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Determining the optimal dose of reactive balance training after stroke – study protocol for a pilot randomized controlled trial

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1. ADMINISTRATIVE INFORMATION

Title: Determining the optimal dose of reactive balance training after stroke – study protocol for a pilot randomized controlled trial

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Contributorship: AM conceived of the study, is the grant holder, and drafted the manuscript. AM, ELI, and CJD developed the intervention. All authors contributed to study design, writing/editing the manuscript, and approved the final manuscript.

2. WHO DATASET

1. **Trial registration:** clinicaltrials.gov, NCT04219696
2. **Date of registration:** 7 January 2020
3. **Secondary identification numbers:** Not applicable
4. **Sources of monetary or material support:** This study is supported by the Heart and Stroke Foundation Canadian Partnership for Stroke Recovery. AM holds a New Investigator Award from the Canadian Institutes of Health Research (MSH-141983). We also acknowledge the support of the Toronto Rehabilitation Institute; equipment and space have been funded with grants from the Canada Foundation for Innovation, Ontario Innovation Trust, and the Ministry of Research and Innovation. These funding sources had no role in the design of this study and will not have any role during its execution, analysis, interpretation of the data, or decision to submit results.
5. **Primary sponsor:** Avril Mansfield
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9. **Public title:** Determining the optimal dose of reactive balance training after stroke
10. **Scientific title:** Determining the optimal dose of reactive balance training after stroke – a pilot study
11. **Countries of recruitment:** Canada
12. **Interventions:** Reactive balance training. A research physiotherapist will oversee reactive balance training (RBT) in collaboration with participants' regular physiotherapists to ensure consistent RBT delivery across participants. Training strategies will be individualized to each

participant, based on their balance impairments and rehabilitation goals. The RBT program includes multi-directional 'internal' and 'external' balance perturbations. Internal perturbations are achieved by asking the participant to complete tasks that challenge balance control, such that they lose balance when attempting to perform the task (e.g., kicking a soccer ball). External perturbations are delivered manually using a push or pull from the physiotherapist. As participants improve their reactive balance control, difficulty will be increased by shifting task requirements along a continuum from stable to mobile, and from predictable to unpredictable, and by increasing perturbation magnitude or imposing sensory or environmental challenges.

13. **Key inclusion and exclusion criteria:** Inclusion criteria: sub-acute stroke; receiving out-patient rehabilitation at the Toronto Rehabilitation Institute; can stand independently for >30 seconds; can walk with or without a gait aid (but without assistance of another person) for >10 metres; and living in the community. Exclusion criteria: completed reactive balance training during in-patient rehabilitation; lower-extremity amputation, weight-bearing restrictions, recent lower-extremity injury or surgery (e.g., fracture), acute back or lower-limb pain, halo, aspen collar, history of fragility fracture and/or severe osteoporosis/osteopenia, contractures that prevent neutral hip or ankle; activity restrictions following cardiac event/surgery, abnormal or unstable cardiovascular responses to exercise, arterial dissection; severe spasticity in the legs; cognitive impairment (i.e., unable to understand the purpose of training and/or to provide informed consent); and/or acute illness (e.g., vomiting, fever), weight > 150 kg (exceeds safety harness weight limits), colostomy bags, indwelling catheter, infection, pressure sore on pelvis or trunk.
14. **Study type:** Pilot parallel randomized controlled trial.
15. **Date of first enrolment:** February 2020 (anticipated).
16. **Target sample size:** 36
17. **Recruitment status:** Pending.
18. **Primary outcome:** Rate of falls in daily life for six months post-discharge from rehabilitation.

19. Secondary outcomes: Rate of accrual, rate of missing data, compliance with the intervention.

3. ABSTRACT

Introduction: Falls risk post-stroke is highest soon after discharge from rehabilitation. Reactive balance training (RBT) aims to improve control of reactions to prevent falling after a loss of balance. In healthy older adults, a single RBT session can lead to lasting improvements in reactive balance control and prevent falls in daily life. While increasing the dose of RBT does not appear to lead to additional benefit for healthy older adults, stroke survivors, who have more severely impaired balance control, may benefit from a higher RBT dose. Our long-term goal is to determine the optimal dose of RBT in people with sub-acute stroke. This assessor-blinded pilot randomized controlled trial aims to inform the design of a larger trial to address this long-term goal.

Methods and analysis: Participants (n=36) will be attending out-patient stroke rehabilitation, and will be randomly allocated to one of three groups: 1, 3, or 6 RBT sessions. RBT will replace a portion of participants' regular physiotherapy so that the total physical rehabilitation time will be the same for the 3 groups. Functional balance, balance confidence, and balance reactions will be assessed: 1) pre-training; 2) post-training; and 3) 6 months post-training. Participants will report falls and physical activity for 6 months post-discharge. Pilot data will be used to plan the larger trial (i.e., sample size estimate using fall rates, and which groups should be included based on between-group trends in pre-to-post training effect sizes for reactive balance control measures). Pilot data will also be used to assess the feasibility of the larger trial (i.e., based on the accrual rate, outcome completion rate, and feasibility of prescribing specific training doses).

Ethics and dissemination: Institutional research ethics approval has been received. Study participants will receive a lay summary of results. We will also publish our findings in a peer-reviewed journal.

4. STRENGTHS AND LIMITATONS

- The intervention will replace a portion of participants routine physiotherapy during out-patient rehabilitation. Therefore, the findings will be directly relevant to clinical practice.
- Conversely, there is a risk that many patients will decline participation in the study as they will not want their rehabilitation care to be disrupted.
- This is a pilot study, so it is unlikely that we will be able to make definitive decisions regarding the optimal dose of reactive balance training post-stroke.

5. INTRODUCTION

5.1 Background and rationale

Falls are the most prevalent complications during all stages of stroke recovery.[1] Along with physical injuries, 88% of people with stroke who fall develop fear of falling.[2] Falls and fear of falling can lead to inactivity, deconditioning, and lower functional capacity, further increasing fall risk[3,4] and reducing quality of life.[5]

Conventional balance training reduces falls in older adults,[6] but not after stroke.[7,8] Reactive balance training (RBT), where clients experience repeated postural perturbations (or loss of balance),[9,10] is a novel type of exercise that aims to improve reactive balance control. RBT can prevent falls in older adults and people with Parkinson's disease.[11] Our non-randomized study suggests that RBT reduces fall rates after discharge from stroke rehabilitation.[12] In our previous study, the intervention was implemented as part of routine care, and the dose of RBT depended on client goals and preferences and length of stay, rather than being prescribed by the study protocol. Participants completed 1-12, 30-minute RBT sessions (median of 6 sessions).[12]

Unlike other forms of exercise,[13] improved reactive balance control with RBT seems to occur with few repetitions, and is maintained for several months without training. Among healthy older adults, just 24 perturbations within a single session of RBT is sufficient to lead to lasting improvements (i.e., 6-12 months) in reactive balance control,[14] and prevent falls in daily life.[15] One study in people with chronic stroke found that improved reactive balance control with a single session of RBT was retained for 3 weeks post-training.[16] While almost doubling the dose of RBT does not appear to lead to additional benefit for healthy older adults,[17] it is possible that those with stroke would benefit from additional RBT as they have more severely impaired balance than healthy older adults.[18] Additional training may also promote sustained training effects beyond 3 weeks.[19] Only two previous studies have investigated RBT in sub-acute stroke.[12,20] This is a crucial period for fall prevention due to the high risk

of falls early after stroke.[21] Therefore, there is a need to establish optimal RBT training parameters in the sub-acute stroke population.

5.2 Objectives and research questions

The long-term goal of this work is ***to determine the optimal dose of RBT in people with sub-acute stroke***. This assessor-blinded pilot randomized controlled trial (RCT) aims ***to inform the design of a larger trial to address this long-term goal***. Specifically, the following questions about the larger trial will be answered with this pilot study:

1) what is the optimal sample size;

2) how long will it take to achieve this sample size;

3) what secondary outcome measures should be used;

4) how feasible is it to prescribe a specific dose of RBT to people with sub-acute stroke; and

5) what two intervention groups should be included in the larger trial?

5.3 Trial design

This is an assessor-blinded pilot RCT (Figure 1). People who are attending out-patient stroke rehabilitation will be randomly assigned to one of three different doses of reactive balance training (RBT). Reactive balance control, functional balance, and balance confidence will be measured pre- and post-training and 6 months post-training. Falls in daily life, physical activity, and participation will be assessed for 6 months post-training.

5.3.1 Patient and public involvement

This study was designed without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes. Some trial design elements

were informed by participant feedback from our previous RBT study.[19] Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

6. METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

6.1 Study setting

This study will take place at the Toronto Rehabilitation Institute, University Health Network. This facility provides specialized in- and out-patient stroke rehabilitation to individuals in the sub-acute stage of stroke recovery. Out-patient stroke rehabilitation at the Toronto Rehabilitation Institute typically includes 45 minutes of physiotherapy 2-5 times/week for at least 4 weeks.

6.2 Participants

Participants will be people with sub-acute stroke (<6-months post-stroke) who are receiving out-patient rehabilitation at the Toronto Rehabilitation Institute. Participants will be eligible if they can: 1) stand independently for >30s; 2) walk with or without a gait aid (but without assistance of another person) for >10m; and 3) are living in the community. Participants will be excluded if they have:

- Completed RBT during in-patient rehabilitation;
- Lower extremity amputation, weight-bearing restrictions, recent lower-extremity injury or surgery (e.g., fracture), acute back or lower-limb pain, halo, aspen collar, history of fragility fracture and/or severe osteoporosis/osteopenia, contractures that prevent neutral hip or ankle;
- Activity restrictions following cardiac event/surgery, abnormal or unstable cardiovascular responses to exercise, arterial dissection;
- Severe spasticity in the legs;
- Cognitive impairment (i.e., unable to understand the purpose of training and/or to provide informed consent), as determined by the healthcare team; and/or

- Acute illness (e.g., vomiting, fever), extreme obesity (exceeds safety harness system weight limits), colostomy bags, indwelling catheter, infection, pressure sore on pelvis or trunk.

After participants provide consent, eligibility will be confirmed using information in the participants' hospital chart, by consulting members of the patient's healthcare team, and by consulting the participant themselves. Participants will still receive their usual care, while participating in the study.

Participants will be informed that they are free to withdraw from the study at any time point, without consequence. If participants ask to be withdrawn from the study, any data collected from them up to that point will be used to answer the research questions. Participants may also be withdrawn from the study due to changes in their health status that affect eligibility.

6.3 Interventions

Participants will be allocated to one of three groups: one, three, or six, 45-minute RBT sessions. RBT will replace a portion of participants' regular physiotherapy, so that the total amount of physical rehabilitation will not be affected by study participation, and will be approximately equal for the three groups. Each 45-minute session will be entirely dedicated to RBT, and will include up to 60 perturbations. The proposed session duration and number of perturbations per session is double that of our previous sub-acute study, whereas the number of sessions is halved.[12] This previous study was conducted during in-patient rehabilitation, where patients are typically provided with 60-minutes of physiotherapy 5 days per week. Within this schedule, patients could easily complete 30 minutes of RBT, leaving 30 minutes per day for other physical therapies. However, as out-patient physiotherapy is only 45 minutes per session, the proposed dosages more easily fit into most out-patient rehabilitation therapy schedules.

