# Exercise-induced cardiac adaptions in rheumatoid arthritis patients during interleukin-6 vs. tumour necrosis factor antibody therapy: Statistical analysis plan for the randomised, controlled RABEX Trial

**Trial Registration**

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**Acronym:** RABEX

**SAP version**:

1.1 (November 3, 2023)

**Protocol version**

This document has been written based on the study protocol version 8.0, 17. December 2021.

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Stastical analysis plan revision history

| Protocol Version | Updated SAP version no. | Section number changed | Description of and reason for change | Date |
|---|---|---|---|---|
| 8.0 | 1.1 | Shell Table 1 | Added IL-6 pg/ml to illustrate differences caused by the medican between IL-6i and TNFi group | November 3rd 2023 |
| 8.0 | 1.1 | Shell Table 1 | Added LV GLS (%). Errounously this was not added to the table. LV GLS (%) was mentioned as an exploratory outcome in SAP version no. 1.0 | November 3rd 2023 |
| 8.0 | 1.1 | Shell Table 2 | Added LV GLS (%). Errounously this was not added to the table. LV GLS (%) was mentioned as an exploratory outcome in SAP version no. 1.0 | November 3rd 2023 |
| 8.0 | 1.1 | Shell Table 3 | Added LV GLS (%). Errounously this was not added to the table. LV GLS (%) was mentioned as an exploratory outcome in SAP version no. 1.0 | November 3rd 2023 |
| 8.0 | 1.1 | Shell Appendix 2 | Added “per day” in the Total physical activity, counts/min per day. Replaced “Walking” with stepping. Stepping was written by mistake. | November 3rd 2023 |
| 8.0 | 1.1 | Shell Appendix 4 | Changed from mg to n(%). Our baseline data regarding concomitant medication do not support a sensible calculation of mean use in mg. Added "Other hypertensive” to include details on all hypertensive medication other than beta blocker. Added relevant comorbidities to differentiate the general health at baseline on the participant. | November 3rd 2023 |

**Abbreviations**

bDMARD: Biological disease modifying anti rheumatic drug

BMI: Body mass index

BSA: Body surface area

CFAS: Centre for physical activity research, Rigshospitalet, Denmark

CI: Confidence interval

CMR: Cardiac magnetic resonance imaging

CONSORT: Consolidated Standards of Reporting Trials

csDMARD: Conventional synthetic disease modifying antirheumatic drugs

CVD: Cardiovascular disease

DAS28-ESR: Disease Activity Score-28 for rheumatoid arthritis with erythrocyte sedimentation rate

GLP: Glucagon-like peptide

HAQ-DI: health assessment questionnaire disability index

HIIT: High intensity interval training

IL-6: Interleukin-6

IL-6i: Interleukin-6 inhibitor

IQR: Interquartile range

ITT: Intention-to-treat

LVM: Left ventricular mass

MAR: Missing at random

NSAID: Non-steroid anti-inflammatory drug

PI: Principal Investigator

PP: Per protocol

RA: Rheumatoid arthritis

SAP: Statistical analysis plan

SD: Standard deviation

SE: Standard error

TNF: Tumour necrosis factor

TNFi: Tumour necrosis factor inhibitor

# Table of contents

# 1 Introduction

## 1.1 Background

Rheumatoid Arthritis (RA) is a chronic autoimmune disease with joint inflammation and destruction, and increasing cardiovascular disease (CVD) risk compared to the background population (1–4). Dysregulated immune response leads to elevated pro-inflammatory proteins like tumour necrosis factor (TNF) and interleukin-6 (IL-6), contributing to systemic inflammation (5,6). Exercise is a corner-stone treatment for RA and has immunomodulatory effects where IL-6 plays a central role (7). Exercise-induced IL-6 has positive effects on fat loss and cardiac function (8,9). High intensity intermitten training (HIIT) is recommended for improving cardiovascular fitness (10). Studies on the impact of IL-6 inhibitors (IL-6i) during exercise in RA patients are lacking, making it valuable to explore in clinical trials. Comparing RA patients treated with IL-6i and TNF inhibitors (TNFi) during exercise training could offer novel insights into the effects of biological disease modifying anti rheumatic drugs (bDMARDs) in relation to exercise.

## 1.2 Deviations from the original protocol

The present statistical analysis plan (SAP) incorporates outcomes of particular interest to exercise-induced cardiac adaptions. Several secondary outcomes denoted in the original protocol and at clinicaltrials.gov were erroneously labeled and indicated as key secondary outcomes and will not feature in the present SAP (Shell Appendix 1). In the original protocol, the trial end criteria were mistakenly denoted in the following way “(…) control and further inclusion rate is below two patients per month.” This has been changed to “(…) control or further inclusion rate is below two patients per month” in the SAP (see Statistical interim analyses and stopping guidance).

