

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	The effectiveness of an anti-inflammatory diet versus low-fat diet for knee osteoarthritis: the FEAST randomised controlled trial protocol
<b>AUTHORS</b>	Law, Lynette; Heerey, Joshua; Devlin, Brooke; Brukner, Peter; Kemp, Joanne; Attanayake, Amanda; Hulett, Mark; De Livera, Alysha; Mosler, Andrea; Morris, Hayden; White, Nathan; Culvenor, Adam

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Juhl, Carsten SEARCH research group, Research Unit of Musculoskeletal Function and Physiotherapy, Institute of Sports Science and Clinical Biomechanics, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark
<b>REVIEW RETURNED</b>	26-Sep-2023

<b>GENERAL COMMENTS</b>	<p>Thank you for giving me the opportunity to read and comment on the protocol for “The effectiveness of an anti-inflammatory diet versus low fat diet for knee osteoarthritis: the FEAST randomized controlled trial protocol”</p> <p>Overall, the protocol describes a very well-planned RCT. The protocol adheres to the SPIRIT guidelines – the interventions are presented using the Template for Intervention Description and Replication (TIDieR) guidelines. The intervention is based on a previous feasibility study showing that the intervention is feasible and well accepted by the participants. However, the previous feasibility study is a single arm feasibility study showing an improvement on KOOS4 on 7.8 and therefore the effect of this intervention in a RCT design may be smaller.</p> <p>This leaves me with one major concern. The sample size is based on the review from Genel et al. showing an effect size of 0.62 (SMD) on physical function. However, this review seems to have misused the SE instead of SD in calculating the effect size and thereby largely overestimate the effect of the low-inflammatory of physical function change when compared to usual diet following 2–4 months of the intervention/control. This means that the sample size may increase largely. I acknowledge that the authors have identified 14 every month and included approx. 5 during Covid-19 and it may be possible to increase the inclusion rate for this study, as the sample size calculation may need to be adjusted the recruitment strategy may need to be adjusted.</p> <p>The author intended to include voluntary participants but did not discuss whether this recruitment strategy will result in a</p>
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	<p>representative sample of participants, or there is a risk that this recruitment strategy may result in a selected sample not representing the general population.</p> <p>One minor typo in line 320 (the 30-second chair-stand test (number of chair-stands from a standardised height chair in 20 seconds) – I guess you mean in 30 sec.</p>
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<b>REVIEWER</b>	Faurot, Keturah University of North Carolina at Chapel Hill School of Medicine, Physical Medicine & Rehabilitation
<b>REVIEW RETURNED</b>	31-Oct-2023

<b>GENERAL COMMENTS</b>	<p>The investigators report on an ongoing trial of a diet purported to be anti-inflammatory compared with the low-fat diet recommended by the Dietary Guidelines. The manuscript is well written and clear for the most part. However, additional details are needed in several areas for the reader to understand the protocol. Suggested areas for including details are listed below.</p> <p><b>Introduction:</b> Additional details supporting the individual components of the anti-inflammatory diet would be helpful as would an explanation of how the diet evolved from a program for diabetes.</p> <p><b>Inclusion/Exclusion criteria:</b> It would be important for the reader to understand the reason for the age restrictions and for the exclusion of individuals treated for diabetes with medications that lower blood sugar levels.</p> <p><b>Blinding:</b> This section requires some work to improve clarity. The researchers correctly identify study participants as assessors for the self-reported data. The protocol needs to state how the dietary interventions will be presented to participants to ensure equal credibility.</p> <p><b>Interventions:</b> It would be helpful to have additional information about the diets such as a sample menu for each of the diets. Similarly, additional details about the foods in the anti-inflammatory diet and their associations with pain and inflammation would be helpful. Additional details are needed to explain the fidelity monitoring of the interventions. Auditing is mentioned, but not described in detail. It is unclear if participants will be actively discouraged from losing weight.</p> <p><b>Assessments:</b> The inclusion of objective assessments of functional status is very helpful. It would be helpful to explain what the EQ-5D-5L instrument assesses in the footnotes of Table 3.</p> <p><b>Data and safety monitoring:</b> It is unusual to have no safety monitor, either internal or external.</p> <p><b>Data analysis:</b> In this section, it would be helpful to restate that the analysis of the primary outcome (and sample size calculations) relies on the mean score for four of the five subscales of the KOOS. The researchers need to define adherence and describe the analysis based on adherence if they plan to include it.</p> <p><b>Qualitative data (here described as Process Evaluation):</b> It would be helpful to know the criteria for purposive sampling. An explanation of "Framework analysis" is needed.</p> <p><b>Community engagement:</b> This is important for the reader to understand how the protocol came about and should be presented earlier in the manuscript. The researchers are commended on their explicit engagement practices!</p> <p><b>Data availability:</b> Will the researchers enable data and sample sharing? Is whole blood to be frozen as well?</p>
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## VERSION 1 – AUTHOR RESPONSE