A research physiotherapist will oversee RBT in collaboration with participants' regular physiotherapists to ensure consistent RBT delivery across participants. Training strategies will be individualized to each participant, based on their balance impairments and rehabilitation goals.[12,19] The

RBT program includes multi-directional 'internal' and 'external' balance perturbations. Internal perturbations are achieved by asking the participant to complete tasks that challenge balance control, such that they lose balance when attempting to perform the task (e.g., kicking a soccer ball). External perturbations are delivered manually using a push or pull from the physiotherapist. As participants improve their reactive balance control, difficulty will be increased by shifting task requirements along a continuum from stable to mobile, and from predictable to unpredictable, and by increasing perturbation magnitude or imposing sensory or environmental challenges.[22]

6.4 Outcome measures

To assess feasibility of the study, we will document rates of accrual (i.e., number of patients approached to participate in the study versus the number who provide consent), number of training sessions attended/missed, reasons for missed sessions, and rate of missing data for the outcomes described below.

Table 1 summarizes additional outcome measures. Demographic, stroke information, and medical history will be extracted from participants' hospital charts. Participants will complete a questionnaire at baseline that asks about their social supports, employment, familial responsibilities, living situation etc., which are factors that could influence fall risk. Many of these questions have been adapted from the Canadian Longitudinal Study on Aging.[23] The National Institutes of Health Stroke Scale (NIH-SS)[24] will be scored at study enrolment. Clinical assessments will be scored by a blinded research assistant at three time points: 1) pre-training; 2) post-training; and 3) 6 months post-training. Tests will include: Chedoke-McMaster Stroke Assessment (CMSA)[25] foot and leg scores; mini-Balance Evaluation Systems Test (mini-BEST);[26] Activities-specific Balance Confidence (ABC) scale;[27] and reactive balance control following unpredictable and novel perturbations.

To assess reactive balance control, participants will be outfitted with reflective markers, and will complete 8-10 walking trials on a movable platform. There will be four force plates embedded in

the movable platform. On two trials, the platform will move forward suddenly on heel strike (i.e., when one of the force plates is loaded) to trigger a slip-like perturbation.[28] On two other trials, the platform will move backward suddenly on toe-off (i.e., when one of the force plates is unloaded) to trigger a trip-like perturbation. The perturbation waveform will consist of a 300 ms square-wave acceleration, followed immediately by 300 ms deceleration (peak acceleration up to 1.5m/s^2).[28] The platform will only move during these four trials, such that the perturbation will be unpredictable to participants. These perturbations differ from what will be used during training, and will measure transfer of training to a novel and ecological loss of balance. Three-dimensional motion capture will record the locations of the reflective markers in space. Biomechanical stability when responding to the perturbation will be measured using an established method that considers the distance between the centre of mass and base of support;[28,29] in general, a more posteriorly- (slip) or anteriorly-located (trip) centre of mass in relation to the perturbed lower limb is considered less stable.

Participants will be asked to report falls ("an event that results in a person coming to rest unintentionally on the ground or other lower level"[30]) in the 6 months post-training. Participants will be provided with stamped, addressed postcards to mail to the research team every 2 weeks for 6 months post-training. Postcards will contain a calendar, on which participants will record falls. The blinded research assistant will call participants who do not return the postcard to determine if any falls occurred. The research assistant will contact participants reporting a fall to complete a short questionnaire determining the cause and consequences of the fall. This method is considered the 'gold standard' for fall reporting.[31]

Participants will also report physical activities using the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD),[32] and participation in daily life using the Subjective Index of Physical and Social Outcome (SIPSO) at 2-, 4- and 6-months post-discharge.

6.5 Sample size

We will aim to recruit 12 participants per group (36 participants total), as recommended for pilot studies.[33]

6.6 Recruitment

Participants will be recruited from the Toronto Rehabilitation Institute University Centre out-patient stroke rehabilitation program. This program admits approximately 200 individuals with stroke per year. Potentially eligible participants will be identified by the patients' primary treating physiotherapist. Participants will be reimbursed for any travel expenses (e.g., public transit, taxi, or parking) they incur to attend data collection appointments; participants will not be reimbursed for travel expenses for the intervention as they were occur as part of routine care. Participants will also receive a $50 gift card upon completion of the study as a modest incentive to participate.

7. METHODS: ASSIGNMENT OF INTERVENTIONS

7.1 Group allocation

Participants will be assigned using blocked randomization to one of the three different doses of RBT (block size: 6). The random allocation sequence will be computer generated. Blocked randomization will ensure equal numbers allocated to each group. Group allocation will be performed centrally by the principal investigator, who will not be involved in recruiting, scoring assessments, or administering the interventions (i.e., concealed allocation).

7.2 Blinding

Outcome measures will be obtained by a research assistant who will be blinded to group allocation. At the post-training and follow-up study visits, the research assistant will be asked to guess the participants' group allocation, and if the research assistant received any information about participant group allocation that led to unblinding. Participants cannot be blinded to group allocation.

8. METHODS: DATA COLLECTION, MANAGEMENT, AND ANALYSIS

8.1 Data collection methods

Data will be collected primarily by the research assistant either directly from the participant or by chart review (see Table 1 for further details). The research assistant will receive training regarding data collection from the principal investigator (AM). Questionnaires will be completed via in person interview at enrolment, and over the telephone at the follow-up time points.

8.2 Data management

Electronic data will be stored on secure institutional severs. Hard copies of files containing de-identified data will be stored in locked cabinets and/or in offices that are locked when not occupied.

8.3 Data analysis

Data analysis will address the research questions as described below.

1. *What is the optimal sample size?* The primary outcome in the larger trial will be rate of falls in daily life. The rate of falls (number of falls per person-year) in the one-session group, and a clinically meaningful 30% reduction in fall rates, will be used to estimate sample size for the larger trial.[34]
2. *How long will it take to achieve this sample size?* We will use the accrual rate from the pilot study (number of participants recruited per month) to estimate how long it will take to achieve the target sample size in the larger trial.
3. *What secondary outcome measures should be used?* Our previous work supports feasibility of data collection using most of the measures in this population.[12] However, we have not previously tested the slip- and trip-like perturbations in this population. We will examine between-group effect sizes for this test to determine if it is useful for revealing training effects. We will also report on

completeness of data collection for this, and other, outcome measures; the larger trial will only include outcomes with ≥80% completion rate.

4. *How feasible is it to prescribe specific dose of RBT to people with sub-acute stroke?* The feasibility of prescribing a specific RBT dose during patients' routine rehabilitation is not known. The dose will be considered feasible if the mean number of sessions and number of perturbations per session is ≥75% of prescribed.
5. *What two intervention groups should be included in the larger trial?* We will use the reactive control sub-scale of the mini-BEST as a measure of effect of RBT on reactive balance control in each group. Scores on this sub-scale have been shown to improve with a high dose of RBT in people with chronic stroke.[19] We will calculate the pre-to-post training effect sizes for this sub-scale for each group (i.e., mean difference in the score from pre-training to post-training). The minimum detectable change for the total mini-BEST score in people with stroke is 3 points[35] (i.e., ~10% of the maximum score). The minimum detectable change for individual sub-scales have not been established, but we will assume that this is 10% of the maximum score for the subscale (i.e., 0.6 points). Therefore, if the pre-to-post training effect sizes are within 0.6 points for the three-session and six-session groups, then the larger trial will include the one-session and three-session groups. However, if effect sizes reveal a trend towards greater improvement for the six-session group, then the larger trial will include the one-session and six-session groups.

Data will be analyzed at the end of the study. Therefore, there is no plan for interim analyses of primary and/or secondary variables.

9. METHODS: MONITORING

9.1 Data monitoring

There is no data monitoring committee for this study; several previous studies have already demonstrated that reactive balance training is safe for people with stroke, with few adverse events reported.[12,16,19,20] Adverse events that meet all three of the following criteria will be reported immediately to the institution's Research Ethics Board, as is routine practice: 1) unexpected in terms of nature, severity, or frequency; 2) related or possibly related to participation in the research; and 3) suggests a potential increased in risk of harm to research participants or others. All adverse events will be collated and evaluated bi-annually by the principal investigator (AM).

9.2 Potential harms

In a previous study, mild adverse events related to RBT in people with stroke were delayed-onset muscle soreness, fatigue, or exacerbation of joint pain (11%, 7%, and 32% of participants, respectively),[19] which did not require medical attention, but resulted in reduced intervention intensity until they resolved (typically by the following session). Of note, the frequency and severity of adverse events are similar for the RBT group and control group, who completed more 'traditional' balance training.[19] Therefore, these types of adverse events are typical of similar exercise programs, and not specific to RBT.

As the assessment and intervention includes tasks that are deliberately challenging to balance control, there is a small risk that participants, upon loss of balance, will fall. Appropriate precautions will be taken to ensure patient safety during these tasks. Interventions will be administered by a trained and licensed physiotherapist who will tailor the training to the patient's abilities. Assessments will be completed by a trained research assistant with a health sciences background. A safety harness attached to a secure point overhead will be worn for all postural perturbations to prevent a fall to the floor if the individual fails to regain stability. Additionally, the research assistant or physiotherapist can provide assistance to prevent a fall. We have administered tens of thousands of postural perturbations to over 500 individuals with varying balance abilities in previous research studies and clinical activities and no

participant suffered an injury as a result of an induced postural perturbation. However, even if the participant is caught by the safety harness or researcher, there is a very small chance that participants will suffer a physical injury (e.g., sprain or bruise). In the event of a minor physical injury, the physiotherapist will provide first aid, will advise the participant regarding follow-up with a medical professional (e.g., family doctor) and home treatment (e.g., rest, ice, compression, elevation), and will follow-up with the participant after a day or two.

The physiotherapist will communicate regularly with the participant's care team about changes in health status that could affect risk profile. Participants will be withdrawn if their health changes such that they would no longer be eligible for the study (i.e., one of the exclusion criteria applies to them).

10. ETHICS AND DISSEMINATION

10.1 Research ethics approval

Research ethics approval has been received by the Research Ethics Board of the University Health Network (Study ID: 19-6001, approved 17 January 2020).

10.2 Protocol amendments

Substantive changes to the design or conduct of the study will require a formal amendment to the study protocol. Such substantive amendments will be agreed upon by the study investigators and will be approved by the Research Ethics Board of the University Health Network prior to implementation. Minor administrative changes to study documents (e.g., correcting a typographical error or clarifying a questionnaire item) may also be implemented, with the Research Ethics Board notified of the changes.

10.3 Consent

Potentially eligible participants will be identified by the patients' primary treating physiotherapist. The physiotherapist will ask patients if they are interested in speaking with a research assistant regarding

the study. If patients agree, they will be approached by a member of the research team (DJ, CJD or a delegate acting on their behalf) who will explain the study and provide patients with the study information sheet and consent form (Appendix). Research personnel will answer the patient's questions about the study. Patients may discuss the study with their friends, family members, or healthcare providers. Patients may take as long as necessary to decide if they wish to participate in the study; however, if a patient has not decided before they are discharged then we will assume they have declined participation. The informed consent process will be documented by research personnel.

