

Official Title: Evaluation of an individualized exercise programme plus behavioural change enhancement strategies for managing general fatigue in community dwelling frail older people: A cluster-randomized controlled trial

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A. Background of Research

Disease-induced fatigue that is manifested by physical or mental illness and / or is a consequence of treatments and medications is a common topic of research in disease management. Such fatigue can be managed by addressing medically treatable causes (15). However, many older people experience general fatigue with no specific known cause. This type of fatigue has been reported in 27-53% of community- dwelling older people worldwide (16). General fatigue is partly caused by age-related bio- physiological changes, such as reduced muscle strength and mass, leading to decreased muscle endurance. This, together with a gradual decline in cardiovascular and pulmonary functions also leads to a reduction in the maximal heart volume and to a decrease in the vital capacity and expiratory volume of older people. These changes predispose older people to reduce their rate of oxygen consumption during activities, and cause them to feel more fatigue when performing even mild daily activities (1). The general fatigue experienced by older people has been likened to a continuum between mild ‘tiredness’ and severe ‘exhaustion’ (17). Exhaustion (a severe level of fatigue) may not be relieved by rest, leading to a decreased capacity for everyday physical and mental activities (17). The terms ‘exhaustion’ and ‘fatigue’ are used interchangeably in most studies, and also in this proposal. Longitudinal studies have shown that older people with self-reported general fatigue have more restricted activities(3), poorer physical function, slower gait speed, and disability(4, 5), increased utilization of home-help and hospital services(6), and even a higher risk of mortality in the long term (i.e., 3-5 years)(18). In fact, exhaustion, together with unintentional weight loss, low levels of activity, a slow walking speed, and a decreased grip strength are the five phenotypes of frailty(7). This physiological state of increased vulnerability to stressors results from a decrease and possible dysregulation of reserves in multiple physiological / biologic systems (8, 19-21). Epidemiological studies have found that exhaustion is one of the most common characteristics exhibited in older people with frailty. A longitudinal study of 420 non-frail older women found that women with exhaustion were 3-5 times more likely to develop frailty seven years later (at which 80% of them developed frailty) when compared with those without exhaustion(2). The empirical evidence shows that general fatigue is prevalent among older people and can predict frailty and disability in the long term. This evidence raises the concern that a decrease in the production of energy or an inability to cope with an increased utilization of energy could be very much a part of the transition to a final common pathway of frailty and disability. Despite this, the management of fatigue has not yet received adequate attention in gerontological care (12).

Likelihood of exercise interventions in managing general fatigue among older people:

Studies investigating the effects of exercise interventions on the general fatigue experienced by older people are currently lacking (15). However, the evidence suggests that patients with disease-induced fatigue feel less exhausted and more energetic as a result of engaging in regular exercise. Fortunately, recent studies have shown that among people who consistently feel exhausted, those who are willing to gradually exceed their perceived energy limits and recondition their bodies by

participating in exercise programmes gradually experience less fatigue (11, 25, 26). Although the causal pathways for different types of fatigue are not the same, the self-perpetuating vicious cycle of fatigue explained under the decondition model is similar between sufferers with different types of fatigue (27). Additionally, exercise targeting the muscle strength, mobility (28, 29), and cardio-respiratory (30) fitness of older people can improve functional capacity, and may improve their perception and condition of fatigue (31).

Rationale for combining exercise therapy with a behavioural change intervention

Older people can only obtain all of the benefits of exercise after they have engaged in regular exercise at their individual attainable level for 3-5 months (32). Over-sensitivity to physical responses such as mild muscle tiredness after exercise may have led to the avoidance of physical activity; thus, high dropout rates were reported among participants with fatigue in the exercise groups (25, 26). A review reported that the dropout rate can be up to 25% when exercise interventions are implemented among older people with various health problems. As pre-existing multiple health problems (such as pain and fatigue) are common among older people, it is not surprising that fatigue was a common cause of their non-adherence or withdrawal in controlled trials of exercise programmes (15, 24). Nevertheless, if prescribed exercise levels are beyond their physical and psychological capabilities, this may also lead to exhaustion, causing them to drop out. To overcome this problem, it is suggested that behavioural change enhancement strategies focusing on enhancing motivation be given alongside an exercise programme (22, 23, 26, 33). The Health Action Process Approach (HAPA) model divides the process of behavioural change into two phases: motivation and volition (34). The motivation phase refers to the goal initiation phase. ‘Self-efficacy’, ‘outcome expectancies’, and ‘increased risk awareness’ are the three attributes that motivate individuals to form an intention / goal to change their unhealthy lifestyle for a healthy lifestyle. The volition phase refers to the process of implementing intentions into actual behaviour through careful planning and action execution (Appendix I: Figure of HAPA). The empirical evidence shows that the HAPA model can be effectively used as a conceptual framework to design concrete strategies to motivate behavioural changes. Used alongside exercise interventions, these strategies can promote adherence to exercise regimes among those undergoing orthopedic rehabilitation (35) and cardiac rehabilitation (36, 37), and among older patients with sedentary lifestyles (38).

B. Research plan and methodology (Appendix 1: Research flowchart)

Aim: The aims of this study are to investigate the effects of an individualized exercise programme with and without BCE strategies for community-dwelling frail older people with general fatigue, so as to reduce their fatigue and improve their physical endurance, exercise self-efficacy, and habitual physical activity, while reducing their symptoms of frailty.