## 1.3 Aim and objectives

*Primary aim:*

To investigate if the effects of exercise training on cardiac structure and function in RA patients vary depending on the concomitant treatment with either TNFi or IL-6i.

*Primary objective:*

To evaluate whether concomitant use of one of the two different bDMARDs impact the effect of 12 weeks of regular supervised exercise, relative to treatment as usual, on changes in left ventricular mass (LVM, measured in grams [g]) measured by cardiac magnetic resonance imaging (CMR) from baseline to week 12, in RA patients in stable treatment with either a TNF- or IL6-inhibitor.

*Key secondary objectives:*

To explore, in patients with RA in stable treatment with either a TNF- or IL-6-inhibitor, whether concomitant use of one of the two different biologics impact the effect of 12 weeks of regular supervised exercise, relative to treatment as usual, after 12 weeks on changes in:

1. Left ventricular stroke volume
2. Left ventricular end diastolic volume
3. Relative $VO_2$peak
4. Disease Activity Score-28 for rheumatoid arthritis based on the erythrocyte sedimentation rate

*Other secondary objectives:*

Further to explore the effect of concomitant use of one of the two different biologics impact the effect of 12 weeks of regular supervised exercise, relative to treatment as usual, after 12 weeks on changes in:

- LVM/body surface area
- Left ventricular global longitudinal strain
- Left ventricular ejection fraction
- Left ventricular end-systolic volume
- Absolute $VO_2$peak
- Total lean mass
- Total fat mass
- Resting heart rate

**1.4 Hypothesis**

We hypothesise that pharmacological inhibition of IL-6 (unlike TNFi) impairs exercise-induced changes in LVM. The null hypotheses are that there is no difference between the exercise and control group, and this apparent null effect cannot be effect modified by the concomitant choice of biological agent (IL-6i vs TNFi).

# 2 Methods

### 2.1 Trial design

All procedures and detailed information about the design, assessments, inclusion and exclusion criteria and interventions has been published elsewhere (11). Briefly, this study is a single-centre, randomised, parallel group, investigator-blinded trial with a primary endpoint of changes in LVM after 12 weeks measured by cMRI. The study was designed to include 80 participants: After patients signed the informed consent form, participants were randomised to either exercise (experimental intervention) or no exercise (control comparator).

### 2.2 Randomisation

The randomisation was based on a 1:1 stratified block randomisation (with blocks of 10). Participants were stratified for bDMARD treatment (TNFi vs IL-6i) and sex (male vs female) as part of the randomisation. The randomisation list was kept in a secure file, accessable only by an employee at Centre for Physical Activity Research (CFAS) not affiliated with this study.

### 2.3 Sample size

The sample size and power considerations is also described in the published protocol (11). For the primary outcome change in left ventricular mass assessed after 12 weeks measured by MRI scan, to detect a change of 12 g (SD 12.3) between exercise groups (TNFi vs IL-6i) assuming a 5% alpha-level in a two-sided unpaired t-test with homoscedasticity and a power of 80% (1−β), a sample size of 16 in each group is needed. To account for potential dropouts, we decided to include 20 patients in each stratum*group (n=80). No previous studies have determined the effect of TNF on cardiac adaptations following exercise, thereby limiting our power analysis to either placebo or IL-6i.

### 2.4 Framework

The study was designed as a superiority trial, testing the effect of exercise compared to control, and explore the possible 'effect modifying impact' of IL6i (11) as a contextual factor. Statistical analyses of RCTs respecting the intention-to-treat population yield a causally valid estimate of the average treatment effect, which is the contrast between the outcomes in the two randomised treatment groups commonly accompanied by a confidence interval. The primary objective of the RABEX Trial however is to examine whether any observed treatment effect varies across patient subgroups; i.e., whether the treatment effect is modified by the value of a variable assessed at baseline (12).

### 2.5 Statistical interim analyses and stopping guidance

No interim analyses were planned. Inclusion period ended 26 months after the first subject had been recruited or if at least 16 subjects in each group have been deemed fully compliant to intervention or control or further inclusion rate was below two patients per month.

### 2.6 Timing of analysis

The analysis described in this SAP will take place once all trial participant has completed either the follow-up cMRI, the follow-up cMRI and the follow-up visit at CFAS or deemed lost to follow-up by the project coordinator or Principial Investigator (PI). The data for the primary outcome is expected to be received by mid October 2023.

