baseline test, during the 12-week training
27
28 310 period, and at a 12-week follow-up. A blind assessor will record fall event based on the
29
30 311 following definition of falling: "a person unintentionally coming to rest on the ground or
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32 312 other lower level, not occurring as a result of a major intrinsic overwhelming
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34 313 hazard." [35] The following approaches will be used to ascertain the fall event: (1)
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36 314 monthly collection of fall diary, (2) monthly phone interview, and (3) self-report from
37
38 315 each assessment.

39
40 316 Falls and fear of falling will be measured with the 14-item Modified Falls Efficacy Scale
41
42 317 (MFES) questionnaire, which reflects self-perceived confidence to engage in activities of
43
44 318 daily living without falling. Each item is scored on a 10-point scale, with a minimum score
45
46 319 of 0 indicating no confidence and a maximum score of 10 indicating full confidence (high
47
48 320 falls efficacy) in performing the tasks without falling. The average score across all 14 items
49
50 321 will be taken, with higher scores indicating greater falls efficacy.[36,37]

51
52 322 The quality of life will be assessed using the 39-item Parkinson's Disease
53
54 323 Questionnaire (PDQ39). It is composed of 39 items grouped in eight domains: mobility,

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4 324 activities of daily living, emotional well-being, stigma, social support, cognition,
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6 325 communication, and bodily discomfort. Each item ranges from 0 (never) to 4 (always). A
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8 326 summary index of eight domain scores ranges from 0 to 100, with higher scores
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10 327 representing worse health related quality of life (HRQoL).[38,39] The data collected are
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12 328 depicted in Table 2.
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329 **Table 2** Changes over time within and between control and experimental groups

Group	Baseline*	12-weeks*	Follow-up*	Mean difference at 12-weeks**	Mean difference at Follow-up**	<i>F(P Value)</i> Time Effect	<i>F(P Value)</i> Group Effect	<i>F(P Value)</i> Interaction Effect
Primary Outcome								
Stride length (cm)								
Integrated Qigong								
Balance training								
Control								
Gait velocity (cm/sec)								
Integrated Qigong								
Balance training								
Control								
Cadence (steps/min)								
Integrated Qigong								
Balance training								
Control								
Stride time Variability (CV)								
Integrated Qigong								
Balance training								
Control								

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NFOG								
Integrated Qigong								
Balance training								
Control								
Secondary Outcome								
FGA								
Integrated Qigong								
Balance training								
Control								
MDS-UPDRS Part-III								
Integrated Qigong								
Balance training								
Control								
Mini-BESTest								
Integrated Qigong								
Balance training								
Control								
Total falls, no.								
Integrated Qigong								
Balance training								
Control								
MFES								
Integrated Qigong								
Balance training								

Control								
PDQ-39								
Integrated Qigong								
Balance training								
Control								

330 *Mean values (standard deviation).

331 **Mean difference (standard error).

332 Abbreviations: CV, coefficient variation; NFOG, new freezing of gait questionnaire; FGA, functional gait assessment; MDS-UPDRS Part-III,
333 movement disorder society unified Parkinson’s disease rating scale, motor subscale; Mini-BESTest, Mini-Balance Evaluation Systems Test; MEFS,
334 falls and fear of fall; PDQ-39, the 39-item Parkinson’s disease questionnaire.

335 **Patient and Public involvement**

336 Participants will not been involved in the study recruitment. The authors conceived the initial research questions and outcome measures, and
337 modified according to the telephone interviews with patients and their guardians by a research assistant. In order to assure the safety and
338 feasibility of the intervention, we invited six patients with mild to moderate PD to learn and practice Integrated Qigong exercise before designing
339 the RCT. Integrated Qigong movements were revised based on the exercise performance and feedback provided by the participants. The burden
340 of the intervention will assessed by patients and their advisors through face-to-face interviews before signing informed consent. The findings of