10.4 Confidentiality

Personal information is any information that could identify participants. If participants agree to join this study, the following personal information will only be accessible to the research team, for contact purposes: name, telephone number, mailing address, and e-mail address (if provided). A number of steps will be taken to ensure protection of personal health information. All information collected during this study, including the participant's personal information, will be kept confidential and will not be shared with anyone outside the study unless required by law. Electronic data will be stored on secure servers for 10 years. After 10 years the data will be deleted from the servers. Electronic files containing patient names and contact information will be password protected, and will be stored separately from study data. Hard copies of files containing de-identified data will be stored in locked cabinets and/or in offices that are locked when not occupied. Consent forms will be stored in locked cabinets/offices separately from other data. Only those individuals who require access to the data for the purpose of this study will be provided with the password to the file containing identifiers and/or the keys to the locked cabinet/office.

10.5 Declaration of interests

The authors declare that they have no competing interests related to this study.

10.6 Access to data

The principal investigator (AM) will have access to the full dataset. There is no current plan to make the participant-level dataset available publicly; however, the dataset may be made available in future via a Data Access Committee, if such a committee is established by the institution.

10.7 Ancillary and post-trial care

The University Health Network will be responsible for providing out-of-pocket expenses to ensure that a participant receives immediate medical care in the event that the participant experiences an adverse health event (e.g., injury) as a result of participation in the study. Patients do not typically receive follow-up after discharge from rehabilitation; therefore, there is no plan for any post-trial care.

10.8 Dissemination policy

Participants will receive a letter of appreciation at the end of the study, which may include a brief summary of the study results. Study results will be shared with the academic community via publication in peer-reviewed journals and presentations at conferences. We will aim to submit a paper describing analysis of the primary and secondary outcomes within 6 months of completing data collection. All individuals who meet the International Committee of Medical Journal Editors criteria for authorship will be included as authors on any publications arising from this work. We will share results directly with physiotherapists through interactive workshops (e.g., at the Canadian Physiotherapy Association meeting). We are developing a toolkit to assist physiotherapists implementing RBT. The results of the larger trial will be incorporated into the toolkit as recommendations for RBT dose in sub-acute stroke.

11. SIGNIFICANCE

A high rate of falling is a common after stroke, and fall risk is highest in the first months post-discharge from rehabilitation.[21] RBT is a novel type of exercise that aims to improve reactive balance control, rather than 'traditional' balance training, which focuses on maintaining stability during voluntary movement. Time in stroke rehabilitation is limited, and physiotherapists report lack of time is a barrier to implementing RBT.[36] The results of the proposed study will inform the design of a larger RCT to establish the optimal dose of RBT in sub-acute stroke. If a low dose of RBT can improve reactive balance control and prevent falls post-stroke, this would allow therapists and patients to more easily include this fall-prevention intervention in rehabilitation, without sacrificing time spent working on other important rehabilitation goals.

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13. TABLES

Table 1: Cohort descriptors and outcome measures.

	Pre-training	Post-training	6-month follow-up
Demographics	✓		
Time post-stroke	✓		
Lesion location	✓		
Medical history	✓		
Medications	✓		
Changes in health/medications		✓	✓
NIH stroke scale[24]	✓		
Chedoke McMaster Stroke Assessment[25]	✓	✓	✓
Mini-Balance Evaluation Systems Test[26]	✓	✓	✓
Activities-specific Balance Confidence scale[27]	✓	✓	✓
Novel unpredictable perturbation	✓	✓	✓
Falls in daily life			✓*
Physical Activity Scale for Individuals with Physical Disabilities[32]			✓*
Subjective Index of Physical and Social Outcome[37]			✓*

*Data collected repeatedly during the 6-month follow-up period.

14. FIGURE CAPTIONS

Figure 1: Trial design.

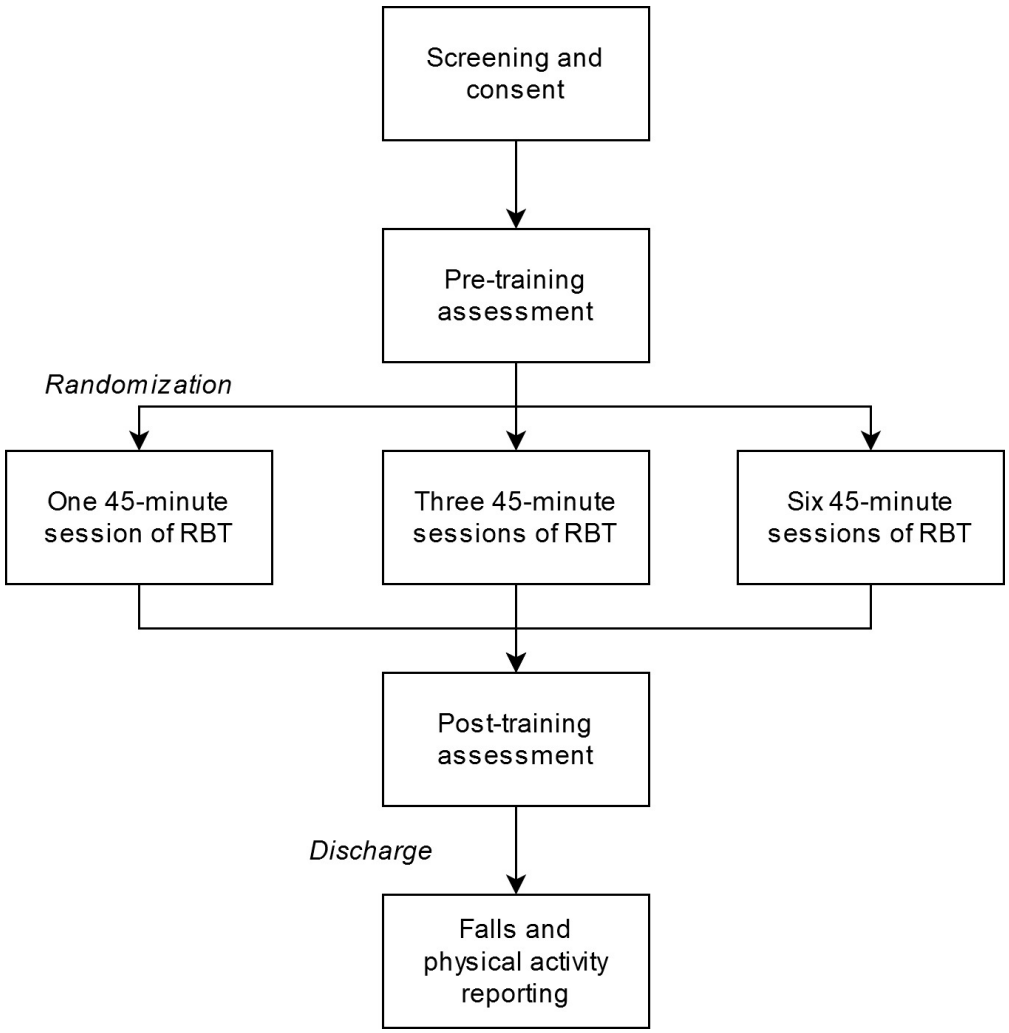

Figure 1: Trial design.

477x487mm (72 x 72 DPI)

CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

Study title: Determining the optimal dose of reactive balance training after stroke ☐a pilot study

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*Please note that communication via e-mail is not absolutely secure. Thus, please do not communicate personal sensitive information via e-mail.

Funding
This study is funded by the Heart and Stroke Foundation Canadian Partnership for Stroke Recovery.

IMPORTANT: You are being invited to take part in a research study. Before you agree to take part, it is important that you read the information below. The information describes the purpose of the study, the risks or benefits to you, and your right to withdraw at any time. You should take as much time as you need to make your decision. You should ask the study doctor or study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish including your friends, family, and family doctor. Participation in this study is voluntary.

Objective of the study

People who have had a stroke tend to walk slower and are more likely to fall than those who have not had a stroke. A new type of reactive balance training, might help reduce fall rates after discharge from stroke rehabilitation. Some studies suggest that people can benefit from even small amounts of reactive balance training, but we do not know how much reactive balance training is necessary to improve balance and prevent falls. Our long-term goal is to determine the ideal number of reactive balance training sessions that will improve reactive balance control and prevent falls. We are currently conducting a small pilot study to determine the feasibility of a larger study to address this long-term goal.

You are being asked to participate because you have had a stroke within the last 6 months, you are attending outpatient rehabilitation at Toronto Rehab, and you are able to walk without assistance of another person.

Up to 36 people will participate in this study and it will take approximately 18 months to recruit all participants.

Study visits and procedures

If you agree to participate in the study, we will review your chart, you will complete balance training, we will test your balance and function, and we will ask you to report falls. The parts of the study are described below.

Chart review

We will review your hospital chart to get some information about your stroke, your previous medical history, and your current prescription medications. We use this information to confirm that you are eligible for the study and to describe the type of people who have participated in the study. You do not need to do anything additional for the chart review.

Reactive balance training

Reactive balance is the kind of balance that you need to stop yourself from falling after you stumble, trip, or get bumped, or jostled. Reactive balance requires you to step very quickly when you have lost your balance, to prevent a fall. In order for you to re-learn reactive balance, you need to lose your balance so that you can practice recovering with rapid steps. This is called **reactive balance training.**

Reactive balance training will be completed by your physiotherapist, and/or by a research physiotherapist. Reactive balance training is done in a safe, supportive, supervised environment. You will wear a harness which is attached to an overhead frame. The harness is worn so that when you lose your balance, you do not risk falling all the way to the floor. The physiotherapist will be there as well to assist you should you be unable to recover your balance on your own.

The physiotherapist will ask you to do exercises that cause you to lose your balance. He or she will do this in one of two ways:

1. he or she will have you practice tasks that gradually challenge your balance and result in a loss of balance, or
2. he or she will gradually pull or push you until you lose your balance.

Images removed for publication

Example of task to challenge balance: tapping on unstable surfaces with alternating feet

Example of 'pull' by physiotherapist to left

You will receive 1, 3, or 6 reactive balance training sessions; each session will be 45-minutes long and will replace 1, 3, or 6 of your regular physiotherapy sessions. The timing of the sessions during your outpatient rehabilitation will be determined by your physiotherapist.

Balance and functional testing

You will be asked to complete three testing sessions: 1) just before you start the reactive balance training; 2) at the time of discharge from rehab; and, 3) 6-months after you finish the training. Each testing session will last 2-2.5 hours. The first session will be longer than the other two. You can take rest breaks as often as you need during the testing sessions. During these test sessions, we will ask you several questions and conduct several tests.

☒ Information about you (10 minutes) ☐we ask you some questions about you and your life. We will ask questions about your employment, education history, and social networks. We use this information to describe the type of people who have participated in this study.