### 2.7 Timing of outcome assessments

Following informed consent, patients underwent baseline assessments at CFAS and the Department of Cardiology, Rigshospitalet. Patients were randomised no later than one day after baseline completion (study day 3, week 0). At week 6 (day 38-45) study participants complete a self-reported three-day kcal intake. The week 12 follow-up visits took place at day 88 – 112 after randomisation. At the follow-up at CFAS, a 5-day activity monitor will be placed on the patient (Shell Appendix 2).

# 3 Statistical principles

### 3.1 Confidence and p-intervals

All *P* values and 95% confidence intervals will be two sided with an alpha-level of 0.05. In principle, *P*<0.05 will be considered statistically significant *per se*; instead of applying explicit adjustments for multiplicity, we will examine and interpret all secondary objectives in a prioritized order using a "gatekeeping procedure" (see 5.1 Outcome definitions) (13). This means we will sequentially assess and interpret the secondary outcomes until either a statistically significant difference is not found, or all analyses have been completed at a statistical significance level of 0.05 following the outcome measure hierarchy listed in this SAP.

### 3.2 Adherence and protocol deviations

Adherence to the study is defined by compliance to the family of bDMARD each participant received prior to enrollment in this study of no less than 80%. Furthermore, adherence to the intervention (exercise) is defined by attendance of no less than 80% of the scheduled sessions (Shell appendix 3).

Adherence to the bDMARD treatment will be calculated as the amount (in mg) of bDMARDs that were taken during the study period divided by the supposed amount to have been taken during the study period:

$$Adherence\ (\%) = \frac{\text{Amount (mg) } of\ bDMARD\ taken\ during\ study\ period}{\text{Amount (mg) } of\ bDMARD\ suppossed\ to\ have\ been\ taken\ during\ study\ period} * 100$$

Adherence to the intervention (exercise) will be calculated as the number of exercise sessions attended divided by the total number of exercise sessions intended in the study (36 sessions) $Adherence\ (\%) = \frac{\text{Exercise sessions attended}}{36} * 100$

Adherence will be reported as number of participants with adherence no less than 80%. The intention-tot-treat (ITT) population will serve as denominator. If protocol deviations are believed to impact the accurate evaluation of the trial, they are categorized as significant and will be managed as violations of the protocol.

The following are considered protocol violations:

1. Non-adherence to bDMARD treatment
2. Non-adherence to the exercise intervention

PI (RHC) and project coordinator (SJ) will review each case and determine if that participant should be excluded from per-protocol (PP) analysis, prior to unblinding. Data regarding protocol deviations will be summarized by group with details for specific deviation(s) given.

### 3.3 Analysis population

The main analyses will be performed on the ITT population. Among patients with baseline data available, the ITT principle asserts the effect of a treatment policy (that is, the planned treatment regimen), rather than the actual treatment given (i.e., it is independent of treatment adherence). Accordingly, participants with a baseline visit at CFAS and a LVM (g) measured by CMR at baseline were subsequently allocated to a treatment group (Exercise and Control, respectively) and were followed up, assessed, and analysed as members of that group, irrespective of their adherence to the planned course of treatment (i.e., independent of withdrawals and cross-over phenomena). In contrast, The PP population is defined as participants who had their baseline measures available and completed the trial without protocol violations and a completed CMR at follow-up.

## 4 Trial Population

### 4.1 Screening data

A complete list of screening data, as well as eligibility (reasons provided), inclusion, exclusion, withdrawals and lost to follow-up (reasons provided) will follow the CONSORT standard flow diagram (Shell Figure 1) (14).

### 4.2 Eligibility criteria

Inclusion and exclusion criteria have previously been published (11).

### 4.3 Recruitment

The recruitment process have previously been published (11).

### 4.4 Baseline characteristics

The demographics and baseline data for the ITT population will be depicted in a table (Shell Table 1 and Shell Appendix 4). The data will be depicted as means and SD (normal distribution) or median and IQR (non-normal distribution). Categorial data will be depicted as numbers and percentages.

# 5 Analysis

### 5.1 Outcomes and definitions

The total list of outcomes is published elsewhere (11).

Outcomes for the current (primary) manuscript are prioritized in the following ranking:

1. Change from baseline in LVM

2. Change from baseline in left ventricular stroke volume

3. Change from baseline in left ventricular end diastolic volume

4. Change from baseline in relative $VO_{2peak}$

5. Change from baseline in DAS28-ESR

*Outcome definitions*

1. LVM refers to the mass or weight (g) of the muscular wall of the left ventricle. Measured by CMR.

2. Left ventricular stroke volume is the amount of blood ejected from the left ventricle of the heart during one contraction (systole) and into the aorta. Measured by CMR.

