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BMJ Open

The effectiveness of an anti-inflammatory diet versus low-fat diet for knee osteoarthritis: the FEAST randomised controlled trial protocol

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Manuscripts

1 The effectiveness of an anti-inflammatory diet versus low- 2 fat diet for knee osteoarthritis: the FEAST randomised 3 controlled trial protocol

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28
29 **Word count:** 3,998

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2
3
4 30 **ABSTRACT**

5
6 31 **Introduction:** Chronic inflammation plays a key role in knee osteoarthritis pathophysiology
7
8 32 and increases risk of comorbidities, yet most interventions do not typically target
9
10 33 inflammation. Our study will investigate if an anti-inflammatory dietary program is superior
11
12 34 to a standard care low-fat dietary program for improving knee pain, function and quality-of-
13
14 35 life in people with knee osteoarthritis.

15 36 **Methods and analysis:** The FEAST (eFEct of an Anti-inflammatory diet for knee
16
17 37 oSTeoarthritis) Study is a parallel-group, assessor-blinded, superiority randomised
18
19 38 controlled trial. Following baseline assessment, 140 participants aged 45-85 years with
20
21 39 symptomatic knee osteoarthritis will be randomly allocated to one of two treatment groups
22
23 40 (1:1 ratio). Participants randomised to the anti-inflammatory dietary program will receive six
24
25 41 dietary consultations over 12 weeks (2 in-person, 4 phone/videoconference) and additional
26
27 42 educational and behaviour change resources. The consultations and resources emphasise
28
29 43 nutrient-dense minimally processed anti-inflammatory foods and discourage pro-
30
31 44 inflammatory processed foods. Participants randomised to the standard care low-fat dietary
32
33 45 program will receive three dietary consultations over 12 weeks (2 in-person, 1
34
35 46 phone/videoconference) consisting of healthy eating advice and education based on the
36
37 47 Australian Dietary Guidelines, reflecting usual care in Australia. Adherence will be assessed
38
39 48 with 3-day food diaries. Outcomes are assessed at 12 weeks and 6 months. The primary
40
41 49 outcome will be change from baseline to 12 weeks in the mean score on four Knee injury
42
43 50 and Osteoarthritis Outcome Score (KOOS₄) subscales: knee pain, symptoms, function in daily
44
45 51 activities and knee-related quality-of-life. Secondary outcomes include change in individual
46
47 52 KOOS subscale scores, patient-perceived improvement, health-related quality-of-life, body
48
49 53 mass and composition using dual-energy X-ray absorptiometry, inflammatory (high-
50
51 54 sensitivity C-Reactive Protein, Interleukins, Tumour Necrosis Factor- α) and metabolic blood
52
53 55 biomarkers (glucose, HbA1c, insulin, liver function, lipids), lower-limb function and physical
54
55 56 activity.

56
57 57 **Ethics and Dissemination:** Approved by La Trobe University Human Ethics Committee.
58
59 58 Results will be presented in peer-reviewed journals and at international conferences.

59 59 **Trial registration:** ACTRN12622000440729
60

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3 60 **Keywords:** Inflammation, Low-carbohydrate, Anti-inflammatory, Pain, Osteoarthritis, Knee,
4
5 61 Chronic disease, Rehabilitation, Diet
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11 63 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
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- 13
14 64 • The anti-inflammatory dietary program was codeveloped and piloted with patients and
15 65 clinicians, with the comparison low-fat dietary program representing usual care.
16
17
18 66 • Sufficiently powered trial evaluating change from baseline to 12 weeks (primary
19 67 endpoint) and 6 months facilitating longer-term effectiveness evaluation of the anti-
20 68 inflammatory dietary program.
21
22
23
24 69 • This trial will evaluate both self-reported and objective outcomes to understand
25 70 potential mechanisms of symptomatic changes.
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29 71 • While outcome assessors are blinded to group allocation, the health professionals
30 72 delivering the interventions and participants are unable to be blinded to group
31 73 allocation due to the type of interventions.
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74 INTRODUCTION

75 Osteoarthritis (OA) is the most common rheumatic disease affecting approximately 15% of
76 the population, with OA of the knee being most prevalent¹. Knee OA and its associated
77 symptoms can be disabling and lead to substantial societal and healthcare costs². In Australia
78 alone, annual OA-related healthcare expenditure exceeds \$2.1 billion³. Although the main
79 symptom of knee OA is pain, individuals with knee OA have an increased risk of other chronic
80 diseases, including cardiovascular disease and diabetes⁴. As many as two-thirds of older
81 adults with knee OA have more than one comorbidity⁵.

82
83 Clinical guidelines for knee OA recommend exercise-therapy and weight-loss as first-line
84 management strategies due to their excellent safety profile and therapeutic effects similar to
85 commonly used analgesics^{2 6}. However, the effectiveness of exercise-therapy has recently
86 been questioned due to its lack of benefit over an open-label placebo⁷, and findings that one-
87 third of people completing an exercise program do not achieve a clinically meaningful
88 improvement in pain^{8 9}. Weight-loss programs in those who are overweight or obese typically
89 consist of caloric restrictive diets, which are challenging to adhere to and sustain¹⁰. A meta-
90 analysis highlighted that, within two years of a calorie-restrictive program, over half of initial
91 weight lost was regained, and by 5 years, this figure jumped to >80%¹¹.

92
93 Anti-inflammatory diets provide an alternative to calorie-restrictive approaches by targeting
94 local and systemic inflammation, both contributors to OA disease onset, progression and
95 symptom burden¹²⁻¹⁴. Anti-inflammatory diets are typically high in minimally processed,
96 nutrient rich foods such as fruit, vegetables, spices and extra virgin olive oil, which are dense
97 in nutrients such as polyphenols, carotenoids, fibre, monounsaturated and polyunsaturated
98 fatty acids¹⁵⁻¹⁸. These nutrients can significantly reduce inflammation even in the absence of
99 weight loss¹⁹ via antioxidant and anti-inflammatory properties by neutralising free radicals
100 and associated cell damage, as well as improved lipid profiles^{15 16 20}. Due to their focus on real
101 foods and consumption to satiety, anti-inflammatory diets are likely more sustainable than
102 traditional calorie-restrictive approaches¹⁶.

