Statistical Analysis Plan (SAP)

Effectiveness of a telehealth physiotherapist-delivered intensive dietary weight loss program combined with exercise in people with knee osteoarthritis and overweight or obesity: the POWER trial

Contents

Section 1. Administrative Information

1. Title

Effectiveness of a telehealth physiotherapist-delivered intensive dietary weight loss program combined with exercise in people with knee osteoarthritis and overweight or obesity: the POWER trial

2. Trial registration

This trial has been prospectively registered with Clinicaltrials.gov (reference: NCT04733053).

3. SAP version

Version 3 (Final). Date: 26 May 2023

4. Protocol Version

This document has been written based on information contained in the POWER study protocol version 3.0 dated 15/6/21. The protocol was published as follows:

Bennell, K.L., Jones, S.E., Hinman, R.S. *et al.* Effectiveness of a telehealth physiotherapist-delivered intensive dietary weight loss program combined with exercise in people with knee osteoarthritis and overweight or obesity: study protocol for the POWER randomized controlled trial. *BMC Musculoskelet Disord* **23**, 733 (2022). https://doi.org/10.1186/s12891-022-05685-z

5. SAP Revisions

Not applicable

6. Names and affiliations

Document prepared by Ms Joanna Ling, Ms Peixuan Li, Dr Anurika De Silva, Dr. Karen Lamb, Professor Kim L. Bennell, and Professor Rana S. Hinman, University of Melbourne.

Emails: J Ling joanna.ling@unimelb.edu.au; P Li li.p4@unimelb.edu.au; A De Silva anurika.de@unimelb.edu.au; K Lamb klamb@unimelb.edu.au; KL Bennell k.bennell@unimelb.edu.au; RS Hinman ranash@unimelb.edu.au

Signatures:

Signature of senior statistician responsible (Dr Anurika De Silva): *Date: 27/04/2023*

Signature of chief investigator (Prof. Kim Bennell): *Date: 29/04/2023*

Section 2: Introduction

7. Background and rationale

Knee osteoarthritis (OA) is a leading and fast growing cause of musculoskeletal pain and disability in Australia, creating a significant burden on the individual and healthcare systems. Having obesity is a significant risk factor for the development and progression of OA, and people who have obesity are more likely to undergo costly joint replacement surgery. On this basis, national and international guidelines for OA management universally recommend losing weight as a core treatment for people with OA who have overweight/obesity, together with exercise, education and use of self-management strategies. Specifically, losing 5-10% of body weight has been shown to lead to clinically meaningful reductions in knee pain in patients with knee OA and overweight/obesity. However, achieving sustainable weight loss is difficult at an individual level, and often requires health practitioner support and supervision for long-term success. In Australia, physiotherapists outnumber dieticians by over 4:1. The scope of the physiotherapy profession is evolving with the public health demands of the 21st century and increasingly, weight management is considered to be within the role of the physiotherapist. Physiotherapists are at the forefront of treatment for knee OA as rehabilitation and exercise specialists and typically have a strong rapport with patients. With recent expansion of advanced scope roles for allied health staff in tertiary hospitals, physiotherapists are employed in advanced practice roles in OA triage clinics in public hospitals. In Victoria, the Victorian model of OA care strongly advocates for innovative models of care for OA that support expanded practice roles for allied health staff, based on the expansion of the existing advanced scope musculoskeletal physiotherapy framework. As such, with additional training, physiotherapists are well placed to deliver combined weight loss and exercise interventions for synergistic benefit for symptoms and weight and fat mass loss without the need for further referrals. Importantly, with respect to patient acceptability, preliminary evidence suggests that patients with musculoskeletal pain believe it is important and appropriate for physiotherapists to address weight in their management.

