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# A protocol of rhythmic auditory stimulation for improving upper-limb movements in patients with Parkinson's disease



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# A protocol of rhythmic auditory stimulation for improving upper-limb movements in patients with Parkinson's disease

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## ABSTRACT

**Introduction** Bradykinesia (i.e., slow movements) is one of the most prominent symptoms of Parkinson's disease (PD) and has a negative impact on quality of life. Rhythmic auditory stimulation (RAS), a widely used and promising treatment technique, has been shown to effectively improve gait speed in PD patients. However, only few studies have explored effects of training involving RAS on upper-limb movements. The purpose of this study is to investigate effects of movement training involving RAS on upper-limb movement speed and function in PD patients.

**Methods and analysis** Patients with PD will be randomly assigned into two groups: the RAS group and the no-RAS group. A 21-day upper-limb training involving RAS (for the RAS group) or without RAS (for the no-RAS group) will be provided to the patients. An assessor will administer the box and block test (BBT) and the Jebsen hand function test (JHFT) before and after training to assess upper-limb movement speed and function. The independent sample t-test will be performed to compare the BBT and JHFT scores between groups to determine the effects of RAS. This randomized controlled trial will provide evidence supporting the effectiveness of upper-limb movement training involving RAS in reducing the severity of bradykinesia in PD patients.

**Ethics and dissemination** Ethical approval has been obtained from the Institutional Review Board of the Hong Kong Polytechnic University with the reference number HSEARS20221027005. Informed consent forms will be gathered from all patients before their participation. Study results will be disseminated through conferences and peer-reviewed academic journals.

**Trial registration number** ClinicalTrials.gov NCT05637593


**Keywords** Acoustic stimulation, Parkinson's disease, Arm, Movement, Bradykinesia

## ARTICLE SUMMARY

### Strengths and limitations of this study

- This is a randomised controlled trial that provides robust evidence supporting effectiveness of upper-limb movement training involving RAS in PD patients.
- Results of this study form a base of evidence-based therapy in clinical practice for tackling bradykinesia in PD patients.
- Effects of home-based training are susceptible to patient compliance, which has been considered and addressed through daily phone calls and completion of a daily training log.

## INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disease caused by neurodegeneration of the substantia nigra, resulting in a decrease in dopamine [1, 2]. The incidence of PD is 14 per 100,000 people per year, and even reaches 160 per 100,000 people over the age of 65 years [3]. Dopamine, a neurotransmitter, is important for the function of the basal ganglia in receiving, modulating, and transmitting signals to various cortical areas, including those associated with movements [4]. Therefore, in PD patients, a decrease in dopamine leads to basal ganglia dysfunction in the cortico-striato-thalamo-cortical circuit, resulting in movement symptoms [5, 6]. Bradykinesia, meaning slowness of movements, is one of the most prominent symptoms of PD [7], extensively interferes with performances of daily activities such as eating, writing, and walking [8], and substantially lowers quality of life in patients [9, 10].

Pharmacotherapy has been shown to alleviate movement symptoms in PD patients. Medications, such as levodopa, are able to adjust activities of the putamen and thalamus, modulate signals from basal ganglia to motor-related cortices, and thus enhance movements in patients [11]. However, long-term use of medications increases medication resistance and thus reduces therapeutic effects, as well as increases side effects of medications such as dyskinesia [12, 13]. Therefore, developing non-pharmacological therapies is warranted and of clinical importance in order to tackle bradykinesia in patients with PD.

Rhythmic auditory stimulation (RAS) is repetitive, discrete sounds with a tempo [14, 15]. Because the tempo of human movements is naturally synchronized with the tempo of RAS [16, 17], RAS has a high potential of being applied to movement training to guide human movement execution [18]. Earlier studies [19] have provided solid evidence that training involving RAS is effective in improving gait performance in PD patients. Earlier classic research [20] examining effects of training involving RAS on gaits in PD patients provided 21-day training with 30 minutes

per day, in which RAS with three different tempi (normal RAS, quick RAS, and fast RAS) was provided. Initially, researchers assessed the baseline walking tempo without the aid of RAS for each patient. For daily training, each patient was given normal RAS (100% of the baseline tempo), quick RAS (105% of the baseline tempo), and fast RAS (110% of the baseline tempo) to guide the gaits. Each RAS was increased by 5% when the time went to next week.

Most previous studies that investigated RAS effects in PD patients focused on lower-limb movements such as gaits [19]. However, upper-limb movements are also important for activities of daily living and directly affect quality of life in humans [21]. In addition, it is commonly seen that rehabilitation training for upper-limb movements involves continuous movement repetition, which supports that RAS may be applicable to upper-limb movement therapy. It is worth investigating if upper-limb training involving RAS is effective for PD patients. To date, only few studies [22, 23] have investigated effects of RAS on upper-limb movements in PD patients. A case report [22] indicated that movement training involving RAS may improve finger tapping speed and finger dexterity in PD patients. In addition, a study using the repeated measures design [23] demonstrated that faster RAS immediately induced faster upper-limb movement speed in PD patients. To date, randomized controlled trials have been needed to determine whether long-term training involving RAS is effective in improving upper-limb movement speed and function in PD patients.

It has been suggested that training involving RAS establishes an internal sense of rhythms in humans because humans keep anticipating subsequent beats of RAS [15]. The established sense of rhythms persists in humans and keeps affecting movement execution even after RAS disappears [15, 24]. In addition, powerful influences of RAS on movements may also be associated with plentiful neural connections between auditory and motor cortices, including the cortico-striato-cortical pathway, the cortico-cerebello-cortical pathway, and auditory-motor neural connections directly in the cortex [25]. Earlier research [26–29] has reported that RAS not only activates neurons in the auditory cortex, but also induces neural firing in motor-related cortical

regions (such as primary motor cortex, premotor and supplementary motor areas) even though examinees are stationary without moving. In PD patients, RAS improves movements possibly by involving the cortico-cerebello-cortical pathway and auditory-motor cortical connections to modulate neural activity of the motor cortex and bypassing the damaged cortico-striato-cortical pathway [25, 30]. Additionally, RAS serves as external cues, can provide timing (tempo) information for PD patients, and thus possibly reduces the dependence of patients' movements on impaired modulation function of basal ganglia.