103

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3 104 Anti-inflammatory diets have garnered much interest in recent years due to their
4
5 105 effectiveness in alleviating symptoms and improving biomarkers for a variety of chronic
6
7 106 diseases, including diabetes¹⁷, cardiovascular disease²¹, epilepsy²² and rheumatoid arthritis²³.
8
9 107 Small studies investigating anti-inflammatory diets for knee OA have demonstrated feasibility
10
11 108 and effectiveness in reducing symptoms and inflammation over 12-16 weeks^{14 24 25}. To date,
12
13 109 no fully powered randomised controlled trial (RCT) has evaluated the effectiveness of an anti-
14
15 110 inflammatory diet in knee OA.

111

112 The primary aim of this RCT is to estimate the average effect of an anti-inflammatory dietary
113 program compared to a standard care low-fat dietary program on knee-related pain, function
114 and quality of life in individuals with knee OA. We hypothesise that the anti-inflammatory
115 dietary program will result in greater improvements in knee-related pain, function and quality
116 of life after 12 weeks (primary endpoint) and 6 months (secondary endpoint) compared to
117 the standard care low-fat dietary program. Secondary aims are to assess 12-week and 6-
118 month effectiveness of the anti-inflammatory dietary program on: i) self-reported global
119 rating of change and achievement of acceptable symptoms; ii) health-related quality of life;
120 iii) body mass and composition using dual-energy X-ray absorptiometry (DXA); iv)
121 inflammatory and metabolic blood biomarkers, global lower-limb function and physical
122 activity.

123

124 **METHODS AND ANALYSIS**

125 **Study Design**

126 This protocol describes a pragmatic, 2-arm, parallel-group assessor-blinded superiority RCT
127 conforming to the Standard Protocol Items: Recommendations for Interventional Trials
128 (SPIRIT) statement²⁶. Reporting of the completed RCT will conform to the Consolidated
129 Standards of Reporting Trials (CONSORT) statement²⁷. The FEAST trial will be conducted at a
130 single site (La Trobe University) in Melbourne, Australia with enrolment anticipated to occur
131 over 24 months (2022-2024) and 6-month follow-up completed in 2024. The primary
132 endpoint will be at 12 weeks, with additional follow-up at 6 months (further longer-term
133 follow-up dependent on funding). The study was prospectively registered on the Australian
134 and New Zealand Clinical Trial Registry (ACTRN 12622000440729).

135

136 **Participants**

137 One hundred and forty adults 45-85 years old with chronic knee pain consistent with a clinical
 138 OA diagnosis using criteria from the National Institute for Health and Care Excellence, which
 139 does not require radiographic evidence²⁸, will be enrolled (table 1).

140

141

142 **Table 1.** Eligibility criteria

Inclusion criteria	Exclusion criteria
Fulfil National Institute for Health and Care Excellence ²⁸ clinical criteria for osteoarthritis: <ul style="list-style-type: none"> • Activity-related joint pain with average knee pain severity ≥ 4 on 11-point numeric rating scale (NRS, where 0 = no pain, 10 = worst pain possible) in the past week; • No morning stiffness or morning stiffness ≤ 30 min; and • Age ≥ 45 years 	Knee injection, injury or surgery in the past 3 months
Age ≤ 85 years – due to potential safety reasons and additional co-morbidities	Had all eligible knee joints replaced by arthroplasty
History of knee pain on most days for at least 3 months	Planning to have knee surgery in next six months
Be willing and able to attend 3-4 phone consults and 12-week and 6-month follow-up assessments	Already strictly following an anti-inflammatory diet (e.g., low carbohydrate, high-fat, paleo, Mediterranean) or strict exclusion diet (e.g., vegan)
Able to understand written and spoken English, and to give informed consent	Unable to follow anti-inflammatory diet (e.g., medically contraindicated, history of food allergy/hypersensitivity, family reasons)
	Taking the following medication that affects blood sugar levels: insulin, SGLT 2 inhibitors, sulfonylureas
	Contraindications for DXA scans (e.g., pregnant, breastfeeding, planning pregnancy in next 6 months, >200 kg body weight)

>5kg weight fluctuation in past 3 months
(i.e., unstable weight)

Dietary intervention (by a qualified dietitian)
in past 3 months

A diagnosed psychiatric disorder (excluding
anxiety and depression), eating disorder or
past bariatric surgery

143 NRS, numeric rating scale; SGLT, sodium glucose co-transporter; DXA, dual-energy X-ray
144 absorptiometry

145

146 **Recruitment and screening procedure**

147 Trial flow is outlined in figure 1. Participants will be recruited from our network of
148 collaborating orthopaedic surgeons in Victoria, Australia. Consistent with our prior work in
149 other musculoskeletal conditions^{29 30}, potentially eligible participants (i.e., individuals aged
150 45-85 years with a history of knee pain for which medical care was sought) will be sent a study
151 information letter inviting them to contact the research team. Additional recruitment
152 strategies will include advertisements in local newspapers, community/university
153 magazines/posters, community market stalls and social media.

154

155 *****FIGURE ONE HERE*******

156

157 Potential participants will be screened for eligibility via telephone. Once eligibility is
158 confirmed, participants will attend a study orientation session via videoconference to explain
159 further study details (e.g., fasting requirements) and be orientated to the dietary assessment
160 tool (3-day food diary). If both knees meet the inclusion criteria, the most symptomatic knee
161 will be considered as the index knee.

162

163 *Randomisation procedure, concealment of allocation and blinding*

164 Upon completion of baseline assessment, participants will be randomised to either the anti-
165 inflammatory dietary program or standard care low-fat dietary program. Study treatments,
166 but not study hypotheses, will be revealed to participants. A computer-generated
167 randomisation schedule has been developed *a priori* by an independent statistician in random
168 permuted blocks of 4-8 and stratified by sex and body mass index ($\geq 30\text{kg.m}^{-2}$ vs $< 30\text{kg.m}^{-2}$).