### Reviewer #1

*Thank you for giving me the opportunity to read and comment on the protocol for “The effectiveness of an anti-inflammatory diet versus low fat diet for knee osteoarthritis: the FEAST randomized controlled trial protocol”*

Author Response: We thank the reviewer for such an in-depth review of our paper.

*Overall, the protocol describes a very well-planned RCT. The protocol adheres to the SPIRIT guidelines – the interventions are presented using the Template for Intervention Description and Replication (TIDieR) guidelines. The intervention is based on a previous feasibility study showing that the intervention is feasible and well accepted by the participants. However, the previous feasibility study is a single arm feasibility study showing an improvement on KOOS4 on 7.8 and therefore the effect of this intervention in a RCT design may be smaller.*

Author Response: We thank the reviewer for the positive comments regarding our paper. We agree that the effect of our intervention in an RCT may be smaller than what we observed in the single-arm feasibility study (Cooper et al., 2022). Based on the subsequent comment from the reviewer, we have revised our sample size calculation to take this into account.

*This leaves me with one major concern. The sample size is based on the review from Genel et al. showing an effect size of 0.62 (SMD) on physical function. However, this review seems to have misused the SE instead of SD in calculating the effect size and thereby largely overestimate the effect of the low-inflammatory of physical function change when compared to usual diet following 2–4 months of the intervention/control. This means that the sample size may increase largely. I acknowledge that the authors have identified 14 every month and included approx. 5 during Covid-19 and it may be possible to increase the inclusion rate for this study, as the sample size calculation may need to be adjusted the recruitment strategy may need to be adjusted.*

Author Response: Thank you for such a detailed review of our sample size calculation. Upon carefully reviewing the systematic review from Genel et al., together with the three original RCTs that were used in the meta-analysis to come up with the SMD of 0.62 for physical function (Skoldstam et al., Dyer et al., Schell et al.), we agree that the measures of variance used for calculating the SMD appear to be incorrect in the systematic review. Furthermore, the study with the largest effect size in the Genel et al., meta-analysis (Schell et al.) was a very different RCT to the FEAST RCT (i.e., cross-over design of a strawberry beverage). As such, we have significantly revised our approach for calculating our sample size.

In our revised sample size calculation, we utilise a conservative effect size estimate from a very recent RCT evaluating the effect of an anti-inflammatory diet vs low-caloric diet in overweight women with knee OA (Dolatkah et al., 2023). In this recent RCT, the standardized mean difference on total WOMAC score (a similar outcome to our primary outcome of KOOS<sub>4</sub>) was 1.0 (95%CI 0.5 to 1.6). For our FEAST RCT sample size calculation, we have now used the lower bound 95% confidence interval (0.5) as a conservative estimate of the effect of our anti-inflammatory diet compared to Australian Dietary Guidelines diet. This effect is also more conservative than the effect we observed in our pilot trial on KOOS<sub>4</sub> (0.68) (Cooper et al., 2022), which, as the reviewer points out, was only a single-arm anti-inflammatory diet trial. With the comparison to a usual care guideline-based control group, we expect the effect in the FEAST RCT to be somewhat attenuated.

With an estimated effect size of 0.5, recruiting 128 participants would yield 80% power to observe such an effect or larger at a two-tailed Type I error rate of 0.05. We initially inflated our sample size to account for a 20% drop-out rate, but we have now been able to account for a much lower drop-out rate of 10% based on the interim report to the grant provider. To account for this estimated 10% drop-out rate, we will recruit 144 participants.

