Statistical analysis plan for FAST (Falls after stroke)

version of 15 December 2024 when data collection ceased, having collected the required sample to completion

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Research questions

In community-dwelling stroke survivors, is a home-based, tailored intervention effective at:

1. reducing the rate of falls and the proportion of people experiencing a fall over a one-year period, and
2. improving community participation, self-efficacy, balance, mobility, physical activity, ADL, depression and health-related quality of life?

Inclusion criteria

- People with stroke
- ≥ 50 years,
- < 5 years since first stroke;
- community-dwelling;
- discharged from formal rehabilitation;
- able to walk 10 m across flat ground (with or without an aid);
- capable of providing consent (< 5 errors on the Short Portable Mental Status Questionnaire).

Exclusion criteria

- moderate to severe receptive aphasia (< 7/10 on the comprehension component of the Frenchay Screening Aphasia Test [Enderby 1986]);
- can walk > 1.4 m/s and had not fallen in the previous year.

Randomisation

- Participants will be randomly allocated into either the experimental group (6 months of habit-forming exercise, safety training and community mobility) or the control group (usual care).
- The allocation of participants to groups will be stratified by level of disability using walking speed because it is associated with community ambulation [Perry 1995].
- Participants will be allocated within each of three strata (< 0.4, 0.4-0.8, > 0.8 m/s preferred walking speed).
- Participants will be allocated to groups randomly after the baseline measurement.
- Randomisation will be offsite, independent and automated service to conceal the schedule from the recruiter.

- Randomisation will be immediate and implemented in REDCap which will be secured by a password.

Intervention

- The experimental group will receive FAST – a home-based intervention consisting of three components – habit-forming exercise, home safety recommendations and a community mobility goal, tailored to their level of disability.
- The faster walkers (> 0.8 m/s) will have an initial emphasis on habit-forming exercise, the slower walkers (< 0.4 m/s) on home safety, and the middle walkers (0.4-0.8 m/s) will have initial emphasis on both habit-forming exercise and home safety. All participants will set a community mobility goal.
- The home-based tailored intervention will be delivered during 7 home visits over Weeks 1-7 followed by three booster sessions at Weeks 13, 15, 23 with two phone calls during Weeks 9 and 19 by an occupational/physical therapist dyad.
- The control group will receive usual care that equates to no active intervention.

Primary outcome measures

- Number of falls will be recorded prospectively from baseline daily until Day 365 on monthly falls calendars and returned by (e)mail or, if not returned, by a phone call and reported as rate of falls.
- Falls are defined according to consensus statements and Cochrane review recommendations as "an unexpected event in which the participant comes to rest on the ground, floor, or lower level" [Lamb 2003].

Secondary outcome measures

- Proportion of participants experiencing a fall over the 12 months.

We will measure the following outcomes at baseline, 6 months (end of intervention) and 12 months (after randomisation) in the home.

- Community participation measured using the disability component (limitation and frequency) of the Late Life Function and Disability Index [Sayers 2004] reported as a score 0 to 100 where 100 is less difficulty with participation. In addition, a self-reported question estimating how much (# outings/wk) participation outside the home.
- Self-efficacy measured as how concerned participants were about falling when carrying out usual activities in the home and the community, rated using a Likert scale where 0 is 'very concerned' and 6 is 'not at all concerned'.
- Balance measured using the balance component of the Short Physical Performance Battery [Guralnik 1994] reported as a score 0 to 4 where 4 is good balance, and the Step Test [Hill 1996] reported as steps/s.
- Mobility measured as preferred and fast walking speed over 5 m [Salbach 2001] reported in m/s. In addition, two self-reported questions estimating maximum duration (using a Likert Scale where 0 is < 5 min and 4 is > 60 min) and maximum distance of walking (using a Likert Scale where 0 is < 100 m and 4 is > 2 km).

- Physical activity measured using the Incidental and Planned Exercise Questionnaire [Delbaere 2010] reported as hr/wk.
- Activities of daily living (ADL) measured using the function component of the Late Life Function and Disability Index [Sayers 2004] reported as a score 0 to 100 where 100 is less difficulty with activities of daily living.
- Health-related quality of life measured using the 0-100 VAS of the EQ-5D (5L) [Kind 2005].
- Depression measured using the Patient Health Questionnaire-2 [Kroenke 2003], reported as a score 0 to 6 where 6 is depression.
- In terms of economic analysis, information will be collected about health care utilisation retrospectively at baseline for the past 12 months and prospectively every 6 months after baseline. Information about regular help with activities of daily living will also be collected using a simple count.
- In order to identify potential barriers and solutions to widespread implementation of the intervention, a qualitative process evaluation will be undertaken using questionnaires (including the Self-Report Behavioural Automaticity Index [Gardner 2012] to explore habit formation) and interviews of participants and therapists via a semi-structured interview.