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4 341 the study will be disseminated to the participants and their guardians.
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8 343 **Statistical Analysis**
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10 344 The statistical analysis will be performed using SPSS 22.0 software (IBM Corp,
11 Armonk, New York). Baseline values of demographic differences in interventional
12 345 groups and the control group will be examined using Chi-squared tests. The primary
13 346 outcomes and secondary outcomes over time (i.e., baseline, 12 weeks, after 12-week
14 347 follow-up) will be analyzed by mixed design repeated-measures analyses of variance
15 348 (RM-ANOVA) for between- and within-group differences. Bonferroni's post hoc test
16 349 will be applied to compare results where main effects are significant. Data will be
17 350 expressed as the mean and standard deviation or standard error, and significance will
18 351 be set at $p < 0.05$. An intention-to-treat analysis will be adopted to deal with missing
19 352 data, including all participants in the analysis based on the initial group allocation. A
20 353 linear mixed model approach (a direct likelihood estimation method) will be applied
21 354 to analyze all continuous as value is missing at random. All analysis will include
22 355 H&Y and MoCA as covariates, as these variables may differ significantly between
23 356 groups.
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41 358 **DISCUSSION**

42 359 Medical treatment integrated with exercise therapy is still an indispensable method to
43 360 manage the motor dysfunction for PD. FOG is common in people with PD which
44 361 contributes to a protective postural response impairment and increases the risk of falls.
45 362 Nevertheless, this balance instability can be improved by extra training.[40] Qigong
46 363 exercise synthesizes training in balance, flexibility, neuromuscular coordination, and
47 364 cognition, it consists of body consciousness, attention, imagination, multiple activities
48 365 and goal-oriented training which may benefit the improvement of gait and postural
49 366 control, beyond conventional single-mode exercise.[41]

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59 367 Patients with PD exhibit difficulty in transitions from static to dynamic states.
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4 368 Transitional activity is a vital component of physical activities, especially gait
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6 369 initiation, turning, and gait termination. Due to the deficiency in postural control,
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8 370 patients generate excessive trunk movement that causes swaying beyond the limits of
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10 371 stability. [42] Moreover, people with PD often manifest impaired protective postural
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12 372 response and postural adjustment in preparation for stepping, thus, increasing the risk
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14 373 of fall.[43,44] Qigong practice requires that the center of gravity moves and changes
15
16 374 to accompany with the movement of the upper limb, slow movement, body control in
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18 375 space, and shifting body weight in different directions. Hence, Qigong practice can be
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20 376 beneficial to improve the ability to focus on the base of support and postural stability,
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22 377 as well as enhance core muscle to stress weight-bearing joints and to increase
23
24 378 proprioception input of trunk and lower limb joints.

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26 379 Most Qigong movements involve closed-chain exercise of the lower limbs, and
27
28 380 contribute to rectifying deficiencies of heel stride and knee extension on gait cycle.
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30 381 [14, 41] In addition, the meditative movement in Qigong exercise can relieve
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32 382 psychological load and consumption, which may benefit for practitioner to reduce
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34 383 muscle tension, and alleviate effect of freezing on stepping forward. [45]
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36 384 Furthermore, Qigong is characterized by slow movement incorporated with
37
38 385 moderated breathing, as well as keeping the mind in a state of calm relaxation. The
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40 386 intensity of Qigong is around 1.5 to 2.6 metabolic equivalents (METs) and the
41
42 387 average induced maximum heart rate ranges from 43% to 49% of the predicted
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44 388 maximum.[13] Therefore, Qigong is a low-intensity physical exercise that has lower
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46 389 risk of muscle strain and overfatigue and is suitable for individuals with PD as a long-
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48 390 term physical exercise program.

49
50 391 There are several limitations in this study. First, it is difficult to achieve a blinded
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52 392 intervention for this study because exercise served as an intervention is widely open to
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54 393 the participants. Second, the control group will have much less contact than training
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56 394 groups, this may induce bias to the study. Future, the impact of attention/social
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58 395 interaction for each participant would be controlled to ensure the equal dosage of
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4 396 training and attention in different interventions. Third, participants are limited to people
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6 397 with mild-to-moderate PD. Therefore, it is unclear whether the results would be valid
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8 398 for people with advanced PD. Forth, the study patients will come from the same
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10 399 geographic area which limits the generalizability and so that it is not a multicenter trial.

