STATISTICAL ANALYSIS PLAN (SAP) FOR:

Effects of treadmill slip and trip perturbation-based balance training on falls in community-dwelling older adults (STABILITY): a randomised controlled trial

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1. Study Synopsis

Falls are common among older adults and can have severe consequences such as disability, decreased quality of life, and premature death [1–4]. Perturbation-based balance training (PBT) has recently gained interest as a potential brief, effective, and sustainable fall preventive strategy [5]. During PBT, participants are exposed to repeated slips and trips during walking while wearing a safety harness in a laboratory. Two meta-analyses, looking at eight and four PBT studies, have shown a vaccination-like effect of almost 50% decreased fall rates after even small dosages (1-8 sessions) [6–8]. Nonetheless, more evidence is needed to evaluate the effects of PBT performed on a treadmill [8]. This assessor-blinded, parallel-group, randomised, controlled trial will evaluate the effects of treadmill-PBT on falls and other relevant physical, cognitive and sociopsychological factors among community-dwelling older adults.

2. Study Objectives, Hypothesis, and Outcomes

2.1. Primary Objective and Outcome (if applicable)

The primary objective of this study is to determine the effects of a four-session PBT intervention on fall rates (number of falls per person-year) in community-dwelling older adults aged 65 or older compared to treadmill walking without perturbations.
The main hypothesis is that treadmill-PBT will decrease the fall rate by up to 50% in the 12 months following the intervention compared to time-matched treadmill walking.

2.2. Secondary Objectives and Outcomes

The secondary objectives are to evaluate the effects on additional fall metrics and the potential transfer effects of PBT to other relevant physical, cognitive, and social-psychological risk factors.
The secondary fall metrics include the proportion of fallers, the time to first fall, the proportion with at least one fall-related fracture, the rate of fall-related fractures, the proportion with at least one fall-related injury, the rate of fall-related injury, the proportion with at least one fall-related health-care contact, and the rate of fall-related health-care contact. It is expected that the proportion of fallers is 50% lower in the PBT-group compared to the treadmill walking group.[6,9] However, we do not have enough evidence regarding the remaining fall-related outcomes to make hypothesis hereof; thus, these outcomes are considered exploratory.
The secondary fall-related risk factors included are single- and dual-task gait speed, reaction time, single- and dual-task static balance, lower extremity performance, executive function, health-related quality of life, and fear of falling. These secondary outcomes were chosen as they all have been identified as fall risk markers [10–16]. However, there is insufficient information about such outcomes following PBT; therefore, we consider these outcomes exploratory.

2.3. Descriptive Outcomes

Descriptive data include height, weight, sex, physical and cognitive function, medication usage, Tilburg Frailty Indicator, highest education level, living arrangements, and fall history, including associated injuries, everyday activity functionality (Vulnerable Elders Survey-13), physical activity levels, and home care usage. Information will be collected through a combination of self-reporting, measurements, questionnaires, and medical/municipality records. Descriptive data will be presented in a table stratified by intervention type as mean and standard deviation (normally distributed continuous variables), median and inter-quartile range (not normally dis-

tributed continuous variables), or number and percentage (categorical variables). Descriptive data will be visually compared to evaluate any potential differences between groups.

2.4. Specification of endpoints

2.4.1. Primary Endpoint

The primary endpoint will be the fall rate 12 months after completion of the third training session, and it will be collected using monthly fall calendars as recommended.[17]

2.4.2. Secondary Endpoints

Secondary outcomes and their endpoints are outlined in table 1 and 2. The secondary fall outcomes will be collected using the fall calendars for 12 months. The fall-related risk factor outcomes will be collected at the pre- and post-training test and the 26- and 52-week follow-up.

3. Study Design

This study is designed as an assessor-blinded, randomised, parallel-group (1:1 ratio), controlled trial

3.1. Sample Size

The sample size calculation was conducted in G*power (version 3.1.9.4, University of Kiel, Kiel, German) using a Poisson regression model. The calculation was made with certain assumptions (80% power, 5% significance level, 50% difference in fall rate (favouring the PBT), and 20% dropout rate) and an expected average fall rate of 0.85.[18–21] This resulted in an estimated required sample size of 70 participants in each group.