Author Action: We have revised the sample size calculation text in the manuscript to reflect the changes described above (page 19, line 447-469):

This trial has been powered to detect a clinically significant between-group difference for the primary outcome of KOOS<sub>4</sub>. A recent RCT comparing an anti-inflammatory diet vs low-caloric diet in overweight women with knee OA observed an effect size (standardised mean difference) on self-reported pain and function of 1.0 (95% confidence interval 0.5 to 1.6) (Dolatkah et al., 2023). Given inherent differences in the FEAST RCT (e.g., Australian Dietary Guideline control group, not specifically targeting overweight participants, inclusion of both women and men), we used the lower bound 95% confidence interval to provide a conservative estimate of the anticipated effect size (0.5). This estimated effect size is also a conservative estimate based on our single-arm anti-inflammatory diet pilot trial, which had an effect size of 0.68 (Cooper et al., 2022). Recruiting 128 participants (equally distributed between two arms) would yield 80% power to observe such an effect or larger at a two-tailed Type I error of 0.05. This sample size estimation is also conservative since it is based on independent samples t-test. Using an ANCOVA model that includes the baseline value as a covariate and is pre-specified for the analysis should provide higher power for the same sample size (Borm, Jaap and Wim, 2007). To account for a potential 10% drop-out, we will recruit 140 participants. This sample size will also be sufficient to detect a minimal important change (MIC) in KOOS<sub>4</sub> estimated at 10 points in patients with knee OA (with a common between-subject standard deviation of 15).

Page 2, line 38: Following baseline assessment, 144 participants aged 45-85 years with symptomatic knee osteoarthritis...

*The author intended to include voluntary participants but did not discuss whether this recruitment strategy will result in a representative sample of participants, or there is a risk that this recruitment strategy may result in a selected sample not representing the general population.*

Author Response: Thank you for raising this important point. In the FEAST RCT, as we have described in the methods section, we employ a range of recruitment strategies to optimise the representativeness of our sample to increase generalisability of our trial results. We appreciate that there remains a risk that our sample will not be representative of the general population with knee OA.

Author Action: We have added text to the discussion section, to acknowledge the potential for selection bias in our RCT (page 22, line 536-545):

The current RCT will be the first full-scale trial to evaluate the symptomatic, inflammatory, functional and body composition benefits of an anti-inflammatory dietary program compared to a standard care low-fat dietary program based on Australian Dietary Guidelines. While outcome assessors are blinded to group allocation, owing to the type of interventions (i.e., dietary advice) blinding of participants will not be possible. We also acknowledge that, like most RCTs, there is a risk that our recruitment strategy may result in a selected sample not representative of the general population. However, using similar recruitment strategies, our prior RCTs have resulted in a representative sample of the culturally and sociodemographically diverse Australian population that has similar characteristics to other international cohorts with the index musculoskeletal condition (Culvenor et al., 2023).

*One minor typo in line 320 (the 30-second chair-stand test (number of chair-stands from a standardised height chair in 20 seconds) – I guess you mean in 30 sec.*

Author Action: Thank you for picking this up. We have amended this error (page 16, line 347):

...the 30-second chair-stand test (number of chair-stands from a standardised height chair in 30 seconds...

## **Reviewer #2**

*The investigators report on an ongoing trial of a diet purported to be anti-inflammatory compared with the low-fat diet recommended by the Dietary Guidelines. The manuscript is well written and clear for*

*the most part. However, additional details are needed in several areas for the reader to understand the protocol. Suggested areas for including details are listed below.*

Author Response: We thank the reviewer for the positive comments regarding our paper and have carefully addressed the suggestions below.

*Introduction: Additional details supporting the individual components of the anti-inflammatory diet would be helpful as would an explanation of how the diet evolved from a program for diabetes.*

Author Response: Thank you for this comment. Firstly, the anti-inflammatory dietary program in the FEAST RCT is a pragmatic diet individualised for each participant based on their eating preferences, rather than a diet with specific prescribed components or intake thresholds (e.g., <50g/day of carbohydrates). Secondly, the anti-inflammatory diet emphasising minimally processed, low-carbohydrate foods has existed for many years and has been utilised in the management of many different chronic diseases (e.g., epilepsy, Alzheimer's, cardiovascular disease, diabetes, Rheumatoid arthritis). It has not specifically evolved from a program for diabetes; rather, we leverage an existing evidence-based digital dietary program (Defeat Diabetes) that has been shown to improve the anti-inflammatory potential of participants. Defeat Diabetes was primarily developed to assist people with diabetes, but its dietary principles can be adapted for any chronic disease (e.g., recipes, modules on inflammation).