11
12 400 For a variety of features of gait pattern, whatever muscle stiffness or abnormal
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14 401 postural control, we may consider the global or specific efficacy of Qigong on gait
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16 402 function in PD.[46] We expect that a 12-week Integrated Qigong exercise can establish
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18 403 positive therapeutic effects on PD patients with FOG. However, gait deficiency in
19
20 404 individuals with PD is a complex syndrome and is associated with neural control
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22 405 regulated by different areas of the brain, particularly the prefrontal lobe and related
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24 406 circuits.[47] In future studies, we might focus on the mechanism of the different forms
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26 407 of Qigong on the relationship between brain activities and FOG, and explore whether
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28 408 Qigong exercise is conducive to restoring brain function and/or preventing brain
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30 409 degeneration. We hope that this trial will demonstrate that the Integrated Qigong
31
32 410 exercise promote the recovery of gait function and prevention of falls for people with
33
34 411 mild and moderate PD. The results of this study may furnish evidence to support the
35
36 412 beneficial effects of Qigong exercise on improvement of walking ability and reduction
37
38 413 of fall risk in people with PD. The findings of this study will provide evidence for a
39
40 414 supplemental therapy to manage gait disorder for clinicians and physical therapist.

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44
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56
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5
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7
8 426 design of the trial, and drafted the manuscript. Guiping Xiao, Kuncheng Jie and Wenhan
9
10 427 Yin participated in trial registration, communication, and monitoring. Yan Jiang and
11
12 428 Tian Wang carried out statistical calculations. Yu Zhang provided medical clearance
13
14 429 and Parkinson's disease stage diagnoses for the participating patients. All authors
15
16 430 participated in revision of the manuscript and approved the final version.

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19 431 **Patient consent** Obtained.

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22 432 **Ethics approval** This work was approved by the ethics committee of science research
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24 433 of Shanghai University of Sport (protocol number: 2018031).

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38 440 non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

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4 568 **Figure Legend**

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6 569 **Figure 1** Flow diagram of study design

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10 571 **Figure 2** Twelve forms of Integrated Qigong exercise.

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12 572 A: Form one: Xu Exercise

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14 573 B: Form two: Chui Exercise

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16 574 C: Form three: Raising the Tiger's Paws

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18 575 D: Form four: Holding the Hands High with Palms Up to Regulate the Internal Organ

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20 576 E: Form five: Drawing a Bow

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22 577 F: Form six: Posing as an Archer Shooting Both Left-and Right-Handed

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24 578 G: Form seven: Pulling Nine Cows by Their Tails

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26 579 H: Form eight: Rub Backbone

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28 580 I: Form nine: Swaying Like a Bear

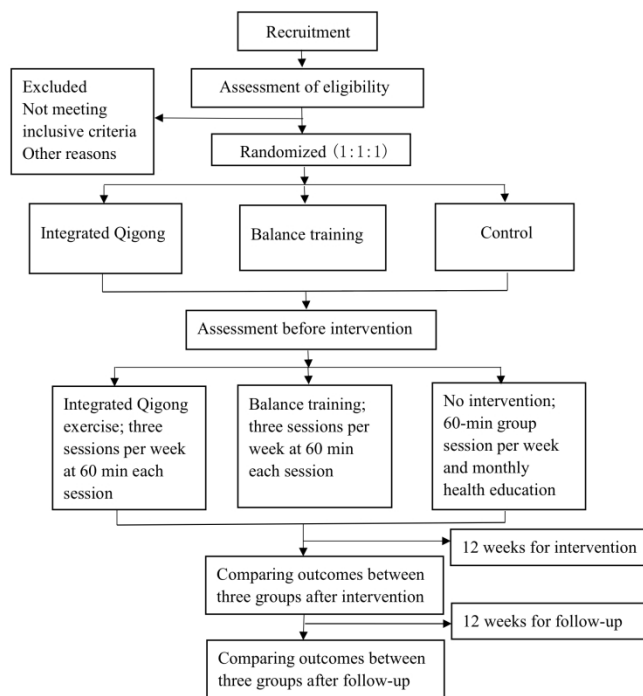
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30 581 J: Form ten: Picking Fruit

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32 582 K: Form eleven: Golden Rooster Heralds the Dawn

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34 583 L: Form twelve: Flying Like a Bird

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45 Flow diagram of study design.

46 209x297mm (300 x 300 DPI)

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Twelve forms of Integrated Qigong exercise.