Blinding

- We will measure outcomes in the home using researchers blind to group allocation.
- It will be not possible to blind participants or therapists to group allocation due to the nature of the intervention.
- A statistician blind to group allocation will conduct statistical analyses.

Sample size

- We estimated the sample size for the primary outcome. A negative binomial model for the number of falls was assumed [Zhu 2014] with alpha (measure of over-dispersion in negative binomial regression model) assumed to be 0.8 and annual rate of falls of the control group assumed to be 1.8 falls/person based on Dean et al [2012].
- Assuming a 15% loss to follow up, with a two-sided level of significance of 5% and power of 80%, a sample size of 185 per group will be recruited to be able to detect a 30% lower rate of falls in the experimental compared with the control group.

Description of participants

- Information describing the characteristics of the participants will be collected and presented according to group (experimental or control) in Table 1 (see below).
- Characteristics of participants lost to follow-up at 12 months will be presented alongside the original cohort so that any trends can be determined.
- Distribution of participants across Australia according to group will also be presented in Table 1 (New South Wales, Victoria, Australian Capital Territory).
- Distribution of participants across walking speeds according to group will also be presented in Table 1 (> 0.8 m/s, 0.4-0.8 m/s, < 0.4 m/s)

Flow of participants through the study

- A flow diagram according to CONSORT statement will be presented as Figure 1 (see below).
- The diagram will present number screened, reasons for inclusion, and final numbers randomised to each group.
- The flow diagram will outline the number of participants who completed the primary outcome (number of falls) for the full 12 months follow-up.
- The flow diagram will also outline number of participants lost to follow-up of the secondary outcomes at 6 and 12 months and the reasons for loss to follow-up.

Description of adherence to intervention

- We will present the mean number of experimental sessions delivered to participants with a 6-month assessment out of a possible 12 per participant as well as the proportion of participants receiving > 80% of the sessions.
- In terms of adherence to the habit-forming exercises, we will present the mean Exercise Adherence Rating Scale score [Newman-Beinart 2017] at 6 and 12 months.
- In terms of home safety recommendations, we will present the proportion of participants implementing recommendations at least partially.
- In terms of community mobility goals, we will present the proportion of participants who set goals.

Statistical analysis

- No interim analyses are planned.
- Not all the outcomes will be presented in the main results paper.
- We will conduct analyses according to this pre-defined plan on an intention-to-treat basis.
- A statistical significance level of 5% will be used, as per the published protocol (Dean, 2020), updated from the registration which specified 1% for secondary outcomes.
- The between-group annual rate of falls will be analysed using negative binomial regression [Robertson 2005] and presented as incidence rate ratio (IRR). Confounding variables such as stroke-specific impairments and demographics factors will be adjusted for, if required. Length of follow-up will be included as an exposure term in these models, i.e. the logarithm of the days of follow-up will be added as an offset.
- The between-group proportion of fallers will be analysed using χ^2 test and presented as relative risk (RR). Although this was published as going to be logistic regression in the protocol [Dean et al 2021], we have decided to present the between-group proportion of fallers as relative risk to be in line with most investigations of interventions to reduce falls.
- Other secondary outcome measures will be analysed using analysis of variance (ANCOVA), adjusted for baseline covariates if appropriate. Ordinal secondary outcomes will be analysed for between-group differences using the nonparametric Mann-Whitney

U statistic. The secondary outcomes will be presented as mean between-group differences (95% CI) in Table 2 (see below).

- Subgroup analyses could be carried out irrespective of whether there is a significant treatment effect on the outcome in order to supplement evidence from the primary analysis. The following subgroups are specified as being of interest for the primary analysis: walking status, fall status.
- Multivariate linear regressions will be used to identify determinants of adherence based on a continuous adherence outcome measure - exercise adherence rating scale (EARS - Newman-Beinart 2016). Further, multivariate modelling will be applied to understand the impact of adherence on the primary and secondary outcome measures on a continuous scale, and dichotomised to represent 'full adherence'.
- The economic evaluation will be conducted from the perspective of the health and community service provider and include the primary and secondary measures as per the protocol. Incremental cost-effectiveness ratios will be calculated using multiple health outcomes, i.e. the incremental cost per a) fall prevented, b) per fall requiring medical attention avoided, c) presentation at emergency department avoided, d) hospital admission avoided, and e) QALY gained (based on the EQ5D-5L). Using the mean costs in each trial arm, and the mean health outcomes in each arm, the incremental cost per health outcome (a-e, above) of the intervention group compared to the control group will be calculated and results will be plotted on a cost- effectiveness plane. Bootstrapping will be used to estimate a distribution around costs and health outcomes, and to calculate the confidence intervals around the incremental cost-effectiveness ratios taking account of joint uncertainty in costs and benefits. One way sensitivity analysis will be conducted around key variables; a cost-effectiveness acceptability curve will be plotted. A cost-effectiveness acceptability curve provides information about the probability that an intervention is cost-effective, given a decision maker’s willingness to pay for each additional health outcome gained.
- In terms of the qualitative process evaluation, verbatim transcripts of interviews will be generated and thematically coded.