☒ Stroke function tests (20 minutes, first visit only) - we will do some quick tests of your vision, memory, sense of touch, and arm and leg function. These tests tell us how your stroke has affected you. We use this information to describe the kind of people who participate in the study.

☒ Questionnaire (10 minutes) - we will ask you to complete a standardized questionnaire about your balance confidence. We would like to know if balance confidence improves after completing the training. You are free to choose not to answer any of the questions. You can take the questionnaire away with you and answer it at home if you like.

☒ Leg and foot recovery (10 minutes) ☐we will ask you to do a few movements with your leg and foot that have been affected by the stroke, such as bending the knee or wiggling the toes. We would like to know if your ability to move the leg and foot improves after completing the training.

☒ Balance test (15 minutes) - we will ask you to do several activities that challenge your balance and mobility, such as walking as quickly as you can, standing with your eyes closed, and recovering your balance once released from a leaning position. A research assistant will stand near you when you complete the tests to provide any assistance you might need. The research assistant will rate how you perform on each test. We would like to know if your ability to perform these tests improves after completing the training.

☒ Balance reaction test (1 hour) - we will test your balance reactions on a movable platform. During this test, you will wear a safety harness attached to an overhead beam and you will be outfitted with reflective markers. We will ask you to walk forward on the platform 8-10 times. During 2 of the walking trials, the platform will move suddenly, requiring you to react to regain your balance. If you are unable to use your own balance reactions to prevent a fall, the safety harness will catch you. We would like to know if your balance reactions improve after completing the exercise program. Setting up for this test takes quite a bit of time, but the tests themselves will only take about 10-15 minutes.

All of the balance tests will be videotaped so that we can check out you performed the tests after you finish your appointment. The videotaping is mandatory for the study. Only study personnel will have access to your video images. We may ask for your permission to show the videos to some people outside the study (e.g., for educational purposes). We will ask you to provide this permission by signing a separate consent form, but you do not have to provide this permission. We will not share the videos with anyone outside of the study without your permission.

Falls reporting

We will ask you to complete a six-month falls monitoring period. When you have completed the assessment at the end of rehabilitation you will be provided with a calendar that you will be asked to fill out daily. You will use this calendar to record any falls or near falls that you experience. We will ask you to return the calendar to us every two weeks. If you experience a fall or a near fall, it is important that you get the medical care you may need. After your medical care is addressed, we will ask you (or a family member) to contact us to answer some questions about the fall or near fall. You can answer these questions over the telephone. The questions include what you were doing when you fell, what you think caused the fall, and whether you have a fear of falling. The questions should take 15-30 minutes to answer.

If you do not return a calendar we will call you to remind you to return it. We will also call you three times during this six month monitoring period (about every 2 months) to ask you questions about your physical activities. These questions should take about 15-30 minutes to answer.

Study design

This is an assessor blind pilot randomized trial.

- $VVHVVRU EOLQG PHDQV WKH SHUVRQV FROOHFWLQJ DOO RI WKH information for the study should not know which exercise program you are in.
- µ3LORW¶ PHDQV D VPDOO VWXG\ to test out the study procedures before planning a larger study.
- µ5DQGRPL]HG¶ PHDQV that you do not have a choice of which group you are in. You have an equal chance of being assigned to one of the three groups and the assignment is decided randomly, like rolling a die.
- µ7ULDO¶ PHDQV WKUHH JURXSV

Potential harms, discomforts and inconveniences

This study involves being assigned to one of three different groups. One group might do better than the other group. If you participate in this study you will get the same or better standard of care than if you did not participate in the study.

There is some extra time involved with participating in this study. You will be asked to do two DVVHVVPHQWV GXULQJ RXWSDWLHQW UHKDELOLWDWLRQ WKDW DUH LQ DGGLWLRQ to your regular physiotherapy. You will be asked to travel to Toronto Rehab for testing one time after your outpatient rehabilitation program is over; this will be approximately 6 months after the end of the reactive balance training sessions. You might find this a burden. If you require a family member to assist you with transport they might also find that it is inconvenient to travel with you to the study appointments.

You might find the balance training or tests to be challenging or tiring. To minimize the risk of physical harm, we do not allow people with certain medical conditions to participate in this study. The sessions will be supervised by a trained physiotherapist who will monitor you for any negative effects. You will be provided regular rest breaks, and can request additional breaks. You can stop the testing or training at any time if you are too tired to continue or are uncomfortable. During the exercises and balance tests, there is a risk that you will not be able to regain balance by yourself and will start to fall. You will wear a safety harness to prevent you from falling to the floor. Additionally, the researchers can help you to regain your balance. There is a very small chance you will have an injury (such as a sprain or a bruise), even if you are caught by the safety harness. However, we have done these types of tests and exercises with hundreds of people with stroke without any injuries.

If you agree to participate in this study you will have to fill out the falls monitoring calendar every day and return it to us every two weeks. We will also call you frequently to ask you questions about your falls and physical activities. You might find that the calendars and the phone calls are inconvenient.

If you have difficulty understanding or speaking English you may need a family member or friend to help you to participate in this study. They may need to translate some of the study documents and questionnaires, speak to our research personnel on the telephone. This may inconvenience your family member or friend.

Potential benefits

If you participate in this study you will participate in reactive balance training. It is possible that this training will benefit your balance.

The results of this study will give us more information about the amount of training that is required to improve balance reaction. These results will be used to inform the next research study and could be used in rehabilitation programs and benefit other stroke patients in the future.

Reminders and responsibilities

It is important to remember the following things during the study:

- ☒ Tell the study staff your health history and medications as accurately as possible. This will help to prevent any harm to you.
- ☒ Ask the study staff about anything that worries you.
- ☒ Tell the study staff if anything about your health has changed.
- ☒ Return the falls calendars regularly and report any falls to the study staff as soon as possible.

Alternatives to being in a study

You do not have to join this study to receive treatment for your stroke. Your outpatient rehabilitation program will be provided as scheduled.

Confidentiality

Your data will be shared as described in this consent form or as required by law. All personal information such as your name, address, and phone number will be removed from the data and will be replaced with a number. A list linking the number with your name will be kept by the study investigator in a secure place, separate from your file.

Personal Health Information

If you agree to join this study, the research team will look at your personal health information and collect only the information they need for the study. Personal health information is any information that could identify you and includes your:

- ☒ name,
- ☒ address,

x age, and,
☒ new or existing medical records, that includes types, dates and results of medical tests or procedures.

Representatives of the University Health Network (UHN) including the UHN Research Ethics Board may look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study is following proper laws and guidelines.

The research team will keep any personal health information about you, including the videos, in a secure and confidential location for 10 years after we have finished collecting data for this study. All information collected during this study, including your personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law. You will not be named in any reports, publications, or presentations that may come from this study.

Research information in shared clinical records
If you participate in this study, information about you from this research project may be stored in your hospital file and in the UHN computer system. The UHN shares the patient information stored on its computers with other hospitals and health care providers in Ontario so they can access the information if it is needed for your clinical care. The study team can tell you what information about you will be stored electronically and may be shared outside of the UHN. If you have any concerns about this, or have any questions, please contact the UHN Privacy Office at 416-340-4800, x6937 (or by email at privacy@uhn.ca).

Alternatives to being in the study
The usual treatment for people with stroke at Toronto Rehab includes the treatment of balance when indicated. Your treatment will include all regular therapy programs as well as the addition of reactive balance training sessions.

Voluntary participation
You are encouraged to ask any questions that you may have about this study. If you do not wish to participate in this study it will not affect any treatment that might receive at Toronto Rehab or the University Health Network in the future. If you chose to participate initially but wish to withdraw at a later date, for any reason, it will not affect any future care that you receive at Toronto Rehab or the University Health Network. We will give you any new information about the study that might affect your decision to stay in the study.

Withdrawal from the study
If you choose to leave the study, the information that was collected before you left the study will still be used in order to help answer the research question. No new information will be collected without your permission.

Costs and reimbursement
You will be reimbursed for any travel expenses that result from the follow-up appointments. These travel expenses may include TTC fare, taxi fare, or parking. You will receive a $50 gift card upon completion of the study.

Rights as a participant
If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost.

By signing this form you do not give up any of your legal rights against the investigators, sponsor or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.

Conflict of interest
Researchers have an interest in completing this study. Their interests should not influence your decision to participate in this study.

Questions about the study
If you have any questions, concerns or would like to speak to the study team for any reason, please call Avril Mansfield at 416-597-3422 extension 7831. **If you have any questions about your rights as a research participant or have concerns about this study, call the Chair of the University Health Network Research Ethics Board (UHN REB) or the Research Ethics office number at 416-581-7849.** The REB is a group of people who oversee the ethical conduct of research studies. The UHN REB is not part of the study team. Everything that you discuss will be kept confidential.

You will be given a signed copy of this consent form.

Consent

This study has been explained to me and any questions I had have been answered.

I know that I may leave the study at any time. I agree to the use of my information as described in this form. I agree to take part in this study.

6WXGHQW SDUWLFLSDQW QDPH	Signature	Date

My signature means that I have explained the study to the participant named above. I have answered all questions.

Name of person obtaining consent	Signature	Date

Was the participant assisted during the consent process? ❑YES ❑NO

If **YES**, please check the relevant box and complete the signature space below:

❑The person signing below acted as an interpreter for the participant during the consent process and attests that the study as set out in this form was accurately interpreted has had any questions answered.

Name of interpreter	Signature	Date

Relationship to participant	Language

❑The consent form was read to the participant. The person signing below attests that the study as set out in this form was accurately explained to, and has had any questions answered.

Name of witness	Signature	Date

Relationship to participant

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	ItemNo	Description	Page no.
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
	2b	All items from the World Health Organization Trial Registration Data Set	2-4
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
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	7
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	8

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	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	8-9
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)	9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	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)	9-10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
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	11-12
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)	Figure 1 Table 1

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	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12-13
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	13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
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
Statistical methods	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	14-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
	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)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	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	n/a
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	16-17
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	17

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)	17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17-18
	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	18
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Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
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	19
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Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Determining the optimal dose of reactive balance training after stroke – study protocol for a pilot randomized controlled trial

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1. ADMINISTRATIVE INFORMATION

Title: Determining the optimal dose of reactive balance training after stroke – study protocol for a pilot randomized controlled trial

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Contributorship: AM conceived of the study, is the grant holder, and drafted the manuscript. AM, ELI, and CJD developed the intervention. AM, ELI, CJD, DJ, TB and AHH contributed to study design, writing/editing the manuscript, and approved the final manuscript.

2. WHO DATASET

1. **Trial registration:** clinicaltrials.gov, NCT04219696
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5. **Primary sponsor:** Avril Mansfield
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9. **Public title:** Determining the optimal dose of reactive balance training after stroke
10. **Scientific title:** Determining the optimal dose of reactive balance training after stroke – a pilot study
11. **Countries of recruitment:** Canada
12. **Interventions:** Reactive balance training. A research physiotherapist will oversee reactive balance training (RBT) in collaboration with participants' regular physiotherapists to ensure consistent RBT delivery across participants. Training strategies will be individualized to each

participant, based on their balance impairments and rehabilitation goals. The RBT program includes multi-directional 'internal' and 'external' balance perturbations. Internal perturbations are achieved by asking the participant to complete tasks that challenge balance control, such that they lose balance when attempting to perform the task (e.g., kicking a soccer ball). External perturbations are delivered manually using a push or pull from the physiotherapist. As participants improve their reactive balance control, difficulty will be increased by shifting task requirements along a continuum from stable to mobile, and from predictable to unpredictable, and by increasing perturbation magnitude or imposing sensory or environmental challenges.

