STATISTICAL ANALYSIS PLAN

Version number and date: 2.0, 08 March 2022

Safety signals and potential efficacy of a low-energy total diet replacement programme with behavioural support to delay disease progression in compensated cirrhosis due to non-alcoholic fatty liver disease: a feasibility randomised controlled trial

Version History

Version:	Version Date:	Changes:
2.0	08 March 2022	Addition of liver frailty index that has been added to the protocol. Addition of information on simulation of one of the primary outcome (cT1) in the appendix

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1 INTRODUCTION

1.1 PREFACE

The Chief Investigator will run the statistical analysis. The investigators and the Trial Steering and Data Monitoring Committee (TSDMEC) will review and approve the statistical analysis plan. The current SAP will support trial protocol v2.1, 03-Feb-22.

Data will be entered in SPSS and analysed using RStudio.

We will aim to follow this SAP unless it is not appropriate to do so and will report deviations from the SAP in the publication.

1.2 PURPOSE AND SCOPE OF THE PLAN

The purpose of the plan is to describe the analysis of the primary, secondary, and exploratory outcome measures as stated in the protocol. No interim analysis is planned.

1.3 TRIAL OVERVIEW

Please see sections 3 (synopsis) and 5 (background) of the protocol.

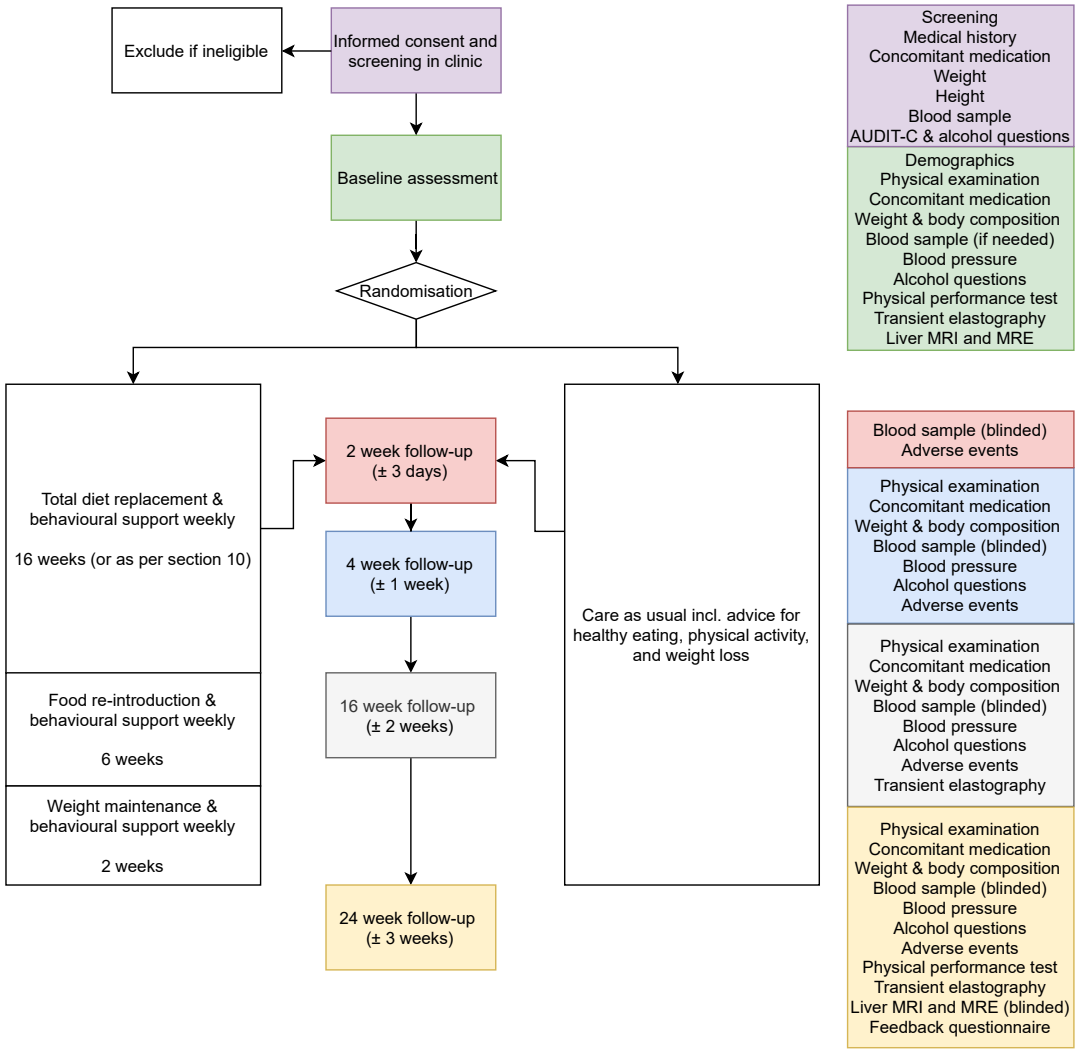
1.4 OBJECTIVES AND OUTCOME MEASURES

	Objectives	Outcome Measures	Timepoint(s)
Primary	i. To assess the safety signals of the intervention	i. Criteria of severe changes in biochemistry (ALT, AST, total bilirubin)	0, 2, 4, 16, & 24
	ii. To assess the potential efficacy of the intervention in improving a marker of liver inflammation/fibrosis	ii. Iron-corrected T1 relaxation time (cT1) values by magnetic resonance imaging (MRI)	0 & 24
	iii. To assess the potential efficacy of the intervention in not worsening MRE-estimated liver stiffness, a marker of liver fibrosis	iii. Liver stiffness by magnetic resonance elastography (MRE)	0 & 24
Secondary	To examine changes in liver stiffness by transient elastography	i. Liver stiffness by transient elastography	0, 16, & 24
		ii. Controlled attenuation parameter	0, 16, & 24
	To examine changes in liver fat	Proton density fat fraction (PDFF)	0 & 24
	To examine changes in blood biomarkers	i. ELF	0 & 24
		ii. UK Model for End-Stage Liver Disease (UKELD) score	0, 4, 16, & 24
		iii. Child-Pugh score	0, 4, 16, & 24

