ORIGINAL STUDY PROTOCOL

1. Project title

The effect of yoga on psychological distress for people with Parkinson's disease: a randomized controlled trial

2. Abstract of project

Background/Objective: Parkinson's disease (PD) is the second most common neurodegenerative diseases affecting our aging population. Psychological distress among people with PD is prevalent. Referring to a local survey, 52.2% of PD population was identified with psychological distress and at risk of anxiety or depression. Regarding the complicated and adverse effects of pharmacological management of psychological distress among PD population, adopting a complementary and alternative approach to improve psychological wellbeing is of vitally importance. The objectives of this study are to determine the effects of yoga on psychological distress among individuals with PD.

Participants: Individual with PD

Design: A single blind, randomized controlled trial with two groups. 126 subjects will be recruited and randomized into either yoga group or stretching and resistance exercise group.

Interventions: The yoga group will receive mindfulness yoga training, which consist of a weekly 90–minute yoga session for eight weeks. The control group will receive a weekly 60–minute stretching and resistance exercise for eight weeks.

Primary outcomes: Psychological disease measured by the Hospital Anxiety and Depression Scale (HADS).

Secondary outcomes: Motor symptoms measured by The Unified Parkinson's Disease Scale- motor examination (UPDRS III); mobility, balance and fall risk measured by the Timed Up and Go test (TUG); spiritual wellbeing measured by the Holistic Wellbeing Scale (HWS); and health–related quality of life (HRQoL) measured by the Parkinson's Disease Questionnaire-8 (PDQ-8).

Impact of the project: With the promising preliminary benefits of yoga on psychological wellbeing, its effect on psychosocial wellbeing among people with PD have rarely been investigated. Research examining effects of yoga is often based on the biomedical model, which overlooked the role of psychosocial factors. The results of this study will identify the effects of yoga on psychosocial, physiological and spiritual wellbeing in enhancing HRQoL among individuals with PD. With the successful implementation of the yoga project among PD population, it is expected that individuals living with chronic illness like PD would demonstrate a reduced level of psychological distress and thus, adopting a more active lifestyle and active role in disease management. Such information will not only provides solid evidence to formulate community exercise programme to enhance HRQoL of PD population, but also inform future research in investigating the underlying mechanism of yoga in promoting psychosocial, physiological and spiritual wellbeing among people with chronic illnesses.

3. Introduction

Tremendous health burden of Parkinson's disease (PD)

PD is a chronic, neurodegenerative disease affecting 1-2% of the population over the age of 65 years(1). It is characterized by four cardinal motor symptoms including resting tremor, stiffness, bradykinesia and postural instability, which greatly impair patients' physical wellbeing and functional capacity. The treatment of PD used to focus solely on management of motor symptoms. However, non–motor symptoms of PD, such as cognitive, neuropsychiatric, sleep, autonomic, sensory and disturbances, have been reported to have a greater impact on health–related quality of life (HRQoL) and gaining increasing attention in the recent decade (2). With the prolonged life expectancy and increasing number of people with Parkinson's disease, demand for long term health care is growing rapidly and one of the most serious challenges facing the healthcare system is how to empower and engage people with PD in adopting a more active role in daily living and chronic disease management.

PD population is at high risks of psychological distress

Psychological distress like anxiety and depressive symptoms are prevalent among PD population, which results from frustration over the loss of body control and diminished feelings of mastery and expression(3). It has been reported that the incidence of anxiety and depression was up to 30% and 40% among PD population, which is much higher than individuals with other chronic illnesses(4).The stress resulting from ineffective coping and uncertainty about life remains as major challenge for individuals with PD(5).

Impact of psychological distress among PD population

Substantial evidence has demonstrated the devastating impact of psychosocial distress on functional status, morbidity and disease progression among PD population. PD individuals with psychological distress were found to be less motivated in social communication and more prone to adopt a sedentary lifestyle, which compromise their daily role functions and self–care capacity, leading to earlier retirement and worsening HRQoL(6). Furthermore, PD individuals with higher psychological distress and depressive symptoms were reported to experience greater disability, faster progression of physical symptoms, increased incidence of relapse, poorer treatment compliance, higher health care utilization and greater caregiver distress(7-9). The impacts of psychological distress among PD population prominently impair their functional status and HRQoL, which greatly increase their need for care and pose tremendous health and socio-economic burden on the healthcare system and society.