13. **Key inclusion and exclusion criteria:** Inclusion criteria: sub-acute stroke; receiving out-patient rehabilitation at the Toronto Rehabilitation Institute; can stand independently for >30 seconds; can walk with or without a gait aid (but without assistance of another person) for >10 metres; and living in the community. Exclusion criteria: completed reactive balance training during in-patient rehabilitation; lower-extremity amputation, weight-bearing restrictions, recent lower-extremity injury or surgery (e.g., fracture), acute back or lower-limb pain, halo, aspen collar, history of fragility fracture and/or severe osteoporosis/osteopenia, contractures that prevent neutral hip or ankle; activity restrictions following cardiac event/surgery, abnormal or unstable cardiovascular responses to exercise, arterial dissection; severe spasticity in the legs; cognitive impairment (i.e., unable to understand the purpose of training and/or to provide informed consent); and/or acute illness (e.g., vomiting, fever), weight > 150 kg (exceeds safety harness weight limits), colostomy bags, indwelling catheter, infection, pressure sore on pelvis or trunk.
14. **Study type:** Pilot parallel randomized controlled trial.
15. **Date of first enrolment:** June 2020 (anticipated).
16. **Target sample size:** 36
17. **Recruitment status:** Pending.

18. Primary outcome: Rate of falls in daily life for six months post-discharge from out-patient rehabilitation.

19. Secondary outcomes: Rate of accrual, rate of missing data, intervention fidelity.

3. ABSTRACT

Introduction: Falls risk post-stroke is highest soon after discharge from rehabilitation. Reactive balance training (RBT) aims to improve control of reactions to prevent falling after a loss of balance. In healthy older adults, a single RBT session can lead to lasting improvements in reactive balance control and prevent falls in daily life. While increasing the dose of RBT does not appear to lead to additional benefit for healthy older adults, stroke survivors, who have more severely impaired balance control, may benefit from a higher RBT dose. Our long-term goal is to determine the optimal dose of RBT in people with sub-acute stroke. This assessor-blinded pilot randomized controlled trial aims to inform the design of a larger trial to address this long-term goal.

Methods and analysis: Participants (n=36) will be attending out-patient stroke rehabilitation, and will be randomly allocated to one of three groups: 1, 3, or 6 RBT sessions. RBT will replace a portion of participants' regular physiotherapy so that the total physical rehabilitation time will be the same for the 3 groups. Balance and balance confidence will be assessed at: 1) study enrolment; 2) out-patient rehabilitation discharge; and 3) 6 months post-discharge. Participants will report falls and physical activity for 6 months post-discharge. Pilot data will be used to plan the larger trial (i.e., sample size estimate using fall rates, and which groups should be included based on between-group trends in pre-to-post training effect sizes for reactive balance control measures). Pilot data will also be used to assess the feasibility of the larger trial (i.e., based on the accrual rate, outcome completion rate, and feasibility of prescribing specific training doses).

Ethics and dissemination: Institutional research ethics approval has been received. Study participants will receive a lay summary of results. We will also publish our findings in a peer-reviewed journal.

4. STRENGTHS AND LIMITATONS

- The intervention will replace a portion of participants routine physiotherapy during out-patient rehabilitation. Therefore, the findings will be directly relevant to clinical practice.
- Conversely, there is a risk that patients will decline participation in the study, which requires consent to being randomized to a specific dose of reactive balance training, as they will not want their rehabilitation care to be disrupted.
- This is a pilot study, so it is unlikely that we will be able to make definitive decisions regarding the optimal dose of reactive balance training post-stroke.

5. INTRODUCTION

5.1 Background and rationale

Falls are the most prevalent complications during all stages of stroke recovery.[1] Along with physical injuries, 88% of people with stroke who fall develop fear of falling.[2] Falls and fear of falling can lead to inactivity, deconditioning, and lower functional capacity, further increasing fall risk[3,4] and reducing quality of life.[5]

Conventional balance training, where the goal is to maintain balance during the balance-challenging exercises, reduces falls in older adults,[6] but not after stroke.[7,8] Reactive balance training (RBT), where clients experience repeated postural perturbations (or loss of balance),[9,10] is a novel type of exercise that aims to improve reactive balance control. RBT can prevent falls in older adults and people with Parkinson's disease.[11] Our non-randomized study suggests that RBT reduces fall rates after discharge from stroke rehabilitation.[12] In our previous study, the intervention was implemented as part of routine care, and the dose of RBT depended on client goals and preferences and length of stay, rather than being prescribed by the study protocol. Participants completed 1-12, 30-minute RBT sessions (median of 6 sessions).[12]

Unlike other forms of exercise (e.g., resistance training or aerobic exercise), where improvements in physical fitness take weeks or months of regular training,[13] improved reactive balance control with RBT seems to occur with few repetitions, and is maintained for several months without training. Among healthy older adults, just 24 perturbations within a single session of RBT is sufficient to lead to lasting improvements (i.e., 6-12 months) in reactive balance control,[14] and prevent falls in daily life.[15] One study in people with chronic stroke found that improved reactive balance control with a single session of RBT was retained for 3 weeks post-training.[16] Almost doubling the dose of RBT does not appear to lead to additional benefit for healthy older adults;[17] however, it is possible that those with stroke would benefit from additional RBT as they have more severely impaired balance than healthy older adults.[18] While additional training may also promote sustained improvements in reactive

balance control beyond 3 weeks,[19-21] in one study that included people with sub-acute stroke reduced fall rates up to six months post-training were reported when 29% of participants completed only one 30-minute session of RBT.[12] The sub-acute phase is a crucial period for reactive balance training, due to the high potential for neuroplasticity in this early phase of recovery,[22] and to the high risk of falls early after stroke.[23] Therefore, there is a need to establish optimal RBT training parameters in the sub-acute stroke population.

5.2 Objectives and research questions

The long-term goal of this work is ***to determine the optimal dose of RBT in people with sub-acute stroke***. This assessor-blinded pilot randomized controlled trial (RCT) aims ***to inform the design of a larger trial to address this long-term goal***. Specifically, the following questions about the larger trial will be answered with this pilot study:

1) what is the optimal sample size;

2) how long will it take to achieve this sample size;

3) are the proposed secondary outcome measures feasible;

4) how feasible is it to prescribe a specific dose of RBT to people with sub-acute stroke within routine out-patient rehabilitation; and

5) what two intervention groups should be included in the larger trial?

5.3 Trial design

The current paper describes the protocol for an assessor-blinded pilot RCT (Figure 1), following the SPIRIT guidelines and checklist.[24] People who are attending out-patient stroke rehabilitation will be randomly assigned to one of three different doses of reactive balance training (RBT). Reactive balance control, functional balance, and balance confidence will be measured at study enrolment (within days of admission to out-patient rehabilitation), discharge from out-patient rehabilitation, and 6 months post-

discharge. Falls in daily life, physical activity, and participation will be assessed for 6 months post-discharge.

5.3.1 Patient and public involvement

This study was designed without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes. Some trial design elements were informed by participant feedback from our previous RBT study.[19] Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

6. METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

6.1 Study setting

This study will take place at the Toronto Rehabilitation Institute, University Health Network. This facility provides specialized in- and out-patient stroke rehabilitation to individuals in the sub-acute stage of stroke recovery. Out-patient stroke rehabilitation at the Toronto Rehabilitation Institute typically includes 45 minutes of physiotherapy 2-5 times/week for at least 4 weeks, with most patients receiving 8 weeks of out-patient rehabilitation.

6.2 Participants

Participants will be people with sub-acute stroke (<6-months post-stroke) who are receiving out-patient rehabilitation at the Toronto Rehabilitation Institute. Participants will be eligible if they can: 1) stand independently for >30s; 2) walk with or without a gait aid (but without assistance of another person) for >10m; and 3) are living in the community. Participants will be excluded if they have:

- Completed RBT during in-patient rehabilitation;

- Lower extremity amputation, weight-bearing restrictions, recent lower-extremity injury or surgery (e.g., fracture), acute back or lower-limb pain, halo, aspen collar, history of fragility fracture and/or severe osteoporosis/osteopenia, contractures that prevent neutral hip or ankle;
- Activity restrictions following cardiac event/surgery, abnormal or unstable cardiovascular responses to exercise, arterial dissection;
- Severe spasticity in the legs that prevents the individual from safely accepting weight on the limb;
- Cognitive impairment (i.e., unable to understand the purpose of training and/or to provide informed consent), as determined by the healthcare team; and/or
- Acute illness (e.g., vomiting, fever), extreme obesity (exceeds safety harness system weight limits), colostomy bags, indwelling catheter, infection, pressure sore on pelvis or trunk.

After participants provide consent, eligibility will be confirmed using information in the participants' hospital chart, by consulting members of the patient's healthcare team, and by consulting the participant themselves. Participants will still receive their usual care, while participating in the study.

Participants will be informed that they are free to withdraw from the study at any time point, without consequence. If participants ask to be withdrawn from the study, any data collected from them up to that point will be used to answer the research questions. Participants may also be withdrawn from the study due to changes in their health status that affect eligibility.

6.3 Interventions

Participants will be allocated to one of three groups: one, three, or six, 45-minute RBT sessions. RBT will replace a portion of participants' regular physiotherapy, so that the total amount of physical rehabilitation will not be affected by study participation, and will be approximately equal for the three groups. Each 45-minute session will be entirely dedicated to RBT, and will include up to 60

perturbations. The proposed session duration and number of perturbations per session is double that of our previous sub-acute study, whereas the number of sessions is halved.[12] This previous study was conducted during in-patient rehabilitation, where patients are typically provided with 60-minutes of physiotherapy 5 days per week. Within this schedule, patients could easily complete 30 minutes of RBT, leaving 30 minutes per day for other physical therapies. However, as out-patient physiotherapy is only 45 minutes per session, the proposed dosages more easily fit into most out-patient rehabilitation therapy schedules. From our team's previous research[12,19] and experience with clinical implementation of RBT in stroke rehabilitation, we expect that participants will be able to tolerate the 45-minute sessions of RBT. Rest breaks will be scheduled into each session, and will be provided when requested by participants.