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3 169 To ensure concealed allocation, the randomisation schedule will be stored electronically in
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5 170 the secure Research Electronic Data Capture (REDCap®) system and only accessible to an
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7 171 unblinded researcher once baseline measures have been obtained, who will communicate
8
9 172 treatment allocation to the participant. Investigators conducting the follow-up assessments
10
11 173 will be blinded to group allocation. As the primary outcome is self-reported, participants are
12
13 174 considered assessors; therefore, participants (and thus assessors) will be blinded to previous
14
15 175 scores. Health professionals delivering the interventions and participants cannot be blinded
16
17 176 to group allocation owing to the type of interventions. An independent statistician, blinded
18
19 177 to group allocation, will perform the primary RCT analysis.
20
21 178

21 179 **Interventions**

23 180 The anti-inflammatory dietary program and standard care low-fat dietary program are
24
25 181 summarised aligning to Template for Intervention Description and Replication (TIDieR)
26
27 182 guidelines³¹ (table 2). The same health professionals will deliver the intervention for both
28
29 183 groups.
30
31 184

33 185 *Anti-inflammatory dietary program*

35 186 Participants allocated to the anti-inflammatory dietary program will receive specific anti-
36
37 187 inflammatory dietary education and an individualised eating plan, as well as a suite of
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39 188 resources to support behaviour change. The anti-inflammatory dietary program will be
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41 189 delivered over 12 weeks by a qualified dietitian or by another health professional specially
42
43 190 trained to deliver the intervention (e.g., physiotherapist).
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45 191

46 192 Participants will be encouraged to follow a diet containing minimal processed foods and high
47
48 193 amounts of healthy fats and nutrient-dense wholefoods known to fight inflammation (e.g.,
49
50 194 fresh fruits low in natural sugar such as berries, non-starchy vegetables, nuts and seeds,
51
52 195 seafood, poultry, red meat, eggs, full-fat dairy). Healthy fats include monounsaturated and
53
54 196 polyunsaturated fats with optimal omega-3: omega-6 ratios as found in seafood, nuts, and
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56 197 extra-virgin olive oil. Participants will be advised to limit processed foods, refined
57
58 198 carbohydrates (e.g., pasta, bread, rice), confectionary and foods with added sugar.
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3 199 Participants will be encouraged to consume a normocaloric diet and to eat to satiety, with no
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5 200 specific percentage of total energy intake targets for carbohydrate, fat or protein.
6

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9 202 An initial in-person consultation (~45 minutes) will occur immediately following group
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11 203 allocation to constructively review participant's current dietary intake (using baseline 3-day
12
13 204 food diary) and develop an individualised meal plan. Participants will be provided with a
14
15 205 comprehensive explanation of anti-inflammatory dietary principles, its rationale (e.g., the role
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17 206 of inflammation in OA, link between foods and inflammation) and its potential benefits and
18
19 207 side-effects, and address questions and/or concerns. The following educational and
20
21 208 behaviour change resources will also be provided at the initial consultation to support
22
23 209 adherence: i) bespoke information booklet providing anti-inflammatory eating information,
24
25 210 example meal plans, and foods that are encouraged and foods to avoid; ii) complimentary
26
27 211 subscription to an anti-inflammatory program (Defeat Diabetes phone app/website),
28
29 212 providing anti-inflammatory recipes, masterclasses, meal plans and educational articles; iii)
30
31 213 complimentary links to recommended documentaries exploring the benefits of anti-
32
33 214 inflammatory nutrition (i.e., Fat Fiction, Cereal Killers, That Sugar Film); and iv) complimentary
34
35 215 copy of a book exploring benefits of anti-inflammatory approach (A Fat Lot of Good³²).
36

37 216

38 217 Follow-up phone/videoconference consultations (~30 minutes) will be scheduled in weeks 2,
39
40 218 4, 6, and 9, with timing to be negotiated between each participant and the health professional
41
42 219 delivering the intervention. A final in-person consultation will be delivered immediately
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44 220 following the completion of the 12-week assessment. These follow-up consultations will
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46 221 provide participants with ongoing support, education and accountability. A 3-day food diary,
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48 222 completed prior to each consultation (see outcomes/adherence section), will guide
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50 223 individualised feedback and support to adapt meal plans to optimise adherence.
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224 **Table 2:** Overview of intervention delivery described according to the TIDieR guidelines

1. BRIEF NAME	Anti-inflammatory dietary program	Standard care low-fat dietary program
2. WHY	Anti-inflammatory diets targeting systemic inflammation assist in the prevention and management of various chronic diseases ¹⁵ . Small pilot studies have shown a positive effect of anti-inflammatory diets to improve knee-related symptoms in people with knee osteoarthritis ²⁵ .	Healthy eating guidelines and dietary advice described in the standard care program booklet was based on Australian Dietary Guidelines (ADGs) ^{33 34} . Two-three dietetic consultations represent usual care for patients referred for dietary management in Australia ^{18 19} .
3. WHAT (MATERIALS)	Participants receive an intervention handbook containing all study details, key anti-inflammatory eating principles, example meal plans, traffic light system of foods encouraged and discouraged, and education (e.g., common myths, tips for eating out, shopping tips); complimentary access to the Defeat Diabetes program app/website; complimentary links to three movies; and a complimentary copy of the book "A Fat Lot of Good" ³²	Participants receive an educational handbook emphasising ADGs healthy eating principles and are provided links to the online resources from the Eat for Health website (https://www.eatforhealth.gov.au/).
4. WHAT (PROCEDURES)	Six consultations providing individualised guidance and support to follow an anti-inflammatory eating pattern, emphasising the consumption of fruits, non-starchy vegetables, fish, poultry, red meat, eggs, full-fat dairy, nuts, seeds, and extra virgin olive oil. Participants will be encouraged to avoid highly processed foods, refined carbohydrates, added sugar, and processed meats.	Three consultations providing general advice and education regarding healthy eating based on the ADGs. The principles focus on consumption of foods from the five food groups, while limiting intake of foods containing saturated fat, added salt, added sugars and alcohol.
5. WHO PROVIDED	A qualified dietitian or health professional specially trained to deliver all components.	A qualified dietitian or health professional specially trained to deliver all components.
6. HOW	Delivered with individual support for 12 weeks, after which, participants will be encouraged to sustain the anti-inflammatory diet unsupported up to 6 months. Consultations are one-to-one.	Delivered with standard healthy eating advice for 12 weeks, after which, participants will be encouraged to sustain the program unsupported up to 6 months. Consultations are one-to-one.
7. WHERE	In-person consultations will occur at La Trobe University Nutrition and Dietetics research laboratory. Additional	In-person consultations will occur at the La Trobe University Nutrition and Dietetics research

