LOFIT

STATISTICAL ANALYSIS PLAN

Study Title:	**Lifestyle front Office For Integrating lifestyle medicine in the Treatment of patients: a novel care model towards community-based options for lifestyle change**
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1. INTRODUCTION

1.1. STUDY BACKGROUND

Non-communicable diseases (NCDs), including cardiovascular disease (CVD) and osteoarthritis, are important contributors to (premature) death and a potent driver of direct and indirect costs in the Netherlands. Lifestyle medicine intends to support patients with healthcare problems to cure or reduce disease burden, disease complications and the intake of medicine. However, implementation of lifestyle medicine is hampered by time constraints and competing priorities of treating physicians. As a consequence, many patients who would benefit do not find their way from hospital care to lifestyle medicine initiatives. Therefore, to optimize patient- referral to lifestyle medicine initiatives a 'lifestyle front office' (LFO) is integrated in hospital care for patients with NCDs. In a LFO dedicated LifeStyle Brokers (LSBs) build, in dialogue with the patient, motivation for lifestyle change and refer patients to local community-based lifestyle change initiatives (f.i. neighbourhood lifestyle coaches, etc.), while maintaining a feedback loop with the treating physician.

1.2. STUDY OBJECTIVES

The primary objective of the LOFIT study is to determine the effectiveness and cost effectiveness of the lifestyle front office. The primary outcome measure is the adapted composite FUSTER-BEWAT CVD risk and lifestyle score. Secondary outcome measures include cardiometabolic biomarkers, anthropometric measures, health behaviour measures, psychological measures, disease related outcome measures, program process measures and cost measures.

1.3. STUDY DESIGN

A parallel conducted, pragmatic randomised controlled trial

1.4. SAMPLE SIZE AND POWER

The study protocol states:

"The primary outcome of this study is a composite health risk and lifestyle score (i.e. adapted Fuster-BEWAT score). The numbers needed in each trial arm (80% power, 5% significance, two-tailed alpha) were calculated assuming a 20% drop-out. To detect a difference of 1.45 change in the adapted Fuster-BEWAT score (with a standard deviation of 3.79), 138 patients will be allocated to each arm (thus a total of 276 patients per sub-trial) [16, 17]. The two randomized controlled trials (musculoskeletal and cardiovascular) will be conducted in parallel. Therefore, the LOFIT trial must include a total of 552 patients."

During the trial under-recruitment was experienced. Therefore, both diagnosis groups (cardiovascular and musculoskeletal) were combined in one trial and we aimed to include a total of 276 patients.

1.5. STUDY POPULATION

1.5.1. INCLUSION CRITERIA

Inclusion criteria are:

- Patients with (an increased risk for) cardiovascular disorders (i.e. cardiovascular disease, hypertension, high cholesterol, diabetes mellitus I and II) or with musculoskeletal disorders (i.e. osteoarthritis, total knee or hip prosthesis). **AND**
- Patients aged ≥18 years. **AND**
- Patients (1) having a body mass index (BMI) of ≥ 25 kg/m2 and/or (2) are smokers.

Exclusion criteria are:

- Patients who are not able to walk at least 100 m safely (e.g. wheelchair-bound)
- Patients who are pregnant
- Patients who are cognitively unable to comply with a healthy lifestyle intervention referral or to complete study measurements
- Patients who are not able to communicate in the Dutch or English language

1.6. STATISTICAL ANALYSIS PLAN (SAP)

1.6.1. SAP OBJECTIVES

The objective of this SAP is to describe the statistical analyses to be carried out for the LOFIT trial.

1.6.2. GENERAL PRINCIPLES

Data will primarily be analysed according to the intention to treat principle, i.e. in relation to randomised group, regardless of participation in the intervention.

Data will be summarised overall, by randomised group, and stratified by disease diagnosis (cardiovascular and musculoskeletal). For all data items, the number of available observations and the number of missing values will be reported. Continuous data will be summarised with the mean, standard deviation, median, quartiles and range. Categorical data will be summarised with frequencies and percentages of non-missing values.

For the primary and secondary outcome analysis at the 12^{th} month follow-up time point, we will use linear mixed effect regression models (or logistic models where applicable) with outcome as the dependent variable on an intention-to-treat basis, the study group (intervention vs. standard care) will be modelled as independent variable, while we will adjust for the baseline value of the outcome. A random intercept on the individual level and site level will be added to take into account the correlated observations within individual and between sites. Sensitivity analyses will be presented without correction for this clustering.

Between-group comparisons will be reported as estimated mean differences with a 95% confidence interval and p-value. Confidence intervals and p-values will be two-sided. For all analyses, a two-tailed significance level of $p<0.05$ will be considered statistically significant.