A research physiotherapist will oversee RBT in collaboration with participants' regular physiotherapists to ensure consistent RBT delivery across participants. Training strategies will be individualized to each participant, based on their balance impairments and rehabilitation goals.[12,19] For example, if a participant has low foot clearance when executing reactive steps, then obstacles will be placed on the floor and the participant will be encouraged to step over the obstacles during voluntary and reactive stepping. If a participant has a goal to return to a specific activity then aspects of that activity will be included in the training sessions (e.g., if returning to golfing is a goal, the participant may train on a compliant surface to simulate uneven outdoor terrain). Further details of the specific balance training approaches that will be used and how training will be tailored to individual participants can be found in our previous paper.[19] The RBT program includes multi-directional 'internal' and 'external' balance perturbations. Internal perturbations are achieved by asking the participant to complete tasks that challenge balance control, such that they lose balance when attempting to perform the task (e.g., kicking a soccer ball). External perturbations are delivered manually using a push or pull from the physiotherapist while the participant is either standing still or doing a voluntary task, like marching on the spot; when the physiotherapist is positioned behind the

participant, the direction and timing of the push or pull can be unpredictable to the participant. As participants improve their reactive balance control, difficulty will be increased by shifting task requirements along a continuum from stable to mobile, and from predictable to unpredictable, and by increasing perturbation magnitude (i.e., by increasing the force of the push/pull) or imposing sensory or environmental challenges.[25]

6.4 Outcome measures

To assess feasibility of the study, we will document rates of accrual (i.e., number of patients approached to participate in the study versus the number who provide consent), number of training sessions attended/missed, reasons for missed sessions, rate of missing data for the outcomes described below, and rate of withdrawal from the study.

Table 1 summarizes additional outcome measures. Demographic, stroke information, and medical history will be extracted from participants' hospital charts. Participants will complete a questionnaire at baseline that asks about their social supports, employment, familial responsibilities, living situation etc., which are factors that could influence fall risk. Many of these questions have been adapted from the Canadian Longitudinal Study on Aging.[26] The National Institutes of Health Stroke Scale (NIH-SS)[27] will be scored at study enrolment. Clinical assessments will be scored by a blinded research assistant at three time points: 1) study enrolment (as soon as possible after admission to out-patient rehabilitation); 2) discharge from out-patient rehabilitation; and 3) 6 months post-discharge. Tests will include: Chedoke-McMaster Stroke Assessment (CMSA)[28] foot and leg scores; mini-Balance Evaluation Systems Test (mini-BEST);[29] Activities-specific Balance Confidence (ABC) scale;[30] and reactive balance control following unpredictable and novel perturbations.

To assess reactive balance control, participants will be outfitted with reflective markers, and will complete 8-10 walking trials on a movable platform. There will be four force plates embedded in the movable platform. On two trials, the platform will move forward suddenly on heel strike (i.e., when

one of the force plates is loaded) to trigger a slip-like perturbation.[31] On two other trials, the platform will move backward suddenly on toe-off (i.e., when one of the force plates is unloaded) to trigger a trip-like perturbation. Each slip or trip trial will be triggered on heel-strike or toe-off, respectively, of each of the left and right limbs. The perturbation waveform will consist of a 300 ms square-wave acceleration, followed immediately by 300 ms deceleration (peak acceleration up to 1.5m/s^2).[31] The platform will only move during these four trials; the remaining 4-6 trials will consist of unperturbed walking. The slip/trip and unperturbed walking trials will be presented in a pseudo-random order to ensure that participants cannot predict the timing, direction, or perturbed limb for these trials. This unpredictability will help ensure that any changes are not simply due to practice effects on the specific task. While there may be some improvement in responses to the perturbation simply due to repetition of the task (i.e., not due to training effects), previous work suggests that experiencing a single slip or trip perturbation does not lead to large and lasting improvements responses to the perturbations.[32,33] These perturbations differ from what will be used during training, and will measure transfer of training to a novel and ecological loss of balance. Three-dimensional motion capture will record the locations of the reflective markers in space. Biomechanical stability when responding to the perturbation will be measured using an established method that considers the distance between the centre of mass and base of support;[31,34] in general, a more posteriorly- (slip) or anteriorly-located (trip) centre of mass in relation to the perturbed lower limb is considered less stable.

Participants will be asked to report falls ("an event that results in a person coming to rest unintentionally on the ground or other lower level"[35]) in the 6 months post-discharge. Participants will be provided with stamped, addressed postcards to mail to the research team every 2 weeks for 6 months post-discharge. Postcards will contain a calendar, on which participants will record falls. The blinded research assistant will call participants who do not return the postcard to determine if any falls occurred. The research assistant will contact participants reporting a fall to complete a short

questionnaire determining the cause and consequences of the fall. This method is considered the 'gold standard' for fall reporting.[36]

Participants will also report physical activities using the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD),[37] and participation in daily life using the Subjective Index of Physical and Social Outcome (SIPSO) at 2-, 4- and 6-months post-discharge.

6.5 Sample size

We will aim to recruit 12 participants per group (36 participants total), as recommended for pilot studies.[38]

6.6 Recruitment

Participants will be recruited from the Toronto Rehabilitation Institute University Centre out-patient stroke rehabilitation program. This program admits approximately 200 individuals with stroke per year. Potentially eligible participants will be identified by the patients' primary treating physiotherapist. Participants will be reimbursed for any travel expenses (e.g., public transit, taxi, or parking) they incur to attend data collection appointments; participants will not be reimbursed for travel expenses for the intervention as they will occur as part of routine care. Participants will also receive a $50 gift card upon completion of the study as a modest incentive to participate.

7. METHODS: ASSIGNMENT OF INTERVENTIONS

7.1 Group allocation

Participants will be assigned using blocked randomization to one of the three different doses of RBT (block size: 6). The random allocation sequence will be computer generated. Blocked randomization will ensure equal numbers allocated to each group. Group allocation will be performed centrally by the

principal investigator, who will not be involved in recruiting, scoring assessments, or administering the interventions (i.e., concealed allocation).

7.2 Blinding

Outcome measures will be obtained by a research assistant who will be blinded to group allocation. At the discharge and follow-up study visits, the research assistant will be asked to guess the participants' group allocation, and if the research assistant received any information about participant group allocation that led to unblinding. Participants cannot be blinded to group allocation. Data analysis will be conducted by an individual who is not blinded to group allocation.

8. METHODS: DATA COLLECTION, MANAGEMENT, AND ANALYSIS

8.1 Data collection methods

Data will be collected primarily by the research assistant either directly from the participant or by chart review (see Table 1 for further details). The research assistant has received training regarding data collection from the principal investigator. Questionnaires will be completed via in person interview at enrolment, and over the telephone at the follow-up time points.

8.2 Data management

Electronic data will be stored on secure institutional servers. Hard copies of files containing de-identified data will be stored in locked cabinets and/or in offices that are locked when not occupied.

8.3 Data analysis

Data analysis will address the research questions as described below.

1. *What is the optimal sample size?* The proposed primary outcome in the larger trial will be rate of falls in daily life. The one-session group is expected to show minimal improvements in reactive

balance control and fall risk. Therefore, the rate of falls (number of falls per person-year) in the one-session group, reported over the 6-months post-discharge, and a clinically meaningful 30% reduction in fall rates, will be used to estimate sample size for the larger trial.[39]

2. *How long will it take to achieve this sample size?* We will use the accrual rate (number of participants recruited per month) and proportion of participants who withdraw from the study to estimate how long it will take to achieve the target sample size in the larger trial.
3. *Are the proposed secondary outcome measures feasible?* Our previous work supports feasibility of data collection using most of the measures in this population.[12] However, we have not previously tested the slip- and trip-like perturbations in this population. We will report between-group effect sizes and completeness of data collection for responses to the slip- and trip-like perturbations, and other outcome measures (i.e., Chedoke-McMaster Stroke Assessment, Mini-Balance Evaluation Systems Test, Activities-specific Balance Confidence Scale, Physical Activity Scale for Individuals with Physical Disabilities, and Subjective Index of Physical and Social Outcome); the larger trial will only include outcomes with ≥80% completion rate.
4. *How feasible is it to prescribe specific dose of RBT to people with sub-acute stroke?* The feasibility of prescribing a specific RBT dose during patients' routine rehabilitation is not known. Participants assigned to the 3- or 6-session groups or their physiotherapists may decline sessions if they feel they is not beneficial to their care. Likewise, participants assigned to the 1- or 3-session groups or their physiotherapists may feel that they can benefit from additional RBT sessions. The dose will be considered feasible if the mean number of sessions and number of perturbations per session is 75-100% of prescribed.
5. *What two intervention groups should be included in the larger trial?* The larger trial will compare one session of RBT with a higher dose. We will use the reactive control sub-scale of the mini-BEST as a measure of effect of RBT on reactive balance control in each group. Scores on this sub-scale have been shown to improve with a high dose of RBT in people with chronic stroke.[19] We

will calculate the pre-to-post training effect sizes for this sub-scale for each group (i.e., mean difference in the score from admission to discharge). The minimum detectable change for the total mini-BEST score in people with stroke is 3 points[40] (i.e., ~10% of the maximum score). The minimum detectable change for individual sub-scales have not been established, but we will assume that this is 10% of the maximum score for the subscale (i.e., 0.6 points). Therefore, if the pre-to-post training effect sizes are within 0.6 points for the three-session and six-session groups, then the larger trial will include the one-session and three-session groups. However, if effect sizes reveal a trend towards greater improvement for the six-session group, then the larger trial will include the one-session and six-session groups.

Data will be analyzed at the end of the study. Therefore, there is no plan for interim analyses of primary and/or secondary variables.

9. METHODS: MONITORING

9.1 Data monitoring

There is no data monitoring committee for this study; several previous studies have already demonstrated that reactive balance training is safe for people with stroke, with few adverse events reported.[12,16,19,20] Adverse events that meet all three of the following criteria will be reported immediately to the institution's Research Ethics Board, as is routine practice: 1) unexpected in terms of nature, severity, or frequency; 2) related or possibly related to participation in the research; and 3) suggests a potential increased in risk of harm to research participants or others. All adverse events will be collated and evaluated bi-annually by the principal investigator.

9.2 Potential harms

In a previous study, mild adverse events related to RBT in people with stroke were delayed-onset muscle soreness, fatigue, or exacerbation of joint pain (11%, 7%, and 32% of participants, respectively),[19] which did not require medical attention, but resulted in reduced intervention intensity until they resolved (typically by the following session). Of note, the frequency and severity of adverse events are similar for the RBT group and control group, who completed more 'traditional' balance training.[19] Therefore, these types of adverse events are typical of similar exercise programs, and not specific to RBT.

As the assessment and intervention includes tasks that are deliberately challenging to balance control, there is a small risk that participants, upon loss of balance, will fall. Appropriate precautions will be taken to ensure patient safety during these tasks. Interventions will be administered by a trained and licensed physiotherapist who will tailor the training to the patient's abilities. Assessments will be completed by a trained research assistant with a health sciences background. A safety harness attached to a secure point overhead will be worn for all postural perturbations to prevent a fall to the floor if the individual fails to regain stability. Additionally, the research assistant or physiotherapist can provide assistance to prevent a fall. We have administered tens of thousands of postural perturbations to over 500 individuals with varying balance abilities in previous research studies and clinical activities and no participant suffered an injury as a result of an induced postural perturbation. However, even if the participant is caught by the safety harness or researcher, there is a very small chance that participants will suffer a physical injury (e.g., sprain or bruise). In the event of a minor physical injury, the physiotherapist will provide first aid, will advise the participant regarding follow-up with a medical professional (e.g., family doctor) and home treatment (e.g., rest, ice, compression, elevation), and will follow-up with the participant after a day or two.