3.2. Randomisation and Blinding

After the pre-training tests, participants will be randomly allocated to either the PBT or treadmill walking group using a permuted block randomisation module in REDCap to ensure similar group sizes (Research Electronic Data Capture; version 9.5.6). Random block sizes (two, four, six, or eight) will ensure that allocation concealment is maintained. The allocation sequence will be generated by a research staff member not involved in enrolling or assigning participants to groups.

4. Study Population

4.1. Subject Disposition

One hundred forty community-dwelling older adults (70 in each group) living in and around Aalborg will be recruited via informal presentations about the trial, local and national newspapers, radio and television spots, flyer hand-outs, and snowball sampling. Participants are eligible if they are 1) ≥65 years old, 2) community-dwelling, and 3) able to walk without a walking aid. Participants will be excluded if they 1) have any of the following self-reported conditions: orthopaedic surgery within the past 12 months, osteoporosis or history of osteoporosis-related fractures (low-impact hip, spine, and wrist fracture), or progressive neurological disease (e.g., Parkinson), 2) have an unstable medical condition that would prevent safe participation, 3) have

a severe cognitive impairment (a score <8 in The Short Orientation-Memory-Concentration Test)[22], or 4) are currently participating in another fall prevention trial.

5. Data handling

All data will be collected and managed using the secure, web-based software platform REDCap hosted in The Region of Northern Denmark.[23,24] The data collection forms in REDCap ensure strong data integrity by applying functions that check for mandatory information, data ranges, and alerts whenever data violates specific limits.[24] To ensure data quality, all outcomes will be visually inspected for implausible values before the dataset is locked. Missing and out-of-range data in REDCap will also be assessed compared to original data files (paper documents for questionnaires and FysioMeter software for balance and reaction time) and corrected in cases of discrepancies. REDCap also logs every record activity, which will be used to monitor data validity.

5.1 Missing data

The number of missing observations and the associated reasons will be reported. For the primary outcome, fall rates, missing data will not be imputed; however, the analysis will be adjusted for follow-up time (days of follow-up will be used as an offset). Likewise, missing data regarding the secondary binary outcomes will neither be imputed, but the modified Poisson regression will be adjusted for person-years (days of follow-up will be used as an offset). For participants who do not return any fall calendars 0 falls and 0 person-years will be registered. However, if more than 10% of data is missing in any outcomes, a sensitivity analysis utilising multiple imputations will be conducted.
Missing data in continuous outcome are expected to be missing at random; thus, they will not be imputed as it has shown that multiple imputations do not add any benefits to a linear mixed-effects model.[25]

6. Statistical Analysis

All statistical tests will be performed using an intention-to-treat approach. Moreover, a per-protocol analysis will also be performed, including only participants who complete 75% or more of the training sessions. The secondary outcome will not be adjusted for multiple comparisons; thus, these results should be considered exploratory.
Count data will be reported as incidence rate ratios (IRR) with 95% confidence intervals (95% CI). Binary outcomes will be reported as risk ratios (RR) and 95% CIs. When appropriate, continuous variables will be reported as either mean and standard deviation or median and interquartile range.

Table 1 Variables, measures, and methods of analysis for fall outcomes.

Primary outcome					
Variable/outcome	**Mode of assessing**	**Time frame**	**Variable type**	**Assumption**	**Methods of analysis**
Fall rate (falls per person-year)	Fall calendars	Continuously for 12 months	Count	Equal mean and variance *	Poisson regression Alternative: Bootstrapping†
Secondary fall outcomes					
Variable/outcome	**Mode of assessing**	**Time frame**	**Variable type**	**Assumption**	**Methods of analysis**
Proportion of fallers	Fall calendars	Continuously for 12 months	Binary	Equal mean and variance *	Poisson regression with robust error variance
Time to first fall	Fall calendars	Continuously for 12 months	Survival	Linear relationship between log hazard and covariate[α]	Cox proportional hazard
Fall-related fracture rate	Fall calendars	Continuously for 12 months	Count	Equal mean and variance *	Poisson regression Alternative: Bootstrapping†
The proportion with a fall-related fracture	Fall calendars	Continuously for 12 months	Binary	Equal mean and variance *	Poisson regression with robust error variance
Fall-related injury rate (other injuries than fractures)	Fall calendars	Continuously for 12 months	Count	Equal mean and variance *	Poisson regression Alternative: Bootstrapping†