Local statistics of psychological wellbeing of PD population

A survey was conducted from February to April, 2016 to investigate the psychological distress and HRQoL among individuals with PD living in the local community. Subjects were recruited from PYNEH and The Hong Kong Society for Rehabilitation. Ninety-two PD patients with a mean age of 69.8 years were interviewed, 54.3% of whom were male. The mean score of Hospital Anxiety and Depression Scale (HADS) was 15.5 with a standard deviation of 7.4. By using a cut-off value of 15 to indicate the presence of psychological distress, 52.2% of this

population was suffering from psychological distress and at risks of anxiety and depression. Despite the high prevalence and substantial negative consequences of psychological distress among PD population, this problem is poorly recognized and addressed by the local healthcare system.

Management for psychological distress among PD population

Conventional interventions for psychological distress consist primarily of pharmacologic agents. However, the pharmacological management of anxiety and depression among PD patients is complicated as there are numerous potential medication interactions between antidepressants and PD treatments. Serotonergic agents may worsen symptoms of PD, bupropion has potential dopamine agonist effect benefitting PD symptoms but potentially worsening psychosis, while selegiline has antidepressant and antiparkinsonian effects but may interact with levodopa and with other antidepressant agents(10). The lack of pharmaceutical treatments for curing PD has led to a growing interest in low-cost behavioral interventions for improving psychological distress and HRQoL among individuals with PD. It has been suggested that exercises may demonstrate neuroprotective effect in slowing PD progression. Increased physical activity have also been recommended to improve both physical and psychological wellbeing for individuals living with PD. However, many older adults in the community who suffer from PD are staying physically inactive, less outgoing and have poorer motivation to adopt an engaging lifestyle. Therefore, exercise programs that are especially tailored to their physical restraint and fragility are needed.

Potential beneficial role of yoga in psychological wellbeing

Yoga, originating from the ancient India, is a form of exercises to promote wellbeing of body, mind and spirit. The beneficial role of yoga on reducing anxiety and depressive symptoms have been demonstrated among individuals with chronic illnesses(11). Throughout the mindfulness practice of a sequence of poses (asana), breathing exercises (pranayama) and meditation (dhyana), the awareness and attention to body is raised and sustained. It is thought that yoga strengthened one's attention to the present moment, which modified the influence of stress on mind and body, minimizing stress, disability and pain. However, previous yoga studies were mainly guided by biomedical model, which emphasized the physiological aspects without acknowledging the role of psychosocial factors in health and illness(12). In view of this, this study aims to investigate the interaction between physiological, psychosocial and spiritual factors of yoga.

Physiologically, musculoskeletal and cardiopulmonary benefits of yoga have been demonstrated. During the practice of yoga, the repetitive extension and flexion of muscles activate the antagonistic neuromuscular systems and tendon–organ feedback, which results in increased strength, flexibility, range of motion and relaxation (13). It is suggested that yoga quiet the body as well as the mind through muscular and vascular relaxation (14). Studies investigating the effect of yoga on autonomic nervous system have reported increase in heart rate variability which indicated reduced stress responses. It has been suggested that yoga–based practice relieved stress and symptoms through a mechanism in correcting the underactivity of parasympathetic nerve system by stimulating the vagal nerves and reducing allostatic load (15).

Psychosocially, yoga has demonstrated beneficial effects on positive mood and social support. It has been suggested that the increased mastery of poses, emotional relieve and the sense of relaxation in restorative poses all contribute to the positive effects on mood, reducing anxiety and depressive symptoms (16). Social support has been reported through practicing exercise in a group, enhancing social wellbeing and HRQoL among individuals with chronic illnesses (17).

For spiritual factors, yoga practice emphasis acceptance and mindful awareness. The non–competitive nature of yoga is different from many forms of exercises which rely upon a comparison to others or pushing oneself beyond limits to define progress. The guiding principle of yoga is to foster the resilience to accept negative situations in life (18). Through regular yoga practice, an individual could redefine the experience of pain, disability or difficulty, and thus, encourage one's acceptance of disability and continue functioning despite physical restraints and difficulties.