	consultations will occur via telephone/videoconference (e.g., Zoom). Participants will integrate the diet principles into their daily consumption of foods and beverages.	laboratory. Additional consultations will occur via telephone/videoconference (e.g., Zoom). Participants will integrate the diet principles into their daily consumption of foods and beverages.
8. WHEN AND HOW MUCH	Two in-person consultations at baseline (~45 mins) and week 12 (~30 mins) Four phone/videoconference follow-up consultations (~30 mins) in week 2, 4, 6, and 9. Total active intervention delivery time: ~3.5 hours Participants are provided with self-management resources to optimise adherence to the anti-inflammatory diet up to the 6-month follow-up.	Two in-person consultations at baseline (~45 mins) and week 12 (~30 mins) One phone/videoconference follow-up consultation (30 mins) in week 6. Total active control delivery time: ~1.5 hours Participants encouraged to sustain their diet up to 6-month follow-up.
9. TAILORING	Individualised anti-inflammatory dietary advice, education, and support aligning with participant preferences and goals.	Advice based on the ADGs.
10. MODIFICATIONS	Any modifications will be reported.	
11. HOW WELL (planned)	Two-three professionals (qualified dietitian and other health professional) receive prior training in how to deliver and supervise the program. Fidelity is assessed through regular auditing. Participant adherence to the anti-inflammatory diet is assessed through consultation attendance, regular 3-day food diaries and self-report.	Two-three professionals (qualified dietitian and health professional) receive prior training in how to deliver and supervise the program. Fidelity assessed through auditing. Participant adherence to the standard care low-fat diet is assessed through consultation attendance, regular 3-day food diaries and self-report.
12. HOW WELL (actual)	This will be reported in the primary paper.	

225 TIDieR, Template for Intervention Description and Replication; ADG, Australian Dietary Guidelines

1
2 226 *Standard care low-fat dietary program*
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5 227 Participants allocated to the standard care low-fat dietary program will receive advice and
6 228 education regarding healthy eating based on the Australian Dietary Guidelines³⁵. These
7 229 government-endorsed guidelines aim to optimise nutrition intake through adequate
8 230 consumption of foods from the five core food groups (grains and cereals; fruit; vegetables and
9 231 legumes; lean meats and poultry, fish, eggs, and tofu; reduced fat dairy or alternatives), while
10 232 limiting intake of foods containing saturated fat, added salt, added sugars and alcohol. They are
11 233 high-carbohydrate and low-fat focused – participants will be encouraged to include at least four
12 234 serves of wholegrains daily (e.g., brown rice, pasta, bread, quinoa, oats) and to choose low-fat
13 235 protein and dairy foods where possible.
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25 237 The program will be delivered through individual consultations with the treating dietitian or other
26 238 specially trained health professional – the first in-person consultation immediately following
27 239 baseline assessment (~45 minutes), the second via phone/videoconference at 6 weeks (~30
28 240 minutes) and the third in-person at 12-week follow-up with timing individualised as required.
29 241 Two to three consultations represents usual care for patients referred for dietary management
30 242 in Australia through the current public healthcare (Medicare) rebate system^{34 36}. During the initial
31 243 in-person consultation, participants will be provided with a bespoke educational booklet and
32 244 advice and education emphasising the Australian Dietary Guideline principles
33 245 (<https://www.eatforhealth.gov.au/guidelines>) and informed of complementary and publicly
34 246 available online resources from the Eat for Health website (<https://www.eatforhealth.gov.au/>).
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46 248 The follow-up phone/videoconference consultation in week-6 and in-person follow-up in week-
47 249 12 will provide participants with ongoing support, education and accountability. The 3-day food
48 250 diary, completed prior to each consultation (see outcomes/adherence section), will guide
49 251 feedback and support to adapt meal plans to optimise adherence. The treating health
50 252 professionals delivering the two dietary programs will be based centrally at La Trobe University
51 253 and will be trained by the senior study dietitian (BLD) until deemed competent in intervention
52 254 delivery.
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1
2 256 Irrespective of group allocation, participants can continue usual medical care and consult with
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4 257 their treating health professionals as necessary (e.g., general practitioner regarding medication
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6 258 changes).

7 259

9 260 **Data collection procedure**

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11 261 Data will be collected at baseline and 6 weeks, 12 weeks and 6 months after randomisation, with
12
13 262 12 weeks the *a priori* primary endpoint as this coincides with completion of supported
14
15 263 interventions (table 3). Where possible, data will be collected and managed using a secure web-
16
17 264 based software platform (REDCap[®]) hosted at La Trobe University³⁷, which has equivalent
18
19 265 measurement properties to paper-based completion³⁸. This strategy was used in our pilot study²⁵
20
21 266 and other trials of musculoskeletal conditions³⁹. Paper versions will also be available if preferred.
22
23 267

25 268 **OUTCOMES**

27 269 **Baseline characteristics**

28
29 270 Participant characteristics including age, sex, ethnicity, knee pain/surgery details, socioeconomic
30
31 271 details (e.g., education level, employment status, living status), medical history and health
32
33 272 literacy (assessed with the Rapid Estimate of Adult Literacy in Medicine (REALM)⁴⁰) will be
34
35 273 collected (table 3).