	Objectives	Outcome Measures	Timepoint(s)
	To examine changes in physical performance	i. Physical performance test ii. Liver frailty index	0 & 24 0 & 24
	To examine adverse events	Adverse events	0, 2, 4, 16, & 24
	To examine changes in weight	Body weight	0, 4, 16, & 24
	To examine changes in total fat-free mass	Total fat-free mass on bioelectrical impedance	0, 4, 16, & 24
	To examine changes in visceral fat	Visceral fat on MRI	0 & 24
	To examine changes in muscle mass	Muscle mass on MRI	0 & 24
Exploratory	To examine changes in medication	Adjustment in the number and dose of medication	0, 4, 16, & 24
	To examine changes in cardiometabolic markers	i. Blood pressure ii. HbA1c iii. Lipid profile	0, 4, 16, & 24 0, 16, & 24 0 & 24
Process measures	To examine feasibility of recruitment	i. Number of potentially eligible participants ii. Proportion of eligible participants randomised iii. Reasons for non-enrolment	0 0 0
	To examine intervention engagement	i. Proportion of sessions attended ii. Reasons for non-engagement	0, 4, 16, & 24
	To examine retention rate	i. Proportion of randomised participants completing a 24-week follow-up visit ii. Reasons for dropout	2, 4, 16, & 24
	To examine satisfaction with the intervention	Feedback questionnaire	24
	To monitor alcohol intake throughout the study	Alcohol intake questions	0, 4, 16, & 24

2 TRIAL DESIGN

Feasibility parallel randomised controlled trial of



2.1 TARGET POPULATION

People with compensated cirrhosis due to non-alcoholic fatty liver disease and body mass index ≥ 30 kg/m^2. Detailed inclusion/exclusion criteria are listed in the protocol.

2.2 SAMPLE SIZE

An 88ms difference in cT1 (co-primary endpoint) is related with a 2-point change in the histological NAFLD activity score and a 1-point difference in histological ballooning (the main NASH feature). In our ongoing pre-post pilot of TDR in NASH with fibrosis stage 2-3 (LiFT), cT1 reduced by a median of 130ms (SD: 70ms) at 12 weeks with similar estimates among the few participants who have already completed the 24-week follow-up.

Given the more advanced stage of the disease, 22 participants (n=15 intervention, n=7 control) will allow detecting a more conservative one-tailed between-group difference of 100ms (pooled SD: 70ms) with 90% power at 5% level (G*Power 3.1, t-test, difference between two independent means) .

Assuming approximately a 10% dropout at 24 weeks as we observed in LiFT, 24 participants are needed (n=16 intervention, n=8 control).