The ketogenic very low calorie diet (VLCD) is a protocolised dietary regime, which has been demonstrated as an effective means of achieving rapid weight loss in the adult population with overweight and obesity. The ketogenic VLCD leads to greater weight loss than low-fat diets in the short term and when delivered using nutritionally complete meal replacement products has been shown to be safe. The restricted carbohydrate feature of the diet causes the body to shift into the physiological state of ketosis, during which low availability of glucose from carbohydrates causes the oxidation of fatty acids in the liver, a process which releases ketones, which then circulate through the body systemically. Ketosis is an important factor in this diet as it overcomes some of the compensatory physiological responses such as increased ghrelin and appetite which usually arise during dieting and weight loss. Though it is widely accepted that ketosis does suppress hunger, the specific mechanism by which ketosis reduces appetite has not been definitively determined. The fact however that a downstream effect of eating a ketogenic VLCD is that it reduces appetite appears to assist individuals to adhere to the diet. A ketogenic VLCD delivered using up to 2 meal replacements per day is an appropriate and simple dietary intervention, with a predicted weight loss of 1.5-2.5 kg per week. This rapid rate of weight loss means that people with overweight or obesity adhering to a ketogenic VLCD frequently achieve a 10-15% weight loss target weight within 12 weeks.

Recent evidence-based recommendations for weight loss programs for knee OA support incorporation of exercise in all dietary weight loss programs. The effectiveness of exercise programs for knee OA, which reflect contemporary clinical practice, is well established. However, whether physiotherapists can effectively deliver a dietary weight loss program in patients with knee OA is unknown.

8. Research question

Is a 6-month physiotherapist-delivered dietary weight loss plus exercise program more effective for improving clinical outcomes than a physiotherapist-delivered exercise program alone in people with knee OA who have overweight or obesity?

9. Objectives

Research hypothesis:

Primary alternative hypothesis: That a physiotherapist-delivered dietary weight loss plus exercise program will

lead to significantly greater reductions in weight, compared to a physiotherapist-delivered exercise program alone at 6 months.

Secondary alternative hypothesis: That a physiotherapist-delivered dietary weight loss plus exercise program will lead to significantly greater benefits on other clinical outcomes (body mass index, weight circumference, waist-to-hip ratio, knee pain, physical function, global change in knee problem, quality of life, physical activity levels, internalized weight stigma, physical performance, quadriceps muscle strength), compared to a physiotherapist-delivered exercise program alone at 6 months.

Study objective:
Primary objective: To determine whether a physiotherapist-delivered dietary weight loss plus exercise program leads to greater weight loss than a physiotherapist-delivered exercise program alone in people with knee OA who have overweight or obesity at 6 months.

Secondary objectives: To compare the effects of a physiotherapist-delivered dietary weight loss plus exercise program and a physiotherapist-delivered exercise program alone on secondary outcomes at 6 months.

Section 3: Trial Methods

10. Trial design

The POWER trial was a two-arm, superiority, parallel-design RCT. Participants were randomised to receive either diet plus exercise or exercise only.

11. Randomisation

Eligible participants were randomised to receive either i) exercise alone or ii) diet plus exercise. The randomisation schedule was computer-generated and prepared by an independent biostatistician. The first list randomly allocated participants to a physiotherapist (no strata). The second list randomly allocated participants to an intervention group using variable permuted block sizes and a randomisation ratio of 1:1, stratified by physiotherapist and participant sex (due to sex differences in weight gain, weight loss, and attitudes to weight loss). If a physiotherapist was unavailable (e.g. sick, on holiday), participants were re-randomised to another available physiotherapist using a third list with variable permuted block sizes and stratified by group allocation and sex. The randomisation schedule was stored on a password-protected website (REDCap^{TM}) at the University of Melbourne and maintained by a researcher not involved in either participant recruitment or administration of primary/secondary outcome measures. Group allocation was revealed by this same researcher after completion of baseline assessment.

12. Sample size

Clinical practice guidelines for knee OA recommend patients who have overweight or obesity should lose at least 5-7.5% of body weight (1). We therefore powered the trial to be able to detect a conservative between-arm difference in weight loss of 5% of body weight assuming no change in weight in the exercise arm based on previous research (1, 2). While the between-participant standard deviation of percentage change in body weight was 5% in another study (1), in this patient population, we were more conservative and assumed a larger standard deviation of 7.5% given that our intervention has substantially less therapist contact (6 in ours, compared with up to 12 individual sessions in the previous study (1)), which could result in more variation in response.