Design: A single-blinded three-arm cluster-RCT is proposed to examine the effect of a 16-week individualized exercise programme with or without BCE strategies for frail older people with general fatigue. To explore the way in which the combined intervention will be implemented (42), a focus group with 30 COMB participants (4-6 per group) will be interviewed by a trained research assistant (RA) to identify the strengths, limitations, and therapeutic components of the combined intervention from their perspectives.

Subjects and Settings: Eligibility criteria for district community health centres are those that are funded by the Hong Kong (HK) government and under the supervision of the Social and Welfare Department of HK, and thus that meet a specific set of standard regulations and criteria on environment and practices. All twelve community centres, which provide similar types of community care and social support services for community dwelling older people, have been invited by a convenience method to work as collaborators in this study. The target population of this study are community-dwelling frail older people with general fatigue with a nonspecific cause who will be recruited through the community centres.

Sample size estimation, recruitment procedures, random allocation, and allocation concealment:
The changes in the mean fatigue scores were -0.58, -5.16, and -2.66 for the control, EXER, and COMB groups respectively, from pre-test to immediately post-intervention in the pilot study. The Cohen's d effect sizes for the EXER and COMB groups were 0.51 and 0.23, respectively; whereas the overall effect size was 0.21. As no similar cluster-RCT has been reported in the literature and the cause of general fatigue is heterogeneous, we assumed that an intra-correlation coefficient would be low (0.01) within each cluster (43). Based on an effect size of 0.21 in the pilot study, and four clusters (community centres) per group with an intraclass correlation of 0.01, a significance level (α) of 0.05, and a power ($1-\beta$) of 0.8 for a two-sided test, the sample size was calculated to be 76 participants per group according to NCSS PASS 14. For a long-term follow-up of 12 months, 285 participants (95 per group) will be recruited after considering an attrition rate of 20%. Using computer-generated random numbers, a biostatistician not affiliated with this study will randomize the centres into either: control, EXER, or COMB. The randomization will be stratified based on the size of the centres. Small-medium centres will be defined as those with < 800 ($n=9$) clients, whereas those with > 800 clients will be defined as large ($n=3$). The number of participants recruited in each centre will be in proportion to the size of the centre (i.e., the total number of clients). We estimate that about 25-50% (4, 16, 44) of the 8,710 members of these centres will be eligible to participate. To avoid selection biases, the allocation to the study groups will be concealed from the researchers until the recruitment of the sample and measurement of the baseline have been completed (please refer to the item 13 in this application for details of the collaborators).

The Inclusion Criteria are: 1) community-dwelling older people aged > 70 years; 2) able to communicate in Cantonese to ensure that they understand our instructions; 3) able to walk with or without an assistive device and able to complete the Time Up and Go (TUG) test with no specific cutoff point to ensure that their mobility and balance is good enough to join the exercise training; and 4) in a frail state with exhaustion as determined using the Fried Frailty Index (FFI)(7), including: i) an unintentional loss of 10% of body weight in the past year; ii) exhaustion: by answering 'Yes' to either 'I felt that everything I did was an effort', or 'I could not get going in the last week'; iii) a slow walk time: with an average walking speed in the lowest quintile stratified by median body height; iv) reduced grip strength: with maximal grip strength in the lowest quintile stratified by body mass index quartile; and v) the Physical Activity Scale for the Elderly-Chinese (PASE-C) score in the lowest quintile (i.e., < 30 for men and < 27.7 for women). The presence of > 3 items indicates frailty, and one criterion indicates that they suffer from exhaustion.

Sample selection for the focus group: Purposive samples of 30 participants (31.5%) from the COMB group will be selected to join in one interview (if needed, a second interview will be organized for follow-up questions and clarifications). To obtain a wide variety of opinions, six focus groups interviews (4-6 participants per group) will be conducted with 10 participants who had a significant positive reduction in their fatigue scores of > 5 out 20 total score, 10 with a minimal reduction in their fatigue scores of between 1-5, and 10 with no or negative changes on their fatigue score between the baseline and post-test 1 measurement.

Interventions: (*Appendix II:* Overview of the combined intervention) A 16-week programme with a combination of exercise and the BCE programme (plus two booster BCE sessions will be held at 2 and 6 months after the programme) will be arranged for the COMB group. Another 16-week programme with a combination of exercise and health talks will be arranged for the EXER group, whereas participants in the control group will attend only the health talks with no other intervention. Two added health talks will be arranged at 2 and 6 months after the programme for the EXER and the control groups. To control the group and social interaction effects of the BCE programme for the COMB group, the number and timing of the health talks for the other two groups will be similar to those in the BCE sessions. All face-to-face sessions will have < 10 participants to maintain good interactions between the participants and the exercise instructor / BCE facilitator/ health talk speakers.

The behavioural change enhancement (BCE) programme in the COMB group (Appendix III: BCE programme protocol) aimed at motivating the participants to develop the intention to actively manage their fatigue; and to encourage them to gradually exceed the perceived limits of their energy and to recondition their bodies by participating in exercise according to their individual exercise regimens. The BCE programme was designed based on the HAPA model and was piloted by the PI

(14). It consists of three phases with six face-to face one-hour sessions plus two booster BCE sessions at 2 and 6 months. The first three weekly sessions will be arranged during the ‘goal initiation’ and ‘planning’ phases. The remaining three sessions and two booster sessions will be offered once per month in weeks 4, 8, and 12 during the programme; and at 2 and 6 months after the programme during the ‘action execution’ phase.