The physiotherapist will communicate regularly with the participant's care team about changes in health status that could affect risk profile. Participants will be withdrawn if their health changes such that they would no longer be eligible for the study (i.e., one of the exclusion criteria applies to them).

10. ETHICS AND DISSEMINATION

10.1 Research ethics approval

Research ethics approval has been received by the Research Ethics Board of the University Health Network (Study ID: 19-6001, approved 17 January 2020).

10.2 Protocol amendments

Substantive changes to the design or conduct of the study will require a formal amendment to the study protocol. Such substantive amendments will be agreed upon by the study investigators and will be approved by the Research Ethics Board of the University Health Network prior to implementation. Minor administrative changes to study documents (e.g., correcting a typographical error or clarifying a questionnaire item) may also be implemented, with the Research Ethics Board notified of the changes.

10.3 Consent

Potentially eligible participants will be identified by the patients' primary treating physiotherapist. The physiotherapist will ask patients if they are interested in speaking with a research assistant regarding the study. If patients agree, they will be approached by a member of the research team (DJ, CJD or a delegate acting on their behalf) who will explain the study and provide patients with the study information sheet and consent form (Appendix). Research personnel will answer the patient's questions about the study. Patients may discuss the study with their friends, family members, or healthcare providers. Patients may take as long as necessary to decide if they wish to participate in the study; however, if a patient has not decided before they are discharged then we will assume they have declined participation. The informed consent process will be documented by research personnel.

10.4 Confidentiality

Personal information is any information that could identify participants. If participants agree to join this study, the following personal information will only be accessible to the research team, for contact purposes: name, telephone number, mailing address, and e-mail address (if provided). A number of steps will be taken to ensure protection of personal health information. All information collected during this study, including the participant's personal information, will be kept confidential and will not be shared with anyone outside the study unless required by law. Electronic data will be stored on secure servers for 10 years. After 10 years the data will be deleted from the servers. Electronic files containing patient names and contact information will be password protected, and will be stored separately from study data. Hard copies of files containing de-identified data will be stored in locked cabinets and/or in offices that are locked when not occupied. Consent forms will be stored in locked cabinets/offices separately from other data. Only those individuals who require access to the data for the purpose of this study will be provided with the password to the file containing identifiers and/or the keys to the locked cabinet/office.

10.5 Declaration of interests

The authors declare that they have no competing interests related to this study.

10.6 Access to data

The principal investigator (AM) will have access to the full dataset. There is no current plan to make the participant-level dataset available publicly; however, the dataset may be made available in future via a Data Access Committee, if such a committee is established by the institution.

10.7 Ancillary and post-trial care

The University Health Network will be responsible for providing out-of-pocket expenses to ensure that a participant receives immediate medical care in the event that the participant experiences an adverse

health event (e.g., injury) as a result of participation in the study. Patients do not typically receive follow-up after discharge from rehabilitation; therefore, there is no plan for any post-trial care.

10.8 Dissemination policy

Participants will receive a letter of appreciation at the end of the study, which may include a brief summary of the study results. Study results will be shared with the academic community via publication in peer-reviewed journals and presentations at conferences. We will aim to submit a paper describing analysis of the primary and secondary outcomes within 6 months of completing data collection. All individuals who meet the International Committee of Medical Journal Editors criteria for authorship will be included as authors on any publications arising from this work. We will share results directly with physiotherapists through interactive workshops (e.g., at the Canadian Physiotherapy Association meeting). We are developing a toolkit to assist physiotherapists implementing RBT. The results of the larger trial will be incorporated into the toolkit as recommendations for RBT dose in sub-acute stroke.

11. SIGNIFICANCE

A high rate of falling is a common after stroke, and fall risk is highest in the first months post-discharge from rehabilitation.[23] RBT is a novel type of exercise that aims to improve reactive balance control, rather than 'traditional' balance training, which focuses on maintaining stability during voluntary movement. Time in stroke rehabilitation is limited, and physiotherapists report lack of time is a barrier to implementing RBT.[41] The results of the proposed study will inform the design of a larger RCT to establish the optimal dose of RBT in sub-acute stroke. If a low dose of RBT can improve reactive balance control and prevent falls post-stroke, this would allow therapists and patients to more easily include this fall-prevention intervention in rehabilitation, without sacrificing time spent working on other important rehabilitation goals.

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13. TABLES

Table 1: Cohort descriptors and outcome measures.

	Study enrolment	Discharge	During six-month follow-up	6-months post-discharge
Demographics	✓			
Time post-stroke	✓			
Lesion location	✓			
Medical history	✓			
Medications	✓			
Changes in health/medications		✓		✓
NIH stroke scale[27]	✓			
Chedoke McMaster Stroke Assessment[28]	✓	✓		✓
Mini-Balance Evaluation Systems Test[29]	✓	✓		✓
Activities-specific Balance Confidence scale[30]	✓	✓		✓
Novel unpredictable perturbation	✓	✓		✓
Falls in daily life			✓*	
Physical Activity Scale for Individuals with Physical Disabilities[37]			✓*	
Subjective Index of Physical and Social Outcome[42]			✓*	

*Data collected repeatedly during the 6-month follow-up period.

14. FIGURE CAPTIONS

Figure 1: Trial design.

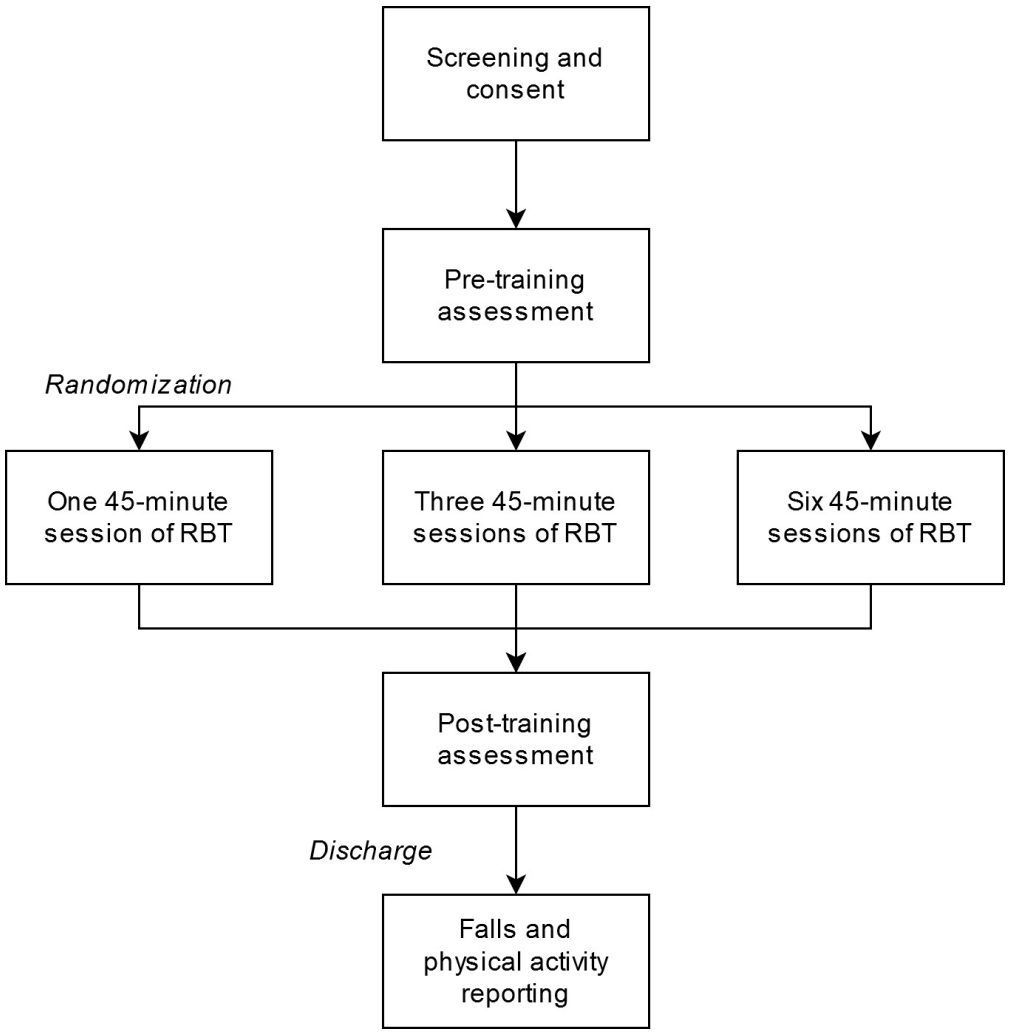

Figure 1: Trial design.

477x487mm (72 x 72 DPI)

CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

Study title: Determining the optimal dose of reactive balance training after stroke – a pilot study

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*Please note that communication via e-mail is not absolutely secure. Thus, please do not communicate personal sensitive information via e-mail.

Funding
This study is funded by the Heart and Stroke Foundation Canadian Partnership for Stroke Recovery.

IMPORTANT: You are being invited to take part in a research study. Before you agree to take part, it is important that you read the information below. The information describes the purpose of the study, the risks or benefits to you, and your right to withdraw at any time. You should take as much time as you need to make your decision. You should ask the study doctor or study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish including your friends, family, and family doctor. Participation in this study is voluntary.

Objective of the study
People who have had a stroke tend to have 'poor' balance and are more likely to fall than those who have not had a stroke. A new type of exercise, called 'reactive balance training', might help reduce fall rates after discharge from stroke rehabilitation. Some studies suggest that people can benefit from even small amounts of reactive balance training, but we do not know how much reactive balance training is necessary to improve balance and prevent falls. Our long-term goal is to determine the ideal number of reactive balance training sessions that will improve reactive balance control and prevent falls. We are currently conducting a small pilot study to determine the feasibility of a larger study to address this long-term goal.

You are being asked to participate because you have had a stroke within the last 6 months, you are attending outpatient rehabilitation at Toronto Rehab, and you are able to walk without assistance of another person.

Up to 36 people will participate in this study and it will take approximately 18 months to recruit all participants.

Study visits and procedures
If you agree to participate in the study, we will review your chart, you will complete balance training, we will test your balance and function, and we will ask you to report falls. The parts of the study are described below.

Chart review
We will review your hospital chart to get some information about your stroke, your previous medical history, and your current prescription medications. We use this information to confirm that you are eligible for the study and to describe the type of people who have participated in the study. You do not need to do anything additional for the chart review.

Reactive balance training
Reactive balance is the kind of balance that you need to stop yourself from falling after you stumble, trip, or get bumped, or jostled. Reactive balance requires you to step very quickly when you have lost your balance, to prevent a fall. In order for you to re-learn reactive balance, you need to lose your balance so that you can practice recovering with rapid steps. This is called **reactive balance training.**

Reactive balance training will be completed by your physiotherapist, and/or by a research physiotherapist. Reactive balance training is done in a safe, supportive, supervised environment. You will wear a harness which is attached to an overhead frame. The harness is worn so that when you lose your balance, you do not risk falling all the way to the floor. The physiotherapist will be there as well to assist you should you be unable to recover your balance on your own.