For a power of 0.8 and a two-tailed significance level of 0.05, we required 37 participants per group. We increased this to 44 participants per group (88 in total) to allow for a 15% loss to follow up. Since physiotherapists treat participants in both arms of the trial, we have not adjusted the sample size calculation for clustering by physiotherapist. Due to unknown correlations between percentage weight loss and baseline weight in this population, sample size calculations are conservative and do not account for the adjustment of baseline weight which will further increase the statistical power.

13. Framework

This trial uses a superiority hypothesis-testing framework between groups for all outcomes.

14. Statistical interim analyses and stopping guidance

Nil

15. Timing of final analysis

Final analysis will be performed on the final total sample size of 88.

16. Timing of outcome assessments

Primary and secondary outcomes are measured at baseline and/or 6 months post-randomisation. The details of timing of each outcome assessments are summarised below. Detailed description of each outcome can be found in Appendix 1.

Name	Time-points measured
Primary Outcome	
Body weight (kg)	Baseline and 6 months
Secondary Outcomes	
Body mass index (BMI)	Baseline and 6 months
Waist circumference (cm)	Baseline and 6 months
Waist to hip ratio	Baseline and 6 months
Severity of knee pain during walking	Baseline and 6 months
Intermittent and constant osteoarthritis pain measure (iCOAP) – intermittent subscale	Baseline and 6 months
Intermittent and constant osteoarthritis pain measure (iCOAP) – constant subscale	Baseline and 6 months
Physical function subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)	Baseline and 6 months
Global overall improvement in knee problems	6 months
Quality of life (AQoL-6D)	Baseline and 6 months
Physical Activity Scale for the elderly (PASE)	Baseline and 6 months
30 sec chair stand test	Baseline and 6 months
40 m fast paced walk test (m/s)	Baseline and 6 months
Stair climb test (s)	Baseline and 6 months
Quadriceps muscle strength (Nm/kg)	Baseline and 6 months
Weight Self-Stigma Questionnaire (WSSQ) total score	Baseline and 6 months

Section 4: Statistical Principles

17. Level of statistical significance

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level.

18. Description of any planned adjustment for multiplicity, and if so, including how the type 1 error is to be controlled

We have one primary outcome (percentage change in body weight over 6 months). We have several secondary outcomes (body mass index, waist circumference, waist-to-hip ratio, knee pain, physical function, global change in knee problem, quality of life, physical activity levels, internalised weight stigma, physical performance, quadriceps muscle strength). All secondary outcomes are exploratory and not powered for. We will therefore not adjust for multiple secondary outcomes but instead report the estimates, confidence intervals, and p values in order to let readers use their own judgment about the relative weight of the conclusions on the effect of diet plus exercise program versus exercise program alone for secondary outcomes. This approach aligns with the usage of p-values favoured by the American Statistical Association (3).

19. Confidence intervals to be reported

All confidence intervals will be 95% confidence intervals.

20. Adherence and protocol deviations

The primary analysis will be based on the principle of intention-to-treat, whereby participants are included in the groups to which they were originally assigned, regardless of their adherence to their assigned treatments. Any protocol deviations (if they occurred), including errors applying inclusion/exclusion criteria and/or administration of the wrong intervention will be summarised in trial results (patient flow diagram/text) by treatment group. Randomisation errors resulting from these errors will be handled according to recommendations (4).

In this study, all participants were advised to perform home strengthening exercises 3 times/week together with a personalised physical activity plan. All participants were asked to self-report adherence to the strengthening exercise program and physical activity plan. Additionally, the diet plus exercise group was asked to self-report adherence with the diet program.

Multiple measures of participant adherence are used in this trial as shown below in the Table and data from these measures will be reported using descriptive statistics as appropriate for each treatment group.