To sum up, the purpose of this study is to investigate effects of movement training involving RAS on upper-limb movement speed and function in PD patients. We hypothesize that movement training involving RAS improves upper-limb movement speed and function in PD patients. Validation of this hypothesis will fill up the knowledge gap regarding whether RAS is applicable to upper-limb training in the PD population and provide clinicians with evidence of non-pharmacological therapy for upper-limb bradykinesia in PD patients. The training program will serve as a reference for clinical practitioners who are interested in using RAS in clinical training for PD patients.

## METHODS AND ANALYSIS

This study follows the SPIRIT (Standard Protocol Items Recommendations for Interventional Trials) guidelines for reporting [31].

### *Study design*

A randomized controlled trial will be used to validate the hypothesis. Patients with PD will be randomly assigned to two groups by using computer-generated random numbers: the RAS group and the no-RAS group. Each sealed envelope with an assigned group will be used. The RAS group will receive upper-limb movement training with the aid of RAS; the no-RAS group will receive upper-limb movement training without the aid of RAS. This study will provide 21-day

training with a session per day and 40 minutes per session. Assessments will be completed face-to-face before and after the 21-day training by a senior therapist. For all participants, training and assessments will be performed during the 'on' state of their anti-Parkinson medication. Daily phone calls and weekly face-to-face meetings with patients will be performed to increase patient retention. We will monitor muscle fatigue during home training by using a daily training log in which self-reported reflections will be recorded.

*Patient and public involvement*

Patients were involved in the design and dissemination of this research. We carefully designed the training duration and content to prevent fatigue in patients according to literature and our pilot study [23]. In addition, we will share key findings of this study with participants at the end of the study.

*Participants*

Patients with PD will be recruited from hospitals. Age, gender and years of education will be recorded. Criteria for selecting patients are as follows: (a) idiopathic PD diagnosed by a neurologist based on the Movement Disorders Society clinical diagnostic criteria [32]; (b) the Hoehn and Yahr stage is 2 or 3, meaning that bilateral movement problems or combination with mild postural instability [33]; (c) a score of Montreal Cognitive Assessment is equal to or higher than 21 to ensure that they understand experimental instructions [34–36]; (d) a score of Edinburgh Handedness Inventory is above 60 to ensure that they are right-handed [37]; (e) Types and doses of medications remain unchanged in the past month right before participation. Exclusion criteria include the presence of medical conditions or diseases that may affect hand movements, vision, or hearing based on self-report. Patients will sign an informed consent form prior to admission to this study.

*Sample size estimation*

Because of no existing PD studies testing effects of training involving RAS on upper-limb movements, we calculated the effect size of training involving RAS ($d$ = 0.51) according to data of the classic study [20] examining effects of training involving RAS on gait speed in PD patients. The G*Power software (version 3.1.9.7) was used. When the effect size $d$ was 0.51, the power was 0.8, and the α level (two-tailed) was 0.05, the estimated required sample size was 62 for each group. Considering the dropout rate of 10%, the final sample size was 69 patients per group, for a total of 138 patients.

*Intervention*

Patients with PD will be randomly assigned into two groups (the RAS group and the no-RAS group). Three-week training will be provided for both groups. The training protocol is mainly based on the classic study [20] examining effects of RAS on gait speed in PD patients and a recent study [38] examining effects of RAS on upper-limb movements in the population exhibiting movement slowness. We increase frequency of breaks during training per day because our pilot study [23] observed that patients with PD had muscle fatigue easily when following RAS to execute upper-limb movements without frequent breaks. The training task of this study will be to use the right hand to move wooden beads one by one from one target bowl to the main bowl on the table (Figure 1A). Three target bowls, labeled as the left, middle, and right target bowl, will be placed on the table at an equal distance from the main bowl. The distance between a target bowl and the main bowl will be set at 30 cm, which is 50% of the upper-limb length (from the shoulder to the middle finger tip) of Hong Kong women [39], to ensure that beads in the target bowls are reachable for research participants. The angle between adjacent target bowls relative to the main bowl will be 30 degrees. Wooden beads with a diameter of 2 cm will be put in target bowls. The main bowl will be placed in front of the patient.

Patients will be asked to use the right hand to take one bead at a time from the left target bowl to the main bowl, repeat this movement for the middle and right target bowls, and keep repeating this order (Figure 1B).

Each daily training will consist of three rounds separated by two 5-minute breaks. Each round (about 10 minutes) will consist of four 2-minute training sessions with a 30-second break between two adjacent sessions. On the first day after the pretest, patients will receive the first training session face-to-face in a hospital. After the first training session, patients will carry all training materials back home for subsequent 6-day home training sessions. Family members or caregivers will be only permitted to assist in setting up the training environment and not allowed to assist the patient during training. On the first day of each subsequent training week, patients will be asked to return to the hospital to receive a face-to-face training session. Research personnel will make phone calls every day to remind patients to complete daily training. In addition, patients will be required to complete a daily training log to ensure compliance.

Before the first-day training, the baseline tempo of executing the training task will be assessed for each patient. The patient will be required to perform the aforementioned upper-limb movement task as fast as possible within 30 seconds without listening to RAS. The obtained number of wooden beads in the main bowl multiplied by two will be the baseline tempo (unit: beat per minute) for each patient [15, 20].

For the RAS group, each patient will receive a 45-minute audio file, which includes briefing the patient about the daily training content (five minutes) and providing RAS (10 minutes per round multiplied by three rounds, plus two 5-minute break time; a total of 40 minutes). The normal RAS (100% of the baseline tempo), the quick RAS (105% of the baseline tempo), and the fast RAS (110% of the baseline tempo) will be provided in the first, second, and third round of training (Table 1). The patient will be asked to pick up a bead when s/he hears a beep sound of RAS. The tempo of the three RAS will be further increased by 5% of the baseline tempo when it goes to a new week. In the face-to-face session (the first day) of each week, the patient will

obtain a new audio file and complete daily training face-to-face in hospital. RAS will be metronome beep sounds generated by a metronome (SQ200, Seiko incorporated). The required tempo of RAS will be adjusted using the computer software Adobe Audition CC 2020. The audio file will be sent to the patient's mobile phone, which will then be used to play the audio file during both face-to-face and home training.