38 275 **Primary Outcome**

39
40 276 The primary outcome is the change from baseline to 12 weeks in the mean score on four Knee
41
42 277 injury and Osteoarthritis Outcome Score (KOOS₄) subscales covering knee pain, symptoms,
43
44 278 function in daily activities and knee-related quality of life. The KOOS is a 42-item patient-reported
45
46 279 outcome measure assessing five separately scored subscales: Pain, Symptoms, Function in Sport
47
48 280 and Recreation (Sport/Rec), Activities of Daily Living (ADL), and Quality of Life. The KOOS₄ and all
49
50 281 KOOS subscale scores range from 0 (extreme problems) to 100 (no problems). The KOOS is a
51
52 282 valid, responsive and reliable questionnaire, with KOOS₄ a primary outcome for other knee OA
53
54 283 trials^{30 41 42}.

54 284

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289 **Table 3.** Overview of data collection

Variable	Baseline	6 weeks	12 weeks	6 months
Participant characteristics				
Age	X			
Sex	X			
Ethnicity	X			
Education level	X			
Health literacy (REALM)	X			
Employment status	X			
Smoking status	X			
Civil status, living situation	X			
Medical history, comorbidities	X			
Knee pain/injury/surgery history	X			
Objective Clinical Outcomes				
Height, weight, waist girth	X		X	X
30-second chair stand test	X		X	X
40 metre walk test	X		X	X
Body composition (DXA)	X		X	X
Blood inflammatory and metabolic biomarkers	X		X	X
Blood pressure	X		X	X
Patient-reported Outcomes				
KOOS subscales	X	X	X	X
Global rating of change		X	X	X
Desire for knee surgery	X	X	X	X
Medication use	X	X	X	X
Knee pain (current and worst in past week)	X	X	X	X
EQ-5D-5L	X	X	X	X
Patient acceptable symptom state	X	X	X	X
Brief Pain Inventory	X		X	X
International Physical Activity Questionnaire	X		X	X
Kessler Psychological Distress Scale (K10)	X		X	X
3-day Food Diaries*	X	X	X	X
Adverse events		X	X	X

290 REALM, Rapid Estimate of Adult Literacy in Medicine; KOOS, Knee injury and Osteoarthritis Outcome
 291 Score; DXA, Dual-Energy X-ray absorptiometry

292 *3-day food diaries are also assessed prior to anti-inflammatory dietary program consultations at 2, 4 and
 293 9 weeks

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2 2943
4 295 **Secondary effectiveness outcomes**5
6 296 *KOOS subscales*

7
8 297 To allow for clinical in-depth interpretation, scores for the five KOOS subscales will be reported
9
10 298 individually (i.e., pain, symptoms, function in sports and recreational activities, activities of daily
11
12 299 living, quality of life)^{9 42}.

13
14 30015
16 301 *Global Rating of Change (GROC) and patient-acceptable state*

17
18 302 Self-perceived change in pain and function will be assessed using a 7-point Likert scale ranging
19
20 303 from 'much worse' to 'much better' in response to the questions: "Overall, how has your knee
21
22 304 pain changed since the start of the study?" and "Overall, how has your knee function changed
23
24 305 since the start of the study?", respectively. Treatment success will be defined as a response of
25
26 306 either 'better' or 'much better'. Satisfaction with current knee function using the self-reported
27
28 307 Patient Acceptable Symptom State (PASS) question⁴³. Participants not satisfied with current knee
29
30 308 function at follow-up assessments will be asked a second question to determine if they
31
32 309 considered the treatment to have failed⁴³.

33 310

34
35 311 *Anthropometrics*

36
37 312 Height and weight will be assessed using a seca 217 stadiometer and seca 703 EMR-validated
38
39 313 column scale (Hammer Steindamm, Hamburg, Germany), respectively. Waist circumference will
40
41 314 be measured using a metal tape measure (Lufkin W606PM ¼ inch x 2m Executive Thinline Pocket
42
43 315 Tape).

44
45 31646
47 317 *Global lower-limb function*

48
49 318 Two performance-based tests of lower-limb function recommended by the OA Research Society
50
51 319 International (OARSI) will be conducted: the 30-second chair-stand test (number of chair-stands
52
53 320 from a standardised height chair in 20 seconds) and 40-metre walk test (time to walk 40 metres
54
55 321 safely, using walking aids if required)⁴⁴.

56
57 322

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59

60

323 *Body composition*

324 A whole-body DXA scan will be acquired using a Hologic Horizon® DXA scanner (Bedford, MA,
325 United States) to assess adiposity (visceral, peripheral) and lean mass⁴⁵.

327 *Inflammatory and metabolic biomarkers*

328 An array of blood inflammatory and metabolic biomarkers will be analysed from samples of blood
329 collected, including high sensitivity C-Reactive Protein (hsCRP), cytokines (IL-1 β , IL-6, IL-8, IL-10,
330 TNF- α), blood glucose, HbA1c, serum insulin, liver function tests (including albumin), and lipids
331 (e.g., high density lipoprotein, triglycerides). Participants will be instructed to fast for at least 10
332 hours prior to blood collection and a single forearm venepuncture will take place to collect a total
333 of \leq 30 mL blood. All samples will be centrifuged (3000ms, 10 minutes), and plasma and serum
334 frozen (-80°C) for later analysis (Supplementary File 2).

336 **Secondary safety outcomes**

337 *Adverse events*

338 Adverse events and serious adverse events will be recorded at 6-week, 12-week and 6-month
339 follow-up via open probe questioning to optimise collection of sufficient detail. Under the
340 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) harms
341 statement, an adverse event is defined as any undesirable experience causing participants to
342 seek medical treatment (e.g., general practitioner)⁴⁶. A serious adverse event is defined as any
343 undesirable event/illness/injury classified as having the potential to significantly compromise
344 clinical outcome or result in significant disability or incapacity, those requiring inpatient or
345 outpatient hospital care, to be life-threatening or result in death.