Adherence	Description	Scale
Attendance at consultations	Recorded by physiotherapist for each consultation	Number of consultations attended
Adherence with strengthening exercise program	Self-reported number of exercise sessions in the last 2 weeks (options of 0, 1,2,3,4,5 and 6)	Range from 0-6 sessions, converted to a % out of the 6 prescribed sessions.
Rating of adherence with strengthening exercise program	Self-reported and scored on a 11-point NRS for “I have been doing my exercise sessions the number of times I was asked to by my POWER physiotherapist (e.g. three times per week)” over the previous 6 months	Ranges from 0 to 10; where 0=strongly disagree and 10=strongly agree
Rating of adherence with physical activity plan	Self-reported and scored on a 11-point NRS for “I	Ranges from 0 to 10; 0=strongly disagree and 10=strongly agree

	followed the physical activity plan that my POWER trial physiotherapist helped me to develop" over the previous 6 months	
Rating of adherence with diet program (diet plus exercise group only)	Self-reported and scored on a 11-point NRS for "I followed the diet plan as it was outlined by my POWER trial physiotherapist" over the previous 6 months	Ranges from 0 to 10; 0=strongly disagree and 10=strongly agree

21. Analysis populations

The primary analysis will be based on the principle of intention-to-treat, whereby participants are included in the groups to which they were originally randomised, regardless of their adherence to their assigned treatments.

Section 5: Trial Population

22. Screening Data

Screening data will be collected and summarised. A CONSORT flow diagram will be created (5). The following summaries will be presented in text and/or flow diagram: time frame for recruitment, the number of participants screened, the number of participants recruited, the number of screened participants not recruited, and the reasons for non-recruitment.

23. Eligibility

Trial inclusion and exclusion criteria are summarised below. Reasons for exclusion will be summarised in the CONSORT flow diagram.

Participants will be eligible for the study if they meet the following inclusion criteria:

i) meet the National Institute for Health and Care Excellence (6) clinical criteria for OA
   i. age≥45 years;
   ii. activity-related knee joint pain;
   iii. morning knee stiffness ≤ 30 mins
ii) report history of knee pain ≥ 3mths
iii) report knee pain on most days of the past month;
iv) report a minimum knee pain score of 4 on an 11-point numeric rating scale during walking over the previous week;
v) have a body mass index (BMI) >27 kg/m^2;
vi) those using hypertensive medication must be willing to have their blood pressure checked (this can be self-monitoring, at a pharmacist or at a GP) if they feel light-headed or dizzy at any point during the study
vii) able to give informed consent and to participate fully in the interventions and assessment procedures.

Participants will be ineligible for the study if they fall into one of the exclusion criteria:

i) weight>150 kgs;
ii) inability to speak English;
iii) on waiting list for/planning knee/hip surgery or bariatric surgery in next 6 months;
iv) previous arthroplasty on affected knee;
v) recent knee surgery on affected knee (past 6 months);
vi) self-reported inflammatory arthritis (e.g. rheumatoid arthritis);
vii) weight loss of > 2 kg over the previous 3 months
viii) already actively trying to lose weight by any of the following mechanisms:
   a. using meal replacements for weight loss
   b. being a member of a slimming club (e.g. weight watchers)
   c. receiving support from another health care professional for weight loss
   d. using any drugs prescribed to aid in weight loss
   e. using structured meal programs for weight loss such as ‘Lite n’ Easy’
ix) unwilling to continue current dietary patterns if randomised to exercise only group;
x) unable to undertake ketogenic VLCD for medical reasons including self-reported:
   a. diagnosis of Type 1 diabetes
   b. Type 2 diabetes requiring insulin or other medication apart from metformin
   c. warfarin use
   d. stroke or cardiac event in previous 6 months
   e. unstable cardiovascular condition
   f. fluid intake restriction
   g. renal (kidney) problems (unless clearance is obtained from GP, including GP confirmation that estimated glomerular filtration rate >30 mL/min/1.73m^2)
xi) any neurological condition affecting lower limbs.

xii) vegan dietary requirements due to complexity of delivering a nutritionally complete diet within the ketogenic diet regime

24. Recruitment

A CONSORT flow diagram will be used to describe the number of people enrolled, randomised, allocated to each treatment group, lost to follow up (including reasons) and analysed.