**Table 1.** RAS tempi that are provided in daily upper-limb training

| Day | Normal RAS in round 1 | Quick RAS in round 2 | Fast RAS in round 3 |
|---|---|---|---|
| 1st – 7th | 100% of the baseline tempo | 105% of the baseline tempo | 110% of the baseline tempo |
| 8th – 14th | 105% of the baseline tempo | 110% of the baseline tempo | 115% of the baseline tempo |
| 15th – 21st | 110% of the baseline tempo | 115% of the baseline tempo | 120% of the baseline tempo |

RAS, rhythmic auditory stimulation.

The no-RAS group will receive a 45-minute audio file, which briefs the patient about the daily training content (five minutes) and instructs the patient to move beads as fast as possible in each round without RAS. The training protocol is the same in the RAS group and the no-RAS group except no RAS is provided for the no-RAS group during training. Similarly, the no-RAS group will perform the training face-to-face on the first day of each week in the hospital and at home on the remaining six days of a week.

*Outcome measures*

The box and block test (BBT) is used to measure gross manual dexterity as well as upper-limb movement speed [40]. It is a 53.7* 25.4 cm box separated into two compartments by a 15.2 cm high erected partition, with 150 blocks in each compartment. Starting from the dominant hand, patients will be asked to move the blocks one by one from the compartment on the hand side to the opposite side (e.g., move the blocks from the right compartment to the left compartment for the right hand test). Patients should move the blocks with their arms raised and crossed over the partition. They have one minute to move the blocks as fast as possible. The score of BBT for each hand is the quantity of blocks transferred between compartments in one minute. A higher score indicates faster upper-limb movements and better dexterity. For the elderly, the BBT has high test-retest reliability (intraclass correlation coefficient of 0.89 to 0.97) and construct validity [41].

The Jebsen hand function test (JHFT) is used to assess unimanual hand function when examinees perform daily activities. Seven items are included in JHFT: writing, turning cards, picking up small objects, simulated feeding, stacking checkers, moving large light objects, and moving large heavy objects [42]. Considering that the patients are Chinese speakers, it is not appropriate to do English writing. According to a previous study conducted in Chinese cultures [43], the JHFT could be modified through excluding the writing item to avoid cultural influences on scores. The score for each item is the completion time. The less time a patient takes, the better hand function s/he has. The JHFT has excellent test-retest reliability (intraclass correlation coefficients of 0.89 to 0.97) for PD patients [44].

*Safety*

To assess the data safety, scientific validity, and integrity of clinical trials, a data monitoring committee will be formed by two senior researchers who are not involved in the group allocation

and protocol implications. After the study is completed, the research data will be retained in demographic and scoring sheets will be retained for five years and destroyed afterwards. In this study, adverse events, defined as any unfavorable medical occurrence in a patient, will be collected and reported to data monitoring committee for records. This study will provide movement training. If participants have muscle fatigue during training, research personnel will provide break time immediately.

*Data collection and statistical analysis*

The general information and results will be kept on a portable hard drive. Authors of this study will conduct interim analysis to re-estimate the required sample size and determine if the study should continue or be modified. Only authors of this study will be allowed to get access to the dataset.

To test the baseline difference, the independent sample t-test (for continuous variables) and the chi-square test (for categorical variables) will be used to examine if age, gender, years of education, Montreal Cognitive Assessment scores, Hoehn and Yahr stages, and pretest scores of BBT and JHFT are the same between the RAS group and the no-RAS group. The independent sample t-test will be performed to compare the difference in posttest scores of BBT and JHFT between groups. The alpha level (two-tailed) will be set at 0.05. It is hypothesized that (a) posttest scores of BBT are higher in the RAS group than the no-RAS group, and (b) posttest scores of JHFT are higher in the RAS group than the no-RAS group. Patients may drop out before the study is completed. The last data point of the patient will be used to handle the missing data. The SPSS package (the 25th version) will be used to conduct statistical analysis.

## DISCUSSION

RAS, a common technique of neuromusic therapy, has been used extensively to improve gait, stride length, and balance in PD patients [19]. Earlier research has provided explanations of

mechanisms of RAS effects in the PD population [25]. Major explanations are that RAS may activate alternative and intact neural pathways or may provide timing information from the beat of RAS so as to improve movement control and alleviate bradykinesia in PD patients [25]. Bradykinesia is also present in upper limbs, in addition to lower limbs, in PD patients and affects daily activities and quality of life in patients [9, 10]. Even though RAS is a promising training technique for bradykinesia, how to apply RAS to upper-limb movement training for PD patients is still unclear. To our best knowledge, scarce training protocols targeting upper-limb movement training involving RAS for the PD population have been available in research. This study presented a pioneering training protocol, which could be used in future randomized controlled trials to validate effects of training involving RAS on improving upper-limb movements in PD patients. The training program shown in this study will serve as a reference for researchers and clinicians who are interested in developing intervention for tackling upper-limb bradykinesia in PD patients.

It is fundamental for training involving RAS to determine a baseline tempo of executing an upper-limb or lower-limb movement (without the aid of RAS), which is used to calculate the speed of normal, quick, and fast RAS in the training. In previous studies regarding walking in PD patients, the baseline tempo was the tempo when the participant walked at a general and comfortable pace, not at the fastest pace [20, 45]. In other words, the baseline tempo of walking in earlier research was a performance patients chose to make, not the best performance patients could make. Therefore, the speed of quick and fast RAS provided in training in earlier research may not be faster than the baseline best walking ability/speed when patients had not received training involving RAS. By contrast, the current study protocol was designed to detect a baseline tempo at participants' fastest pace and thus able to provide participants with quick and fast RAS with speed faster than their baseline best movement abilities. This design may contribute to optimizing effects of RAS incorporated in movement training.

Our previous empirical study has reported immediate effects of RAS on inducing faster upper-limb movements in PD patients [23]. However, we observed that although RAS with speed of 110% and 120% of baseline tempos was effective, patients had muscle fatigue easily to follow the beat of RAS on a movement task. Considering this study protocol provided daily movement training lasting for 40 minutes, it adopted quick and fast RAS with speed of 105% and 110% of baseline tempos as well as increased the frequency of break during training to reduce muscle fatigue in patients.

To sum up, this study protocol will support healthcare providers in academia and clinical settings to provide promising non-pharmacological therapy, that is, training involving RAS, for tackling upper-limb bradykinesia in PD patients.

