Statistical Analysis Plan

# BOOSTSITLESS

Remote 3-week Booster Intervention to Reduce Sedentary Time in Patients With Coronary Artery Disease: A randomized controlled trial

Radboudumc, Nijmegen, the Netherlands

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**Roles and responsibility**:


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# 2. Introduction

## 2.1 Brief background and rationale

High levels of sedentary time (ST) are observed in patients with coronary artery disease (CAD) and are associated with adverse health outcomes. Behavioral interventions targeting ST are effective in the short-term, but effects seem to diminish at long-term follow-up. Short-term (telephonic) Booster programs can induce sustainable physical activity behavioral changes. However, the effects of a Booster ST reduction program are unknown in patients with CAD. Therefore, we aimed to assess the effect of the SIT LESS Booster on ST and physical activity levels in patient with coronary artery disease who participated in cardiac rehabilitation.

## 2.2 Objectives

Research hypothesis

The null hypothesis is that there is no difference in the change-from-baseline of ST between the SIT LESS Booster and control group. The alternative hypothesis is that there is a difference between the two groups.

Study objectives

The primary objective is to examine the effectiveness of a remote 3-week Booster behavior intervention compared to usual care on reducing ST.

Secondary objectives are:

a) To examine the effectiveness of a remote 3-week Booster behavior intervention compared to usual care on improving sedentary behavior defined as number of prolonged sedentary bouts and prevalence of a ST ≥9.5 h/day.
b) To examine the effectiveness of a remote 3-week Booster behavior intervention compared to usual care on improving physical activity characteristics.

# 3. Study Methods

## 3.1 Trial design

A parallel-group randomized controlled trial is conducted to determine the effectiveness of a Booster intervention: a 3-week, fully remote and personalized behavior change intervention with a primary focus on reducing and interrupting ST in patients with CAD. All participants receive usual care, whereas Booster participants additionally receive a 3-week remote behavioral change intervention consisting of education, goal-setting, motivational interviewing, and telemonitoring.

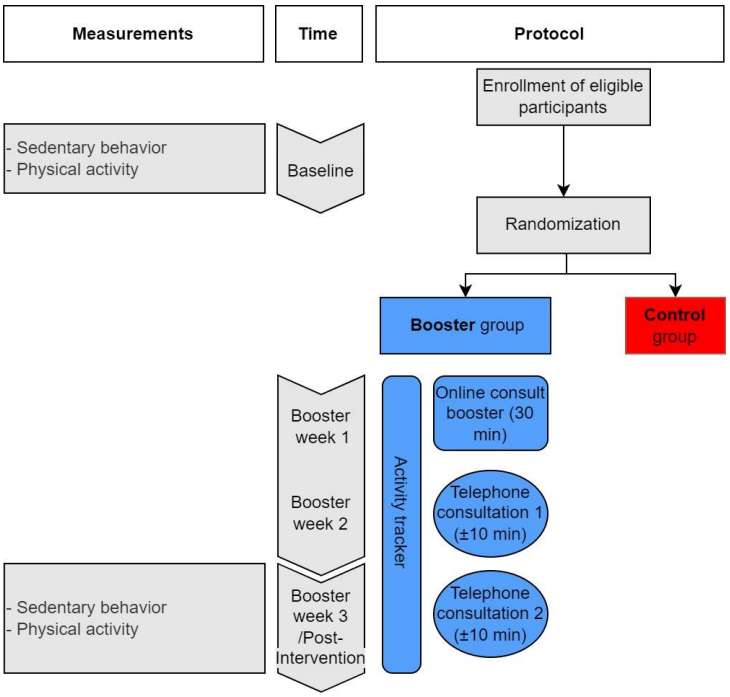


**Figure 1**. Overview of the BOOSTSITLESS randomized controlled trial.

### 3.2 Randomization

The researcher randomly allocates (1:1) the participant into the control or Booster group with allocation concealment in random block sizes ranging from two to six participants, using a computerized algorithm (Castor Electronic Data Capture 2021, Ciwit B.V., Amsterdam, The Netherlands). Randomization is stratified by gender to ensure balance of the treatment arms. Due to the nature of the intervention, the research team and participants are not blinded to the treatment allocation. The outcome assessment of ST is blinded for the research team as an automatized script is used based on a unique participant identification number, independent from the randomization procedure.

### 3.3 Sample Size

As our study has an explorative character, no formal sample size calculation was performed prior to trial initialization. For the original SIT LESS study, a sample size calculation was performed and described[1]. Based on that calculation, 106 patients were needed in the SIT LESS arm of the trial. Participants in this study arm will be eligible for participation in the BOOSTSITLESS.

In the original SIT LESS study, we found an effect size Cohen D of 0.3 [2] with an alpha of 0.05 and beta of 0.2 (power 0.8). The estimated sample size, based on previously mentioned parameters and repeated-measures ANOVA, needed for BOOSTSITLESS was 24 participants (12 in each study arm)(**Figure 2**) suggesting that the included sample size (n=42) is large enough to run meaningful analyses.