Exercise intervention in the EXER and the COMB groups: A weekly 45-60 minute centre-based exercise programme, which designed according to the American Heart Association’s recommendations on exercise for older people (48), will be arranged from weeks 4-16 during the execution phase. This programme will consist of balance training, such as sideways walking (15-20 minutes); resistance exercises, such as using resistance bands to improve muscle strength in both the upper and lower limbs (10-20 minutes); aerobics training, such as walking (10 minutes) and with 10 minutes of warm-up and cool-down exercises at the beginning and at the end. All participants will receive circuit training with set exercises, but the dosage of different components will be tailor-made for each participant based on his/her physical conditions. The first assessment will be in week 4 (i.e., the first week of the exercise programme), and subsequent monthly assessments will be held in weeks 8 and 12 by a physiotherapist. The dosage of exercises will gradually increase by increasing the number of repetitions, the duration of the exercises, and also by using progressively heavier wrist and ankle weights maintained at approximately 12-14 on the Borg Rate of Perceived Exertion Scale(28, 49), based on the participants’ progress. The dosage of exercise recommended to each participant by the physiotherapist will be recorded. Demonstrations and return demonstrations will be performed during the training to ensure that the participants are able to do the exercises properly. A compact disc and a pamphlet describing the different types of exercises used in this programme will be disseminated to all participants to encourage them to continually practice their exercises at home for approximately 30 minutes at least 3 times per week. Although this set of exercises was used in the pilot study with no reports of adverse effects, safety guidelines on exercise for older people will be discussed with all of the participants.

The Control Condition: Participants in the control and EXER groups will attend centre-based health talks on the management of different health issues with the exception of fatigue. Another RA, who will not be involved in other procedures of this study, will run the health talks.

Instruments and Measures

Participants will be assessed on a variety of outcomes (described below) at week 8 (T1 at mid-term programme), 1 week (T2 immediate effect), 6 and 12 months after the programme (T3 and T4), which will be compared with the baseline assessment (T0). All assessments will be carried out by a part-time RA, regarded as an independent assessor, who will be blinded to the group assignments.

Socio-demographic data: The following data will be collected: 1) age, gender, marital status,

exercise habits, living conditions, and level of education, 2) the participants' health-related information, including cognitive status and medications. Additionally, their levels of comorbidity will be assessed using the Chinese version of the Charlson comorbidity index (C-CCI). The C-CCI score is the sum of the comorbidity and age scores, in which scores of 0, 1-2, 3-4, and > 5 represent the comorbidity level as none, low, medium, and high, respectively⁵⁰. The health services utilization of the parents in the past 12 months and during the study period, such as the number, duration, and causes of hospital admissions and scheduled/non-scheduled clinical visits, will be collected during each measurement time point and will be treated as a co-variate if needed.

Primary outcome measurement: Fatigue will be assessed using the 20-item Chinese Multidimensional Fatigue Inventory (CMFI-20)⁽⁵¹⁾. This scale was validated among 385 local cancer patients. A factor analysis revealed that it contains three factors (namely, physical, mental, and spiritual) with a factor loading ranging from 0.52 to 0.75. The Cronbach's α was between 0.7 and 0.8 for three domains and the total of the CMFI-20 score. It supports the view that the CMFI-20 is a reliable and valid instrument.

Secondary outcome measurements

Physical Endurance will be evaluated using different physical tests. First, the participants' lower-limb and upper-limb strength will be assessed using a 30-second chair stand test⁽⁵²⁾ and a handheld Jamar Hydraulic Hand Dynamometer⁽⁵³⁾, respectively. Their mobility and overall physical endurance will be assessed through the TUG test and by their gait speed (6-m walk).

Exercise Self-efficacy: The participants' self-confidence in their ability to exercise in a variety of circumstances (e.g., when feeling tired) will be assessed using the 9-item Chinese Self-Efficacy for Exercise scale (CSEE) (54, 46). The CSEE was validated on 192 Chinese older people. Discriminant validity was shown by the CSEE total score, which significantly differentiated between individuals with or without regular exercise. The Cronbach's α was 0.75, which showed an acceptable level of internal consistency.

Frailty status: This will be assessed based on the FFI mentioned in the sample inclusion criteria (7).

Physical activity level will be assessed using the 10-item PASE-C⁽⁵⁵⁾ to measure self-reported occupational, household, and leisure activities for the last week. Its total score is calculated by multiplying the amount of time spent in each activity (hours / week) by the weight of the pre-set item. PASE-C has been shown across different studies to be a reliable and valid instrument (56, 57).

Depressive Mood: A 15-item C-GDS⁴⁵ will be used on all participants to measure the exhibition of depressive symptoms. The scores '0 to 4', '5 to 9', and '10 to 15' indicate 'normal', 'mild', and 'moderate to severe' depressive mood, respectively. The C-GDS is commonly used in both clinical and research settings, and has shown good reliability and validity^{45, 58}.

Formative or Process Evaluation is aimed at exploring the COMB group participants' perceptions of the strengths and limitations of the intervention. The data will provide valuable insights for the research team to realize / identify the positive components of the combined intervention and the barriers and difficulties faced by the participants in attending/adhering to the intervention.