## Contributors

Wei Fan: Study conception and design. Execution. Writing of the first draft.

Kenneth N. K. Fong: Review and critique.

Shu-Mei Wang: Study conception and design. Review and critique.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Competing interests:

None declared.

## Ethics and dissemination:

Ethical approval has been obtained from the Institutional Review Board of the Hong Kong Polytechnic University with the reference number HSEARS20221027005. It has been registered on ClinicalTrials.gov under the identifier NCT05637593.

Patients who are eligible will be well-informed about the objectives and timeline of this study. Informed consent forms will be gathered from all patients before their participation. The general health condition of patients will be monitored via daily phone calls and weekly face-to-face meetings. Training will be suspended or terminated when there are adverse events. Study results will be disseminated through conferences and peer-reviewed academic journals. Identifiable information of patients will not be disclosed during result dissemination.

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**Figure captions**

**Figure 1.** (A) The setup of the upper-limb training task. (B) The patient picks up one bead from one target bowl and is going to move the bead to the main bowl.

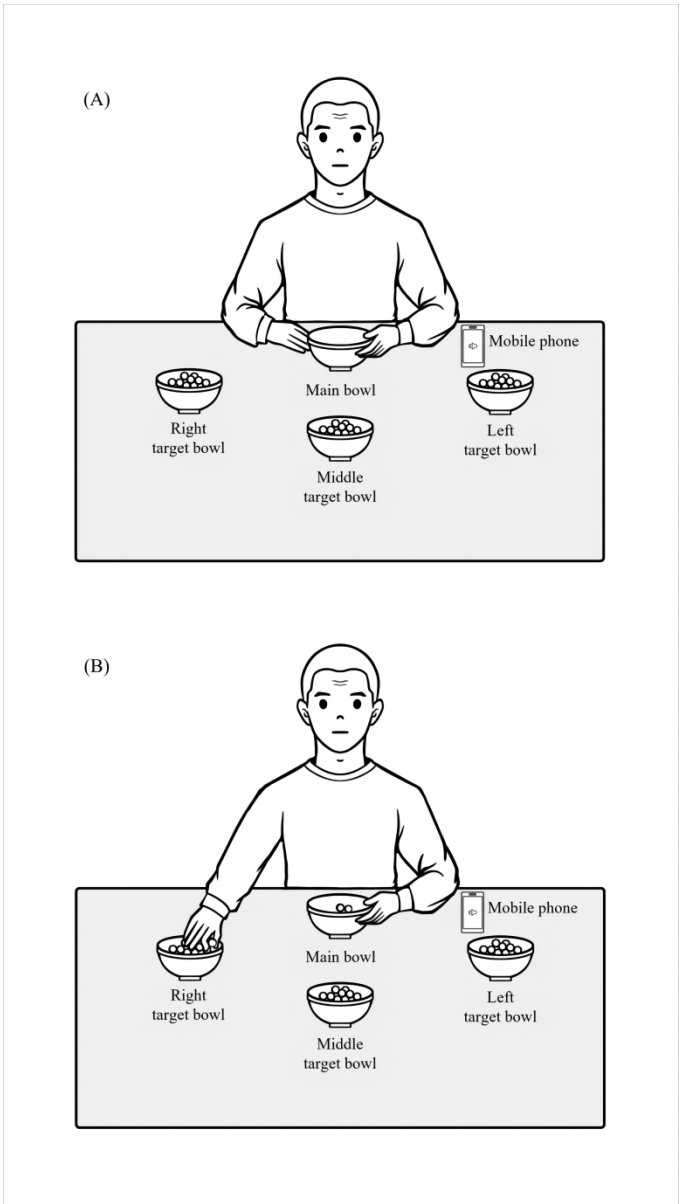


Figure 1

530x940mm (216 x 216 DPI)

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

| | | Reporting Item | Page Number |
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| **Administrative information** | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | 2 |
| Protocol version | #3 | Date and version identifier | n/a |
| Funding | #4 | Sources and types of financial, material, and other support | 15 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 15 |

| | | | |
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| Roles and responsibilities: sponsor contact information | #5b | Name and contact information for the trial sponsor | 1 |
| Roles and responsibilities: sponsor and funder | #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 | 15 |
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| Consent or assent: ancillary studies | #26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
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| Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | n/a |
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| Biological specimens | #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 | n/a |

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# Effects of training involving patterned sensory enhancement on improving upper-limb movements in patients with Parkinson's disease: protocol of a randomised controlled trial



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# Effects of training involving patterned sensory enhancement on improving upper-limb movements in patients with Parkinson's disease: protocol of a randomised controlled trial

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## ABSTRACT

**Introduction** Bradykinesia (i.e., slow movements) is one of the most prominent symptoms of Parkinson's disease (PD) and has a negative impact on quality of life. Rhythmic auditory stimulation (RAS), a widely used and promising treatment technique, has been shown to effectively improve gait speed in PD patients. The upper-limb movements, which also suffer from bradykinesia, are essential for daily life and directly impact quality of life. The term, patterned sensory enhancement (PSE) instead of RAS, is used when movement training targets the human body except lower limbs. Up until now, scarce studies have explored effects of training involving PSE on upper-limb movements. The purpose of this study is to investigate effects of movement training involving PSE on upper-limb movement speed and function in PD patients.

**Methods and analysis** A total of 138 patients with PD will be randomly assigned into two groups: the PSE group and the no-PSE group. A 21-day upper-limb training involving PSE (for the PSE group) or without PSE (for the no-PSE group) will be provided to the patients. An assessor will administer the box and block test and the Jebsen hand function test before and after training to assess upper-limb movement speed and function. The one-way analysis of covariance will be performed. This randomised controlled trial will provide evidence supporting effectiveness of upper-limb movement training involving PSE on reducing severity of bradykinesia in PD patients.

**Ethics and dissemination** Ethical approval has been obtained from the Institutional Review Board of the Hong Kong Polytechnic University with the reference number HSEARS20221027005. Informed consent forms will be gathered from all patients before their participation. Study results will be disseminated through conferences and peer-reviewed academic journals.