Impact of the project

With the promising preliminary benefits of yoga on psychological wellbeing, its effect on psychosocial wellbeing among people with PD have rarely been investigated. Research examining effects of yoga is often based on the biomedical model, which overlooked the role of psychosocial factors. The results of this pilot study could provide preliminary data regarding effects of yoga on promoting both psychosocial, physiological and spiritual wellbeing among people with PD.

With the successful implementation of the yoga project among PD population, it is expected that individuals living with chronic illness like PD would demonstrate a reduced level of psychological distress and thus, adopting a more active lifestyle and active role in disease management. Such information will not only provides solid evidence to formulate community exercise programme to enhance HRQoL of PD population, but also inform future research in investigating the underlying mechanism of yoga in promoting psychosocial, physiological and spiritual wellbeing among people with chronic illnesses.

4. Aim & Objectives

This study aims to examine the effect of yoga on the psychological well–being of individuals with mild–to–moderate PD. The objectives will be as follows: To investigate the effect of a structured mindfulness yoga program on (i) psychological well–being, (ii) physiological well–being, (iii) spiritual well–being, and (iv) HRQoL in individuals with mild–to–moderate PD.

Hypotheses

We hypothesize that (1) the structured mindfulness yoga programme will be effective in improving psychological well–being, physiological well–being, spiritual well–being, and HRQoL in individuals with mild–to–moderate PD, and (2) the structured mindfulness yoga programme will be superior compared to stretching and resistance training exercise in improving psychological well–being, physiological well–being, spiritual well–being, and HRQoL in individuals with mild–to–moderate PD.

5. Plan of investigation

Study design

This study is a single–blind, randomized controlled trial (RCT). Eligible participants will be randomized into experimental or control group with an allocation of 1:1, through a permuted block randomization. The flow diagram and data collection plan of the study is shown in Figure 1 and Figure 2.