The proportion with fall-related injuries (other injuries than fractures)	Fall calendars	Continuously for 12 months	Binary	Equal mean and variance *	Poisson regression with robust error variance
Fall-related hospital contact rate	Fall calendars	Continuously for 12 months	Count	Equal mean and variance *	Poisson regression Alternative: Bootstrapping†
The proportion with a fall-related fracture	Fall calendars	Continuously for 12 months	Binary	Equal mean and variance *	Poisson regression with robust error variance
All-cause fracture rates	Fall calendars	Continuously for 12 months	Count	Equal mean and variance *	Poisson regression Alternative: Bootstrapping†
The proportion with an all-cause fracture	Fall calendars	Continuously for 12 months	Binary	Equal mean and variance *	Poisson regression with robust error variance
Patient Global Impression of Change	7-item questionnaire and 11-point Likert scale; proportion "4 – somewhat better") and 0-11 points on the Likert scale (lower score indicates better performance)	52-week follow-up	7-item questionnaire: Binary VAS: Continuous (Ordinal)	VAS-scale: Normal distributionϕ Homogeneity of varianceϕ	7-item questionnaire: Fisher's Exact VAS-scale: Unpaired t-test Alternative: Unpaired two-sample Wilcoxon test‡
Laboratory-induced overall fall rate	Visual inspection of video recording of a level 1 slip and trip perturbation; fall (1) or no fall (0)	Pre-training test; post-training test; 26- week follow-up; 52-week follow-up	Count	Equal mean and variance *	Poisson regression Alternative: Bootstrapping†

Laboratory-induced slip falls	Visual inspection of video recording of a level 1 slip perturbation; fall (1) or no fall (0)	Pre-training test; post-training test; 26- week follow-up; 52-week follow-up	Binary	-	Fisher's Exact
Laboratory-induced trip falls	Visual inspection of video recording of a level 1 trip perturbation; fall (1) or no fall (0)	Pre-training test; post-training test; 26- week follow-up; 52-week follow-up	Binary	-	Fisher's Exact

* Similarity of the calculated mean and variance; † If mean is not equal to variance; α Visual inspection of residual plots; ϕ Examined by visual inspection of histograms and QQ-plots; ‡ If data is not normal-distributed; O Participants ID as randoms effect - only participants, who did not fall during the perturbation at pre-training test was included

Table 2 Variables, measures, and analysis methods for fall-related risk factors.

Variable/outcome	Mode of assessing	Time frame	Variable type	Assumption	Methods of analysis
Single- and dual-task gait speed	6-meter walking test; walking speed (m/s)	Pre-training test; post-training test; 26- week follow-up; 52-week follow-up	Continuous (ratio)	Normal distribution of residuals and random effects*ϕ Homogeneity of variance⊕ϕ	Linear mixed-effects model O

Single- and dual-task sway	30-second balance test on WBB[‡]; centre of pressure area (mm^2) and velocity (mm/s)	Pre-training test; post-training test; 26- week follow-up; 52-week follow-up	Continuous (ratio)	Normal distribution of residuals and random effects[*ϕ] Homogeneity of variance[⊕ϕ]	Linear mixed-effects model[O]
Choice stepping reaction time (CSRT)	CSRT on WBB[‡]; reaction time (ms)	Pre-training test; post-training test; 26- week follow-up; 52-week follow-up	Continuous (ratio)	Normal distribution of residuals and random effects[*ϕ] Homogeneity of variance[⊕ϕ]	Linear mixed-effects model[O]
Short physical performance battery	2x4 meter walking time, 3x10 second static balance with 3 different foot positions, and 5 chair raises; score from 0-12 (higher score indicates better performance)	Pre-training test; post-training test; 26- week follow-up; 52-week follow-up	Continuous (ordinal)	Normal distribution of residuals and random effects[*ϕ] Homogeneity of variance[⊕ϕ]	Linear mixed-effects model[O]
Trial-making-test Part A and B; time and error	Part A and Part B of the Trail-making-test; time (s) and errors (n). Difference in time-to-complete between Part A and Part B; time (s)	Pre-training test; post-training test; 26- week follow-up; 52-week follow-up	Continuous (ratio)	Normal distribution of residuals and random effects[*ϕ] Homogeneity of variance[⊕ϕ]	Linear mixed-effects model[O]
Short Falls Efficacy Scale	7-item questionnaire; score from 7-28 (lower score indicates better performance)	Pre-training test; post-training test; 26- week follow-up; 52-week follow-up	Continuous (ordinal)	Normal distribution of residuals and random effects[*ϕ] Homogeneity of variance[⊕ϕ]	Linear mixed-effects model[O]