Results will be presented in the first instance without imputation of missing data. In case of missing data or unexpected patterns of missing data in the primary outcome, results for the primary outcome will also be presented from sensitivity analyses using multiple imputation

for missing data. Since the primary outcome is a composite score multiple imputation will be considered for the missing sub-scores and afterwards combined to a new composite score.

1.6.3. CURRENT PROTOCOL

The current study protocol at the time of writing is version 6, dated 22 February 2022. Future amendments to the protocol will be reviewed for their impact on this SAP, which will be updated only if necessary.

1.6.4. DEVIATIONS TO THOSE SPECIFIED IN STUDY PROTOCOL

This SAP does represent a deviation from the analyses specified in the study protocol.

- In the study protocol the analysis would have been performed for the two disease diagnosis groups (CVD and muscular disorders) separately. However, due to under-recruitment both disease diagnosis groups will be combined in the primary analysis. Secondary analysis will stratify for the two disease diagnosis groups, even though the trial is underpowered.

Should any further SAP-deviations be required, based on the characteristics of the study data, these will be justified and documented in the final study report.

1.6.5. ADDITIONAL ANALYSES TO THOSE SPECIFIED IN STUDY PROTOCOL

This SAP does not include any analyses additional to those specified in the study protocol. Should any additional analyses be considered worthwhile, these will be included in a Supplementary Statistical Analysis Plan and presented as such in any upcoming presentations.

1.6.6. SOFTWARE

All analyses will be carried out using recognised statistical software. This is likely to be SPSS 28.0 (SPSS Inc. Chicago, Illinois, USA) or STATA/SE 17.0 (StataCorp LLC, Texas, USA), or more recent versions of these programs.

2. ANALYSIS

2.1. STUDY POPULATIONS

The numbers of participants who were screened will be reported overall and for the disease diagnosis groups. The number and percentage of those screened who were randomised will be presented overall and by disease diagnosis group. For those not randomised, the reasons for exclusion will be summarised overall. For all randomised participants, the number and percentage who provided data at each time point will be reported. The number and percentage of participants who have withdrawn from the study between baseline and 12 months will be reported for all randomised participants and by randomised group. Reasons for withdrawal will also be summarised.

2.2. BASELINE CHARACTERISTICS

Baseline characteristics will be summarised for all randomised participants and by randomised group and by disease diagnosis group. In line with the CONSORT guidelines, no statistical

comparisons will be made between randomised groups at baseline. The following baseline characteristics will be presented:

- Age (years)
- Gender
- Ethnicity
- Marital status
- Number of children
- Employment status
- Household income
- Education level
- Health literacy
- ASA physical status classification
- Comorbidity (CCI)
- Family history of diseases

Primary outcome

- Adapted FUSTER-BEWAT

Secondary outcomes

Objective measured lifestyle behaviour

- ActivPAL step-count, steps/d
- ActivPAL sitting time, standing time, stepping time, cycling time, waking wear time, min/d

Self-reported lifestyle behaviours

- Moderate to vigorous intensity physical activity (IPAQ short), min/d
- Walking (IPAQ short), min/d
- Moderate physical activity (IPAQ short), min/d
- Vigorous physical activity (IPAQ short), min/d
- Total physical activity (IPAQ short), MET-min/week
- Meeting the recommendation for physical activity of 150 min/wk (IPAQ short), y/n
- Sedentary behaviour weekday, weekend-day, total (Marshall), min/d
- Sedentary behaviour weekday, weekendday, domain-specific (Marshall): occupational, transportation, television, computer, leisure, min/d
- Fitness (FitMax)
- Sleep insomnia (ISI)
- Sleep quality (Brief-PSQI)
- Obstructive Sleep Apnoea Syndrome (OSAS)
- Alcohol intake (AUDIT)
- Diet intake score
- Fruit & vegetable consumption, serves/d
- Wholegrain products type
- Legumes, times/week
- Nuts, g/week
- Fish, times/month
- Fats and oils type
- Red and Processed meat, times/week
- Sweetened beverages, glass/d
- Unhealthy snack, times/week
- Smoking, type of smoker and units/d
- Smoking status (FTND)

Anthropometric assessments

- Waist circumference, cm
- Neck circumference, cm
- Body weight, kg
- Body height, m
- Body Mass Index, $kg \cdot m^{-2}$
- Resting Systolic blood pressure, mm Hg
- Resting Diastolic blood pressure, mm Hg

Psychological assessments

- Wellbeing (Cantril Ladder)
- Quality of life (EQ-5D-5L)
- Resilience (BRS)
- Self-rated health (EQ VAS)
- General Self-efficacy scale (GSES)
- Stage of change

Cardiometabolic biomarkers

- Blood glucose, serum lipids (total, LDL and HDL cholesterol, and triglycerides), insulin, HbA1C, liver function (GGT, ALT, AST), kidney function (creatinine) mg/dL

Work-related outcomes

- Sickness absenteeism (iPCQ)
- Presenteeism (iPCQ)

Disease-related outcomes

- Medication use
- PROMS Functional limitation (HOOS-PS/KOOS-PS)

Baseline characteristics will also be summarised in relation to whether participants provided Adapted Fuster BEWAT data at 12 months follow up. Those with and without outcome data will be compared using t-tests or Wilcoxon-Mann-Whitney tests as appropriate, for continuous or ordinal variables, and Fisher's Exact test for categorical variables.