Procedures: (*Appendix IV*: Detailed Ethical Considerations; *Appendix V*: CONSORT diagram of the Cluster RCT) Ethical and access approval will be obtained from the Ethics Review Committee of The University and study venues, respectively. Potential participants will be referred to the research team by the collaborators. An RA will screen all potential participants for their eligibility to participate in this study. Written informed consent will then be obtained from all of the participants, to whom all aspects of the study will be explained and questions answered. They will then be interviewed to obtain their health-socio-demographic data, and baseline assessment. After that, the twelve community centres will be randomized to either the control, EXER, or COBM group. Participants from each centre will be placed into their centre's corresponding group to avoid 'contamination' effects across participants. At the mid-term programme, 1 week, 6 months, and 12 months post-intervention, an independent assessor who is blinded to the group allocations will assess the participants' outcomes, which will be compared with the baseline assessment. Focus group interviews will be conducted by the trained RA after the first post-test 1 (one-week post-intervention). Purposive samples of 30 participants from the COMB group will be selected to take part in one interview (4-6 per group). They will be asked to comment on their experiences and (dis)satisfaction regarding the programme, perceptions of its positive/negative aspects, concerns and difficulties in participating and adhering to the programme, and ways of improving the intervention. A semi-structured interview guide will be developed for these interviews, which will be conducted in Cantonese, and all interviews will be audio-recorded for content analysis. Examples of interview questions include: "What are your opinions and comments on your participation in the programme?" and "What are your changes and / or difficulties in adherence to the exercise regimen during and after the 16-week programme?"

Intervention fidelity and RA training: The PI will train an RA on how to use all of the outcome instruments with reference to the latest user guidelines for the instruments, so that the RA can act as an independent outcome assessor. The RA will practise using all of the instruments, with clinical vignettes and on-site practise. The inter-/intra-rater reliabilities will be evaluated by the intra-class correlations (ICC). Acceptable levels of reliability (ICC > 0.9) will be established by comparing the scores rated by the assessor and the PI prior to the start of the study, and checking them on a monthly basis throughout the data collection period. These procedures are to ensure that quality assessments are performed as intended. The protocols of the exercise and BCE programmes have been developed and tested in the pilot study (14). They will be used to guide the implementation of all interventions in different sub-groups to ensure standardization throughout the study. The pre-intervention practice of the BCE facilitator and the exercise instructor will be supervised by the research team on one or two small groups of older adults with general fatigue. All BCE and exercise sessions must follow the programme protocol and will be run by the same facilitator/exercise instructor to ensure intervention consistency. Intervention fidelity checking will be conducted in the training period and then monthly to bimonthly during the intervention period based on the BCE facilitation/exercise checklist.

Achieving a fidelity rate of > 90% will be considered acceptable based on the recommendations of the NIH Behaviour Change Consortium (59). This is to ensure that all of the interventions are executed by the exercise instructor or the BCE facilitator as intended. Monthly quality control meetings with all research personnel (the exercise instructor, BCE facilitator, and RAs) will be arranged to evaluate their instruction/facilitation skills in this study.

References:

1. Avlund K. Fatigue in older adults: an early indicator of the aging process? *Aging Clin Exp Res.* 2010; 22(2): 100-15.
2. Xue Q-L, Bandeen-Roche K, Varadhan R, Zhou J, Fried LP. Initial manifestations of frailty criteria and the development of frailty phenotype in the women's health and aging study II. *J Gerontol A Biol Sci Med Sci.* 2008; 63(9): 984-90.
3. Gill TM, Desai MM, Gahbauer EA, Holford TR, Williams CS. Restricted activity among community-Living older persons: incidence, precipitants, and health care utilization. *Ann Intern Med.* 2001; 135(5):313-21.
4. Schultz-Larsen K, Avlund K. Tiredness in daily activities: A subjective measure for the identification of frailty among non-disabled community-living older adults. *Arch Gerontol Geriatr.* 2007; 44(1): 83-93.
5. Hardy SE, Studenski SA. Fatigue and function over 3 years among older adults. *J Gerontol A Biol Sci Med Sci.* 2008; 63(12): 1389-92.
6. Avlund K, Damsgaard MT, Schroll M. Tiredness as determinant of subsequent use of health and social services among nondisabled elderly people. *J Aging Health.* 2001; 13(2): 267-86.
7. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001; 56(3): M146-M57.
8. Drey M, Pfeifer K, Sieber CC, Bauer JM. The Fried Frailty Criteria as inclusion criteria for a randomized controlled trial: personal experience and literature review. *Gerontology.* 2011; 57(1): 11-8.
9. Moschny A, Platen P, Klaaßen-Mielke R, Trampisch U, Hinrichs T. Barriers to physical activity in older adults in Germany: a cross-sectional study. *Int J Behav Nutr Phys Act.* 2011; 8(1): 121-31.
10. Rasinaho M, Hirvensalo M, Leinonen R, Lintunen T, Rantanen T. Motives for and barriers to physical activity among older adults with mobility limitations. *J Aging Phys Act.* 2007; 15(1): 90-102.
11. Clark LV, White PD. The role of deconditioning and therapeutic exercise in chronic fatigue syndrome (CFS). *Journal of Mental Health.* 2005; 14(3): 237-52.
12. Yu DSF, Lee DTF, Man NW. Fatigue among older people: a review of the research literature. *Int J Nurs Stud.* 2010; 47(2): 216-28.
13. Smets EMA, Garssen B, Bonke B, De Haes JCJM. The multidimensional Fatigue Inventory

(MFI) psychometric qualities of an instrument to assess fatigue. *Journal of Psychosomatic Research*. 1995; 39(3):315-25.