3. Left ventricular end diastolic volume is the amount of blood present in the left ventricle at the end of the diastolic phase. Measured by CMR.

4. Relative VO2peak, or maximal oxygen consumption per kg (ml/min/kg), is a measure of the maximum amount of oxygen an individual can use during intense aerobic exercise. Measured by indirect calorimetric measurements at CFAS (11).

5. DAS28-ESR is a composite numerical score used to assess the disease activity and monitor the progress of RA patients. The DAS28-ESR score takes into account 28 tender and swollen joint

counts, the ESR and the patient's assessment of their overall well-being on a visual analogue scale.

### 5.2 Analysis methods

The main analysis (primary outcome) will compare TNFi and IL-6i in terms of change of LVM from baseline to follow-up after an exercise intervention of 12 weeks (Shell Table 2 and Shell Figure 2). We will assess this superiority analysis based on the ITT population. Change from baseline will be calculated as the value collected after 12 weeks minus the initial value; An increase in LVM indicates cardiac adaptions to exercise. To analyse the change from baseline, we will use an ANCOVA model, and report the least squares means with standard errors. For the main analyses, missing values will be replaced by a simplistic non-responder imputation technique (i.e., baseline observation carried forward). The model will include the level at baseline as a covairiate, and fixed effect factors for sex, group (Exercise vs Management as usual), and concomitant bDMARD use (TNFi vs. IL-6i). For the purpose of sensitivite analysis, we will also attempt to account for baseline values and previous bDMARDs treatment (number of drugs used prior to the treatment at enrollment).

$$\Delta LVM = Group + sex + bDMARD + Group*bDMARD + \boldsymbol{f}(LVM_{baseline})$$

The primary analysis will be conducted following week 12based on the change from baseline variable (e.g., ΔLVM). We will report the difference between the randomised groups with a 95% CI and the associated P-value, which tests the null hypothesis of no difference between the groups.

We will claim superiority if the calculated 95% CI of the estimated group difference in the change from baseline does not include 0 in the ITT population. To ensure the validity of our model, several assumptions will be assessed. These include checking for normal distribution of the residuals and assessing the homogeneity of the variance by examining the standardized residuals in relation to the predicted values. In cases where variables do not meet the model assumptions, appropriate transformations will be applied to address the issue. However, if no suitable transformation is found, the results will be reported in terms of median change along with interquartile ranges. In such instances, suitable non-parametric statistical tests will be employed for analysis and testing.

Analysis of secondary outcomes will follow the same method as described above. Results will be presented in Shell table 2.

### 5.3 Sensitivity analysis

We will conduct sensitivity analyses for both primary and secondary outcomes. Initially, we will reiterate the primary analysis, but this time employing the Per Protocol (PP) population instead of the Intention-to-Treat (ITT) population.

$$\Delta\text{Variable} = \text{Group} + \text{sex} + \text{bDMARD} + \text{Group*bDMARD} + f(\text{Variable}_{\text{baseline}}) + \text{Previous\_bDMARD} + \text{Radiagnosis\_years}$$

Results will be presented as illustrated in Shell table 3.

### 5.4 Missing data

The database will undergo a thorough examination of all variables, including derived ones, to detect any missing values, outliers, or inconsistencies. Outliers will be identified by visually inspecting the maximum and minimum values, comparing them to the values recorded in the eCRF, and noting any significantly high or low values. If any outliers are found to be incorrect, they will be corrected if possible. Otherwise, they will be treated as missing data. Since the trial is being monitored by the external Good Clinical Practice Unit at Copenhagen University Hospitals, we anticipate minimal occurrence of faulty data points. The monitor has conducted pre-trial site visits and regular inspections throughout the trial, ensuring compliance with trial procedures, safety assessments, as well as data recording and verification.

## 5.5 Harms

All participants will undergo evaluations of adverse events (AEs), adverse reactions (ARs), serious adverse events (SAEs), serious adverse reactions (SARs), and suspected unsuspected serious adverse reactions (SUSARs). The frequency (and proportion) of participants encountering AEs and SAEs will be reported for each treatment group, classified according to their severity. Each participant's record will only show the highest level of severity experienced for each type of event

or reaction. No formal statistical analysis will be conducted. If needed, the classification categories for events and reactions will be expanded (Shell appendix 5).

### 5.6 Statistical software

Statistical analysis will be done in R (version 4.2.2 or more updated version). Figures will be done in either R or GraphPad Prism (most updated version available).