2.3. EFFECTIVENESS OUTCOMES

2.3.1. DATA SUMMARIES

All effectiveness outcome measures will be summarized at 12 months after randomization.

2.3.2. PRIMARY OUTCOME

The primary study outcome is the adapted Fuster BEWAT score at 12th months after baseline. The adapted Fuster BEWAT is a composite score of blood pressure, physical activity, sedentary time, body mass index, fruit and vegetable consumption and smoking (see Table 1 for the scoring). All other variables are considered secondary outcomes.

The following outcome measures will be reported for the 12th month follow-up time point separately:

Primary outcome

- Adapted FUSTER-BEWAT score

Secondary outcomes

Objective measured lifestyle behaviour

- ActivPAL step-count, steps/d

- ActivPAL sitting time, standing time, stepping time, cycling time, waking wear time, min/d

Self-reported lifestyle behaviours

- Moderate to vigorous intensity physical activity (IPAQ short), min/d
- Walking (IPAQ short), min/d
- Moderate physical activity (IPAQ short), min/d
- Vigorous physical activity (IPAQ short), min/d
- Total physical activity (IPAQ short), MET-min/week
- Meeting the recommendation for physical activity of 150 min/wk (IPAQ short), y/n
- Sedentary behaviour weekday, weekend-day, total (Marshall), min/d
- Sedentary behaviour weekday, weekendday, domain-specific (Marshall): occupational, transportation, television, computer, leisure, min/d
- Fitness (FitMax),
- Sleep insomnia (ISI)
- Sleep quality (Brief-PSQI)
- Obstructive Sleep Apnoea Syndrome (OSAS)
- Alcohol intake (AUDIT)
- Diet intake score
- Fruit & vegetable consumption, serves/d
- Wholegrain products type
- Legumes, times/week
- Nuts, g/week
- Fish, times/month
- Fats and oils type
- Red and Processed meat, times/week
- Sweetened beverages, glass/d
- Unhealthy snack, times/week
- Smoking, type of smoker and units/d
- Smoking status (FTND)

Anthropometric assessments

- Waist circumference, cm
- Neck circumference, cm
- Body weight, kg
- Body Mass Index, $kg \cdot m^{-2}$
- Resting Systolic blood pressure, mm Hg
- Resting Diastolic blood pressure, mm Hg

Psychological assessments

- Wellbeing (Cantril Ladder)
- Quality of life (EQ-5D-5L)
- Resilience (BRS)
- Self-rated health (EQ VAS)
- General Self-efficacy scale (GSES)
- Stage of change

Cardiometabolic biomarkers

- Blood glucose, serum lipids (total, LDL and HDL cholesterol, and triglycerides), insulin, HbA1C, liver function (GGT, ALT, AST), kidney function (creatinine) mg/dL

Work-related outcomes

- Sickness absenteeism (iPCQ) (12 months and as part of the economic evaluation)
- Presenteeism (iPCQ) (12 months and as part of the economic evaluation)

Disease-related outcomes

- Medication use
- PROMS Functional limitation (HOOS-PS/KOOS-PS)

Table 1. Scoring of the adapted FUSTER-BEWAT primary outcome measure.

Score	0	1	2	3	4
Systolic/diastolic blood pressure* (mm Hg)	≥140/90	134-139/87-89	128-133/84-86	121-127/81-83	≤120/80
Physical activity (steps/d)	<5500	5500-6999	7000-8499	8500-9999	≥10000
Sitting (h/d)	≥12.5	11-<12.5	9.5-<11	8-<9.5	<8
BMI (kg/m^2) †	≥32	30-31.9	27-29.9	25-26.9	<25
Fruit & vegetable consumption (serves/d)	≤1	2	3	4	≥5
Smoking (units/d)	>20	10-20	1-9	<1	0

Total score range 0-24, with a higher score indicating a lower risk score.
* If systolic and diastolic blood pressure do not fall in the same category, then the participant is assigned to the category with the relatively highest blood pressure (i.e. systolic or diastolic)
† At follow-up visits, a >5% decrease in BMI will add 1 extra point in the BMI score, except for those participants who have changed BMI categories since baseline or who are already in the normal weight category (BMI<25). Similarly, a >5% increase in BMI at follow-up will mean 1 point less in the BMI score, except for participants who have changed BMI categories since baseline or with BMI≥32.

