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# Breaking up sitting time after stroke – How much less sitting is needed to improve blood pressure after stroke (BUST-BP-Dose): Protocol for a dose-finding study

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ABSTRACT

Excessive sitting is detrimentally associated with cardiovascular disease and all-cause mortality. Frequent breaks in prolonged sitting can improve cardiometabolic responses in non-stroke populations. However, this has not been established in stroke survivors. This study will determine the most effective dose of activity breaks that (i) produce clinically meaningful improvements in mean systolic blood pressure (primary outcome), postprandial glucose, and insulin responses (secondary outcomes), and (ii) is safe and feasible. We hypothesis that systolic blood pressure, postprandial insulin, and glucose responses will improve with increasing doses of activity and be most effective at the maximum safe and feasible dose of activity. Thirty participants in the most effective dose will provide 80% power to detect a within-person, between-condition, difference of 3.5 mmHg in systolic blood pressure assuming a SD of 15 mmHg, within-person correlation of 0.9, and $\alpha = 0.05$. Stroke survivors will complete 3 experimental conditions in a within-participant, dose escalation design including (i) uninterrupted sitting (8 h), (ii) Dose 1: uninterrupted sitting with bouts of light-intensity exercises while standing (initial dose involves two 5-min breaks), and (iii) Dose 2: two additional 5-min breaks above Dose 1. Ambulatory blood pressure will be collected every 30 min during experimental conditions and hourly for 24-h post-experimental conditions. Blood samples will be collected every 30 min during 2-h postprandial periods. This study will identify the most effective dose of light-intensity exercises while standing to improve cardiometabolic responses in stroke survivors.

## 1. Introduction and rationale

Prolonged sitting is associated with adverse health effects including an increased risk of cardiovascular disease (CVD), all-cause mortality, and diabetes [1,2]. Stroke survivors are a high-risk population that spend 75% of their waking hours sitting and 52% in prolonged bouts of sitting (≥30 min) [3], thus placing them at greater risk of further cardiovascular events. Hypertension is the leading modifiable risk

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**Abbreviations**

| | |
|---|---|
| ABP | ambulatory blood pressure |
| ABPM | ambulatory blood pressure monitor |
| AUSDRISK | Australian type 2 diabetes risk assessment tool |
| Bld | blood sample |
| BMI | body mass index |
| BORG | rating of perceived exertion scale |
| BP | blood pressure |
| CVD | cardiovascular disease |
| DLT | dose-limiting threshold |
| EDTA | ethylenediaminetetraacetic acid |
| ELISA | enzyme-linked immunosorbent assay |
| FAC | functional ambulation classification |
| $Kg/m^2$ | kilograms per metre squared |
| m/s | metres per second |
| min/week | minutes per week |
| mL | millilitre |
| mmHg | millimetres of mercury |
| SBP | systolic blood pressure |
| SD | standard deviation |
| STAND-EX | light-intensity exercises while standing |

factor associated with first stroke and recurrent stroke [4,5]. Interrupting prolonged sitting with frequent bouts of physical activity (e.g. standing activities or walking) in non-stroke populations significantly reduces blood pressure (BP) [6], postprandial glucose and insulin concentrations [7,8]. In stroke survivors, our previous trial found that breaking up prolonged sitting with frequent, short breaks of light-intensity exercises while standing (STAND-EX) significantly reduced systolic blood pressure (SBP) by an average of 3.5 mmHg [9]. This improvement in SBP following frequent bouts of STAND-EX might present a promising target to reduce recurrent stroke risk amongst stroke survivors. While demonstrating proof of concept, the schedule of activity breaks (3 min every 30 min) is not clinically applicable in every-day life. Therefore, this new study builds on our previous BUST-Stroke trial [9,10] and aims to investigate the dose-response of STAND-EX bouts to reduce recurrent stroke risk and improve cardiometabolic health in stroke survivors.

The aims of this study are to determine the most effective dose of activity breaks that (i) produce clinically meaningful improvements in mean SBP (primary outcome), postprandial glucose, and insulin responses (secondary outcomes), and (ii) is safe and feasible.