The physiotherapist will ask you to do exercises that cause you to lose your balance. He or she will do this in one of two ways:

1. he or she will have you practice tasks that gradually challenge your balance and result in a loss of balance, or
2. he or she will gradually pull or push you until you lose your balance.

Images removed for publication

Example of task to challenge balance: tapping on unstable surfaces with alternating feet

Example of 'pull' by physiotherapist to left

You will receive 1, 3, or 6 reactive balance training sessions; each session will be 45-minutes long and will replace 1, 3, or 6 of your regular physiotherapy sessions. The timing of the sessions during your outpatient rehabilitation will be determined by your physiotherapist.

Balance and functional testing

You will be asked to complete three testing sessions: 1) just before you start the reactive balance training; 2) at the time of discharge from rehab; and, 3) 6-months after you finish the training. Each testing session will last 2-2.5 hours. The first session will be longer than the other two. You can take rest breaks as often as you need during the testing sessions. During these test sessions, we will ask you several questions and conduct several tests.

- Information about you (10 minutes) – we ask you some questions about you and your life. We will ask questions about your employment, education history, and social networks. We use this information to describe the type of people who have participated in this study.

- Stroke function tests (20 minutes, first visit only) - we will do some quick tests of your vision, memory, sense of touch, and arm and leg function. These tests tell us how your stroke has affected you. We use this information to describe the kind of people who participate in the study.

- Questionnaire (10 minutes) - we will ask you to complete a standardized questionnaire about your balance confidence. We would like to know if balance confidence improves after completing the training. You are free to choose not to answer any of the questions. You can take the questionnaire away with you and answer it at home if you like.

- Leg and foot recovery (10 minutes) – we will ask you to do a few movements with your leg and foot that have been affected by the stroke, such as bending the knee or wiggling the toes. We would like to know if your ability to move the leg and foot improves after completing the training.

- Balance test (15 minutes) - we will ask you to do several activities that challenge your balance and mobility, such as walking as quickly as you can, standing with your eyes closed, and recovering your balance once released from a leaning position. A research assistant will stand near you when you complete the tests to provide any assistance you might need. The research assistant will rate how you perform on each test. We would like to know if your ability to perform these tests improves after completing the training.

- Balance reaction test (1 hour) - we will test your balance reactions on a movable platform. During this test, you will wear a safety harness attached to an overhead beam and you will be outfitted with reflective markers. We will ask you to walk forward on the platform 8-10 times. During 2 of the walking trials, the platform will move suddenly, requiring you to react to regain your balance. If you are unable to use your own balance reactions to prevent a fall, the safety harness will catch you. We would like to know if your balance reactions improve after completing the exercise program. Setting up for this test takes quite a bit of time, but the tests themselves will only take about 10-15 minutes.

All of the balance tests will be videotaped so that we can check out you performed the tests after you finish your appointment. The videotaping is mandatory for the study. Only study personnel will have access to your video images. We may ask for your permission to show the videos to some people outside the study (e.g., for educational purposes). We will ask you to provide this permission by signing a separate consent form, but you do not have to provide this permission. We will not share the videos with anyone outside of the study without your permission.

Falls reporting

We will ask you to complete a six-month falls monitoring period. When you have completed the assessment at the end of rehabilitation you will be provided with a calendar that you will be asked to fill out daily. You will use this calendar to record any falls or near falls that you experience. We will ask you to return the calendar to us every two weeks. If you experience a fall or a near fall, it is important that you get the medical care you may need. After your medical care is addressed, we will ask you (or a family member) to contact us to answer some questions about the fall or near fall. You can answer these questions over the telephone. The questions include what you were doing when you fell, what you think caused the fall, and whether you have a fear of falling. The questions should take 15-30 minutes to answer.

If you do not return a calendar we will call you to remind you to return it. We will also call you three times during this six month monitoring period (about every 2 months) to ask you questions about your physical activities. These questions should take about 15-30 minutes to answer.

Study design

This is an assessor blind pilot randomized trial.

- 'Assessor blind' means that the person who is collecting all of the information for the study should not know which exercise program you are in.
- 'Pilot' means a small study to test out the study procedures before planning a larger study.
- 'Randomized' means that you do not have a choice of which group you are in. You have an equal chance of being assigned to one of the three groups and the assignment is decided randomly, like rolling a die.
- 'Trial' is another word for 'study'.

Potential harms, discomforts and inconveniences

This study involves being assigned to one of three different groups. One group might do better than the other group. If you participate in this study you will get the same or better standard of care than if you did not participate in the study.

There is some extra time involved with participating in this study. You will be asked to do two assessments during outpatient rehabilitation that are 'in addition' to your regular physiotherapy. You will be asked to travel to Toronto Rehab for testing one time after your outpatient rehabilitation program is over; this will be approximately 6 months after the end of the reactive balance training sessions. You might find this a burden. If you require a family member to assist you with transport they might also find that it is inconvenient to travel with you to the study appointments.

You might find the balance training or tests to be challenging or tiring. To minimize the risk of physical harm, we do not allow people with certain medical conditions to participate in this study. The sessions will be supervised by a trained physiotherapist who will monitor you for any negative effects. You will be provided regular rest breaks, and can request additional breaks. You can stop the testing or training at any time if you are too tired to continue or are uncomfortable. During the exercises and balance tests, there is a risk that you will not be able to regain balance by yourself and will start to fall. You will wear a safety harness to prevent you from falling to the floor. Additionally, the researchers can help you to regain your balance. There is a very small chance you will have an injury (such as a sprain or a bruise), even if you are caught by the safety harness. However, we have done these types of tests and exercises with hundreds of people with stroke without any injuries.

If you agree to participate in this study you will have to fill out the falls monitoring calendar every day and return it to us every two weeks. We will also call you frequently to ask you questions about your falls and physical activities. You might find that the calendars and the phone calls are inconvenient.

If you have difficulty understanding or speaking English you may need a family member or friend to help you to participate in this study. They may need to translate some of the study documents and questionnaires, speak to our research personnel on the telephone. This may inconvenience your family member or friend.

Potential benefits

If you participate in this study you will participate in reactive balance training. It is possible that this training will benefit your balance.

The results of this study will give us more information about the amount of training that is required to improve balance reaction. These results will be used to inform the next research study and could be used in rehabilitation programs and benefit other stroke patients in the future.

Reminders and responsibilities

It is important to remember the following things during the study:

- Tell the study staff your health history and medications as accurately as possible. This will help to prevent any harm to you.
- Ask the study staff about anything that worries you.
- Tell the study staff if anything about your health has changed.
- Return the falls calendars regularly and report any falls to the study staff as soon as possible.

Alternatives to being in a study

You do not have to join this study to receive treatment for your stroke. Your outpatient rehabilitation program will be provided as scheduled.

Confidentiality

Your data will be shared as described in this consent form or as required by law. All personal information such as your name, address, and phone number will be removed from the data and will be replaced with a number. A list linking the number with your name will be kept by the study investigator in a secure place, separate from your file.

Personal Health Information

If you agree to join this study, the research team will look at your personal health information and collect only the information they need for the study. Personal health information is any information that could identify you and includes your:

- name,
- address,

- age, and,
- new or existing medical records, that includes types, dates and results of medical tests or procedures.

Representatives of the University Health Network (UHN) including the UHN Research Ethics Board may look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study is following proper laws and guidelines.

The research team will keep any personal health information about you, including the videos, in a secure and confidential location for 10 years after we have finished collecting data for this study. All information collected during this study, including your personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law. You will not be named in any reports, publications, or presentations that may come from this study.

Research information in shared clinical records

If you participate in this study, information about you from this research project may be stored in your hospital file and in the UHN computer system. The UHN shares the patient information stored on its computers with other hospitals and health care providers in Ontario so they can access the information if it is needed for your clinical care. The study team can tell you what information about you will be stored electronically and may be shared outside of the UHN. If you have any concerns about this, or have any questions, please contact the UHN Privacy Office at 416-340-4800, x6937 (or by email at privacy@uhn.ca).

Alternatives to being in the study

The usual treatment for people with stroke at Toronto Rehab includes the treatment of balance when indicated. Your treatment will include all regular therapy programs as well as the addition of reactive balance training sessions.

Voluntary participation

You are encouraged to ask any questions that you may have about this study. If you do not wish to participate in this study it will not affect any treatment that might receive at Toronto Rehab or the University Health Network in the future. If you chose to participate initially but wish to withdraw at a later date, for any reason, it will not affect any future care that you receive at Toronto Rehab or the University Health Network. We will give you any new information about the study that might affect your decision to stay in the study.

Withdrawal from the study

If you choose to leave the study, the information that was collected before you left the study will still be used in order to help answer the research question. No new information will be collected without your permission.

Costs and reimbursement
You will be reimbursed for any travel expenses that result from the follow-up appointments. These travel expenses may include TTC fare, taxi fare, or parking. You will receive a $50 gift card upon completion of the study.

Rights as a participant
If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost.

By signing this form you do not give up any of your legal rights against the investigators, sponsor or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.

Conflict of interest
Researchers have an interest in completing this study. Their interests should not influence your decision to participate in this study.

Questions about the study
If you have any questions, concerns or would like to speak to the study team for any reason, please call Avril Mansfield at 416-597-3422 extension 7831. **If you have any questions about your rights as a research participant or have concerns about this study, call the Chair of the University Health Network Research Ethics Board (UHN REB) or the Research Ethics office number at 416-581-7849.** The REB is a group of people who oversee the ethical conduct of research studies. The UHN REB is not part of the study team. Everything that you discuss will be kept confidential.

You will be given a signed copy of this consent form.

Consent

This study has been explained to me and any questions I had have been answered.

I know that I may leave the study at any time. I agree to the use of my information as described in this form. I agree to take part in this study.

Study participant's name	Signature	Date

My signature means that I have explained the study to the participant named above. I have answered all questions.

Name of person obtaining consent	Signature	Date

Was the participant assisted during the consent process? ❑YES ❑NO

If **YES**, please check the relevant box and complete the signature space below:

❑The person signing below acted as an interpreter for the participant during the consent process and attests that the study as set out in this form was accurately interpreted has had any questions answered.

Name of interpreter	Signature	Date

Relationship to participant	Language

❑The consent form was read to the participant. The person signing below attests that the study as set out in this form was accurately explained to, and has had any questions answered.

Name of witness	Signature	Date

Relationship to participant

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	ItemNo	Description	Page no.
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
	2b	All items from the World Health Organization Trial Registration Data Set	2-4
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
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	7
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	8

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	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	8-9
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)	9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	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)	9-10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
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	11-12
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)	Figure 1 Table 1

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	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12-13
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	13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
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
Statistical methods	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	14-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
	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)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	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	n/a
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	16-17
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	17

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)	17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17-18
	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	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
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	19
Dissemination policy	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	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.