Missing data

- All participants with partial falls calendars collected will be entered into binomial regression model.
- Only participants for whom secondary measures was collected will be included in the between-group analysis at 6 and 12 months, ie, missing data will not be imputed.
- During periods of COVID restrictions, data will be collected via phone or (e)mail for falls and those outcomes that are questionnaires. Data for outcomes that require the physical presence of the measurer will not be collected but the data missing due to COVID will be reported.

Data monitoring body

- All adverse events will be reported to the relevant ethics committees.
- Regular fidelity checks of the intervention will be undertaken.

- Data safety and monitoring will be overseen by an experienced researcher independent of the trial after every 50 participants.
- Recruitment will be stopped in the case of multiple serious adverse events.

References

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Figure 1. Design and flow of participants through the trial.

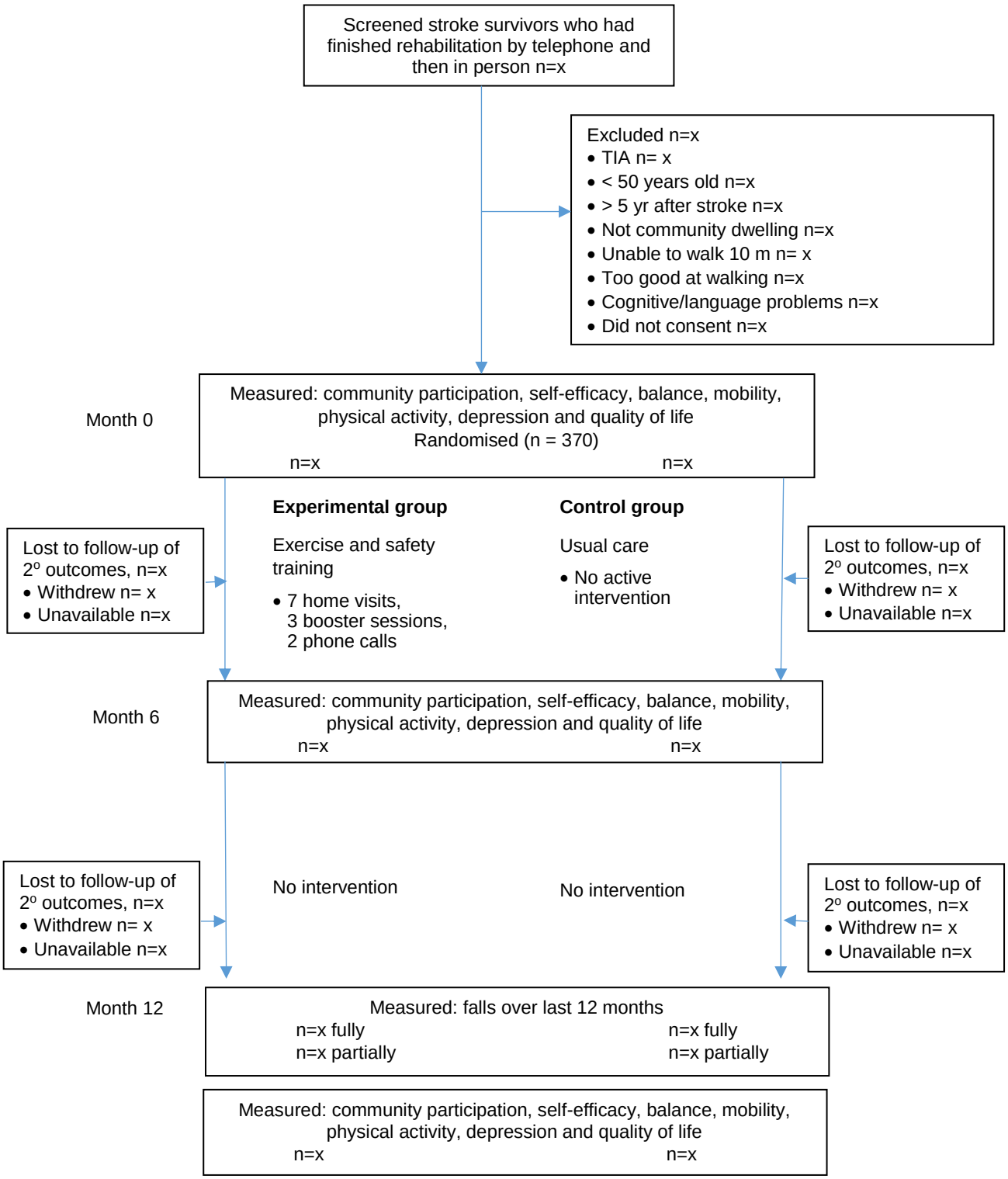

Table 1. Participants' characteristics and distribution across states and walking speeds