Figure 1. Flow diagram of the study

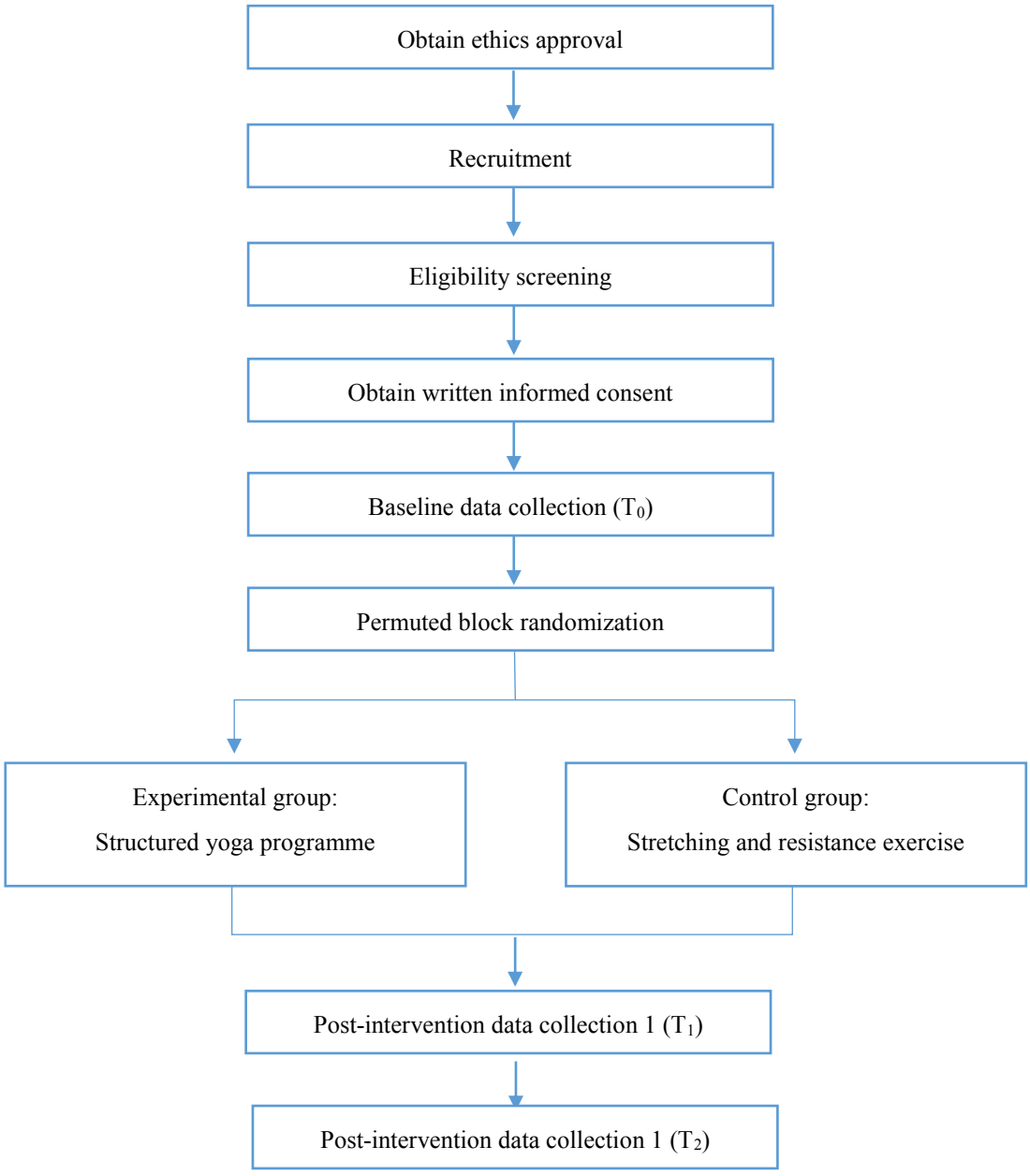

Figure 2. Data collection plan

	Baseline (T_0)	Implementation of intervention/ control	Post-intervention (T_1)	Post-intervention (T_2)
Eligibility screening	✓			
Informed consent	✓			
Demographic Sheet	✓			
Baseline assessment	✓			
Randomization	✓			
I: Intervention C: Control		✓		
HADS; TUG; MDS UPDRS III; HWS; PDQ-8;	✓		✓	✓

Time points for data collection:

T_0= before the intervention (baseline)

T_1= post-intervention 1 (at completion of intervention)

T_2= post-intervention 2 (three months following the completion of intervention)

Subject

People who have been diagnosed with idiopathic PD will be recruited with the following eligibility criteria. Inclusion criteria include the following: (a) a clinical diagnosis of idiopathic PD, with a disease severity rating of stage I to III on the Hoehn and Yahr scale; (b) age above 18 years old; (c) ability to stand unaided and walk with or without an assistive device; and (d) participants who can give written consent. Exclusion criteria are the following: (a) participants who are currently receiving treatment for mental disorders or with uncontrolled mood disorders; (b) current participation in any other behavioral or pharmacological trial or instructor–led exercise program; (c) cognitive impairment as indicated by the abbreviated mental test lower than 6; and (d) other debilitating conditions except PD, e.g. hearing or vision impairment, that can impede full participation in the study.

Sampling method

Convenience sampling will be used. Potential study participants will be recruited through two major sources: (1) local PD support groups like the Hong Kong PD Association and Hong Kong Society of Rehabilitation; and (2) local medical clinics.

Sample size calculation

According to a meta–analysis of the effects of yoga on depression compared with aerobic exercise, a moderate effect size of 0.59 was reported for individuals with elevated levels of depression.

In addition, a moderate to large effect size of 0.79 on anxiety was found when comparing yoga with relaxation (19). To anticipate the effect size of at least 0.59 for our primary outcomes (depression and anxiety) and using the power analysis software Gpower 3.1, 47 subjects per arm give a two–arm RCT 80% power to detect an effect size of at least 0.59 at 5% level of significance. Considering previous RCTs of mind–body interventions among people with PD (20), an attrition rate of 25% is taken into consideration. Therefore, 126 subjects with 63 per arm will be recruited.