25. Withdrawal/follow-up

If a participant withdraws from the study, the nature, timing of and reasons for withdrawal will be described (provided the participant responds to requests for information by the research team). Any data provided up to the point of withdrawal will be analysed in accordance with intention-to-treat analyses, unless the participant specifically requests to withdraw their data from the study. Losses to follow-up (including reasons) will be summarised in the CONSORT flow diagram by treatment group.

26. Baseline characteristics

Baseline characteristics will be summarised by treatment group and presented in a table:

- Age
- Sex
- Height
- Body mass
- Body mass index
- Educational level
- Duration of study knee symptoms
- Pain at other sites
- Current employment status
- Co-morbidities
- Dieting history (attempts)
- Knee OA treatments used in past 6 months
- Current medication use
- Expectation of treatment outcome

Baseline characteristics will be summarised as appropriate (means and standard deviations for continuous variables that appear to be distributed approximately symmetrically, medians and interquartile ranges for other continuous variables, counts and percentages for categorical variables). Tests of statistical significance will not be undertaken for comparing baseline characteristics of treatment groups; rather the clinical importance of any imbalance will be noted.

If more than 5% of participants are missing the primary outcome at 6 months, an appendix table will provide summaries of baseline characteristics and baseline levels of primary and secondary outcomes. This table is to compare these characteristics between two groups: those participants who provide the primary outcome at 6 months, and those participants who are missing the primary outcome.

Section 6: Analysis

27. Endpoint and outcome definitions

Primary outcome:

- Percentage change in body weight (baseline-follow up/baseline x100%) from baseline to 6 months follow-up. Body weight is measured using calibrated digital laboratory platform scales (TCS-2 series) in kilograms precise to 2 decimal places. However, in some participants it was not possible to obtain the follow-up body weight measure using the calibrated digital laboratory platform scales (TCS-2 series). For these participants, we obtained the follow-up body weight measure via self report over the telephone with participants measuring their weight using their own set of scales.

Secondary outcomes: Where change scores at 6 months are used, these will be calculated as baseline – follow up difference.

- Change in body mass index (BMI). BMI is calculated as weight/height^2 with unit kg/m^2.

- Change in waist circumference. Waist circumference is measured at mid-abdomen level at its smallest circumference using a tape measure in centimetres precise to 1 decimal place.

- Change in waist to hip ratio. The waist to hip ratio is calculated by dividing the waist circumference by the hip circumference at its widest part, measured using a tape measure.

- Change in severity of knee pain during walking. The self-reported severity of knee pain during walking is scored on an 11-point numerical rating scale (NRS) for average knee pain during walking in the last week. This ranges from 0 to 10; where 0=no pain and 10=worst pain possible.

- Change in intermittent and constant osteoarthritis pain measure (iCOAP) intermittent subscale. iCOAP is an 11-item tool. The scores range from 0 to 24 for the intermittent subscale with higher scores indicating worse pain.

- Change in intermittent and constant osteoarthritis pain measure (iCOAP) constant subscale. iCOAP is an 11-item tool. The scores range from 0 to 20 for the constant pain subscale with higher scores indicating worse pain.

- Change in physical function subscale score of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). This is scored using 17 questions regarding knee function in the last 48 hours, with 4-point Likert response options ranging from no dysfunction to extreme dysfunction. The total subscale score ranges from 0 (no dysfunction) to 68 (maximum dysfunction).

- Global overall improvement in knee problems at 6 months. Global overall improvement in knee problems is scored using a 7-point global rating of change Likert scale with response options ranging from “much worse” to “much better” when compared to baseline. Participants indicating they are “moderately better” or “much better” will be classified as improved. All other respondents will be classified as not improved.

- Change in Quality of life (AQoL-6D). AQoL-6D is scored using the 20-item Assessment of Quality of Life II Instrument (6D version), which covers the topics of Independent Living, Relationships, Mental Health, Coping, Pain and Senses to come up with one overall value representing quality of life. The total score ranges from −0.04 to 1.00; higher scores indicate better quality of life.