**Trial registration number** ClinicalTrials.gov NCT05637593

**Keywords** Acoustic stimulation, Parkinson's disease, Arm, Movement, Bradykinesia

**Strengths and limitations of this study**

- This is a randomised controlled trial with one experimental group with PD receiving 21-day upper-limb movement training with the aid of PSE and one control group with PD receiving the same training without the aid of PSE.
- PSE is three tempi of metronome beat that are based on the participant's fastest upper-limb movement speed before the training and gradually increase by each week.
- Movement speed and quality are assessed using the box and block test and the Jebsen hand function test.
- One possible concern of this training combining face-to-face sessions and home training sessions is whether participants will adhere to the home training protocol, which will be addressed via real-time video meetings during all home training sessions.

## INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disease caused by neurodegeneration of the substantia nigra, resulting in a decrease in dopamine [1, 2]. The incidence of PD is 14 per 100,000 people per year, and even reaches 160 per 100,000 people over the age of 65 years [3]. Dopamine, a neurotransmitter, is important for the function of the basal ganglia in receiving, modulating, and transmitting signals to various cortical areas, including those associated with movements [4]. Therefore, in PD patients, a decrease in dopamine leads to basal ganglia dysfunction in the cortico-striato-thalamo-cortical circuit, resulting in movement symptoms [5, 6]. Bradykinesia, meaning slowness of movements, is one of the most prominent symptoms of PD [7], extensively interferes with performances of daily activities such as eating, writing, and walking [8], and substantially lowers the quality of life in patients [9, 10].

Pharmacotherapy has been shown to alleviate movement symptoms in PD patients. Medications, such as levodopa, are able to adjust activities of the putamen and thalamus, modulate signals from basal ganglia to motor-related cortices, and thus enhance movements in patients [11]. However, long-term use of medications increases medication resistance and thus reduces therapeutic effects, as well as increases side effects of medications such as dyskinesia [12, 13]. Therefore, developing non-pharmacological therapies is warranted and of clinical importance in order to tackle bradykinesia in patients with PD.

Rhythmic auditory stimulation (RAS) is repetitive, discrete sounds with a tempo [14, 15]. Because the tempo of human movements is naturally synchronized with the tempo of RAS [16, 17], RAS has a high potential of being applied to movement training to guide human movement execution [18]. Earlier studies [19] have provided solid evidence that training involving RAS is effective in improving gait performance in PD patients. Earlier classic research [20] examining effects of training involving RAS on gaits in PD patients provided 21-day training with 30

minutes per day, in which RAS with three different tempi (normal RAS, quick RAS, and fast RAS) was provided. Initially, researchers assessed the baseline walking tempo without the aid of RAS for each patient. For daily training, each patient was given normal RAS (100% of the baseline tempo), quick RAS (105% of the baseline tempo), and fast RAS (110% of the baseline tempo) to guide the gaits. Each RAS was increased by 5% when the time went to the next week.

The term, patterned sensory enhancement (PSE) instead of RAS, is used when movement training targets the human body except lower limbs [21]. Most previous studies that investigated RAS effects in PD patients focused on lower-limb movements such as gaits [19]. However, upper-limb movements are also important for activities of daily living and directly affect quality of life in humans [22]. In addition, it is commonly seen that rehabilitation training for upper-limb movements involves continuous movement repetition, which supports that PSE may be applicable to upper-limb movement therapy. It is worth investigating if upper-limb training involving PSE is effective for PD patients. To date, only few studies [23, 24] have investigated effects of PSE on upper-limb movements in PD patients. A case report [23] indicated that movement training involving PSE may improve finger-tapping speed and finger dexterity in PD patients. In addition, a study using the repeated measures design [24] demonstrated that faster PSE immediately induced faster upper-limb movement speed in PD patients. To date, randomised controlled trials have been needed to determine whether long-term training involving PSE is effective in improving upper-limb movement speed and function in PD patients.

It has been suggested that training involving RAS/PSE establishes an internal sense of rhythm in humans because humans keep anticipating subsequent beats of RAS/PSE [15]. The established sense of rhythms persists in humans and keeps affecting movement execution even after RAS/PSE disappears [15, 25]. In addition, powerful influences of RAS/PSE on movements may also be associated with plentiful neural connections between auditory and motor cortices,

including the cortico-striato-cortical pathway, the cortico-cerebello-cortical pathway, and auditory-motor neural connections directly in the cortex [26]. Earlier research [27–30] has reported that RAS/PSE not only activates neurons in the auditory cortex, but also induces neural firing in motor-related cortical regions (such as primary motor cortex, premotor, and supplementary motor areas) even though examinees are stationary without moving. In PD patients, RAS/PSE improves movements possibly by involving the cortico-cerebello-cortical pathway and auditory-motor cortical connections to modulate neural activity of the motor cortex and bypassing the damaged cortico-striato-cortical pathway [26, 31]. Additionally, RAS/PSE serves as external cues, can provide timing (tempo) information for PD patients, and thus possibly reduces the dependence of patients' movements on impaired modulation function of basal ganglia [15].

To sum up, the purpose of this study is to investigate effects of movement training involving PSE on upper-limb movement speed and function in PD patients. We hypothesize that movement training involving PSE improves upper-limb movement speed and function in PD patients. Validation of this hypothesis will fill up the knowledge gap regarding whether PSE is applicable to upper-limb training in the PD population and provide clinicians with evidence of non-pharmacological therapy for upper-limb bradykinesia in PD patients. The training program will serve as a reference for clinical practitioners who are interested in using RAS/PSE in clinical training for PD patients.

## METHODS AND ANALYSIS

This study follows the SPIRIT (Standard Protocol Items Recommendations for Interventional Trials) guidelines for reporting [32].

*Study design*

A randomised controlled trial will be used to validate the hypothesis. Patients with PD will be randomly assigned to two groups by using computer-generated random numbers: the PSE group and the no-PSE group. Each sealed envelope with an assigned group will be used. The PSE group will receive upper-limb movement training with the aid of PSE; the no-PSE group will receive upper-limb movement training without the aid of PSE. This study will provide 21-day training with a session per day and 40 minutes per session. Assessments will be completed face-to-face before and after the 21-day training by a senior therapist who is blinded to the group allocation. Blinding of patients and people who provide training is not feasible in this study because patients and training providers know group allocation. For all participants, training and assessments will be performed during the 'on' state of their anti-Parkinson medication. We will conduct weekly face-to-face meetings with patients and real-time video meetings during all home training sessions to ensure the adherence of participants to the training program. We will monitor muscle fatigue during home training by using a daily training log. The study is expected to commence in August of 2023 and is anticipated to be completed within two years.