### 5.7 Changes to protocol

Inclusion criteria: DAS28-ESR was changed from 2.8 to 3.2 on December 17, 2021, to increase enrollment. A DAS28-ESR score of 3.2 as well as 2.8 suggests low disease activity.

## 6 Tables and figures

| Shell Table 1. Baseline Characteristics | | Exercise | Control | Overall |
|---|---|---|---|---|
| Demographics | | | | |
| Female/Male, n | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| Age, years | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| BMI, kg/m$^2$ | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| RA characteristics | | | | |
| Duration of RA, years | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| DAS28-ESR | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| HAQ-DI | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| Sero-positive RA, n (%) | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| SR,mm | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| IL-6, pg/ml | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| Cardiac Measures | | | | |
| LVM, g | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| LVSV, ml | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |

| | | | | |
|---|---|---|---|---|
| LVEDV, ml | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| LVM/BSA, g/m$^2$ | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| LV GLS (%) | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| LVEF, % | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| LVESV, ml | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| Resting HR, bpm | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| SBP, mmHg | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| DBP, mmHg | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| Metabolic measures | | | | |
| Total lean mass, kg | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| Total fat mass, kg | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| Fitness measures | | | | |
| Absolute Vo2peak, ml/min | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| Relative Vo2peak, ml/min/kg | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |

Shell Table 1. Baseline Characteristics. Values are depicted in means (SD) or number and percentage. BMI, body mass index; RA, rheumatoid arthritis; DAS28-ESR, Disease Activity Score-28 for rheumatoid arthritis with erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire disability index; SR, sedimentation rate; IL-6, interleukin.6; bDMARD, biological disease modifying anti rheumatic drug; LVM, left ventricular mass; LVSV; left ventricular stroke volume; LVEDV; left ventricular end-diastolic volume; BSA, body durface area; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure

| Shell Table 2. Outcomes after 12 weeks in ITT population | | Exercise | Control | Difference between groups (95% CI) | Interaction |
|---|---|---|---|---|---|
| ∆LVM, g | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ***Key secondary outcomes*** | | | | | |
| ∆LVSV, ml | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ∆LVEDV, ml | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ∆/Relative Vo2peak, ml/min | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ∆DAS28-ESR | Total | | | | |
| | TNFi | | | | |

| | | | | | |
|---|---|---|---|---|---|
| | IL-6i | | | | |
| ***Other secondary outcomes*** | | | | | |
| ΔLVM/BSA, g/m$^2$ | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ΔLV GLS (%) | | | | | |
| | | | | | |
| | | | | | |
| ΔLVEF, % | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ΔLVESV | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ΔAbsolute Vo2peak, ml/min | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ΔTotal lean mass, kg | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ΔTotal fat mass, kg | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ΔResting HR, bpm | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |

Shell Table 2. Values are depicted in least square means [95% CI]. LVM, left ventricular mass; LVSV; left ventricular stroke volume; LVEDV; left ventricular end-diastolic volume; DAS28-ESR, Disease Activity Score-28 for rheumatoid arthritis with erythrocyte sedimentation rate; BSA, body durface area; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; HR, heart rate

| Shell Table 3. Outcomes after 12 weeks in PP population | | Exercise | Control | Difference between groups (95% CI) | Interaction |
|---|---|---|---|---|---|
| ΔLVM, g | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ***Key secondary outcomes*** | | | | | |
| ΔLVSV, ml | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ΔLVEDV, ml | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| Δ/Relative Vo2peak, ml/min | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ΔDAS28-ESR | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ***Other secondary outcomes*** | | | | | |
| ΔLVM/BSA, g/m$^2$ | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ΔLV GLS (%) | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ΔLVEF, % | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ΔLVESV | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |

| | | | | | |
|---|---|---|---|---|---|
| ∆Absolute Vo2peak, ml/min | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ∆Total lean mass, kg | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ∆Total fat mass, kg | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| ∆Resting HR, bpm | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |

Shell Table 3. Values are depicted in least square means [95% CI]. LVM, left ventricular mass; LVSV; left ventricular stroke volume; LVEDV; left ventricular end-diastolic volume; DAS28-ESR, Disease Activity Score-28 for rheumatoid arthritis with erythrocyte sedimentation rate; BSA, body durface area; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; HR, heart rate

| Shell Appendix 1. Secondary outcomes documented in Clinical trials that are not covered in the present statistical analysis plan. | |
|---|---|
| Clinical trials secondary outcome number | Outcome |
| 1 | Visceral adipose tissue mass |
| 3 | Left atrial end-diastolic volume |
| 6 | E/A |
| 7 | E/é |
| 8 | Left atrial end-systolic volume |
| 9 | Left atrial volume index |
| 10 | Interventricular septum thickness |
| 11 | Left ventricular posterior wall thickness |
| 12 | Aortic and pulmonary disensibility and pulse wave velocity |
| 13 | Subcutaneous, visceral and epicardial adipose tissue |
| 14 | Intramyocardial triglyceride content |
| 16 | Dynamic spirometry |
| 17 | Whole body plethysmography |
| 18 | Diffusion capacity |
| 20 | Oral glucose tolerance test |
| 23 | Blood sample (cholesterol, LDL, HDL) |
| 24 | Blood sample (triglycerides) |
| 25 | RA disease specific outcomes 1 (66/68 tender and swollen joint) |
| 26 | RA disease specific outcomes 2 (VAS) |
| 28 | RA disease specific outcomes 4 (SF-36) |
| 30 | RA disease specific outcomes 6 (CDAI) |
| 31 | RA disease specific outcomes 7 (ACR 20/50/70) |
| 32 | RA disease specific utcomes 8 (EULAR none/good/moderate) |

Shell Appendix 1. E/A, early (E) to late (A) ventricular filling velocities; E/é, early mitral inflow velocity and mitral annular early diastolic velocity; LDL, low density lipoprotein; HDL, high density lipoprotein; VAS, visual analog scale; SF, short form; CDAI, clinical disease activity index; ACR, american college of rheumatology; EULAR, european league against rheumatism

| Shell appendix 2. Self-reported diet, self-reported physical activity prior to enrollment, and measured free-living physical activity | | Exercise | Control | Difference |
|---|---|---|---|---|
| Diet | | | | |
| Energy intake (kcal/day) | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| Physical Activity | | | | |
| Self-reported weekly exercise sessions at baseline, n | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| Free living physical activity | | | | |
| Valid days, n | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| Wear time, h/day | Total | | | |
| | TNFi | | | |

| | | | | |
|---|---|---|---|---|
| | IL-6i | | | |
| Total physical activity, counts/min per day | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| MVPA, min/day | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| Sedentary, min/day | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| Walking, min/day | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |

Shell appendix 2. Values are presented as mean (SD) or median and interquartile range. h, hour; MVPA, moderate and vigorous physical activity

| Shell appendix 3. Adherence to exercise and bDMARDs | | Exercise | Control | Difference in groups (95% CI) |
|---|---|---|---|---|
| Exercise intervention | | | | |
| Total sessions attended, n | Total | | - | |
| | TNFi | | - | |
| | IL-6i | | - | |
| Time in heart rate zone 1 (<70% HR max), min | Total | | - | |
| | TNFi | | - | |
| | IL-6i | | - | |
| Time in heart rate zone 2 (70-74% HR max), min | Total | | - | |
| | TNFi | | - | |
| | IL-6i | | - | |
| Time in heart rate zone 3 (75-79% HR max), min | Total | | - | |
| | TNFi | | - | |
| | IL-6i | | - | |
| Time in heart rate zone 4 (80-84% HR max), min | Total | | - | |
| | TNFi | | - | |
| | IL-6i | | - | |
| Time in heart rate zone 5 (≥85% HR max), min | Total | | - | |
| | TNFi | | - | |
| | IL-6i | | - | |
| Watt outputs during HIIT intervals, watt | Total | | - | |
| | TNFi | | - | |
| | IL-6i | | - | |
| Average BORG | Total | | - | |
| | TNFi | | - | |
| | IL-6i | | - | |
| bDMARD treatment | | | | |
| bDMARD compliance, % | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |

Shell appendix 3. Values are presented as mean (SD) or median and interquartile range. HR, heart rate; bDMARD, biological disease modifying antirheumatic drug; TNFi, tumour necrosis factor inhibitor; IL-6i, interleukin-6 inhibitor; FU, follow-up

| Shell Appendix 4. Supplemental baseline characteristics | | Exercise | Control | Overall |
|---|---|---|---|---|
| Concomitant medications | | | | |
| Oral steroids, n(%) | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| csDMARD, n(%) | Total | | | |
| | TNFi | | | |
| | IL-6i | | | |
| Betablocker, n(%) | Total | | | |