The sample size has been based on the above calculation.

An additional analysis of the sample size calculation has explored the potential of the study to be powered for the MRI stiffness outcomes. In the ongoing LiFT study, preliminary estimates suggest that MRE reduced by -0.56 kPA on average (median: -0.40kPA, SD: 0.45). LiFT2 will have 80% power at 5% level to detect a similar 0.54 kPA difference between groups, assuming a one-tailed test, 10% dropout, and a 0.45 pooled SD. There was no adjustment for multiple testing in this analysis.

No sample size calculation has been performed for the severe changes in biochemistry, as these are safety signals.

2.3 Randomisation and blinding in the analysis stage

With minimisation (based on BMI and type 2 diabetes) and 2:1 ratio. Details incl. the allocation concealment mechanism are described in the 9.4 section of the protocol.

3 Analysis – General considerations

3.1 Descriptive statistics

A table will present the baseline characteristics. This table will include age, sex, ethnic group, weight, BMI, education, marital status, smoking status, health conditions, alcohol consumption, liver markers, and summary of medication. Continuous variables will be summarised using means and standard deviations. Medians with interquartile ranges will be presented where appropriate. Categorical variables will be summarised using counts and percentages.

In the case where a trial is terminated early, or when the sample size achieved is too small for formal statistical analysis, the analysis will be by means of descriptive analysis only.

3.2 Characteristics of participants

Baseline/screening and demographic characteristics of the study population (overall and by group) will include age, sex, ethnic origin weight, BMI, education, marital status, smoking status, health conditions, alcohol consumption, liver markers, and summary of medication.

3.3 Definition of population for analysis

Safety analysis (severe biochemistry changes): This will include participants who commenced the intervention compared against all participants following usual care.

Primary analysis (cT1 and MRE stiffness): Given the feasibility nature of the study, all randomised participants with available data on the outcome of interest will be included in the primary intention-to-treat analysis in the group they were randomised.

Sensitivity analysis: The per protocol population is characterised by:

- Achieving ≥10% weight loss at 16 weeks (participants in the intervention group only) AND
- Having no major protocol violations, including the violation of entry criteria.

3.4 Data Monitoring Committee and Interim analysis

Given the small scale of the trial, it is unlikely that an interim analysis of the MRI and MRE (PDFF, cT1, and liver stiffness) data will provide definitive evidence of the efficacy of the intervention. Therefore, no interim analysis of the MRI and MRE data has been planned.

Therefore, the TSDMEC will not have routine access to the follow-up MRI and MRE data (collected at 16 and 24 weeks) during their scheduled meetings. This aims to avoid inflation of the type 1 error in the primary analysis. However, the TSDMEC might access these data if they regard it as necessary (e.g., to balance a possible safety risk against a possible gain in efficacy). In such a scenario where an unplanned interim analysis of the MRI/MRE data is required, the p-value of the final analysis will be adjusted using the O'Brien/Fleming approach (EMA 2005).

As an initial approach, the TSDMEC should compare the safety profile (liver biochemistry and adverse events) between intervention and control groups.

In case where there are no occurrences of biochemistry signals for intervention discontinuation in the control group, it is challenging to assess relative risk (see potential examples in Appendix). This is a plausible and likely scenario. In such a scenario, assessing only the intervention group participants that have started treatment would be considered based on one-sample test for binomial proportion (assuming no missing data).

As a guideline, the TSDMEC may consider recommending stopping the study if the lower bound of the 95% CI is at least 30% (in the 1st TSDMEC meeting that occurs when 4 out of 6 intervention participants discontinue and, in the 2nd TSDMEC meeting, when 7 out of 12 intervention participants discontinue). [Note: The 95% CIs are based on the Wilson score interval method. This method produces the tightest CIs (i.e. CIs based on Fisher's exact are much wider) (Sullivan 2022).]