*Patient and public involvement*

Patients were involved in the design and dissemination of this research. We carefully designed the training duration and content to prevent fatigue in patients according to literature and our pilot study [24]. In addition, we will share key findings of this study with participants at the end of the study.

*Participants*

Patients with PD will be recruited from hospitals through posters and physician referrals. At pretest, this study will collect demographic and clinical data, including age, gender, disease duration, the more-affected side, and medication dosage. The more-affected side (left or right)

refers to the side of the body exhibiting more severe bradykinesia, which will be determined visually by an experienced physician. In addition, we will calculate the levodopa equivalent dose [33] to measure medication dosage. Criteria for selecting patients are as follows: (a) idiopathic PD diagnosed by a neurologist based on the Movement Disorders Society clinical diagnostic criteria [34]; (b) the Hoehn and Yahr stage is 2 or 3, meaning that bilateral movement problems or combination with mild postural instability [35]; (c) a score of Montreal Cognitive Assessment is equal to or higher than 21 to ensure that they understand experimental instructions [36–38]; (d) a score of Edinburgh Handedness Inventory is above 60 to ensure that they are right-handed [39]; (e) Types and doses of medications remain unchanged in the past month right before participation. Exclusion criteria include the presence of medical conditions or diseases that may affect hand movements, vision, or hearing based on self-report. Patients will sign an informed consent form prior to admission to this study.

*Sample size estimation*

Because of no existing PD studies testing effects of training involving PSE on upper-limb movements, we calculated the effect size of training involving PSE ($f = 0.255$) according to data of the classic study [20] examining effects of training involving RAS on gait speed in PD patients. The G*Power software (version 3.1.9.7) was used to estimate the required sample size under the following conditions: analysis of covariance as the statistical test, an effect size $f$ of 0.255, the power of 0.8, the alpha level of 0.05, two groups, and 10 covariates (age, gender, the Hoehn and Yahr stage, disease duration, the more-affected side, medication dosage, the number of training sessions the participant completes, the score of the depression item in the first part of the Movement Disorder Society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS) at pretest, the score of the anxiety item in the first part of MDS-UPDRS at pretest, and a pretest score of an outcome variable, including the score of the box and block test

(BBT), the error rate during executing BBT, the score of the Jebsen hand function test (JHFT), and the domain score of the third part of MDS-UPDRS). The estimated total sample size was 124. Considering the dropout rate of 10%, the final total sample size was 138 patients (69 patients per group).

*Intervention*

Patients with PD will be randomly assigned into two groups (the PSE group and the no-PSE group). Three-week training will be provided for both groups. The training protocol is mainly based on the classic study [20] examining effects of RAS on gait speed in PD patients and a recent study [40] examining effects of PSE on upper-limb movements in the population exhibiting movement slowness. We increase the frequency of breaks during training per day because our pilot study [24] observed that patients with PD had muscle fatigue easily when following PSE to execute upper-limb movements without frequent breaks. The training task of this study will be to use the right hand to move wooden beads one by one from one target bowl to the main bowl on the table (Figure 1A). Three target bowls, labelled as the left, middle, and right target bowl, will be placed on the table at an equal distance from the main bowl. The distance between a target bowl and the main bowl will be set at 30 cm, which is 50% of the upper-limb length (from the shoulder to the middle finger tip) of Hong Kong women [41], to ensure that beads in the target bowls are reachable for research participants. The angles between adjacent target bowls relative to the main bowl will be 30 degrees. Wooden beads with a diameter of 2 cm will be put in target bowls. The main bowl will be placed in front of the patient. Patients will be asked to use the right hand to take one bead at a time from the left target bowl to the main bowl, repeat this movement for the middle and right target bowls, and keep repeating this order (Figure 1B).

The training sessions will be conducted during the "ON" period of medication. Specifically, the participant will be required to conduct daily training after 1 hour of taking medications. Each daily training will consist of three rounds separated by two 5-minute breaks. Each round (about 10 minutes) will consist of four 2-minute training sessions with a 30-second break between two adjacent sessions. On the first day after the pretest, patients will receive the first training session face-to-face in a hospital. After the first training session, patients will carry all training materials back home for subsequent 6-day home training sessions. Family members or caregivers will be only permitted to assist in setting up the training environment and not be allowed to assist the patient during training. On the first day of each subsequent training week, patients will be asked to return to the hospital to receive a face-to-face training session. We will conduct real-time video meetings during all home training sessions to ensure adherence to the treatment plan. We will also ask participants to complete daily training logs to record training completion and monitor the degrees of fatigue. In addition, we will calculate the number of training sessions the participant completes.

Before the first-day training, the baseline tempo of executing the training task will be assessed for each patient. The patient will be required to perform the aforementioned upper-limb movement task as fast as possible within 30 seconds for three times without listening to PSE. The obtained average number of wooden beads in the main bowl multiplied by two will be the baseline tempo (unit: beat per minute) for each patient [15, 20].

For the PSE group, each patient will receive a 45-minute audio file, which includes briefing the patient about the daily training content (five minutes) and providing PSE (10 minutes per round multiplied by three rounds, plus two 5-minute break times; a total of 40 minutes). The normal PSE (100% of the baseline tempo), the quick PSE (105% of the baseline tempo), and the fast PSE (110% of the baseline tempo) will be provided in the first, second, and third round of

training (Table 1). The patient will be asked to pick up a bead when s/he hears a beep sound of PSE. The tempo of the three PSE will be further increased by 5% of the baseline tempo when it goes to a new week. In the face-to-face session (the first day) of each week, the patient will obtain a new audio file and complete daily training face-to-face in the hospital. PSE will be metronome beep sounds generated by a metronome (SQ200, Seiko incorporated). The required tempo of PSE will be adjusted using the computer software Adobe Audition CC 2020. The audio file will be sent to the patient's mobile phone, which will then be used to play the audio file during both face-to-face and home training.