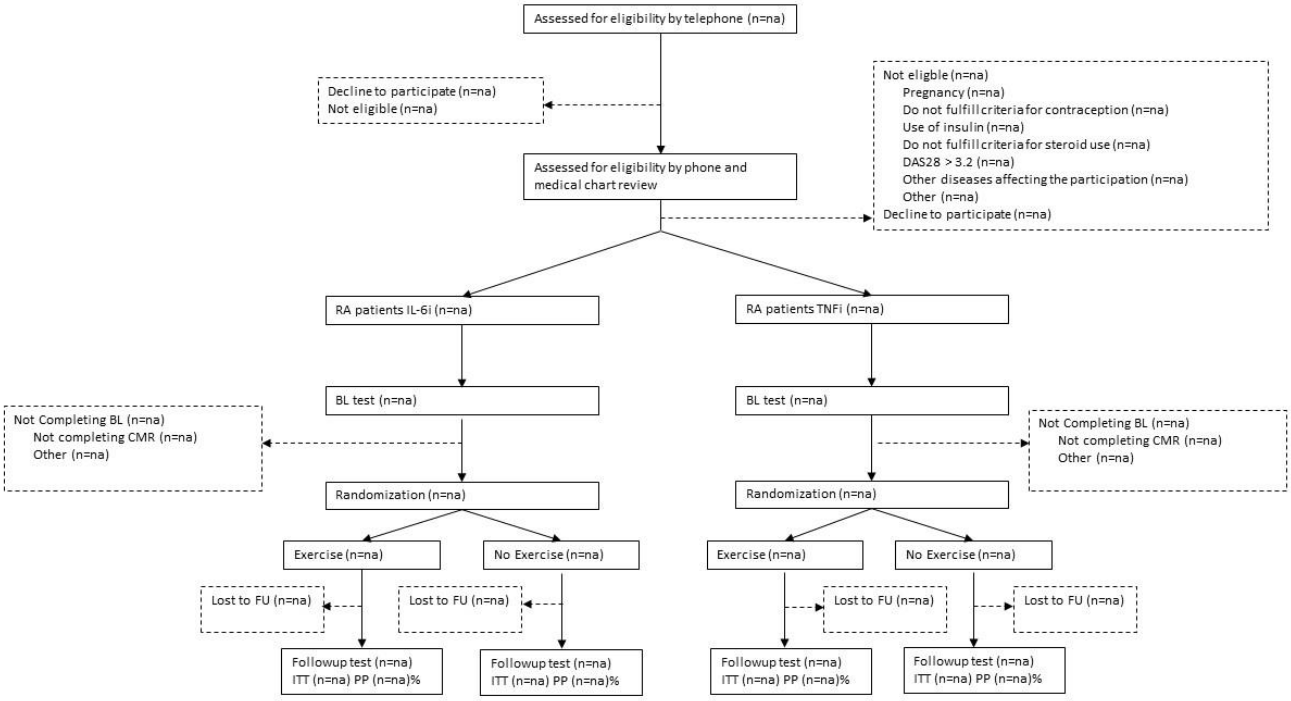
| | | | | | |
|---|---|---|---|---|---|
| | TNFi | | | | |
| | IL-6i | | | | |
| Other antihypertensive, n(%) | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| NSAIDs, n(%) | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| Statins, n(%) | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| Comorbidites | | | | | |
| Muskoskeletal disease, n (%) | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| Cardiovascular disease, n (%) | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| Pulmonary disease, n (%) | Total | | | | |
| | TNFi | | | | |
| | IL-6i | | | | |
| Prior bDMARD use | Total | 0: n(%) | | | |
| | | 1: n(%) | | | |
| | | ≥2: n(%) | | | |
| | TNFi | 0: n(%) | | | |
| | | 1: n(%) | | | |
| | | ≥2: n(%) | | | |
| | IL-6i | 0: n(%) | | | |
| | | 1: n(%) | | | |
| | | ≥2: n(%) | | | |

Shell Appendix 4. Values are mean (SD) unless noted otherwise. csDMARD, conventional synthetic disease modifying antirheumatic drugs; NSAIDs, non-steroid anti-inflammatory drug..