## 2. Methods

### 2.1. Design

Community dwelling stroke survivors will be recruited to this laboratory based, dose-escalation study. Each participant will complete a familiarisation session followed by an uninterrupted sitting condition and two dose-escalation conditions (Fig. 1). Ethics was obtained and approved by the Hunter New England Human Research Ethics Committee (17/06/21/4.04) and registered with the University of Newcastle's Human Research Committee (H-2017-0296). The trial is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12617001517369).

### 2.2. Patient population

Stroke survivors with a moderate walking disability will be recruited to each cohort ($n = 10$/cohort).

*Inclusion criteria:* Stroke survivors > 3 months post-stroke; Functional Ambulation Classification (FAC) ≥ 3 (able to ambulate on level surfaces with or without supervision); walking speed ≥ 0.4 m/s; able to stand from sitting with minimal assistance (≤1 person); sit ≥ 7 h during waking hours; aged ≥ 18 years.

*Exclusion criteria:* Regularly engage in physical activity (≥150 min/week); Body Mass Index (BMI) > 45 $kg/m^2$; smoker; pregnant; clinically diagnosed with an illness or condition that limits their ability to complete each condition; urinary frequency or urgency; diabetes or taking diabetic medication other than metformin.

### 2.3. Recruitment strategies

Participants will be recruited from the Hunter Stroke Research Volunteer Register, through advertisement, social media posts and presentations. Each participant will enrol in only one cohort.

### 2.4. Intervention

#### 2.4.1. Familiarisation session

Baseline characteristics, including stroke profile (National Institutes of Health Stroke Scale [11], Oxfordshire classification [12] and the Fatigue Assessment Scale [13]), walking ability (10 m walk test, FAC), Australian diabetes risk (AUSDRISK assessment tool [14]) and BP will be measured. Dietary intake will be recalled (24-h recall) under guidance of a dietitian. Participants will be fitted with a thigh-worn

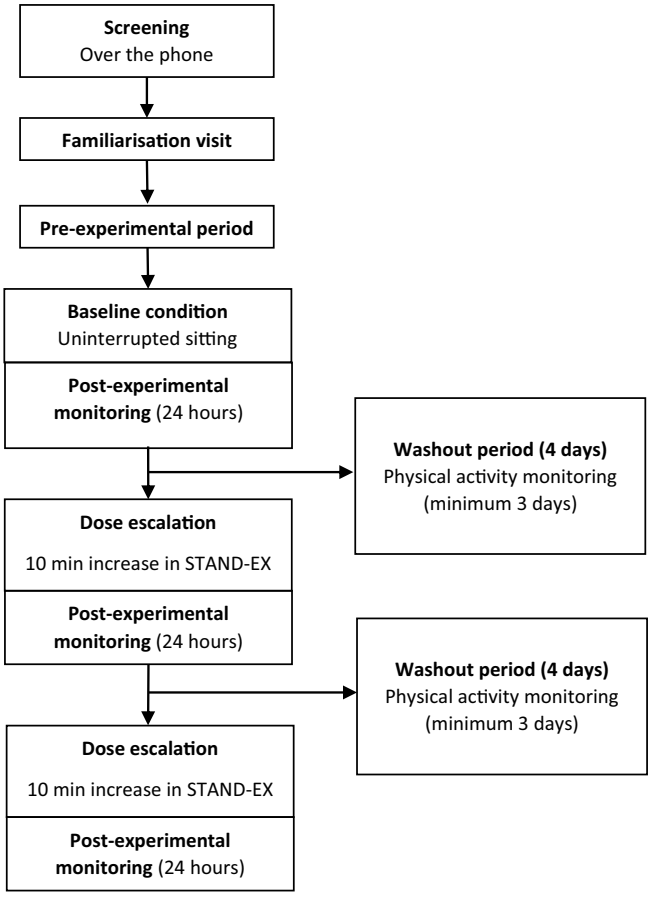
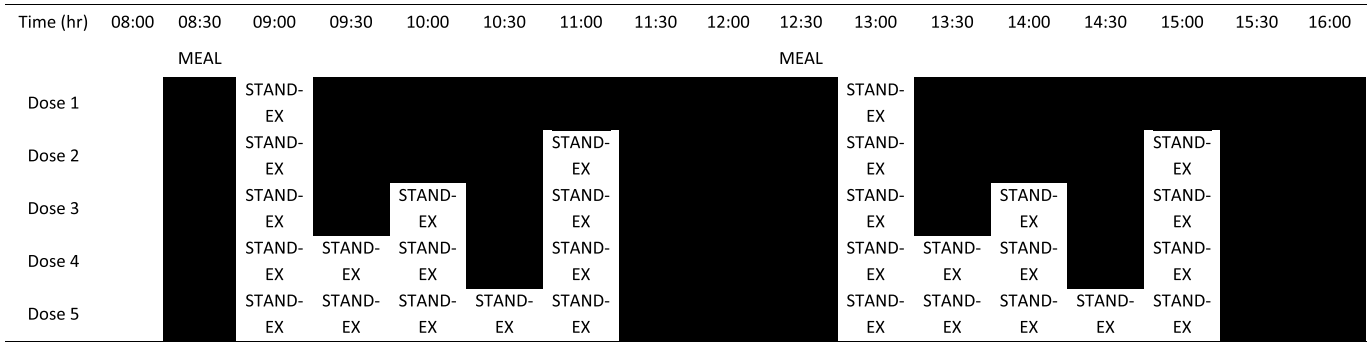