14. Liu JY-W, Lai CK, Siu PM, Kwong E, Tse MM. An individualized exercise programme with and without behavioural change enhancement strategies for managing fatigue among frail older people: A quasiexperimental pilot study. *Clin Rehabil*. 2016.
15. Egerton T. Self-reported aging-related fatigue: a concept description and its relevance to physical therapist practice. *Phys Ther*. 2013; 93(10): 1403-13.
16. Hellström Y, Persson G, Hallberg IR. Quality of life and symptoms among older people living at home. *J Adv Nurs*. 2004; 48(6): 584-93.
17. Ream E, Richardson A. Fatigue: a concept analysis. *Int J Nurs Stud*. 1996; 33(5): 519-29.
18. Avlund K, Pedersen AN, Schroll M. Functional decline from age 80 to 85: influence of preceding changes in tiredness in daily activities. *Psychosom Med*. 2003; 65(5): 771-7.
19. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci*. 2004; 59(3): M255-M63.
20. Santos-Eggimann B, Cuénoud P, Spagnoli J, Junod J. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. *J Gerontol A Biol Sci Med Sci*. 2009; 64A(6): 675-81.
21. Ble A, Cherubini A, Volpato S, Bartali B, Walston JD, Windham BG, et al. Lower plasma vitamin E levels are associated with the frailty syndrome: the InCHIANTI Study. *J Gerontol A Biol Sci Med Sci*. 2006; 61(3): 278-83.
22. Cramp F, Byron - Daniel J. Exercise for the management of cancer - related fatigue in adults. *The Cochrane Database Syst Rev* 2012; 11: CD006145.
23. Neill J, Belan I, Ried K. Effectiveness of non-pharmacological interventions for fatigue in adults with multiple sclerosis, rheumatoid arthritis, or systemic lupus erythematosus: a systematic review. *J Adv Nurs*. 2006; 56(6): 617-35.
24. Martin KA, Sinden AR. Who will stay and who will go? A review of older adults' adherence to randomized controlled trials of exercise. *J Aging Phys Act*. 2001; 9(2): 91-114.
25. Larun L, Brurberg KG, Odgaard-Jensen J, Price JR. Exercise therapy for chronic fatigue syndrome. Status and date: New search for studies and content updated (no change to conclusions), published in. 2015; (2).
26. Edmonds M, McGuire H, Price J. Exercise therapy for chronic fatigue syndrome. *Cochrane Database Syst Rev*. 2004; 3.
27. Jones DEJ, Gray JC, Newton J. Perceived fatigue is comparable between different disease groups. *QJM*. 2009.
28. Liu Cj, Latham NK. Progressive resistance strength training for improving physical function in older adults. *Cochrane Database Syst Rev*. 2009; 3: CD002759.
29. Nash KC. The effects of exercise on strength and physical performance in frail older people: a

systematic review. *Rev Clin Gerontol.* 2012; 22(4): 274.

- 30. Simons R, Andel R. The effects of resistance training and walking on functional fitness in advanced old age. *J Aging Health.* 2006; 18(1): 91.
- 31. Network NCC. NCCN clinical practice guideline in oncology: cancer-related fatigue. Available from: www.nccn.org. 2013.
- 32. Theou O, Stathokostas L, Roland KP, Jakobi JM, Patterson C, Vandervoort AA, et al. The effectiveness of exercise interventions for the management of frailty: a systematic review. *J Aging Res.* 2011; 2011.
- 33. Pinto BM, Frierson GM, Rabin C, Trunzo JJ, Marcus BH. Home-based physical activity intervention for breast cancer patients. *J Clin Oncol.* 2005; 23(15): 3577-87.
- 34. Schwarzer R. Modeling health behavior change: How to predict and modify the adoption and maintenance of health behaviors. *Appl Psychol-Int Rev.* 2008; 57(1): 1 - 29.
- 35. Lippke S, Ziegelmann JP, Schwarzer R. Behavioral intentions and action plans promote physical exercise: a longitudinal study with orthopedic rehabilitation patients. *J Sport Exerc Psychol.* 2004; 26(3): 470.
- 36. Scholz U, Sniehotta F, Burkert S, Schwarzer R. Increasing physical exercise levels-Age-specific benefits of planning. *J Aging Health.* 2007; 19(5): 851 - 66.
- 37. Ghisi GLdM, Grace SL, Thomas S, Oh P. Behavior determinants among cardiac rehabilitation patients receiving educational interventions: an application of the health action process approach. *Patient Educ Couns.* 2015; 98(5): 612-21.
- 38. Evers A, Klusmann V, Schwarzer R, Heuser I. Adherence to physical and mental activity interventions: coping plans as a mediator and prior adherence as a moderator. *Br J Health Psychol.* 2012; 17(3): 477-91.
- 39. Chien WT, Bressington D. A randomized controlled clinical trial of a nurse-led structured psychosocial intervention program for people with first-onset mental illness in psychiatric outpatient clinics. *Psychiatry Res.* 2015; 229(1-2): 277-86.
- 40. Chien WT, Mui JH, Cheung EF, Gray R. Effects of motivational interviewing-based adherence therapy for schizophrenia spectrum disorders: a randomized controlled trial. *Trials.* 2015; 16(1): 270.
- 41. Tan PJ, Khoo EM, Chinna K, Hill KD, Poi PJ, Tan MP. An individually-tailored multifactorial intervention program for older fallers in a middle-income developing country: Malaysian Falls Assessment and Intervention Trial (MyFAIT). *BMC Geriatr.* 2014; 14(1): 1.
- 42. Craig P, Dieppe P, Macintyre S, Mitchie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ.* 2008; 337(7676): 5.
- 43. Hemming K, Girling AJ, Sitch AJ, Marsh J, Lilford RJ. Sample size calculations for cluster randomized controlled trials with a fixed number of clusters. *BMC Med Res Methodol.* 2011; 11(1): 1.