Author Action: We have added text to the introduction to provide more detail regarding the individual components of the anti-inflammatory diet, as suggested (page 4, line 100-105):

Omega-3 fatty acids, abundant in nuts, seeds and fish, are also a key part of anti-inflammatory dietary approaches and help to achieve a more desirable omega-6 to omega-3 ratio (Russo, 2009). In contrast, omega-6 fatty acids can be converted into arachidonic acid, a precursor for proinflammatory eicosanoids (Ricker & Haas, 2017). An elevated omega-6:omega-3 ratio exacerbates oxidative stress, which increases the risk and severity of chronic disease, including OA (Strath et al, 2020).

Author Action: We have edited and added content to the anti-inflammatory intervention description to further clarify its components (page 9, lines 216-219):

Participants will be encouraged to follow a diet containing minimally-processed foods and vegetable oils and higher amounts of healthy fats and nutrient-dense wholefoods known to fight inflammation (e.g., fresh fruits low in natural sugar such as berries, non-starchy vegetables, nuts and seeds, seafood, poultry, red meat, eggs, full-fat dairy).

*Inclusion/Exclusion criteria: It would be important for the reader to understand the reason for the age restrictions and for the exclusion of individuals treated for diabetes with medications that lower blood sugar levels.*

Author Response: The reasons for age restrictions are provided in Table 1. Age eligibility is set at ≥45 years as this is the clinical criteria to diagnose OA using the well-established NICE guidelines (National Institute for Health and Clinical Excellence, 2014). The upper age limit of 85 years was set due to potential safety reasons and additional co-morbidities that may hinder the capacity for dietary adherence. We excluded individuals with diabetes who were being treated with certain antihyperglycemic medications (insulin, SGLT 2 inhibitors, sulfonylureas) to mitigate the risk of hypoglycaemia or ketoacidosis if assigned to the anti-inflammatory dietary program.

Author Action: We have edited and added content to the eligibility criteria for clarity (Table 1):

Age ≤85 years – due to potential safety reasons and additional co-morbidities that may hinder capacity for dietary adherence.

Taking the following diabetic medication that lowers blood sugar levels (i.e., insulin, SGLT 2 inhibitors, sulfonylureas) to mitigate risk of hypoglycaemia/ketoacidosis

*Blinding: This section requires some work to improve clarity. The researchers correctly identify study participants as assessors for the self-reported data. The protocol needs to state how the dietary interventions will be presented to participants to ensure equal credibility.*

Author Response: We agree that more detail is needed around how the dietary interventions were presented to ensure equal credibility.

Author Action: We have added content to the relevant section (page 8, lines 192-197):

As the primary outcome is self-reported, participants are considered assessors; therefore, they will be blinded to previous scores. Health professionals delivering the interventions and participants cannot be blinded to group allocation owing to the type of interventions. The health professionals delivering the interventions will deliver the intervention for both groups. Specific protocols for both interventions (including consultation content and format, and accompanying resources) have been developed, and the health professionals have received training to ensure equal credibility. Random observations of intervention delivery will be conducted by the principal investigators to ensure treatment delivery credibility and fidelity.

*Interventions: It would be helpful to have additional information about the diets such as a sample menu for each of the diets. Similarly, additional details about the foods in the anti-inflammatory diet and their associations with pain and inflammation would be helpful. Additional details are needed to explain the fidelity monitoring of the interventions. Auditing is mentioned, but not described in detail. It is unclear if participants will be actively discouraged from losing weight.*

Author Response: Thank you for these suggestions. Firstly, we have now included a sample of the two intervention group booklets in the supplementary material, which include a sample meal plan, among other things. Secondly, as described in our response to the previous comment, fidelity monitoring of intervention consultations is conducted at intervals throughout the trial period by members of the principal investigator team. Thirdly, participants are not actively discouraged from losing weight. It is anticipated that a positive side-effect of both interventions will be weight loss, but weight loss itself is not emphasised as a primary target of the interventions.

Author Action: As per our response to the previous comment, we have revised the text to describe our fidelity assessment process (Table 2, page 11):

Fidelity is assessed through random auditing by members of the principal investigator team (AC or BD).

We have also added text to emphasise that weight loss was not actively discouraged, but was described as a potential positive side-effect of the interventions (page 9, line 205-206):

The anti-inflammatory dietary program and standard care low-fat dietary program are summarised aligning to Template for Intervention Description and Replication (TIDieR) guidelines (table 2). Participants in both intervention groups were not actively discouraged to lose weight, but weight loss was described as a potential outcome of the interventions.