**Table 1.** PSE tempi that are provided in daily upper-limb training

| Day | 1st round: Normal PSE | 2nd round: Quick PSE | 3rd round: Fast PSE |
|---|---|---|---|
| 1st – 7th | 100% of the baseline tempo | 105% of the baseline tempo | 110% of the baseline tempo |
| 8th – 14th | 105% of the baseline tempo | 110% of the baseline tempo | 115% of the baseline tempo |
| 15th – 21st | 110% of the baseline tempo | 115% of the baseline tempo | 120% of the baseline tempo |

PSE, patterned sensory enhancement.

The no-PSE group will receive a 45-minute audio file, which briefs the patient about the daily training content (five minutes) and instructs the patient to move beads as fast as possible in each round without PSE. The training protocol is the same in the PSE group and the no-PSE group, except no PSE is provided for the no-PSE group during training. Similarly, the no-PSE group will perform the training face-to-face on the first day of each week in the hospital and at home on the remaining six days of a week.

Our previous empirical study has reported immediate effects of PSE on inducing faster upper-limb movements in PD patients [24]. However, we observed that although PSE with the speed of 110% and 120% of the baseline tempo was effective, patients had muscle fatigue easily when following the beat of PSE on an upper-limb movement task. This study protocol provides daily 40-minute upper-limb movement training at the fastest speed for 40 minutes, which is very intensive and easily causes muscle fatigue. To reduce muscle fatigue in patients, we will adopt PSE with the tempo speed starting from 100%, 105%, and 110% of the baseline tempo in the first-week training instead of 100%, 110%, and 120%, and will increase the frequency of training breaks.

*Outcome measures*

The MDS-UPDRS is a commonly used tool in clinical settings and research to assess influences of PD on multiple aspects in patients [35]. It consists of four parts, including (the first part) non-motor subjective experiences of daily living, (the second part) motor-related subjective experiences of daily living, (the third part) the motor examination, and (the fourth part) motor complications [35]. We will calculate the domain score of the third part of MDS-UPDRS, which is used to reflect objective severity of movement symptoms in patients. Larger scores indicate more severe movement symptoms. We will also use the score of the depression item and that of the anxiety item separately in the first part of MDS-UPDRS to detect levels of depression and anxiety in patients.

The BBT is used to measure gross manual dexterity as well as upper-limb movement speed [42]. It is a 53.7* 25.4 cm box separated into two compartments by a 15.2 cm high erected partition, with 150 blocks in each compartment. Starting from the dominant hand, patients will be asked to move the blocks one by one from the compartment on the hand side to the opposite side (e.g., move the blocks from the right compartment to the left compartment for the right hand

test). Patients should move the blocks with their arms raised and crossed over the partition. They have one minute to move the blocks as fast as possible. The score of BBT for each hand is the number of blocks that are successfully transferred between compartments in one minute. A higher BBT score indicates faster upper-limb movements and better dexterity. In addition, the number of dropping blocks during the blocks moving tasks of BBT in each hand will be recorded as the error score. We will calculate the error rate of executing BBT in each hand by dividing the error score by the sum of the error score and the BBT score to assess the accuracy of upper-limb movements. The higher error rate indicates less accurate upper-limb movements. For the elderly, the BBT has high test-retest reliability (intraclass correlation coefficient of 0.89 to 0.97) and construct validity [43].

The JHFT is used to assess unimanual hand function when examinees perform daily activities. Seven items are included in JHFT: writing, turning cards, picking up small objects, simulated feeding, stacking checkers, moving large light objects, and moving large heavy objects [44]. Considering that the patients are Chinese speakers, it is not appropriate to do English writing. According to a previous study conducted in Chinese cultures [45], the JHFT could be modified by excluding the writing item to avoid cultural influences on scores. The score for each item is the completion time. The less time a patient takes, the better hand function s/he has. We will calculate the total score of these six items as one dependent variable. The JHFT has excellent test-retest reliability (intraclass correlation coefficients of 0.89 to 0.97) for PD patients [46].

*Safety*

To assess the data safety, scientific validity, and integrity of clinical trials, a data monitoring committee will be formed by two senior researchers who are not involved in the group allocation and protocol implications. After the study is completed, the research data will be retained for five years and destroyed afterwards. In this study, adverse events, defined as any unfavorable medical

occurrence in a patient, will be collected and reported to data monitoring committee for records. This study will provide movement training. If participants have muscle fatigue during training, research personnel will provide break time immediately.

*Data collection and statistical analysis*

The general information and results will be kept on a portable hard drive. Authors of this study will conduct an interim analysis to re-estimate the required sample size and determine if the study should continue or be modified. Only authors of this study will be allowed to get access to the dataset.

A one-way analysis of covariance will be conducted to examine effects of group (the PSE group versus the no-PSE group) on each dependent variable, including BBT scores, the error rate during executing BBT, JHFT scores, and the domain score of the third part of MDS-UPDRS at posttest. The 10 potential confounding factors are age, gender, the Hoehn and Yahr stage, disease duration, the more-affected side, medication dosage, the number of training sessions the participant completes, the score of the depression item in the first part of MDS-UPDRS at pretest, the score of the anxiety item in the first part of MDS-UPDRS at pretest, and a pretest score of an outcome variable (including BBT scores, the error rate during executing BBT, JHFT scores, and the domain score of the third part of MDS-UPDRS). The alpha level (two-tailed) will be set at 0.05. It is hypothesized that after controlling for confounding influences, PSE increases scores of BBT, and decreases JHFT scores, the domain score of the third part of MDS-UPDRS, and the error rate of BBT. Patients may drop out before the study is completed. The last data point of the patient will be used to handle the missing data. The SPSS package (the 25th version) will be used to conduct statistical analysis.

**Contributors**

Wei Fan: Study conception and design. Execution. Writing of the first draft.

Kenneth N. K. Fong: Review and critique.

Shu-Mei Wang: Study conception and design. Review and critique.

**Data Availability Statement:**

The data supporting the findings of this study will be available upon reasonable request to the corresponding author.

**Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Competing interests:**

None declared.

**Ethics and dissemination:**

Ethical approval has been obtained from the Institutional Review Board of the Hong Kong Polytechnic University with the reference number HSEARS20221027005. It has been registered on ClinicalTrials.gov under the identifier NCT05637593. Patients who are eligible will be well-informed about the objectives and timeline of this study. Informed consent forms will be gathered from all patients before their participation. The general health condition of patients will be monitored via daily video meetings and weekly face-to-face meetings. Training will be suspended or terminated when there are adverse events. Study results will be disseminated through conferences and peer-reviewed academic journals. Identifiable information of patients will not be disclosed during result dissemination.

