Brief summary:

People with Parkinson’s disease (PD) often show gait impairments such as shuffling gait, short steps and gait asymmetry and irregularity. These gait problems are already apparent in the early disease stages, having an immense effect on daily life functioning. Especially Freezing of Gait (FOG), where the patients are not able to initiate or continue their movement despite their intention to do so. It is thought that lack of gait adaptability could be an underlying cause of FOG. With a split-belt treadmill the speed of both legs can be controlled independently, which forces participants to actively adapt their gait to the new situation. In a previous study performed at our lab results showed that only one session of split-belt training (SBT) where the speed of one leg was reduced, improved gait adaptability and other gait features compared to tied-belt training (TBT). Furthermore, overground turning speed improved after only one single training session and this was even retained 24 hours later, indicating training induced long-term potentiation. Since the short-term effects of SBT are promising the objective of this study is to investigate if 4 weeks of SBT, 3 times a week, has an effect on gait deficits found in individuals with PD, compared to 4-weeks, 3 times a week, of TBT.

Primary outcome:

Participants will be instructed to turn 360 degrees in alternating directions (clockwise/counterclockwise) for 60 seconds. The instruction is to turn as quickly as possible, while still feeling safe doing this. The average overground turning speed will be determined by the use of APDM Opal accelerometers, which will be worn on both shins, wrists and the lower back.

The primary outcome will be the immediate training effect measured at Retest 1 after the 4 week intervention compared to the results of the measurement before the intervention.

Secondary outcomes:

- Change in Retention ST turning speed
- Change in Pre-Post DT turning speed
- Change in Retention DT turning speed

Main analysis:

The main analysis will be based on intention to treat in that participants will be analysed according to the group to which they were allocated irrespective of the extent of intervention received. The primary outcome will be compared between experimental and control group using a constrained longitudinal data analysis approach using mixed model specification. We will consider Hoehn and Yahr stage, freezing status and centre as possible covariates, depending on between group differences and determined in a blind review of the data.

Freezing and other binary secondary outcomes will be examined using logistic regression models or a negative binomial model, with Hoehn and Yahr stage, freezing status, and centre as possible
covariates, see above. Other secondary outcomes will be examined in mixed models for repeated measurements T1, T2 and T3 controlling for centre, Hoehn and Yahr score, including participants with incomplete follow-up information in the analysis.

**Sensitivity analysis:**

Sensitivity analyses will be conducted to examine the impact of missing data to using worst-case scenario analysis and by exploring a multiple imputation method, if missing data for the primary outcome exceeds 5%. We will also conduct a per protocol analysis in that we will include patients only who had more than 80% compliance or more than 80% of the intensity of training dose. Data on compliance and any adverse events listed in both groups will be collected by the trainers and therefore will not be collected in a blind fashion. No formal interim analyses are planned, but descriptive data of patients included will be compared in the two groups 6 months into the trial for recruitment purposes. The statistical analysis plan will be finalized before the blinding is broken shortly before the main analysis commences.

**Secondary analysis**

A planned secondary analysis of the primary outcome will be performed within the subgroups of freezers and non-freezers. The planned analysis of the primary outcome will be also performed within the subgroups of participants with UPDRS scores of 26 and under (less severe) and 27 and over (more severe) (1). The comparison of the intervention effect between subgroups will be tested as an interaction.