Example 1: Potential 1st TSDMEC meeting after n=8 randomised and completed their 4-week follow-up (assuming n=6 intervention, n=2 control)

# of participants discontinuing intervention due to severe biochemistry changes	% with 95% CI based on Wilson score (pre-post)
1 of 6	17 (3-56)
2 of 6	33 (10-70)
3 of 6	50 (19-81)
4 of 6	67 (30-90)
5 of 6	83 (44-97)
6 of 6	100 (61-100)

Example 2: Potential 2nd TSDMEC meeting after n=16 randomised and completed their 4-week follow-up (assuming n=11 intervention, n=5 control)

# of participants discontinuing intervention due to severe biochemistry changes	% with 95% CI based on Wilson score (pre-post)
1 of 11	9 (2-38)
2 of 11	18 (5-48)
3 of 11	27 (10-57)
4 of 11	36 (15-65)
5 of 11	45 (21-72)

6 of 11	55 (28-79)
7 of 11	64 (35-85)
8 of 11	73 (43-90)
9 of 11	82 (52-95)
10 of 11	91 (62-98)
11 of 11	100 (68-100)

4 PRIMARY ANALYSIS

4.1 CO-PRIMARY OUTCOMES

A. **Severe changes in biochemistry** (ALT, AST, total bilirubin) based on
   - Enhanced observation (appendix D of protocol)
   - Intervention discontinuation (appendix E of protocol)

Initially, data will be plotted in the following tables

Table 1: N (%) of participants meeting the pre-specified criteria for enhanced observation

	Intervention				Control			
Week	2	4	16	24	2	4	16	24
ALT								
AST								
Total bilirubin								

Table 2: N (%) of participants meeting the pre-specified criteria for intervention discontinuation (the % control group will stand as reference).

	Intervention				Control			
Week	2	4	16	24	2	4	16	24
ALT								
AST								
Total bilirubin								

If sufficient non-zero data are available, we may consider estimating the ORs between groups using logistic mixed effects model adjusted for

- treatment group
- and a variable with 4 strata based on the two factors included in the minimisation algorithm (BMI<35/no T2D, BMI<35/T2D, BMI≥35/no T2D, BMI≥35/T2D) (Kahan and Morris 2012, 2013).

B. **cT1** – a marker of liver inflammation/fibrosis
   - H1: The intervention is more effective than usual care in reducing cT1 at 24 weeks.
   - H0: The intervention and usual care are equally effective in reducing cT1 at 24 weeks.

cT1 at 24 weeks will be analysed with a linear effects model adjusting for

- treatment group

- baseline cT1 value
- and a variable with 4 levels based on the two factors included in the minimisation algorithm (BMI<35/no T2D, BMI<35/T2D, BMI≥35/no T2D, BMI≥35/T2D) (Kahan and Morris 2012, 2013).

C. **MRE stiffness** – a marker of liver fibrosis
   - H1: The intervention is more effective than usual care in not worsening MRE stiffness at 24 weeks.
   - H0: The intervention and usual care are equally effective in not worsening MRE stiffness at 24 weeks.

MRE stiffness at 24 weeks will be analysed with a linear effects model adjusting for

- treatment group
- baseline MRE stiffness value
- and a variable with 4 strata based on the two factors included in the minimisation algorithm (BMI<35/no T2D, BMI<35/T2D, BMI≥35/no T2D, BMI≥35/T2D) (Kahan and Morris 2012, 2013).

4.2 SECONDARY OUTCOMES

The secondary outcomes measures that are continuous will be analysed following the principles outlined in the continuous co-primary outcomes. This will include linear models adjusting for treatment group, baseline value of the dependent variable, and a stratification factor. Continuous secondary outcomes will be:

- Liver stiffness by transient elastography
- Controlled attenuation parameter
- Proton density fat fraction (PDFF)
- ELF
- Physical performance test
- Liver frailty index
- Visceral fat on MRI
- Muscle mass on MRI

Continuous outcomes that are evaluated at more than 2 time points will be analysed with linear mixed effects models. These will include:

- Body weight
- Total fat-free mass on bioelectrical impedance
- UK Model for End-Stage Liver Disease (UKELD) score
- Child-Pugh score

4.3 EXPLORATORY OUTCOMES

The secondary outcomes measures that are continuous will be analysed following the principles outlined in the continuous co-primary outcomes. This will include linear models adjusting for treatment group, baseline value of the dependent variable, and a stratification factor. Continuous exploratory outcomes will be:

- Lipid profile
    - Total cholesterol/HDL ratio
    - Total cholesterol
    - HDL cholesterol
    - LDL cholesterol
    - Triglycerides

Continuous outcomes that are evaluated at more than 2 time points will be analysed with linear mixed effects models. These will include:

- Blood pressure
- HbA1c

Regarding medication adjustment, two ordinal variables will be created (one for medication for T2D and one for medication for hypertension) with levels “reduced”, “unchanged”, and “increased”. Reduced and increased will be coded if a reduction or increase, respectively, will occur in the dose or number of at least one medication for either T2D or hypertension. This will be compared between group using an ordinal logistic regression. Detailed adjustments in the number and dose of medication will be presented descriptively.