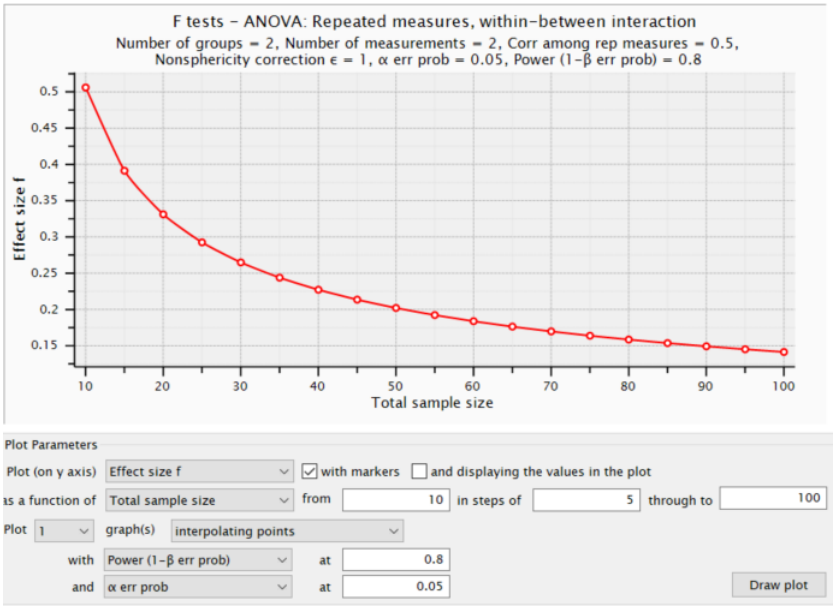


**Figure 2.** Sample size calculation using G*power (version 3.1)

### 3.4 Framework

A superiority hypothesis testing framework will be used, in which we will compare whether the Booster intervention is superior to the usual care.

### 3.5 Statistical analyses and stopping guidelines

No pre-specified interim analyses are performed, and therefore, a stopping guidance was not applicable.

### 3.6 Timing of final analysis

The final analyses will be performed after the finalization of the data collection and processing of the primary and secondary outcomes.

### 3.7 Timing of outcome assessment

The primary and secondary outcomes will be assessed at baseline and post intervention (3 weeks).

## 4. Statistical principles

### 4.1 Confidence intervals and P values

All statistical tests will be two-tailed. P for significance will be set at 0.05 and 95% confidence intervals will be estimated.

### 4.2 Adherence and protocol deviations

For participants randomized to the Booster-arm, the adherence will be assessed by counting the number of valid wear days of the activity tracker (≥ 10 h/day), and by dividing the number of valid days by the total number of days of the intervention period x 100%.

The adherence to the daily use of the activity tracker will be reported as the mean ± standard deviation (when normally distributed) or as median [interquartile range] (when not-normally distributed).

All protocol deviations made to the protocol (e.g. change in pre-defined inclusion/exclusion criteria, baseline and post-intervention, data cleaning/processing) will be reported and described.

### 4.3 Analysis populations

We plan to do an intention-to-treat analysis. This analytical cohort includes all randomized participants. With this approach, all randomized participants are included in the analysis, based on the groups to which they were initially randomly assigned. This imply that some participants will have valid data in both time points, while some might have missing data at baseline or post-intervention assessment.

## 5. Trial population

### 5.1 Screening Data

No screening was needed as participants who participated in the intervention group during the original SIT LESS study were eligible for inclusion.

### 5.2 Eligibility

Eligible patients were defined on the inclusion and exclusion criteria. In general, patients with coronary artery disease who followed cardiac rehabilitation with a special sedentary reduction program (SIT LESS) were included. Specific inclusion and exclusion criteria are:

Inclusion Criteria:

1. Participation in the SIT LESS intervention group of the original SIT LESS study. Inclusion criteria of the SIT LESS study were:
    a. Patients aged ≥ 18 years old
    b. Referred to CR because of stable CAD, an acute coronary syndrome, and/or after coronary revascularization.

Exclusion Criteria:

1. Unable to give informed consent.
2. Wheelchair-bounded / not physically able to stand or walk.
3. Dutch Language barrier.
4. Coronary arterial bypass graft surgery expected within 8 weeks after inclusion.
5. New York Heart Association class III or IV heart failure.
6. Participation in another interventional study targeting sedentary behavior or physical activity.

### 5.3 Recruitment

A CONSORT flow diagram will be used to summarize the number of patients who were:

- Eligible for study participation based on participation in the SIT LESS study without dropping out.
- Approached for study participation (Reasons for no approach will be given*).
- Included in the study.
- Randomized.
- Received the randomized allocation .
- Did not receive the randomized allocation*.
- Lost to follow-up*.
- Discontinued the intervention*.
- Randomized and included in the primary analysis.
- Randomized and excluded from the primary analysis*.