44. Wijeratne C, Hickie I, Brodaty H. The characteristics of fatigue in an older primary care sample. *Journal of Psychosomatic Research*. 2007; 62(2): 153-8.
45. Woo J, Ho SC, Lau J, Yuen YK, Chiu H, Lee HC, et al. The prevalence of depressive symptoms and predisposing factors in an elderly Chinese population. *Acta Psychiatr Scand*. 1994; 89(1): 8-13.
46. Lee L, Arthur A, Avis M. Using self-efficacy theory to develop interventions that help older people overcome psychological barriers to physical activity: A discussion paper. *Int J Nurs Stud*. 2008; 45(11): 1690 - 9.
47. Hinrichs T, Moschny A, Brach M, Wilm S, KlaaSZen-Mielke R, Trampisch M, et al. Effects of an exercise programme for chronically ill and mobility-restricted elderly with structured support by the general practitioner's practice (HOMEfit) - study protocol of a randomised controlled trial. *Trials*. 2011; 12(1): 263.
48. Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc*. 2007; 116(9): 1094.
49. Chin A Paw MJM, de Jong N, Schouten EG, Hiddink GJ, Kok FJ. Physical exercise and/or enriched foods for functional improvement in frail, independently living elderly: A randomized controlled trial. *Arch Phys Med Rehabil*. 2001; 82(6): 811-7.
50. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987; 40(5): 373-83.
51. Tian J, Hong J-S. Validation of the Chinese version of Multidimensional Fatigue Inventory-20 in Chinese patients with cancer. *Support Care Cancer*. 2012; 20(10): 2379-83.
52. Rikli R, Jones C. Development and validation of a functional fitness test for community-residing older adults. *J Aging Phys Act*. 1999; 7(2): 129 - 61.
53. Yang XJ, Hill K, Moore K, Williams S, Dowson L, Borschmann K, et al. Effectiveness of a targeted exercise intervention in reversing older people's mild balance dysfunction: a randomized controlled trial. *Phys Ther*. 2012; 92(1): 24-37.
54. Resnick B, Jenkins LS. Testing the Reliability and Validity of the Self-Efficacy for Exercise Scale. *Nurs Res*. 2000; 49(3): 154-9.
55. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol*. 1993; 46(2): 153-62.
56. Ku P-W, Sun W-J, Chang C-Y, Chen L-J. Reliability and validity of the Chinese version of the Physical Activity Scale for the Elderly. *Sports & Exercise Research*. 2013; 15(3): 309-19.
57. Ngai SP, Cheung RT, Lam PL, Chiu JK, Fung EY. Validation and reliability of the Physical Activity Scale for the Elderly in Chinese population. *J Rehabil Med*. 2012; 44(5): 462-5.
58. Chan AC-M. Clinical validation of the geriatric depression scale (GDS) Chinese version. *Journal of Aging and Health*. 1996; 8(2): 238-53.

59. Bellg AJ, Borrelli B, Resnick B, Hecht J, Minicucci DS, Ory M, et al. Enhancing treatment fidelity in health behavior change studies: best practices and recommendations from the NIH Behavior Change Consortium. *Health Psychol.* 2004; 23(5): 443.

60. Stevens JP. Applied multivariate statistics for the social sciences: Routledge; 2012.

61. Krippendorff K. Content analysis: An introduction to its methodology: Sage; 2004.

Appendix I: Figure of HAPA

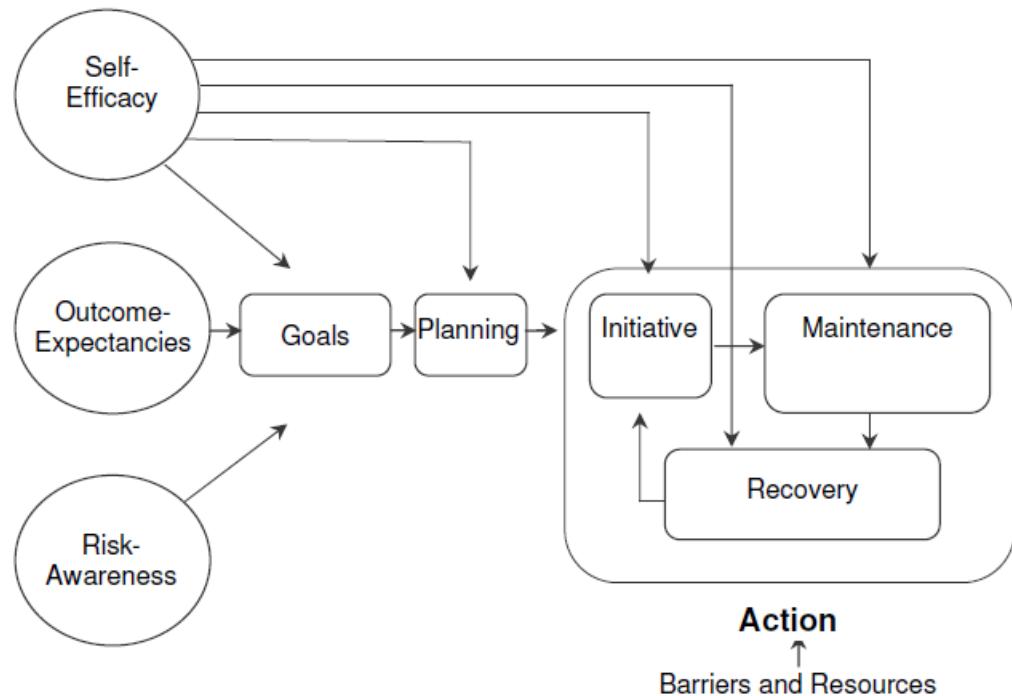


Figure 1: The Health Action Process Approach (HAPA).