- Change in Physical Activity scale for the elderly (PASE) total score. The PASE is scored via 10 questions about frequency and duration of recreational, household and occupational physical activity undertaken over the past 7 days. The total score ranges from 0 to 400+ with higher scores indicating greater levels of physical

activity.

- Change in the Weight Self-Stigma Questionnaire (WSSQ) total score. The WSSQ is a self-reported 12-item questionnaire scored on two 6-item sub-scales (self-devaluation and fear of enacted stigma). Each item will be rated on a 5-point Likert scale where from 1=completely disagree to 5=completely agree. The two subscale scores range from 6-30 with the total score ranging from 12-60 with higher scores indicating greater internalized weight stigma.

- Change in the 30 seconds chair sit-to-stand test. The 30 seconds chair sit-to-stand test measures the number of complete chair stands in 30 seconds. A greater number of complete chair stands indicates better function.

- Change in the 40 m fast paced walk test. This is measured as the time taken to walk 4 x 10 m quickly but safely in metres/second (m/s). Greater speed indicates better function.

- Change in 6-step stair climb test. The total time taken to ascend and descend a flight of six stairs with optional use of the handrail. Shorter completion times indicate better physical function.

- Change in the quadriceps muscle strength (Nm/kg). Quadriceps muscle strength is measured by the maximum voluntary isometric strength assessed using an isokinetic dynamometer with the knee at 60 degrees knee flexion. Peak torque over 3 maximal efforts lasting 5 seconds will be recorded. Higher scores indicate greater strength.

28. Analysis methods

Primary outcome:

Main comparative analyses between groups (exercise plus diet compared to exercise only) will be performed using intention-to-treat. If more than 5% of the primary outcome is missing, multiple imputation will be applied. If not, complete-case analysis will be applied. For the primary hypothesis, differences in mean percentage change in body weight (baseline minus 6-month follow-up) will be compared between groups using linear regression modelling adjusted for baseline weight and the stratification variables of sex and physiotherapist. Results will be presented as mean differences between groups with 95% confidence intervals, and p-values will also be reported. To aid clinical interpretation, the primary outcome will also be dichotomized into those who do and do not achieve a: 1) 5% or more weight loss and 2) 10% or more weight loss. Counts and percentages of participants experiencing weight loss of at least 5% and of at least 10% will be reported and compared in each treatment group at 6 months using log-binomial regression, adjusting for baseline weight and the stratification variables of sex and physiotherapist, with results reported as risk ratios and risk differences.

Secondary outcomes:

Similar analyses will be conducted for continuous secondary outcomes. Binary outcomes will be compared between groups using log-binomial regression, adjusting for the stratification variables of sex and physiotherapist, with results reported as risk ratios and risk differences. Counts and percentages of participants experiencing improvement will be reported in each group. Should the log-binomial regression models fail to converge, logistic regression models adjusting for the stratifying variables will be fitted, with results reported as risk ratios and risk differences. For all between-group comparisons, 95% confidence intervals for comparisons and p-values will be reported. Standard diagnostic plots will be used to check model assumptions.

29. Statistical Methods – adjustment for covariates

For all outcomes, adjustment is as described in the relevant section (Section 28, 30 and 31). In additional analyses of the primary and secondary outcomes, any baseline characteristics that appear to exhibit a meaningful imbalance between treatment groups will be adjusted for, and the sensitivity of the conclusions drawn as a result of these additions will be assessed.

30. Statistical Methods – sensitivity analyses

As noted in Section 27, the self-reported follow-up body weight will be used for the primary outcome (Percentage change in body weight (baseline-follow up/baseline x100%)) where using the calibrated digital laboratory platform scales (TCS-2 series) is impossible. A sensitivity analysis will be performed to estimate the effect of diet plus exercise compared to exercise alone on the primary outcome of percentage change in body weight, excluding those participants who self-reported follow-up body weight from the analysis.

If multiple imputation is required to handle missing data, complete-case analyses of primary and secondary outcomes will be undertaken in sensitivity analysis.