*reasons will be provided

### 5.4 Withdrawal/follow-up

The number, timing, and reasons (e.g. adverse events, lost motivation to continue with the study, withdraw consent, could not or did not want to attend to the post-intervention evaluations) for withdrawal will be noted and described.

### 5.5 Baseline patient characteristics

A baseline table will be created to describe the characteristics of the study population. The characteristics include participant characteristics (e.g. age, gender, body mass index, alcohol use, smoking), disease characteristics (e.g. comorbidities, medication use) and objectively measured sedentary behavior and physical activity levels. The characteristics of the total study population and each study arm will be summarized using mean (SD) or median (interquartile range) for normally and not normally distributed continuous variables, respectively, and as number (percentage) for categorical variables.

## 6. Analysis

### 6.1 Outcome definitions

Primary outcome

Change in daily ST (h/day; baseline and post-intervention).

ST is objectively assessed using a validated accelerometer (ActivPAL3$^{TM}$micro, PAL Technologies Ltd., Glasgow, United Kingdom)[3]. The ActivPAL is a small device (25x45x5 mm), waterproof attached to the participant's thigh using hypoallergenic tape. The ActivPAL combines a tri-axial accelerometer with an inclinometer which accurately distinguishes between sitting, standing and walking[3]. Participants are instructed to wear the ActivPAL 24 h/day for 8 consecutive days and to fill in a diary with sleep times and moment of attachment and detachment. Raw data is analyzed by a modified version of the script of Winkler et al.[4]. Total ST (Metabolic Equivalent of Task score (METs) ≤1.5 while awake in a sitting, lying or reclining posture)[5] is expressed in h/day.

Secondary outcomes

- Change in number of prolonged sedentary (bouts/day; baseline and post-intervention). Prolonged sedentary bouts are defined as an accumulation of ST (≥30 min) and based on ActivPAL data.

- Prevalence of an average ST >9.5 h/day (number, (%); baseline and post-intervention). Daily ST will be dichotomized using 9.5 h/day as cut-off as it was previously shown that exceeding this upper limit of normal was associated with an increased risk of morbidity and mortality[6]. ActivPAL data will be used for this outcome.
- Change in the prevalence of a sitting time ≥9.5 h/day.
- Change in daily time spent in light-intensity physical activity (LIPA in h/day; baseline and post-intervention). The ActivPAL data will be used and LIPA is categorized as physical activity with MET levels < 3.
- Change in daily time spent in moderate-to-vigorous intensity physical activity (MVPA in h/day; baseline and post-intervention). The ActivPAL data will be used and MVPA is categorized as physical activity with MET levels ≥ 3.
- Change in step count (steps/day; baseline and post-intervention). The ActivPAL data will be used for this outcome.

### 6.2 Analysis methods

The primary and secondary outcome analyses will performed on an intention-to-treat basis using a constrained (i.e. baseline adjusted) linear mixed-model analysis to handle missing data and to avoid baseline imbalances between treatment arms[7]. Time (categorical) and time*group will be included in the model. In addition, we evaluate the difference between the control and Booster group in the proportion of participants with ST ≥9.5 h/day post-intervention by constrained logistic mixed model analysis.

### 6.3 Missing data

The number of missing data will be reported, and patterns of missing data will be explored. Based on previous experience, we expect that missing data will be assumed as missing at random. Therefore, the linear mixed model analyses will handle our missing data. However, once the data processing is finalized, we reconsider this assumption. In case we believe this assumption does not hold, we will take appropriate measures for the data analyses by using e.g. other multiple imputation techniques.

### 6.4 Additional analyses

To assess the presence of potential selection bias among study participants, sedentary behavior and physical activity characteristics at 3 months post-CR (i.e. last assessment of previous RCT) will be compared between our analytical cohort and non-participants using an independent samples t-test (continuous normally distributed data), Wilcoxon-signed rank test (continuous not-normally distributed data) or $\chi^2$ test (categorial data).

To assess the long-term effects of CR on sedentary behavior and PA characteristics taking into account the results of the original SITLESS, linear (continuous data) and logistic (categorical data) mixed-model analyses with time as a categorical variable will be used. The BOOSTSITLESS is taken as reference and compared to measurements at pre-CR, post-CR and 3 months post-CR measurements of the previous (SITLESS) RCT.

### 6.5 Harms

The number and reasons of adverse events (e.g. falls, injuries, musculoskeletal problems, major cardiovascular disease events, and any other events potentially related to the implementation of the trial protocol) at each time point will be collected, reported, and described separately for each study arm. No formal statistical testing will be undertaken.

### 6.6 Statistical software

The analyses will be performed using R. For the main analyses we will use the 'lme4' or 'LMMstar' package. The use of packages will be reported in the manuscript.

### 6.7 References

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