Furthermore, cirrhosis-related blood markers will also be graphically presented as continuous variables by treatment group (but will not be statistically analysed):

- ALT
- AST
- ALP
- Total bilirubin
- Conjugated bilirubin
- INR
- PT

4.4 PROCESS OUTCOMES

The following outcomes will be presented descriptively

- Number of potentially eligible participants
- Proportion of eligible participants randomised
- Reasons for non-enrolment
- Proportion of sessions attended
- Reasons for non-engagement
- Proportion of randomised participants completing a 24-week follow-up visit
- Reasons for dropout
- Feedback questionnaire
- Alcohol intake questions
    - AUDIT-C score at baseline
    - Alcohol units consumed within the last 7 days at each time point

4.5 HANDLING MISSING DATA

Given the nature of the study and the small sample size, it is likely that techniques to impute data will be of limited value. Therefore, available cases for each regression model will be used. We do not anticipate that we will impute data but will report the reasons for missing data.

4.6 HANDLING OUTLIERS

The safety analysis primarily relies on identification of outliers. These will be included in the analysis.

For the analysis of the co-primary outcomes (cT1), we do not expect significant outliers based on our definition of population for analysis (section 3.3). Data outliers will be defined as being at least three standard deviations from the mean of its distribution in the variable at that time-point. We will investigate and report the reasons for outliers. Outliers will be included in the analysis and a sensitivity analysis will be conducted by setting outliers to be missing.

4.7 MULTIPLE COMPARISONS AND MULTIPLICITY

As the comparisons have been pre-specified, we will not correct for multiple testing (Li et al. 2017).

The level of statistical significance will be set at $p<0.05$. The 95% confidence intervals will be presented but regarded nominal and descriptive.

4.8 MODEL ASSUMPTIONS

Residuals will be plotted against the explanatory variable, against the fitted values, and as a histogram. Where concern is indicated, a transformation and/or a nonparametric method may be used to address gross deviations from the assumptions.

5 SENSITIVITY ANALYSIS

The primary analysis will be repeated in the per protocol population as defined in section 3.3

6 SUBGROUP ANALYSES

Given the sample size, it is expected that the data will not be normally distributed and the statistical power to detect differences beyond the primary outcome will be limited. Therefore, we have not planned to statistically analyse subgroups.

Descriptive statistics ((mean [SD], median [IQR], count [%])) on each outcome, as appropriate, will be presented stratified by baseline cT1, Child-Pugh score, MELD score, type 2 diabetes status, and median BMI.

7 ADDITIONAL EXPLORATORY ANALYSIS

We have not planned any additional exploratory analysis.

8 ADVERSE EVENTS

Adverse events will be presented descriptively

- classified by system,
- as mild, moderate, severe, and
- as serious vs. non-serious.

Using a Chi-squared or Fisher's exact test as appropriate, we will also compare between groups:

- The proportion of participants reporting at least one adverse event
- The proportion of participants reporting at least one moderate or severe adverse event
- The proportion of participants reporting at least one serious adverse event
- The proportion of participants developing at least one event of hepatic decompensation as defined in the protocol

9 PROGRESSION CRITERIA TO A FULL TRIAL

	Criterion Decision	**Green** **Progress**	**Amber** **Progress with changes**	**Red** **Stop**
1	Recruitment (Proportion of eligible patients that have been randomised)	≥25%	11-24%	≤10%
2	Adherence (Proportion of participants in the intervention group who commenced the programme with ≥10% weight loss at 16 weeks)	≥60%	46-59%	≤45%
3	Retention (Proportion of randomised participants completing a 24-week follow-up visit)	≥85%	66-84%	≤65%
4	Safety profile	Based on adverse and serious adverse reactions. Adjudicated by the TSDMEC.		

10 VALIDATION

The TSDMEC (incl. the TSDMEC statistician) will review the analysis plan as well as the code and output of the co-primary outcome measures.

11 CHANGES TO THE PROTOCOL OR PREVIOUS VERSIONS OF SAP

Version:	Version Date:	Changes:
2.0	08 March 2022	Addition of liver frailty index that has been added to the protocol. Addition of information on simulation of one of the primary outcome (cT1) in the appendix

12 REFERENCES

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13 APPENDICES

Simulation of relative risks of severe biochemistry changes. Indicative relative risks for the 1st TSDMEC meeting, assuming 5 and 3 randomised to intervention and control, respectively.