**Fig. 1.** Study schematic.

**Table 1**
Break protocol for light-intensity exercises while standing.




STAND-EX, light-intensity exercises while standing (calf-raises, mini-squats and marching on the spot)

activity monitor (activPAL3; PAL Technologies Ltd) and ambulatory blood pressure monitor (ABPM 7100; Welch Allyn, Inc.) and instructed in the pre-experimental day dietary and activity restrictions.

### 2.4.2. Pre-experimental day protocol

To reduce dietary-induced variations in glucose and insulin, dietary intake will be standardised 24 h prior to, and during, each experimental condition based on the procedures employed in our previous trial [9,10]. Participants will follow a dietitian prescribed meal plan and be provided with a standardised pre-experimental day evening meal and asked to abstain from alcohol, caffeine and moderate-to-vigorous physical activity for 48 h before the experimental conditions.

### 2.4.3. Physical activity and ambulatory blood pressure monitoring

Physical activity and sedentary time will be recorded using an activPAL3 for a minimum of 3 days prior to, and following, each experimental day. Ambulatory blood pressure (ABP) monitoring will continue for 24 h after each experimental day, with hourly ABP recordings. Participants will be asked to remain still whilst ABP measurements are taken. All monitors will be positioned on the participant's non-paretic limb.

### 2.4.4. Experimental day protocol

The protocol is adapted from a previous study completed in stroke survivors (BUST-Stroke) [15]. Participants will arrive at 07:30 on each experimental day and have their health status (presence of cold/flu-like symptoms) and adherence to pre-experimental day protocols determined. An intra-venous cannula will be inserted and fasting blood samples will be collected (08:00am and 08:30am). Blood samples will then be collected every 30 min during each 2 h postprandial period. BP (measured with ABPM) will also be measured every 30 min, with researchers and participants blinded to recordings. BP and blood samples will be taken before bouts of STAND-EX. A standardised breakfast and lunch meal will be provided at approximately 08:30am and 12:30pm, respectively. Participants will be required to consume standardised meals within 30 min. Heart rate, perceived exertion (using the BORG 0–10 scale) and time on task will be measured before and immediately after each bout of STAND-EX, which will vary according to dose escalation (Table 1). Fatigue will be assessed periodically throughout the experimental day using a visual analogue scale. Water will be consumed *ad libitum* during the baseline condition, with total intake recorded and kept consistent between experimental conditions. Toilet breaks will be noted and timed. Table 2 summarises the testing day procedures.

The three experimental conditions will consist of:

1. *Uninterrupted sitting* – 8 h of prolonged, uninterrupted sitting in a comfortable lounge chair (excluding toilet breaks).
2. *Dose escalation 1* – Complete the prescribed dose of STAND-EX (calf-raises, mini-squats and marching on the spot; BORG ≤ 3).
3. *Dose escalation 2* – Complete an additional 10 min of STAND-EX above Dose escalation 1.

Each 5-min bout of STAND-EX will be completed in the following order and repeated 5 times: 20 s calf-raises, 20 s small amplitude squats, and 20 s marching on the spot. Table 1 describes the schedule of STAND-EX for each dose.