Participants	Randomised (n=370)		Lost to Month 12 2º outcomes (n=x)	
	Exp n=x	Con n=x	Exp n=x	Con n=x
Characteristics				
Age *(yr),* mean (SD)	x (x)	x (x)	x (x)	x (x)
Sex, n female (%)	x (x)	x (x)	x (x)	x (x)
Time since stroke (*mth*), mean (SD)	x (x)	x (x)	x (x)	x (x)
Side affected, n hemiplegic (%)	x (x)	x (x)	x (x)	x (x)
Depression, n yes (%)	x (x)	x (x)	x (x)	x (x)
Aphasia (mild receptive), n yes (%)	x (x)	x (x)	x (x)	x (x)
Comorbidities (Groll Scale 0 to 18), mean (SD)	x (x)	x (x)	x (x)	x (x)
Arthritis, n (%)	x (x)	x (x)	x (x)	x (x)
Congestive heart failure, n (%)	x (x)	x (x)	x (x)	x (x)
Diabetes, n (%)	x (x)	x (x)	x (x)	x (x)
Obesity, n (%)	x (x)	x (x)	x (x)	x (x)
Visual impairment, n (%)	x (x)	x (x)	x (x)	x (x)
Falls history				
Fallers/last 12 mth, n (%)	x (x)	x (x)	x (x)	x (x)
Annual fall rate (#/participant), mean (SD)	x (x)	x (x)	x (x)	x (x)
Living arrangements, n alone (%)	x (x)	x (x)	x (x)	x (x)
Distribution across Australia, n participants (%)				
New South Wales	x (x)	x (x)	x (x)	x (x)
Victoria	x (x)	x (x)	x (x)	x (x)
Australian Capital Territory	x (x)	x (x)	x (x)	x (x)
Distribution across walking speeds, n participants (%)				
> 0.8 m/s	x (x)	x (x)	x (x)	x (x)
0.4-0.8 m/s	x (x)	x (x)	x (x)	x (x)
< 0.4 m/s	x (x)	x (x)	x (x)	x (x)

Table 2. Mean (SD) of groups, mean (SD) difference within groups, and mean (95% CI) difference between groups of secondary outcomes.

Secondary outcome	Groups						Difference within groups				Difference between groups	
	Month 0		Month 6		Month 12		Month 6 minus 0		Month 12 minus 0		Month 6 minus 0	Month 12 minus 0
	Exp (n=x)	Con (n=x)	Exp (n=x)	Con (n=x)	Exp (n=x)	Con (n=x)	Exp	Con	Exp	Con	Exp minus Con	Exp minus Con
Depression PHQ-2 *(0 to 6)*	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x to x)	x (x to x)
Self-efficacy Likert *(0 to 6)*	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x to x)	x (x to x)
Balance SPPB *(0 to 4)*	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x to x)	x (x to x)
Step Test *(steps/s)*	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x to x)	x (x to x)
Mobility Walking speed pref 5-m Walk Test *(m/s)*	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x to x)	x (x to x)
Walking speed fast 5-m Walk Test *(m/s)*	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x to x)	x (x to x)
Walking duration Likert *(1 to 5)*	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x to x)	x (x to x)
Walking distance Likert *(1 to 5)*	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x to x)	x (x to x)
Physical Activity IPEQ (*hr/wk)*	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x to x)	x (x to x)
ADL LLFDI function *(0 to 100)*	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x to x)	x (x to x)
Participation												
LLFDI disability (limitation) *(0 to 100)*	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x to x)	x (x to x)
LLFDI disability (frequency) *(0 to 100)*	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x to x)	x (x to x)
Getting out frequency *(#/wk)*	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x to x)	x (x to x)
Health related QOL EQ-5D VAS *(0 to 100)*	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x to x)	x (x to x)

PHQ-2 = Patient Health Questionnaire-2, SPPB = Short Physical Performance Battery, IPEQ = Incidental and Planned Exercise Questionnaire, ADL = activities of daily living, LLFDI = Late Life Function and Disability Index, QOL = quality of life, VAS = visual analogue scale