EuroQoL 5D-5L	5-item questionnaire and visual analogue scale; index from 0-1 (higher score indicates better performance) Visual analogue scale from 0-100 (higher score indicates better performance)	Pre-training test; post-training test; 26- week follow-up; 52-week follow-up	Continuous (ordinal)	Normal distribution of residuals and random effects[*ϕ] Homogeneity of variance[⊕ϕ]	Linear mixed-effects model[O]

[*] Examined by visual inspection of histograms and QQ-plots; [⊕] Examined by visually inspecting residuals plotted against fitted values; [†] If data is not normal-distributed; [ϕ] Violations of assumptions will be noted; however, no alternative method will be used, as the linear mixed-effects model is robust against such violations; [O] Participant ID as the random effect

Sensitivity analysis

Fall outcomes

For the primary outcome (fall rates) and secondary fall outcomes, a sensitivity analysis adjusting for known confounders (age, sex, and previous falls) will be conducted to evaluate the robustness of the results. Furthermore, if the count variable data is over-dispersed, a poisons regression with bootstrapping will be performed; however, a sensitivity analysis without bootstrapping will also be carried out. These analyses were planned before the commencement of data collection. Additional fall rate sensitivity analyses 1) only including participants with no prior history of falls 12 months before study commencement and 2) only including participants with a history of falls 12 months before study commencement will also be conducted. These sensitivity analyses were planned after data collection began.

Fall-related risk factor outcomes

Before data collection commenced, it was determined to conduct a sensitivity analysis on the secondary fall-related risk factors adjusting for age, sex, and previous falls will be carried out.

6.3. Major Protocol Deviations

Major protocol deviations will be reported in the trial registration at ClinicalTrials.gov (NCT04733222), the local ethics committee, and the SAP.

7. Implementation of Analysis Plan

The data will be exported from REDCap to the statistical program STATA. An external statistician not involved in the study will assist with the statistical test.

STATA CODE

Poisson regression (example of code for fall rate):
poisson fallrate ib1.group, irr exposure(personyear)

Poisson regression with bootstrapping (example of code for fall rate):
poisson fallrate ib1.group, irr exposure(personyear) vce(bootstrap, reps(1000))

Poisson regression adjusting for age, sex, and fall history (*example of code for fall rate)*:
poisson fallrate ib1.group age i.sex i.prev_faller, irr exposure(personyear)

Poisson regression with robust error variance (*example of code for proportion of fallers)*:
glm faller ib1.group, fam(poisson) link(log) vce(robust) eform

Poisson regression with robust error variance adjusting for age, sex, and fall history (*example of code for proportion of fallers)*:
glm faller ib1.group age i.sex i.prev_faller, fam(poisson) link(log) vce(robust) eform

Cox survival analysis (example of code for time to first fall):
stset firstfall, failure(faller==1)
stcox group

Cox survival analysis adjusted for age, sex, and fall history (example of code for time to first fall):
stset firstfall, failure(faller==1)
stcox group age i.sex i.prev_faller

unpaired t-test (example of code for Global Patient Impression of Change (gpic)):
ttest gpic, by(group) unpaired

Unpaired two-sample Wilcoxon test (example of code for Global Patient Impression of Change):
ranksum gpic, by(group)

Fisher's exact (example of code for the proportion of fallers following slip perturbation at pre-training (t1)):
tabulate lab_slip_t1 group, exact

Linear mixed-effects model (*example of code for single-task gait speed)*:
mixed gaitspeed_st group time || record_id:, var reml
In case of significant interaction effect, a posthoc analysis adjusted using the Bonferroni method is employed using the following code:
contrast rb1.time#group, mcompare(bonferroni)

Linear mixed-effects model adjusting for age, sex, and fall history (*example of code for single-task gait speed)*:
mixed gaitspeed_st age i.sex i.prev_faller group##time || record_id:, var reml
In case of a significant interaction effect, posthoc tests was conducted using the following code:
contrast rb1.time#group

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