31. Statistical Methods – subgroup analyses

To assess whether the effect of diet plus exercise compared to exercise alone on the primary outcome of percentage change in body weight is moderated by obesity (BMI $\geq$ 30 kg/m^2), a linear regression model will be fit for the primary outcome with obesity (as a binary moderator, Yes versus No), treatment group, the stratification variables of sex and physiotherapist, baseline weight, and an interaction between treatment group and obesity.

32. Missing data reporting and assumptions/statistical methods to handle missing data

If more than 5% of participants are missing the primary outcome at 6 months, baseline characteristics of participants with the primary outcome missing at 6 months will be compared to those of participants with the primary outcome, as outlined in Section 26. If more than 5% of participants are missing the primary outcome at 6 months, multiple imputation will be applied. The number of imputed datasets will be approximately equal to the proportion of participants with missing primary outcomes. Missing baseline characteristics will be imputed using single mean imputation. Missing outcome values will be imputed separately by treatment group, using chained equations and predictive mean matching, using the five nearest neighbours. Imputation models will include baseline levels of outcomes and baseline characteristics that appear to be different between participants who provide complete follow up data and participants who do not. Initially, imputation models will include all primary and secondary outcomes together, with outcomes broken into subsets if imputation models do not converge. Imputed datasets will be compared to complete data using density plots for continuous outcomes and plots of proportions for binary outcomes. To assess the potential impact of the violation of the missing at random (MAR) assumption on conclusions for the primary outcome, an analysis will be conducted using the delta-adjustment method under the pattern-mixture modelling framework in the context of multiple imputation (7).

33. Additional Analyses

Nil

34. Harms

The number (and percentage) of participants experiencing any related adverse events will be summarised for each treatment group and the nature of the event(s) described. An adverse event is defined as any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the treatment. Adverse events will also be self-reported in the 6-month questionnaire, where participants are asked to provide details of the nature of adverse event(s), how long they lasted for, what action, if any, they took (e.g. taking medication or seeing a health professional), and whether they believe the adverse event was caused by participation in the trial (likely, unlikely, or unsure). A serious adverse event is defined as any untoward medical occurrence that; i) results in death; ii) is life-threatening; iii) requires hospitalisation or prolongation of existing inpatients hospitalisation; iv) results in persistent or significant disability or incapacity; v) is a congenital anomaly or birth defect, or; vi) any other important medical condition which, although not included in the above, may require medical or surgical intervention to prevent one of the outcomes listed. The Chief Investigator along with other trial investigators will determine causality. If the event is deemed related or possibly related to the trial, it is deemed to be a related adverse event.

We will report:

- the number and proportion of participants that withdraw from the trial due to a related adverse event;
- the number and proportion of participants that experience one or more serious related adverse events and their types;
- the number and proportion of participants that experience one or more non-serious related adverse events

and their types.

35. Statistical Software

Stata v17.0 will be used (StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC)

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Appendix 1

MEASURES

Name	Description	Scale	Variable in data set
Primary Outcome			
Body weight	Measured using calibrated digital laboratory platform scales (TCS-2 series), the percentage of body weight change (baseline-follow up/baseline x100%) will be calculated as the primary outcome*. Note: In some participants, the follow up weight is self-reported via the telephone using the participant's own set of scales	Kilograms to 2 decimal places	weight 0M [Baseline] weight 6M [6 months] weight status 6M [1=study scales, 2=self-report with own scales]
Secondary Outcomes			
Body mass index (BMI)	Calculated from height and weight*	Kg/m^2	bmi 0M [Baseline] bmi 6M [6 months]
Waist circumference	Measured using a tape measure*	Centimetres to 1 decimal place	waist 0M [Baseline] waist 6M [6 months]
Waist to hip ratio	Measured using a tape measure*	Ratio derived from waist circumference and hip circumference at baseline and 6 months	waist hip ratio 0M [Baseline] waist hip ratio 6M [6 months]
Severity of knee pain during walking	Scored on an 11-point NRS for average knee pain during walking in the last week	Ranges from 0 to 10; where 0=no pain and 10=worst pain possible	NRS walking pain 0M [Baseline] NRS walking pain 6M [6 months]
Intermittent and constant osteoarthritis pain measure (iCOAP) – intermittent pain subscale	11-item tool with constant and intermittent pain subscales	Ranges 0 to 24 for intermittent subscale	iCOAP intermittent pain 0M [Baseline] iCOAP intermittent pain 6M [6 months]
Intermittent and constant osteoarthritis pain measure (iCOAP) – constant pain subscale	11-item tool with constant and intermittent pain subscales	Ranges from 0 to 20 for constant pain subscale	iCOAP constant pain 0M [Baseline] iCOAP constant pain 6M [6 months]
Intermittent and constant osteoarthritis pain measure (iCOAP) – total pain score	Sum of iCOAP intermittent and constant pain subscales	Ranges from 0 to 44 for total pain score	iCOAP total pain 0M [Baseline] iCOAP total pain 6M [6 months]
Physical function subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)	Scored using 17 questions regarding knee function in the last 48 hours, with Likert response options ranging from no dysfunction to extreme dysfunction	Ranges from 0 (no dysfunction) to 68 (maximum dysfunction)	WOMAC function 0M [Baseline] WOMAC function 6M [6 months]
Global overall	Scored using a 7-point	Participants who indicate	Global improvement 6M [6