Finally, we have included the intervention group booklets as supplementary material and cited in the text (page 10, line 231-5):

The following educational and behaviour change resources will also be provided at the initial consultation to support adherence: i) bespoke information booklet providing anti-inflammatory eating information, example meal plans, and foods that are encouraged and foods to avoid (supplementary file 3 and 4);

*Assessments: The inclusion of objective assessments of functional status is very helpful. It would be helpful to explain what the EQ-5D-5L instrument assesses in the footnotes of Table 3.*

Author Response: We thank the reviewer for this suggestion to clarify the use of the EQ-5D-5L instrument.

Author Action: We have added a footnote to Table 3 as suggested (page 16, lines 319-2320):

^Assesses health-related quality of life across 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and a visual analogue scale (0-100) of current overall health status.

*Data and safety monitoring: It is unusual to have no safety monitor, either internal or external.*

Author Response: The approving Human Research Ethics Committee at La Trobe University deemed that a formal data and safety monitoring committee was not necessary for this trial due its low risk (i.e., both interventions are considered safe and easily accessible to members of the general public). As we have described in the paper, all unexpected serious adverse events or outcomes will be discussed by the trial management committee and reported to the ethics committee who will monitor the trial for safety. This approach is the same as we have taken in our other current low-risk RCTs (e.g., exercise-therapy interventions) (Culvenor et al., 2023)

Author Action: We have included a reference to our other trial with a similar approach (page 19, line 441-4):

This is the same approach we have taken with other low risk RCTs (Culvenor et al., 2023). Any unexpected serious adverse events or outcomes will be discussed by the trial management committee (authors of this protocol) and reported to the approving human research ethics committee for monitoring.

*Data analysis: In this section, it would be helpful to restate that the analysis of the primary outcome (and sample size calculations) relies on the mean score for four of the five subscales of the KOOS. The researchers need to define adherence and describe the analysis based on adherence if they plan to include it.*

Author Response: While there is no gold standard objective measures of dietary intake and adherence, we use multiple measures of adherence in our trial: evaluation of participant self-reported 3-day food diaries; blood biomarkers collected at three timepoints; self-reported adherence measures (Visual Analogue Scale and 5-point Likert scale) where responses can be further clarified in consultations; and attendance at regular phone follow-ups with the study dietitian or suitably-trained health professional, who will assess how reported dietary intakes differ compared with recommendations. We defined satisfactory adherence as participants reporting both  $\geq 80\%$  on the VAS and 'Most days' or 'Every day' on the Likert scale, at both the 6-week and 12-week timepoints.

Author Action: We have revised the data analysis section, restating the primary outcome, as suggested (page 20, line 477-480):

For the primary hypothesis, a linear model with baseline value, sex and BMI ( $\geq 30$  vs  $< 30$  kg.m<sup>-2</sup>) as covariates and treatment condition as a fixed factor will evaluate the treatment effect on the primary outcome of KOOS<sub>4</sub> (mean score of four of the five subscales of the KOOS) at 12 weeks.

(page 19, lines 421-425):

Adherence will be assessed by a self-reported visual analogue scale (0=not at all adherent, 100=extremely adherent) and 5-point Likert scale at 6 weeks, 12 weeks and 6 months and evaluation of 3-day food diaries by consulting health professionals. Satisfactory adherence is defined as a self-report of both  $\geq 80$  on the VAS and 'Most days' or 'Every day' on the Likert scale, at both the 6-week and 12-week timepoints.

*Qualitative data (here described as Process Evaluation): It would be helpful to know the criteria for purposive sampling. An explanation of "Framework analysis" is needed.*

Author Response: We thank the reviewer for these suggestions. We have added further details to the text as suggested.

Author Action:

We clarified details to the text (page 21, lines 499-501):

Purposive sampling will be used to recruit interview participants based upon characteristics (anti-inflammatory dietary program vs standard care low-fat dietary program, men vs women) and outcomes of the trial (good vs poor outcome).

(Page 21, line 501-5):

Interviews will be audio recorded, transcribed and analysed using Framework Analysis, a flexible technique allowing researchers to identify, compare and contrast data according to inductively- and deductively-derived themes. The five stages of framework analysis are: familiarisation, theme identification, indexing, charting and summarising, and interpretation."