90x90mm (600 x 600 DPI)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title(P0)	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration(P2)	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding(P21)	4	Sources and types of financial, material, and other support
Roles and responsibilities (P21-22)	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	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
	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)
Introduction		
Background and rationale(P3)	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
	6b	Explanation for choice of comparators
Objectives(P4)	7	Specific objectives or hypotheses

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2 Trial design(P5) 8 Description of trial design including type of trial (eg, parallel group,
3 crossover, factorial, single group), allocation ratio, and framework (eg,
4 superiority, equivalence, noninferiority, exploratory)
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8 **Methods: Participants, interventions, and outcomes**
9

10 Study setting(P7) 9 Description of study settings (eg, community clinic, academic hospital)
11 and list of countries where data will be collected. Reference to where
12 list of study sites can be obtained
13

14 Eligibility 10 Inclusion and exclusion criteria for participants. If applicable, eligibility
15 criteria(P5-6) criteria for study centres and individuals who will perform the
16 interventions (eg, surgeons, psychotherapists)
17

18 Interventions 11a Interventions for each group with sufficient detail to allow replication,
19 (P7-10) including how and when they will be administered
20
21

22 11b Criteria for discontinuing or modifying allocated interventions for a
23 given trial participant (eg, drug dose change in response to harms,
24 participant request, or improving/worsening disease)
25

26 11c Strategies to improve adherence to intervention protocols, and any
27 procedures for monitoring adherence (eg, drug tablet return,
28 laboratory tests)
29

30 11d Relevant concomitant care and interventions that are permitted or
31 prohibited during the trial
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34 Outcomes 12 Primary, secondary, and other outcomes, including the specific
35 (P10-15) measurement variable (eg, systolic blood pressure), analysis metric
36 (eg, change from baseline, final value, time to event), method of
37 aggregation (eg, median, proportion), and time point for each
38 outcome. Explanation of the clinical relevance of chosen efficacy and
39 harm outcomes is strongly recommended
40
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42 Participant 13 Time schedule of enrolment, interventions (including any run-ins and
43 timeline(Figure1) washouts), assessments, and visits for participants. A schematic
44 diagram is highly recommended (see Figure)
45

46 Sample size(P6- 14 Estimated number of participants needed to achieve study objectives
47 7) and how it was determined, including clinical and statistical
48 assumptions supporting any sample size calculations
49

50 Recruitment(P5) 15 Strategies for achieving adequate participant enrolment to reach
51 target sample size
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54 **Methods: Assignment of interventions (for controlled trials)**
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56 Allocation:
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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation(P7)		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions
8			
9			
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13	(P7)		assigned
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16	(P7)		and who will assign participants to interventions
17			
18	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
19	(masking)		participants, care providers, outcome assessors, data analysts), and
20	(P7)		how
21			
22		17b	If blinded, circumstances under which unblinding is permissible, and
23			procedure for revealing a participant's allocated intervention during
24			the trial
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Methods: Data collection, management, and analysis

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30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods(P10)		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol
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37			
38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44	(P19-20)		range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol
46			
47			
48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
49	methods(P19-20)		Reference to where other details of the statistical analysis plan can be
50			found, if not in the protocol
51			
52		20b	Methods for any additional analyses (eg, subgroup and adjusted
53			analyses)
54			
55		20c	Definition of analysis population relating to protocol non-adherence
56			(eg, as randomised analysis), and any statistical methods to handle
57			missing data (eg, multiple imputation)
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Methods: Monitoring

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24	Data monitoring (n/a)	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Harms (n/a)	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
	Auditing (n/a)	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Research ethics approval (P5)	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
	Protocol amendments (n/a)	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
	Consent or assent (P5)	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
	Confidentiality (see informed consent)	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
	Declaration of interests (n/a)	28	Financial and other competing interests for principal investigators for the overall trial and each study site
	Access to data (n/a)	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
	Ancillary and post-trial care (n/a)	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

1 2 3 4 5 6 7 8 9 10 11 12 13	Dissemination policy (n/a)	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
		31b	Authorship eligibility guidelines and any intended use of professional writers
		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

14 15 16 17 18 19 20 21 22 23 24 25	Informed consent materials (see informed consent)	32	Model consent form and other related documentation given to participants and authorised surrogates
26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Biological specimens (n/a)	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

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