2.3.3. Intervention Effects

Each outcome measure will be summarised for all randomised participants and by randomised group (intervention and comparison), and stratified by the two disease diagnosis groups (cardiovascular disorders and musculoskeletal disorders) and will be analysed using regression models as described in section 1.6.2.

2.3.4. Multiple Imputation

In case of missing data or unexpected patterns of missing data in the primary outcome, results will also be presented from sensitivity analyses using multiple imputation for missing data. The prediction model used will be based on available baseline data and will be described in full in the final statistical outputs.

2.3.5. Stratified Analyses and Interaction Tests

The primary outcome and all the under 2.3.2 described secondary outcomes will be analysed stratified by the two disease diagnosis groups to address the original study objective.

Interaction tests in the primary outcome model will also be performed in order to determine if the intervention effectiveness differs by age (<50 and 50+), gender (woman and man) and disease diagnose group (cardiovascular and musculoskeletal), and if stratification by age, gender and disease diagnosis group is warranted.

We will also explore the potential effect of (change in) blood pressure medication usage on blood pressure and consequently on the Fuster-BEWAT score.

2.4. COST-EFFECTIVENESS ANALYSES

The cost-effectiveness analyses will take a societal and healthcare perspective. When the societal perspective is applied, all costs will be included, whereas only those costs accruing to the formal Dutch healthcare sector will be included when the healthcare perspective is applied. In line with the effect analysis, analyses will be performed according to the intention-to-treat principle. In the main analysis, missing cost and effect data will be imputed using Multivariate Imputation by Chained Equations (MICE). Each imputed dataset will be evaluated as outlined below, after which Rubin's rules will be used to pool the results. Multilevel (i.e. participant level, hospital level) linear regression analyses will be used to estimate cost and effect differences between LOFIT and usual care, while adjusting for confounders if necessary. Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the differences in costs across groups by the differences in clinical outcomes (i.e. adapted Fuster-BEWAT) and QALYs. Bias-corrected and accelerated bootstrapping with 5000 replications will be used to estimate 95% confidence intervals around the cost differences and statistical uncertainty surrounding the ICERs. Uncertainty surrounding ICERs will be graphically presented on cost-effectiveness planes. Cost-effectiveness acceptability curves will be estimated showing the probability that LOFIT is cost-effective in comparison with usual care for a range of different ceiling ratios, thereby showing decision uncertainty. To assess the robustness of the results, sensitivity analyses will be performed using methods such as complete-case analysis, CART imputation, and replacing multilevel regression with seemingly unrelated regression.

2.5. PROCES EVALUATION ANALYSES

To evaluate the process data of this study descriptive statistics (mean, SD, proportions) will be used to report patients', physicians' and lifestyle brokers' characteristics and results of pre-structured questions from the questionnaire lifestyle broker logs. All interviews will be audiotaped, fully transcribed verbatim and anonymized. The qualitative data will be analyzed using a thematic analysis method. All reported (suggestions and reasons for) adaptations to the program and any other answers to open-ended questions will be listed, analyzed and summarized. A framework analysis approach will be used to identify barriers and facilitators for adoption, implementation and continuation. A dose response analysis will be performed within the intervention group for the primary outcome (i.e. FUSTER-BEWAT), whereby those that received more LOFIT intervention components get a higher score for dose.

2.6. ADDITIONAL ANALYSES

Following the completion of the analyses specified in this SAP, some additional sensitivity analyses might be carried out to further understand the study results. In any case, a Supplementary Statistical Analysis Plan will be agreed before any additional analyses are carried out.

2.6.1. MULTIPLE IMPUTATION

After considering the intervention effects on the secondary outcome measures, and the impact of possible multiple imputation on the primary analyses, similar imputation procedures may be applied to selected secondary outcome measures.

2.6.2. SUBGROUP ANALYSES

In case of substantial baseline differences between the intervention and control group, sensitivity analyses might be carried out to explore the effects of these baseline differences.

2.6.3. OTHER ANALYSES

If any additional analyses not covered in this SAP are considered worthwhile, they will be included in a Supplementary Statistical Analysis Plan.

3. DOCUMENT HISTORY

This is v2 of the SAP for the LOFIT trial, dated 24 June 2025.

4. TABLES & FIGURES

Dummy tables and figures will be produced during the development of the statistical analysis programs for review and feedback. Approval of the content of the final statistical outputs will be a requirement for database lock.