Appendix II: Overview of the combined intervention

		@week 8 (half-way point of the intervention)			@1 week after the intervention + Focus groups for 30 participants	@6 months & 12 months after completing the entire programme
		T ₀	T ₁	T ₂	T ₃ and T ₄	
Week		1-2	3	4-16	2 and 6 months after completing of entire programme	
HAPA Phases	Phase 1 Goal Initiation	Phase 1 Goal Initiation	Phase 2 Plan Formation	Phase 3 Action Execution		
	Behavioural Change Enhancement Programme	2 sessions	1 session	<ul style="list-style-type: none"> 3 sessions – 1 session per month in weeks 4, 8, and 12 (i.e., the 1st week of each month in the action execution phase) 	<ul style="list-style-type: none"> 2 booster sessions – 1 session 2 months after completing the entire programme and 1 session 6 months after completing the entire programme 	
Intervention Components	Exercise			<ul style="list-style-type: none"> 12-week centre-based exercise programme on 1) balance 2) resistance exercises, and 3) aerobic training Physiotherapist tailor-made individualized exercise regimen for participants based on an individual physical assessment at weeks 4, 8, and 12 	<ul style="list-style-type: none"> Continue to regularly practise the exercises 	

Appendix III: HAPA Based-behavioural Change Enhancement Programme Protocol

Expected outcomes: The participants will:

- 1) demonstrate a sense of self-control and confidence in managing their fatigue-related health issues,
- 2) agree to gradually exceed their perceived energy limits and recondition their bodies through participating in exercise according to their own exercise regimen.

Size of group: Maximum of 10.

Phases	Session No	Aims	Contents
Goal Initiation	1	<ul style="list-style-type: none"> • To establish the intention to adhere to strategies that address issues related to fatigue • To understand the expected outcomes of the programme • To increase awareness of the negative impacts of unmanaged fatigue • To strengthen self-efficacy 	<ul style="list-style-type: none"> • To get the participants to share their experiences with fatigue • To explain the expected outcomes of the programme and how these outcomes can match the personal goals of the participants • To introduce the participants to the impacts of unmanaged fatigue on physio-psychosocial wellbeing • To introduce the participants to the deconditioning model of fatigue (i.e., avoiding physical activity exacerbates fatigue-related physical symptoms) • To discuss the participants' intention to complete the programme
	2		<ul style="list-style-type: none"> • To introduce the connection between exercise and fatigue • To understand the expected outcomes in older people resulting from regular exercise • To recognize correct / incorrect beliefs about exercise for older people • To recognize and overcome barriers to staying or becoming physically active • To identify the negative impacts of leading a sedentary lifestyle
Plan Formulation	3	<ul style="list-style-type: none"> • To create an action plan and coping plan for adhering to the exercise regimen • To set sub-goals 	<ul style="list-style-type: none"> • To evaluate the participants' current preferences relating to exercise • To set achievable sub-goals with the participants based on the physical and cognitive abilities of individuals • To reassure the participants that the final goals will be divided into several achievable sub-goals according to an individual's progress throughout the programme • To create a detailed action plan of when, where, and how to practise the desired action • To identify an alternative coping plan
Action Execution	4	<ul style="list-style-type: none"> • To encourage action execution • To continue strategies that can enhance the participants' self-efficacy, which include <ul style="list-style-type: none"> • obtaining performance accomplishments • generating social persuasion • gaining vicarious experience • perceiving the positive physiological and emotional responses of engaging in regular exercise 	<ul style="list-style-type: none"> • To self-evaluate levels of compliance with the action plans and the achievement of the sub-goals, so as to let the participants experience success by achieving the (sub) goals • To provide positive feedback and encouragement from peers and the BCE facilitator • To observe peers with similar physical and psychological difficulties related to fatigue adhering to the action plan, participants will be provided with chances to learn about the successful experiences of their peers during the sharing sessions • To continue to refine the sub-goals and the action and coping plans according to the progress, if necessary • To promote positive perceived responses (such as vitalization-enjoyment and improved endurance) after exercise • To guide the participants to develop their own plan for the sustainability of their actions in the future • To round up the participants in the final session (S6) and encourage them to continue the action in the future
	5		
	6		
	Booster Session at 2 nd and 6 th Month		<ul style="list-style-type: none"> • To recap all strategies used in previous sessions during action execution, so as to reinforce the participants' self-efficacy • To review and modify long-term goals / action plans / exercise regimens, etc. • To practise exercises together • To share experiences and thoughts related to <ul style="list-style-type: none"> - Compliance with regular exercise - Fatigue management