### 2.4.5. Dose-escalation

Escalation of STAND-EX will be completed in 10 min increments (2 x 5-min activity breaks). If a dose-limiting threshold (DLT) is not met, the next cohort will commence dose escalation at the final dose completed by the previous cohort. Once DLT is met, a final cohort will repeat the dose escalation of the penultimate cohort to confirm this is the maximum tolerable dose. Table 3 summarises dose escalation procedures.

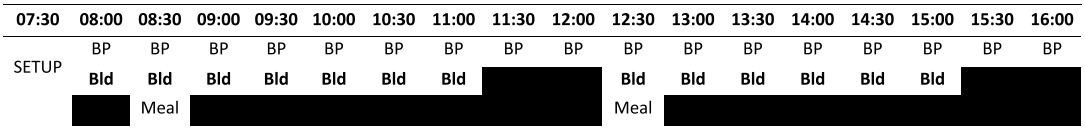
### 2.4.6. Dose-limiting threshold

The DLT is failure to achieve at least 80% of the target time in STAND-EX due to fatigue, pain or effort. The maximum dose for a cohort will be considered reached if 70% or more of the cohort have met the DLT.

### 2.4.7. Blood sampling and analysis

Blood samples will be collected in a 4 mL EDTA tube at each sampling time-point (Table 2) to measure plasma glucose and insulin

**Table 2**
Testing day procedure.




BP, blood Pressure; Bld, blood sample

**Table 3**
Dose-escalation protocol, representing a most effective dose of 40 min.

| | Uninterrupted sitting | Dose 1 (10 minutes) | Dose 2 (20 minutes) | Dose 3 (30 minutes) | Dose 4 (40 minutes) | Dose 5 (50 minutes) |
|---|---|---|---|---|---|---|
| Cohort A |  |  |  | | | |
| Cohort B |  | |  |  | | |
| Cohort C |  | | |  |  | |
| Cohort D |  | | | |  |  |
| Cohort E |  | | |  |  | |

concentrations. Samples will be immediately refrigerated, centrifuged within 60 min of collection, aliquoted and stored in a −80 °C freezer for later analysis. Enzyme-linked immunosorbent assay (ELISA) will be used to measure plasma insulin concentrations. Plasma glucose concentrations will be measured using the point of care i-STAT handheld blood analysis device (i-STAT, Abbot Point of Care Inc.).

### 2.5. Study outcomes

The primary outcome is mean SBP (within-participant, between condition differences) during and 24-h post experimental days. Secondary outcomes are within-participant, between-condition differences for plasma glucose and insulin. Safety will be measured by the number of adverse events, e.g. pain and discomfort from activity breaks. Feasibility assessments will include measures of protocol adherence and completion of activity breaks.

### 2.6. Sample size estimates

At study end, we will have data from n = 30 participants at the maximum tolerable dose of STAND-EX. With an assumed SD of 15 mmHg (based on previous exercise trials in stroke survivors) and a within-person correlation of 0.9, we will have 80% power to detect a within-person, between condition difference of 3.5 mmHg in SBP ($\alpha = 0.05$).

### 2.7. Statistical analysis

SBP, blood glucose and insulin concentrations will be assessed using generalised linear mixed models with random intercepts to account for repeated measures on participants. On achieving the DLT, mean SBP, blood glucose and insulin will be compared with baseline to identify between condition differences. Safety and feasibility outcomes will be evaluated descriptively, and by comparing odds of adverse events across experimental conditions.

### 2.8. Study organisation and funding

This study is supported by a Hunter Medical Research Institute project grant (2016) and Heart Foundation Vanguard Grant (2017 - #101727). PhD Candidate Paul Mackie is supported by a University of Newcastle PhD scholarship, A/Prof English is supported by a Heart Foundation Future Leader Fellowship (#101177).

## 3. Discussion

As an extension to previous research [15], this trial will aim to ascertain the dose of light-intensity exercises most effective to improve mean SBP of stroke survivors that might reduce the risk of recurrent stroke. Results from this trial will inform future studies aiming to reduce the recurrent risk of stroke in stroke survivors.

## 4. Conclusion

This dose escalation trial will further develop our understanding of frequently interrupting prolonged sitting as a strategy to reduce blood pressure and recurrent stroke risk.

## Conflicts of interest disclosures

Nil.

## Acknowledgments

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2018.100310.

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