Experimental group

A structured yoga programme will be provided to the participants in the experimental group. Participants will attend a 90–minute yoga session once a week and be encouraged to perform a 20–minute home–based practice twice a week for eight weeks. A class size of 15 participants is planned in order to provide adequate instructional attention to each participant and to allow the intervener to perform the required training routines. For yoga intervention, yoga instructor with certification of recognized organizations (e.g. Yoga Alliance) and at least two years of yoga teaching experience among individuals with chronic illnesses will be recruited.

Twelve basic Hatha yoga poses, which is known as sun salutations (surya namaskar), with controlled breathing (pranayama) and mindfulness meditation (dhyana) will be taught. This set of yoga motions and postures has been described as the most complete yoga exercise available, which is a gentle yet dynamic form of exercises, involving static stretching while exerting optimal stress on the cardiorespiratory system. During the mindful practice of sun salutations, participants are taught to control their breathing and to envisage vital energy flowing

freely between body and mind, forming a deep connectedness to mind and spirit, reaching a state of equanimity. In order to assure the ecological validity of the novel intervention, including appropriateness and applicability, the yoga protocol will be reviewed by a representative panel of seven experts with clinical expertise. The expert panel will consist of one neurologist, one physiotherapist, one occupational therapist, one nurse specialized in Parkinson's disease, one experienced researcher specialized in physical education relating to balance and fall among aging population, two yoga instructors with experienced working with individuals with chronic illnesses.

Control group

To enhance the internal validity of the study, the participants in the control group will receive a weekly 60–minute stretching and resistance exercise and be encouraged to perform a 20–minute home–based practice twice a week for eight weeks. This set of stretching and resistance exercise has been validated in previous study for older adults with osteoarthritis knee (Lee, 2011), an allied health professional will be recruited to deliver the intervention. These regular gatherings aim to balance the emotional effect of the weekly gathering of the experimental groups during the study period. No information relating to yoga, mindfulness meditation and psychological distress will be covered in stretching and resistance exercise classes. A class size of around 30 participants is planned.

Outcome measurements

1. Primary outcome
    (i) Psychological distress:

    HADS (Chinese–Cantonese Version). The HADS is a self–reported questionnaire used to measure the level of psychological distress (21). It is an instrument designed for screening mood disorders in general, non–psychiatric settings. It has been suggested for use in PD population as somatic symptoms which may potentially overlapping parkinsonian manifestations were not assessed in this scale (22-24). It is a 14–item scale that consists of an anxiety and depression subscales, with a total score of 42. Each subscale consists of seven statements which is rated by a four–point scale. Higher scores represent greater level of anxiety or depression. Regarding the psychometric properties of Chinese–Cantonese version of HADS, it demonstrated good reliability with a Cronbach's alpha of 0.86 for the overall scale, 0.82 for the depression subscale and 0.77 for the anxiety subscale. Satisfactory construct validity was reported through factor analysis. Satisfactory concurrent validity has been demonstrated by the close correlation with the Hamilton Rating Depression Scale of Depression ($r = 0.67$, $p < 0.001$) and Hamilton Rating Depression Scale of Anxiety($r = 0.63$, $p < 0.001$). Criterion validity has been established to successfully discriminate people with or without adjustment disorder and major depression. A cut–off value of 15 for the full scale is used to indicate the presence of psychological distress, with a sensitivity of 0.79 (95% CI = 0.66–0.90) and a specificity of 0.80 (95% CI = 0.69–0.91) (25).

2. Secondary outcomes

(i) Motor symptoms:

Movement Disorders Society – Unified Parkinson's Disease Rating Scale – Part III Motor Examination (MDS–UPDRS III) is an 18–item assessor–rated instrument assessing severity of PD motor symptoms. Each item is scored on a "0" to "4" on a categorical scale, in which "0" indicates no impairment and "4" represents severe impairment. The total score is 132. Higher scores indicate more motor disabilities. This scale has demonstrated excellent internal consistency with a Cronbach's alpha of 0.93. Excellent concurrent validity has been demonstrated by the good correlation with the original UPDRS ($r = 0.96$, $p < 0.001$) (44).