"Bad" outcome: exceeding the liver biochemistry thresholds (incl. developing decompensation) that trigger intervention discontinuation as per the protocol. These cut-offs are based on earlier pharmacotherapy RCTs and the FDA guidance. For context, no one in the ongoing LiFT study has reached or approached these cut-offs.

Relative risk calculator

Exposed group

Number with positive (bad) outcome:	1	*a*
Number with negative (good) outcome:	4	*b*

Control group

Number with positive (bad) outcome:	0	*c*
Number with negative (good) outcome:	3	*d*

Test

Results

Relative risk	2.0000
95% CI	0.1057 to 37.8317
z statistic	0.462
Significance level	P = 0.6440
NNT (Harm)	8.000
95% CI	1.600 (Harm) to ∞ to 2.666 (Benefit)

Relative risk calculator

Exposed group

Number with positive (bad) outcome:	4	*a*
Number with negative (good) outcome:	1	*b*

Control group

Number with positive (bad) outcome:	0	*c*
Number with negative (good) outcome:	3	*d*

Test

Results

Relative risk	6.0000
95% CI	0.4309 to 83.5488
z statistic	1.333
Significance level	P = 0.1824
NNT (Harm)	1.600
95% CI	8.007 (Harm) to 0.889 (Harm)

For the 2nd TSDMEC meeting – assuming 11 vs 5 randomised to intervention and control, respectively.

Relative risk calculator

Exposed group

Number with positive (bad) outcome:	6	*a*
Number with negative (good) outcome:	5	*b*

Control group

Number with positive (bad) outcome:	0	*c*
Number with negative (good) outcome:	5	*d*

Test

Results

Relative risk	6.5000
95% CI	0.4349 to 97.1454
z statistic	1.357
Significance level	P = 0.1749
NNT (Harm)	2.182
95% CI	33.256 (Harm) to 1.128 (Harm)

Relative risk calculator

Exposed group

Number with positive (bad) outcome:	2	*a*
Number with negative (good) outcome:	9	*b*

Control group

Number with positive (bad) outcome:	0	*c*
Number with negative (good) outcome:	5	*d*

Test

Results

Relative risk	2.5000
95% CI	0.1412 to 44.2659
z statistic	0.625
Significance level	P = 0.5320
NNT (Harm)	8.000
95% CI	2.059 (Harm) to ∞ to 4.244 (Benefit)

Note 1: Where zeros cause problems with computation of the relative risk or its standard error, 0.5 is added to all cells (a, b, c, d) (Pagano & Gauvreau, 2000; Deeks & Higgins, 2010).

Note 2: If 1 “bad” outcome is observed in the control group, the mean RR reduces significantly in each scenario.

Simulation of the regression analysis of the co-primary outcome cT1

In the previous single-arm trial LiFT, we observed a correlation of 0.4 between cT1 values at baseline and follow-up. Previous studies suggest that cT1 and MRE data are not normally distributed in the general population but are skewed to the left, since most people do not have liver inflammation/fibrosis and therefore have normal values. However, we assume that the data in the LiFT2 study will approach normal distribution, because the study entry criteria will exclude people at both ends of the tail.

Assuming a normal distribution (mean cT1: 950, SD: 70), a 0.4 correlation between pre-post cT1 values, and that the null hypothesis is true (cT1 remains unchanged from baseline compared with control), the probability of a *significant* p-value ($p<0.05$) for the treatment group was 1% over 100 simulations in a regression model adjusting for treatment group, baseline value, and minimisation factors (lm(cT1_24 ~ cT1_0 + group + strata))).

In a second simulation assuming we reject the null hypothesis (cT1 reduces by 100 units on average in the intervention compared with control), the probability of a *non-significant* p-value ($p>0.05$) for the treatment group was 1% over 100 simulations in a regression model adjusting for treatment group, baseline value, and minimisation factors (lm(cT1_24 ~ cT1_0 + group + strata))).

Furthermore, a previous 2-arm trial (n=24 and n=19 per group) analysed cT1 with a similar method using analysis of covariance with treatment group and baseline values as covariates, indicating that the assumptions for regression modelling are likely to hold in LiFT2 (Harrison et al. 2020).