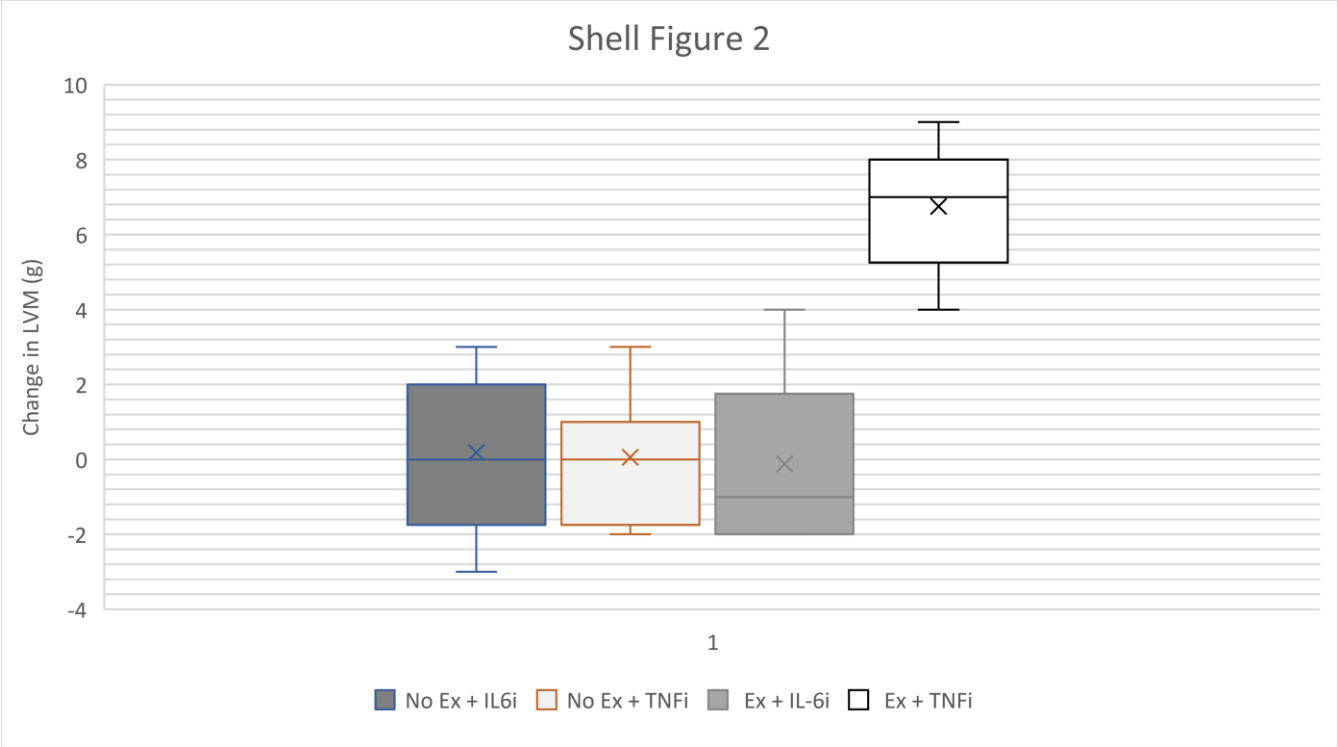
| Shell appendix 5. Adverse events | | Exercise | Control |
|---|---|---|---|
| SAE, no. (%) | Total | | |
| | TNFi | | |
| | IL-6i | | |
| All AE | | | |
| Muskuoloskeletal pain and injuries | | | |
| Lower extremities, no. (%) | Total | | |
| | TNFi | | |
| | IL-6i | | |
| Upper extremities, no. (%) | Total | | |
| | TNFi | | |
| | IL-6i | | |
| Back pain, no. (%) | Total | | |
| | TNFi | | |
| | IL-6i | | |
| Other, no. (%) | Total | | |
| | TNFi | | |
| | IL-6i | | |
| Infections | | | |
| Bacterial infections, no. (%) | Total | | |
| | TNFi | | |
| | IL-6i | | |
| Viral infections, no. (%) | Total | | |
| | TNFi | | |
| | IL-6i | | |
| Other, no. (%) | Total | | |
| | TNFi | | |
| | IL-6i | | |
| Cardiovascular disorders | | | |
| Pectoral Angina, no. (%) | Total | | |
| | TNFi | | |
| | IL-6i | | |
| Arrythmia, no. (%) | Total | | |

| | | | |
|---|---|---|---|
| | TNFi | | |
| | IL-6i | | |
| Other, no. (%) | Total | | |
| | TNFi | | |
| | IL-6i | | |
| Neurological disorders | | | |
| Headaches, no. (%) | Total | | |
| | TNFi | | |
| | IL-6i | | |
| Dizziness, no. (%) | Total | | |
| | TNFi | | |
| | IL-6i | | |
| Other, no. (%) | Total | | |
| | TNFi | | |
| | IL-6i | | |

Shell appendix 5. Values are number and percentage (%) of participants with AE for each group. SAE; serious adverse event, AE; adverse event.




Shell Figure 1. Flowchart. BL, baseline; FU, Follow-up




Shell Figure 2: Simulation. Hypothetical changes in LVM fra baseline to follow-up in the ITT population. LVM, left ventricular mass; ITT, intention-to-treat.

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