347 **Exploratory outcomes**

348 *Dietary Analysis*

349 Participants will record food and beverage intake over three days via the smartphone application
350 *Australia Calorie Counter - Easy Diet Diary* (Xyris Software Pty Ltd) or on paper (personal
351 preference). Easy Diet Diary is a commercial calorie counter and food diary that allows users to
352 email recorded diaries to treating professionals. Once received by the treating health
353 professional, the 3-day food diaries will be imported into, and analysed using, Foodworks®

1
2 354 Premium Edition nutrient analysis software (Version 10, Brisbane, Australia 2019) and Australian
3
4 355 food composition databases. Paper-based 3-day food diaries will be manually entered into
5
6 356 FoodWorks®. Total energy intake, macronutrients, micronutrients and core food group analysis
7
8 357 will be reported. Dietary analysis data will also be used to calculate the inflammatory potential
9
10
11 358 of participants' diets (e.g., Dietary Inflammatory Index)⁴⁷.

12 13 360 *Quality of life*

14
15 361 Health-related quality of life will be assessed with the EQ-5D-5L generic health index, which
16
17 362 comprises five dimensions of health (mobility, self-care, usual activities, pain or discomfort,
18
19 363 anxiety or depression) and a Visual Analogue Scale (VAS) of current overall health status⁴⁸. Both
20
21 364 validity and reliability has been demonstrated in arthritic populations⁴⁹.

22 23 365 24 25 366 *Knee pain and interference*

26
27 367 Self-reported knee pain (current, worst over past week, average over past week) will be assessed
28
29 368 using a 100mm VAS (0=no pain, 100=worst pain imaginable). The degree to which knee pain
30
31 369 interferes with participant's daily functioning will be assessed using the Brief Pain Inventory⁵⁰, a
32
33 370 tool with reliability and validity demonstrated in knee pain populations^{51 52}.

34 35 371 36 37 372 *Change in analgesic medication use*

38
39 373 Change in analgesic medication use from baseline to 12-week and 6-month follow-up will be
40
41 374 assessed with a 7-point Likert scale (much less to much more).

42 43 375 44 45 376 *Physical activity*

46
47 377 Physical activity will be assessed using the International Physical Activity Questionnaire (IPAQ)⁵³,
48
49 378 a standardised and valid questionnaire providing an estimate of physical activity and sedentary
50
51 379 behaviour, which has been widely validated^{53 54 55}. Respondents are asked to report time spent
52
53 380 in physical activity across three intensities (walking, moderate, vigorous). Using the IPAQ scoring
54
55 381 protocol⁵⁶, total weekly physical activity can be estimated by weighting time spent in each activity
56
57 382 intensity with its estimated metabolic equivalent (MET) energy expenditure⁵⁷.

1
2 384 *Blood pressure*
3

4 385 A pair of seated blood pressure measurements will be obtained using an automated monitor
5
6 386 (Omron Model HEM-7121). The blood pressure cuff is placed over the mid-upper arm with the
7
8 387 participant seated.
9

10 388

11
12 389 *Self-perceived wellness*
13

14 390 Self-reported sleep quality, hunger, fatigue and energy levels will be assessed using a 100mm
15
16 391 VAS (0=worst outcome, 100=best outcome).
17

18 392

19
20 393 *Intervention adherence*
21

22
23 394 In both randomised groups, intervention adherence will be collected via: i) secure online app
24
25 395 (e.g., Foodworks® 3-day food diary) and/or self-reported paper logbooks as preferred, completed
26
27 396 in the week prior to each consultation and follow-up assessment; and ii) overall adherence rating
28
29 397 (e.g., 5-point Likert scale) at each follow-up assessment.
30

31 398

32
33 399 **DATA MANAGEMENT**

34 400 Most outcome data will be collected and managed electronically via REDCap© web-based
35
36 401 software hosted at La Trobe University. Other data (e.g., DXA reports) will be stored electronically
37
38 402 on the La Trobe University secure research drive. All electronic data will be de-identified
39
40 403 (participant code) and exported for data analysis and saved in a password protected database on
41
42 404 the La Trobe University research drive only accessible to the research team. Paper-based
43
44 405 identifying documents (e.g., consent forms) will be securely stored in a locked filing cabinet
45
46 406 accessible only to members of the research team and separately from re-identifiable (i.e., coded)
47
48 407 data.
49

50 408

51 409 Due to the minimal known risks associated with the interventions being evaluated, our study will
52
53 410 not have a formal data monitoring committee and does not require an interim analysis. Any
54
55 411 unexpected serious adverse events or outcomes will be discussed by the trial management
56
57 412 committee (authors of this protocol) and reported to the approving human research ethics
58
59 413 committee for monitoring.
60

60 414

415 **Sample size calculation**

416 This trial has been powered to detect a clinically significant between-group difference for the
417 primary outcome of KOOS₄. The estimated effect size for low-inflammatory diets on self-reported
418 pain and function in individuals with arthritis is at least moderate (Cohen's d 0.62)⁵⁸. Recruiting
419 112 participants (equally distributed between two arms) would yield 90% power to observe such
420 an effect or larger at a two-tailed Type I error of 0.05. This sample size estimation is conservative
421 since it is based on independent samples t-test. Using an ANCOVA model that includes the
422 baseline value as a covariate and is pre-specified for the analysis should provide higher power for
423 the same sample size. To account for a potential 20% drop-out, we will recruit 140 participants.
424 This sample size will be sufficient to detect a minimal important change (MIC) in KOOS₄ estimated
425 at 10 points in patients with knee OA (with a common between-subject standard deviation of
426 15). Including 140 participants will also provide ≥90% power to detect a statistically significant
427 between-group difference (two-tailed $\alpha=0.05$) on the secondary outcome of inflammatory
428 biomarkers (anticipated effect size: Cohen's d 2.33 for hsCRP/IL-6)⁵⁸.