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**Figure captions**

**Figure 1.** (A) The setup of the upper-limb training task. (B) The patient picks up one bead from one target bowl and is going to move the bead to the main bowl.

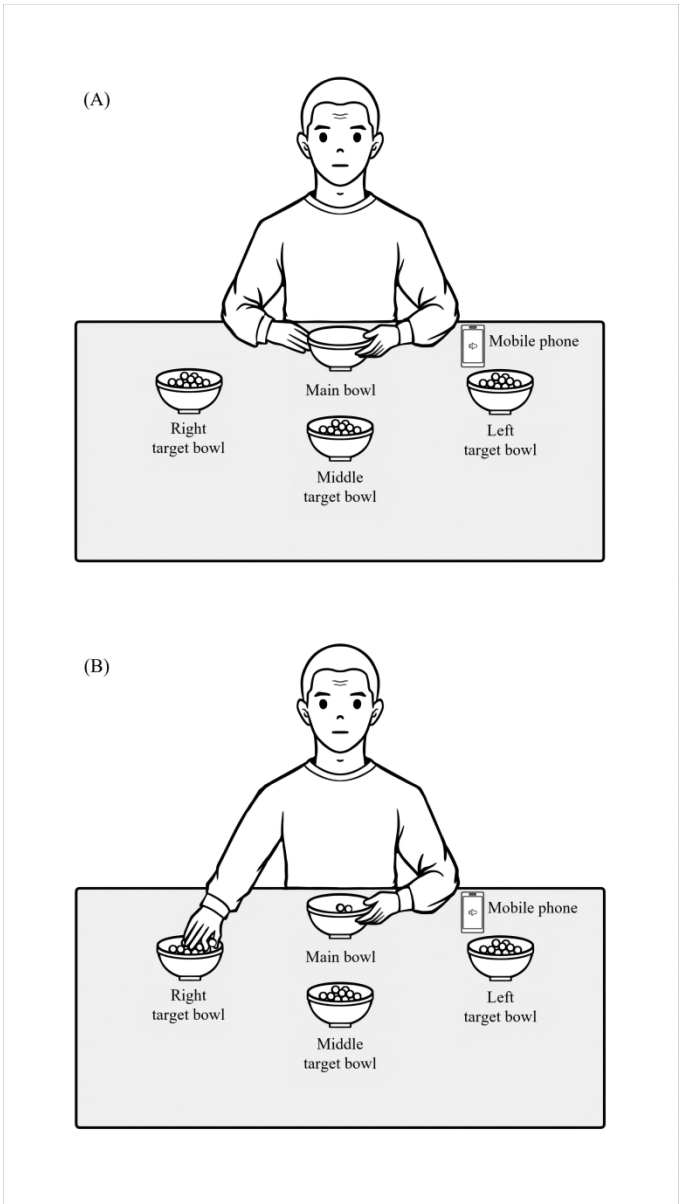


Figure 1

530x940mm (216 x 216 DPI)

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

| | | Reporting Item | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, | 2 |

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| | | name of intended registry | |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | 2 |
| Protocol version | #3 | Date and version identifier | n/a |
| Funding | #4 | Sources and types of financial, material, and other support | 16 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 16 |
| Roles and responsibilities: sponsor contact information | #5b | Name and contact information for the trial sponsor | 1 |
| Roles and responsibilities: sponsor and funder | #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 | 16 |
| Roles and responsibilities: committees | #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 | 16 |

| | | | |
|---|---|---|---|
| | | applicable (see Item 21a for data monitoring committee) | |
| **Introduction** | | | |
| Background and rationale | #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 | 5-7 |
| Background and rationale: choice of comparators | #6b | Explanation for choice of comparators | 5-7 |
| Objectives | #7 | Specific objectives or hypotheses | 7 |
| Trial design | #8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory) | 8 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | #9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 8 |

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| Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 8 |
| Interventions: description | #11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 9-13 |
| Interventions: modifications | #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) | 9-13 |
| Interventions: adherance | #11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) | 11 |
| Interventions: concomitant care | #11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 11 |
| Outcomes | #12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 13-14 |

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| Participant timeline | #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) | 10-11 |
| Sample size | #14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 9 |
| Recruitment | #15 | Strategies for achieving adequate participant enrolment to reach target sample size | 8 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: sequence generation | #16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 8 |
| Allocation concealment mechanism | #16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to | 8 |

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| | | conceal the sequence until interventions are assigned | |
| Allocation: implementation | #16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 8 |
| Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 8 |
| Blinding (masking): emergency unblinding | #17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | n/a |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 13-14 |
| Data collection plan: retention | #18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be | 11 |

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| | | collected for participants who discontinue or deviate from intervention protocols | |
| Data management | #19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 14-15 |
| Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 15 |
| Statistics: additional analyses | #20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 15 |
| Statistics: analysis population and missing data | #20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 15 |
| **Methods: Monitoring** | | | |
| Data monitoring: formal committee | #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 | 14-15 |

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| | | protocol. Alternatively, an explanation of why a DMC is not needed | |
| Data monitoring: interim analysis | #21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 14-15 |
| Harms | #22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 14-15 |
| Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | n/a |
| **Ethics and dissemination** | | | |
| Research ethics approval | #24 | Plans for seeking research ethics committee / institutional review board (REC / IRB) approval | 16 |
| Protocol amendments | #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) | 15 |
| Consent or assent | #26a | Who will obtain informed consent or assent from | 16 |

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| | | potential trial participants or authorised surrogates, and how (see Item 32) | |
| Consent or assent: ancillary studies | #26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| Confidentiality | #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 | 16 |
| Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 16 |
| Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 15 |
| Ancillary and post trial care | #30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | n/a |
| Dissemination policy: trial results | #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 | 8 |

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| Dissemination policy: authorship | #31b | Authorship eligibility guidelines and any intended use of professional writers | 1 |
| Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | n/a |

## Appendices

| | | | |
|---|---|---|---|
| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | Supplemental Material |
| Biological specimens | #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 | n/a |