*Community engagement: This is important for the reader to understand how the protocol came about and should be presented earlier in the manuscript. The researchers are commended on their explicit engagement practices!*

Author Response: We thank the reviewer for the positive comment regarding our community engagement strategies. We agree that the Patient and Public Involvement statement should be presented earlier in the manuscript to demonstrate the extensive co-design approaches utilised in our study planning phase.

Author Action: We have updated the manuscript order so that the Patient and Public Involvement statement (originally on page 20, line 461-468) is now integrated into the Methods (page 6, lines 142-150).

*Data availability: Will the researchers enable data and sample sharing?*

Author Response: Deidentified data will be shared upon reasonable request to the principal investigator. We have clarified this in the Ethics and Dissemination section of the manuscript (page 22, line 530-3):

Deidentified data will be made available upon reasonable request to the principal investigator (AGC) after publication (except where the sharing of data is prevented by privacy, confidentiality, or other ethical matters, or other contractual or legal obligations) according to La Trobe University Research Data Management Policy.

*Is whole blood to be frozen as well?*

Author Action: We have added detail to clarify our blood collection samples (page 17, line 361-3):

Plasma and serum samples will be centrifuged (3000ms, 10 minutes), and all samples (plasma, serum, whole blood) frozen at -80°C for later analysis.

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Juhl, Carsten SEARCH research group, Research Unit of Musculoskeletal Function and Physiotherapy, Institute of Sports Science and Clinical Biomechanics, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark
<b>REVIEW RETURNED</b>	29-Jan-2024

<b>GENERAL COMMENTS</b>	The authors have answered my concerns appropriately - thanx
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<b>REVIEWER</b>	Faurot, Keturah University of North Carolina at Chapel Hill School of Medicine, Physical Medicine & Rehabilitation
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<b>REVIEW RETURNED</b>	23-Feb-2024
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<b>GENERAL COMMENTS</b>	The authors have addressed the comments of both reviewers fully. Among issues that can be addressed, a lingering concern is the impact of weight loss on the outcomes. The authors clarified that weight loss is allowed in the trial although not encouraged. Weight loss can be associated with improvements in knee pain and related function. Since the weight loss is occurring post randomization, it could be considered a confounding covariate. The authors are monitoring weight loss, waist circumference, and body composition. I would encourage the authors to consider a sensitivity analysis accounting for weight loss or changes in lean mass in their pre-specified statistical analysis plans.
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### VERSION 2 – AUTHOR RESPONSE

#### Reviewer #1

*The authors have answered my concerns appropriately – thanx*

Author Response: We thank the reviewer for the positive comments regarding our paper.

#### Reviewer #2

*The authors have addressed the comments of both reviewers fully. Among issues that can be addressed, a lingering concern is the impact of weight loss on the outcomes. The authors clarified that weight loss is allowed in the trial although not encouraged. Weight loss can be associated with improvements in knee pain and related function. Since the weight loss is occurring post randomization, it could be considered a confounding covariate. The authors are monitoring weight loss, waist circumference, and body composition. I would encourage the authors to consider a sensitivity analysis accounting for weight loss or changes in lean mass in their pre-specified statistical analysis plans.*

Author Response: The reviewer is correct that weight loss is allowed in the trial, and it can be associated with improvement in pain and function. Our trial's study design takes into account the potential confounding effect of baseline body composition as our randomisation process is stratified by BMI. As weight loss occurs after randomisation and likely contributes to the overall effect of the anti-inflammatory diet intervention (similar to changes in inflammation biomarkers), to estimate the total effect, it is not appropriate to adjust our analysis for changes in weight (or inflammation). However, we are planning to conduct a mediation analysis (evaluating changes in weight and inflammation) following publication of the primary trial results to estimate direct and indirect effects.

Author Response: We have added content to the statistical analysis section to briefly describe this (page 20, line 472-4):

Following publication of the primary trial results, we will also perform a formal mediation analysis to estimate direct and indirect (e.g., through weight and inflammation change) effects.

### VERSION 3 – REVIEW

<b>REVIEWER</b>	Faurot, Keturah University of North Carolina at Chapel Hill School of Medicine, Physical Medicine & Rehabilitation
<b>REVIEW RETURNED</b>	05-Mar-2024

<b>GENERAL COMMENTS</b>	The authors have addressed my concerns.
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