(ii) Mobility, balance and fall risk:

Time Up and Go test (TUG) is a simple test used to assess mobility, balance and fall risk in older adults. It counts the time required for a participant to rise from chair, walk for three meters, turn around, walk back to the chair and sit down. Satisfactory test–retest reliability has been demonstrated among PD population with ICC ranging from 0.80 to 0.85 (26). Excellent concurrent validity was demonstrated by the good correlation with the Berg Balance Scale ($–r = 0.78$, $p < 0.001$) (27). The minimal detectable change for Chinese population with PD is 3.5 seconds (26). The cut off score for fall prediction among PD is 11.5 seconds with a sensitivity of 0.66 and specificity of 0.62 (28).

(iii) Spiritual wellbeing

Holistic Wellbeing Scale (HWS) is used to measure the perceived state of holistic wellbeing. It is a 30–item questionnaire to evaluate two domains of holistic wellbeing, including (i) the absence of affliction characterized by bodily irritability, emotional vulnerability and spiritual disorientation; and (ii) the presence of equanimity in terms of general vitality, mindful awareness, non–attachment and a spiritual self–care. Each item is rated by a '0–10' scale, '0' represents totally disagree while '10' indicates totally agree. Full marks of HWS is 300, the higher scores indicate a worse state of holistic wellbeing. The Cronbach's alphas and ICC for the novel three factors ranged from 0.708 to 0.885 and from 0.894 to 0.930, respectively, which indicated high internal consistency reliability and high stability (29).

(iv) HRQoL

PDQ–8 (Traditional Chinese Hong Kong version). PDQ–8 is a short–form eight–item questionnaire used to quantify the impact of PD on HRQoL of patients (30). It assesses eight domains including mobility, activities of daily living, emotional wellbeing, stigma, social support, cognitions, communication and bodily discomfort. A PDQ–8 summary index will be generated, higher scores indicate worse HRQoL. It has been widely used to assess the effects of alternative therapies like Tai Chi and dance in the management of PD (31, 32). The internal consistency of Chinese PDQ–8 has been validated with a Cronbach's alpha of 0.87, and construct validity has been demonstrated against the Hoehn and Yahr stage and UPDRS motor scores (33).

Data collection

Eligibility of potential participants will be screened by the principal investigator. For those eligible individuals, information sheet of the study will be provided and written informed consent will be sought. After signing the written informed consent, information related to demographics and health background will be collected by the principal investigator.

The randomization sequence will be generated by a statistician with the use of computer software. Details of the group allocation will be concealed on cards inside a sequentially–numbered series of sealed opaque envelopes. Envelopes will then be passed to a research assistant who is responsible for allocating and contacting participants to their assigned group. The names of participants will be coded and replaced by numbers.

All primary and secondary measures will be assessed at baseline (T0), two months (T1; completion of intervention) and three months following the completion of the intervention (T2). The principal investigator, who is blinded to the subject allocation, will be responsible for all clinical assessment and data collection. All assessment will be conducted one hour after participants taking their usual PD medications ("on" state), so as to minimize motor fluctuation and variability of motor symptoms among participants. Baseline and post–intervention assessments will be performed within one week of the predefined time–point. Participants will be instructed to follow their normal medication schedule and physical activity, and not to start any new exercise programme throughout the study peroid. Participants will be instructed not to reveal their group status to the study assessors at any time–point.

Progress evaluation, including semi–structured interviews of both participants and instructors, will be performed at the end of the programme. Any problems encountered will be recorded and modification will be made accordingly for future full scale study.

Data analysis

Baseline characteristics will be summarized and presented using appropriate descriptive statistics. Normality of the variables will be assessed by using the skewness statistic and normal probability plot. Baseline characteristics between two groups will be compared using independent–t test for continuous variables and the chi–square or Fisher's Exact test for categorical variables. Generalized estimating equations (GEE) analysis will be adopted to adjust for any significant differences in baseline characteristics. Baseline characteristics of the participants who completed the study will be compared with those who did not finish the study. All primary and secondary outcomes will be compared between groups on the basis of intention–to–treat (ITT) principle. GEE models will be used to assess differential change of each primary and secondary outcomes across different time–points between two groups. IBM SPSS 22.0 software will be used for all statistical analysis. Two–tailed test will be used and statistical significance will be set at a p–value < 0.05.