improvement in knee problems	global rating of change Likert scale with response options ranging from "much worse" to "much better" when compared to baseline	that they are "moderately better" or "much better" will be classified as improved. All other respondents will be classified as not improved	months]
Quality of life (AQoL-6D)	Scored using the 20-item Assessment of Quality of Life II Instrument (6D version), which covers the topics of Independent Living, Relationships, Mental Health, Coping, Pain and Senses to come up with one overall value representing quality of life	Total score ranges from −0.04 to 1.00; higher scores indicate better quality of life	AQoL 0M [Baseline] AQoL 6M [6 months]
Physical Activity scale for the elderly (PASE)	Scored via 10 questions about frequency and duration of recreational, household and occupational physical activity undertaken over the past 7 days	Scores range from 0 to 400+; higher scores indicate greater levels of physical activity	PASE 0M [Baseline] PASE 6M [6 months]
30 sec chair stand test	Number of complete chair stands completed in 30 secs	Number. Greater number indicates better function	30s STS 0M [Baseline] 30s STS 6M [6 months]
40 m fast paced walk test	Time to taken to walk 4 x 10 m quickly but safely	Metres/Second. Greater speed indicates better function	40m walk 0M [Baseline] 40m walk 6M [6 months]
Stair climb test	Time taken for participant to ascend and descend a flight of stairs	Seconds. Shorter time indicates better function	Stair climb 0M [Baseline] Stair climb 6M [6 months]
Quadriceps muscle strength	Maximum voluntary isometric strength will be assessed using an isokinetic dynamometer with the knee at 60 degrees knee flexion. Peak torque over 3 maximal efforts lasting 5 seconds will be recorded	Nm/kg	Quads strength 0M [Baseline] Quads strength 6M [6 months]
Weight Self-Stigma Questionnaire (WSSQ) self-devaluation subscale	Self-reported and scored on a 6-item subscale Each item rated on a 5-point Likert scale where from 1=*completely disagree* to 5=*completely agree.*	The subscale scores range from 6-30 with higher scores indicating greater internalized weight stigma.	WSSQ self-deval 0M [Baseline] WSSQ self-deval 6M [6 months]
Weight Self-Stigma Questionnaire (WSSQ) fear of enacted stigma subscale	Self-reported and scored on a 6-item subscale Each item rated on a 5-point Likert scale where from 1=*completely disagree* to 5=*completely agree.*	The subscale scores range from 6-30 with higher scores indicating greater internalized weight stigma.	WSSQ fear stigma 0M [Baseline] WSSQ fear stigma 6M [6 months]
Weight Self-Stigma Questionnaire (WSSQ) total score	The total WSSQ score is the sum of the self-devaluation and fear of enacted stigma subscales.	The two subscale scores range from 12-60 with the total score ranging from 12-60 with higher	WSSQ total 0M [Baseline] WSSQ total 6M [6 months]

		scores indicating greater internalized weight stigma.	