430 **Statistical analyses**

431 Analysis will be performed according to the Estimands Framework⁵⁹ with a statistical analyst
432 blinded to group allocation. All outcomes and analyses are prospectively categorised as primary,
433 secondary or exploratory. For the primary hypothesis, a linear model with baseline value, sex and
434 BMI (≥ 30 vs < 30 kg.m⁻²) as covariates and treatment condition as a fixed factor will evaluate the
435 treatment effect on KOOS₄ at 12 weeks. A linear mixed model utilising repeated measures at all
436 time-points for secondary hypotheses will allow non-biased estimates of treatment effect in the
437 presence of any potential missing cases, providing data are missing at random. A sensitivity
438 analysis using pattern-mixture model to investigate the deviation from the missingness-at-
439 random assumption will be carried out⁶⁰. For secondary binary outcomes (e.g., treatment
440 success), mixed-effect logistic regression models will be used to assess the effect of treatment. A
441 subsequent analysis of participants classified as adherent to the protocol will be performed.

443 **Healthcare resource use**

444 Healthcare resource utilisation (e.g., hospitalisations, medical imaging, healthcare visits,
445 medication use) will be assessed by participant self-report to estimate costs associated with the
446 trial programs (e.g., hospital admissions, medication use, clinician visits, imaging tests, out-of-
447 pocket expenses).

448

449 **Process Evaluation**

450 Semi-structured interviews will be conducted on a subset of consenting participants (until data
451 saturation reached) at 6 months. Interviews will explore experiences, knowledge and
452 understanding of interventions received including potential benefits; acceptability and perceived
453 effectiveness of the intervention; and reasons for adhering (or not) to the allocated diet.
454 Purposive sampling will be used to recruit interview participants who will then be stratified based
455 upon characteristics and outcomes of the trial (good outcome; poor outcome). Interviews will be
456 audio recorded, transcribed and analysed using Framework Analysis⁶¹. Data will be coded and an
457 inductive thematic analysis will be applied until no new themes emerge.

459 *Patient and public involvement*

460 Participants and clinicians co-designed the anti-inflammatory intervention, research questions
461 and study methods. This input was gained from: i) qualitative interviews with participants from
462 the pilot study as part of formal process evaluation strategies²⁵; ii) participant and clinician focus
463 groups providing feedback on study recruitment material and participant handbooks; and iii)
464 discussion with experienced clinicians managing knee OA and dietary intervention strategies as
465 part of FEAST development. Patients and clinicians will provide input into the dissemination of
466 study results by assisting with the decision on what information to share and in what format.

468 **ETHICS AND DISSEMINATION**

469 This study complies with the Declaration of Helsinki and has received approval from La Trobe
470 University Human Ethics Committee (HEC-22044). Written informed consent will be obtained
471 from participants prior to enrolment (Supplementary File 1). Anti-inflammatory diets are
472 associated with minimal and transient adverse events, thus there are minimal safety
473 considerations associated with this trial.

474
475 Study outcomes will be widely disseminated through a variety of sources. Results will be reported
476 in peer-reviewed publications and presented at key national and international conferences. Only
477 aggregate data will be reported. A lay summary report will be available for study participants.
478 Any important protocol amendments will be reported to the approving ethics committee,
479 registered at ANZCTR and communicated in the primary RCT paper. Any serious adverse events
480 will be recorded and reported to the approving ethics committee.

481

DISCUSSION

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.

The evaluation of a non-pharmacological anti-inflammatory dietary program to improve pain, symptoms, and quality of life for individuals with OA could have important individual and socio-economic benefits – decreased healthcare dollars spent on managing OA and reduced surgery waiting lists. Another benefit is that anti-inflammatory diets are also effective at combating metabolic syndrome, a key risk factor for chronic diseases, and thus the benefits from treating OA could stretch further to improving other medical co-morbidities⁶². This fully-powered RCT represents a crucial step towards the development of a sustainable and cost-effective therapy that can both supplement and complement existing treatment strategies to optimise OA outcomes.

AUTHOR CONTRIBUTIONS

AGC, BLD, PB and JLK conceived the study and obtained funding. AGC, BLD, PB, and JLK designed the study protocol with input from LL, JJH and ABM. ADL provided statistical expertise and will conduct primary statistical analysis. MDH provided blood analysis expertise and will lead inflammatory and metabolic marker analyses. HGM and NPW assisted with participant recruitment from their clinical population with knee osteoarthritis. LL drafted the manuscript with input from AGC, JJH, BLD, PB, JLK, AA, MDH, ADL, ABM, HGM and NPW. All authors read and approved the final manuscript.

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COMPETING INTERESTS STATEMENT

1
2 515 PB is the founder of Defeat Diabetes and author of “A Fat Lot of Good”. PB contributed to study
3
4 516 design but has no role in study execution, data management, analysis or the decision to publish.
5
6 517 The NHMRC has no role in study design and will not have any role in its execution, data
7
8 518 management, analysis and interpretation or on the decision to submit the results for publication.
9
10 519 JLK is an editor of the British Journal of Sports Medicine (British Medical Journal Group). AGC is
11
12 520 an associate editor of British Journal of Sports Medicine (British Medical Journal Group). All other
13
14 521 authors have no competing interests.
15
16 522

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17
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19
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21
22 526 Melbourne Pathology for providing pathology collection kits and analysis of biomarkers from
23
24 527 blood specimens.
25
26 528

27 529 **FIGURE LEGENDS**

28
29 530 **Figure 1.** Flow of participants through the trial. DXA, Dual X-ray Absorptiometry; KOOS, Knee
30
31 531 injury and Osteoarthritis Outcome Score
32
33 532 *Optional qualitative interview for process evaluation at 6 months
34
35 533
36
37 534

38 535 **SUPPLEMENTARY FILES**

39
40 536 **Supplementary File 1.** Patient information and consent form
41
42 537 **Supplementary File 2.** Standard Operating Procedures for blood collection, processing and
43
44 538 storage
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48 49 540 **REFERENCES**

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Participant Information Sheet/Consent Form