Ethical considerations

Permissions to conduct this study in the selected patient support associations will be sought from the association–in–charge. Written informed consent will be obtained from the eligible participants. The participation is on

voluntary–basis and participants could withdraw from the study at any time–point. All data will be kept in a locked and secured cabinet in an office located in The Chinese University of Hong Kong. This protocol is stated in compliance with the declaration of Helsinki.

Participants are instructed to report any unexpected or unusual symptom to the principal investigator. A project adverse log will be used to document the event of adverse events. Any major serious adverse event will be reported immediately to the ethics committee.

6. References

1. Bach JP, Ziegler U, Deuschl G, Dodel R, Doblhammer-Reiter G. Projected numbers of people with movement disorders in the years 2030 and 2050. Movement disorders : official journal of the Movement Disorder Society. 2011;26(12):2286-90.

2. Pfeiffer RF. Non-motor symptoms in Parkinson's disease. Parkinsonism & related disorders. 2016;22 Suppl 1:S119-22.

3. Simpson J, Lekwuwa G, Crawford T. Predictors of quality of life in people with Parkinson's disease: evidence for both domain specific and general relationships. Disability and rehabilitation. 2014;36(23):1964-70.

4. Quelhas R, Costa M. Anxiety, depression, and quality of life in Parkinson's disease. The Journal of neuropsychiatry and clinical neurosciences. 2009;21(4):413-9.

5. Soundy A, Stubbs B, Roskell C. The experience of Parkinson's disease: a systematic review and meta-ethnography. TheScientificWorldJournal. 2014;2014:613592.

6. Simpson J, McMillan H, Reeve D. Reformulating psychological difficulties in people with Parkinson's disease: the potential of a social relational approach to disablism. Parkinson's disease. 2013;2013:608562.

7. Leentjens AF, Driessen G, Weber W, Drukker M, van Os J. Mental health care use in Parkinson's disease: a record linkage study. Neuroepidemiology. 2008;30(2):71-5.

8. Menza M, Dobkin RD, Marin H, Mark MH, Gara M, Buyske S, et al. The impact of treatment of depression on quality of life, disability and relapse in patients with Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 2009;24(9):1325-32.

9. Ravina B, Marder K, Fernandez HH, Friedman JH, McDonald W, Murphy D, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. Movement disorders : official journal of the Movement Disorder Society. 2007;22(8):1061-8.

10. Hales DJ, Rapaport, M. H., & Moeller, K. . Major Depressive Disorder: Maintenance of Certification Workbook. Arlington, VA: American Psychiatric Association; 2012.

11. Herring MP, Puetz TW, O'Connor PJ, Dishman RK. Effect of exercise training on depressive symptoms among patients with a chronic illness: a systematic review and meta-analysis of randomized controlled trials. Archives of internal medicine. 2012;172(2):101-11.

12. Lindau ST, Laumann EO, Levinson W, Waite LJ. Synthesis of scientific disciplines in pursuit of health: the Interactive Biopsychosocial Model. Perspectives in biology and medicine. 2003;46(3 Suppl):S74-86.

13. Riley D. Hatha yoga and the treatment of illness. Alternative therapies in health and medicine. 2004;10(2):20-1.

14. Monroe R, Nagarathana, R., & Nagendra, H. R. Yoga for common ailments. New York/ London: Simon &

Schuster; 2010.

15. Streeter CC, Gerbarg PL, Saper RB, Ciraulo DA, Brown RP. Effects of yoga on the autonomic nervous system, gamma-aminobutyric-acid, and allostasis in epilepsy, depression, and post-traumatic stress disorder. Medical hypotheses. 2012;78(5):571-9.

16. Woolery A, Myers H, Sternlieb B, Zeltzer L. A yoga intervention for young adults with elevated symptoms of depression. Alternative therapies in health and medicine. 2004;10(2):60-3.