Appendix IV: Detailed Ethical Considerations

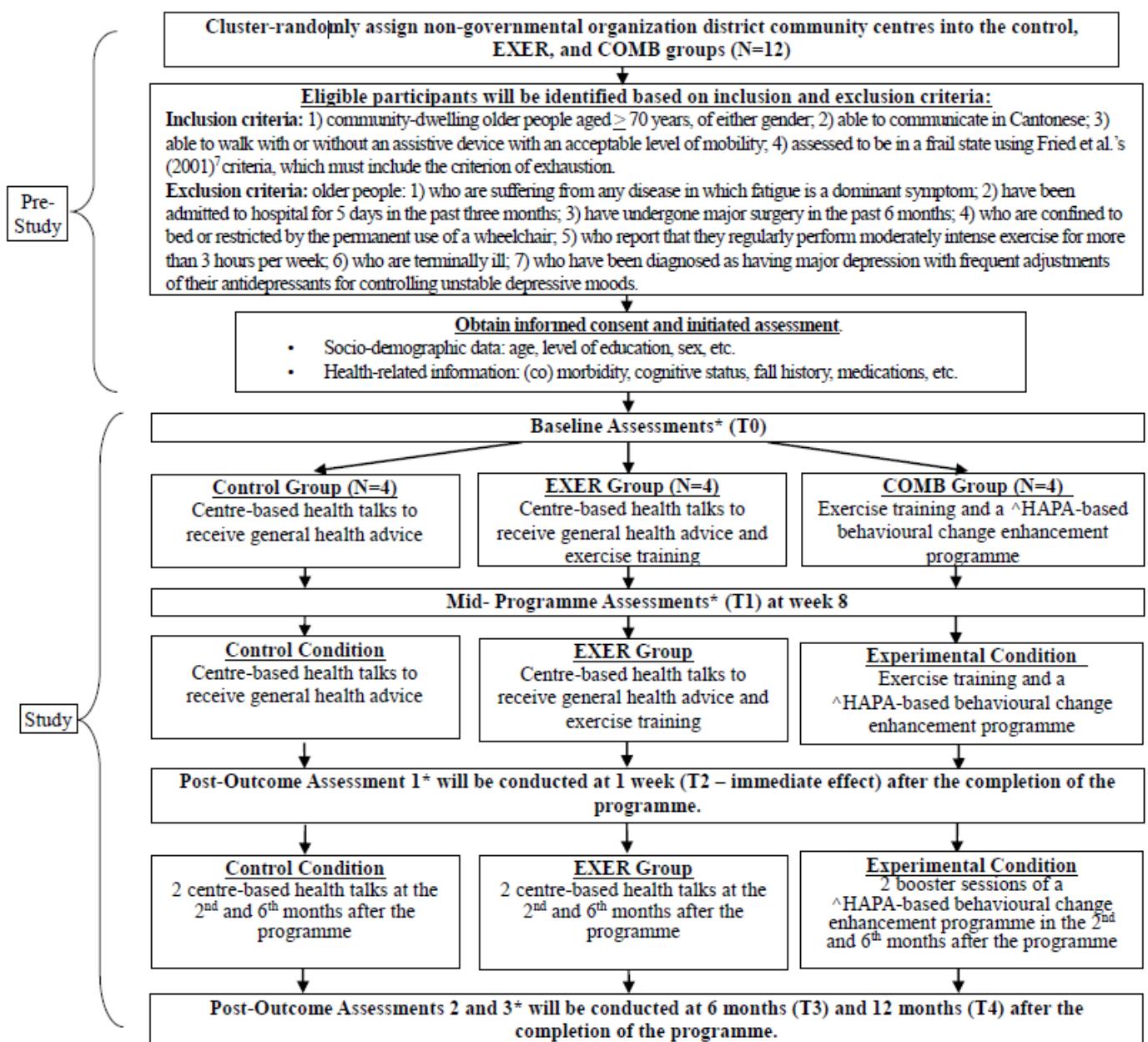
The principle of protecting research subjects in accordance with the Helsinki Declaration will be observed. The data will be kept confidential in accordance with Hong Kong's Privacy Ordinance. All of the research personnel involved will work closely together to monitor the occurrence of untoward effects on the participants. Standard guidelines for managing symptoms of intolerance will be used. For example, a target heart rate (THR) will be identified for each participant. Those at the beginner level will be advised not to exceed 50% to 60% of their THR, with the figure being 60% to 70% for those at the intermediate level. The physiotherapist / the PI (a registered nurse) will give individual participants advice on an ad hoc basis to ensure their safety. Below please see an example of the safety guidelines for preventing falls while exercising at home.

Guidelines for managing older people who fall while doing exercises at home:

After slipping and falling, elderly people should take the following steps to help themselves:

1. Keep calm.
2. Assess the level of injury; move slowly if not severe.
3. Move along the ground to walls or stable furniture, then climb up with the support of the furniture.
4. If you cannot stand up, you may make a call by using the Personal Emergency Link Service / opening the main door and loudly asking for help.
5. Clean the wound first if you get an abrasion.
6. Consult a doctor quickly if you note any problems. You may have a fracture if you have difficulty moving or are in severe pain, even without any obvious wound.
7. All fall accidents should be reported to the research team.
8. In all cases, a follow-up call by phone will be conducted by the PI, who is a registered nurse.

Appendix V: The CONSORT diagram of the cluster randomized controlled trial



*Baseline & Outcome Assessments: Fatigue, Physical Endurance, Exercise Self-efficacy Fried Frailty Index, Habitual Physical Activity, Depressive Mood, Exercise Adherence (only for the EXER & COMB groups);

[^]HAPA: Health Action Process Approach