17. McHugh JE, Lawlor BA. Exercise and social support are associated with psychological distress outcomes in a population of community-dwelling older adults. Journal of health psychology. 2012;17(6):833-44.

18. Salmon P, Lush, E., Jablonski, M., & Sephton, S. E. . Yoga and mindfulness: Clinical aspects of an ancient mind/body practice. Cogn Behav Pract. 2009;16(1):59-72.

19. Cramer H, Lauche R, Langhorst J, Dobos G. Yoga for depression: a systematic review and meta-analysis. Depress Anxiety. 2013;30(11):1068-83.

20. Kwok JY, Choi KC, Chan HY. Effects of mind-body exercises on the physiological and psychosocial well-being of individuals with Parkinson's disease: A systematic review and meta-analysis. Complement Ther Med. 2016;29:121-31.

21. Leung CM, Ho S, Kan CS, Hung CH, Chen CN. Evaluation of the Chinese version of the Hospital Anxiety and Depression Scale. A cross-cultural perspective. Int J Psychosom. 1993;40(1-4):29-34.

22. Mondolo F, Jahanshahi M, Grana A, Biasutti E, Cacciatori E, Di Benedetto P. The validity of the hospital anxiety and depression scale and the geriatric depression scale in Parkinson's disease. Behav Neurol. 2006;17(2):109-15.

23. Rodriguez-Blazquez C, Frades-Payo B, Forjaz MJ, de Pedro-Cuesta J, Martinez-Martin P, Longitudinal Parkinson's Disease Patient Study G. Psychometric attributes of the Hospital Anxiety and Depression Scale in Parkinson's disease. Mov Disord. 2009;24(4):519-25.

24. Schrag A, Barone P, Brown RG, Leentjens AF, McDonald WM, Starkstein S, et al. Depression rating scales in Parkinson's disease: critique and recommendations. Movement disorders : official journal of the Movement Disorder Society. 2007;22(8):1077-92.

25. Leung CM, Wing YK, Kwong PK, Lo A, Shum K. Validation of the Chinese-Cantonese version of the hospital anxiety and depression scale and comparison with the Hamilton Rating Scale of Depression. Acta psychiatrica Scandinavica. 1999;100(6):456-61.

26. Huang SL, Hsieh CL, Wu RM, Tai CH, Lin CH, Lu WS. Minimal detectable change of the timed "up & go" test and the dynamic gait index in people with Parkinson disease. Physical therapy. 2011;91(1):114-21.

27. Brusse KJ, Zimdars S, Zalewski KR, Steffen TM. Testing functional performance in people with Parkinson disease. Physical therapy. 2005;85(2):134-41.

28. Nocera JR, Stegemoller EL, Malaty IA, Okun MS, Marsiske M, Hass CJ. Using the Timed Up & Go test in a clinical setting to predict falling in Parkinson's disease. Archives of physical medicine and rehabilitation. 2013;94(7):1300-5.

29. Chan CH, Chan, T. H., Leung, P. P., Brenner, M. J., Wong, V. P., Leung, E. K., ... & Chan, C. L. . Rethinking Well-Being in Terms of Affliction and Equanimity: Development of a Holistic Well-Being Scale. Journal of Ethnic And Cultural Diversity in Social Work. 2014;23(3-4):289-308.

30. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's Disease Questionnaire (PDQ-

39): development and validation of a Parkinson's disease summary index score. Age Ageing. 1997;26(5):353-7.

31. Li F, Harmer P, Liu Y, Eckstrom E, Fitzgerald K, Stock R, et al. A randomized controlled trial of patient-reported outcomes with tai chi exercise in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 2014;29(4):539-45.

32. Cugusi L, Solla P, Zedda F, Loi M, Serpe R, Cannas A, et al. Effects of an adapted physical activity program on motor and non-motor functions and quality of life in patients with Parkinson's disease. NeuroRehabilitation. 2014;35(4):789-94.

33. Tan LC, Lau PN, Au WL, Luo N. Validation of PDQ-8 as an independent instrument in English and Chinese. Journal of the neurological sciences. 2007;255(1-2):77-80.