Interventional study - Adult providing own consent

Title	Optimising outcomes for people with knee pain through food: FEAST randomised controlled trial
Short Title	The FEAST trial
Ethics Reference Number	HEC22044
Project Sponsor	La Trobe University
Coordinating Principal Investigator/ Principal Investigator	Dr Adam Culvenor (School of Allied Health, Human Services and Sport (SAHHSS), La Trobe University)
Associate Investigator(s)	Dr Brooke Devlin (School of Human Movement and Nutrition Sciences, University of Queensland) Prof. Peter Brukner (SAHHSS, La Trobe University) Ass. Prof. Joanne Kemp (SAHHSS, La Trobe University) Prof. Kay Crossley (SAHHSS, La Trobe University) Dr Andrea Mosler (SAHHSS, La Trobe University) Dr Josh Heerey (SAHHSS, La Trobe University) Ms Lynette Law (PhD student, SAHHSS, La Trobe University) Ms Amanda Attanayake (SAHHSS, La Trobe University)
Location	La Trobe University

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project because you have knee pain. This research project aims to assess the effectiveness of two different programs provided through advice and education by a qualified dietitian to improve your knee pain, function and quality of life.

This information sheet tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the project. Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Your participation is voluntary

Participation in this research is completely voluntary and there will be no cost to you. If you don't wish to take part, you don't have to. If you decide you want to take part, you will be given a copy of this Participant Information Sheet and asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participation Information Sheet and Consent Form to keep.

2 What is the purpose of this research?

As you may be aware, knee pain is very common and is often associated with knee osteoarthritis. Osteoarthritis is the most common form of arthritis and is a leading cause of disability in Australia. Currently, there is no cure for osteoarthritis, therefore it is important to investigate treatments that can improve the main symptoms associated with osteoarthritis: pain, swelling, stiffness and movement difficulties. We will recruit 140 adults who have knee pain.

This study is being conducted by researchers at La Trobe University and is partly funded by the National Health and Medical Research Council (NHMRC) of Australia and Dr Peter Brukner. All assessments and consultations will be at **no cost** to you.

3 Who can participate?

You can participate in this study if you meet all the following:

- Between 45-85 years of age and understand written and spoken English
- Activity-related knee pain on most days of the past month
- Knee pain for at least 3 months
- No morning knee stiffness, or morning stiffness that lasts less than 30mins
- Willing to complete the assigned 12-week eating program and attend all appointments (detailed below)

You are not eligible and cannot participate in this study if you meet any of the following:

- Knee pain not primarily due to osteoarthritis (e.g., fibromyalgia, referred pain)
- Bilateral knee replacement
- Already strictly following a specific diet (e.g., low-carb, paleo, Mediterranean, Vegan)
- Received treatment from a dietitian, or knee injection, in the past 3 months
- Experienced ≥ 5 kg weight loss in the past 3 months or body weight ≥ 200 kg
- Planning to have knee surgery in the next 6 months
- Pregnant or breastfeeding
- History of psychiatric or eating disorder (excluding anxiety/depression) or bariatric surgery

4 What does participation in this research involve?

This study will be conducted over 6 months in total (see flowchart on next page).

Pre-baseline (online/phone) appointment

You will be asked to attend a 30-minute Zoom/telephone appointment prior to your first face-to-face appointment. At this appointment, we will discuss the consent form, outline the fasting process needed to complete your blood test and DEXA scan, and answer any questions you might have. We will also explain how to complete a 3-day food diary, which will be done using a smart phone application or paper-based food diary (personal preference).

Baseline (first) appointment

This appointment will be arranged at a convenient time for you at La Trobe University, Bundoora and will take approximately 2 hours. You will be asked to not eat/drink anything or conduct any exercise in the morning of your appointment (i.e., fasting for 12-hours) for the purpose of a blood test. At the appointment, we will assess your:

- Height, weight, waist circumference and blood pressure
- Body composition measured via a Dual-energy X-ray Absorptiometry Scan (DEXA).
This involves laying on the scanner bed for ~7 mins. The machine uses small doses (<1% yearly dose) of radiation to assess tissue density (how much muscle and adipose tissue you have). The total effective dose of radiation has been calculated by a Medical Physicist (see risks below). Light clothing with no metal (e.g., zips, clips, underwire) should be worn (gown provided if needed). All measures will be taken by trained

researchers who hold Victorian Government radiation licenses and comply to the Code of Practice set out by the Australian Radiation Protection and Nuclear Safety Agency.

- Blood test: A trained researcher qualified to take blood will collect a small amount of blood (~25 mL, equivalent to ~4 teaspoons) from a forearm vein to assess inflammation levels.
- Questionnaires assessing your pain, activity level and quality of life and food intake
- Functional tests: i) how many times you can stand from a chair in 30 secs; and ii) how fast you can walk 40 metres.

We will provide a snack/drink as soon as you complete the DEXA and blood tests.

Random assignment to one of two different treatments

At the end of the first appointment at La Trobe University, you will be randomly assigned (50:50 chance, like a coin toss) to receive a program (from qualified dietitians) to either:

- minimise processed foods that are known to promote inflammation and optimise foods shown to reduce inflammation; or
- minimise foods that are known to be high in fat content.

This means neither you nor the researchers will be able to choose which group you are assigned to. We do not know which treatment is best; to find out we need to compare the two programs. Although the two programs involve modifying some types of food that you eat, you can eat as much as you like of these foods. **You do not need to restrict the amount of food that you eat.**

Irrespective of which group you are assigned to, you will receive specific education and advice from an Accredited Practising Dietitian (APD) in a dietary consultation at the start of the study (at the end of your first appointment at La Trobe University). Your dietitian will also work with you to develop a personalised management plan to support you throughout the study. You will be asked to follow the program for 12 weeks (but you can continue for as long as you like). We will ask you to record your food intake for 3 days at up to six different times throughout the study.

Support phone calls

To support you throughout the study and answer any questions you have, we will arrange up to four follow-up consultations to be conducted over the phone/online during the 12 weeks. This phone call will take approximately 15-20 minutes. At these times, we will also ask you to complete some of the same questionnaires online (via a secure link provided by e-mail).

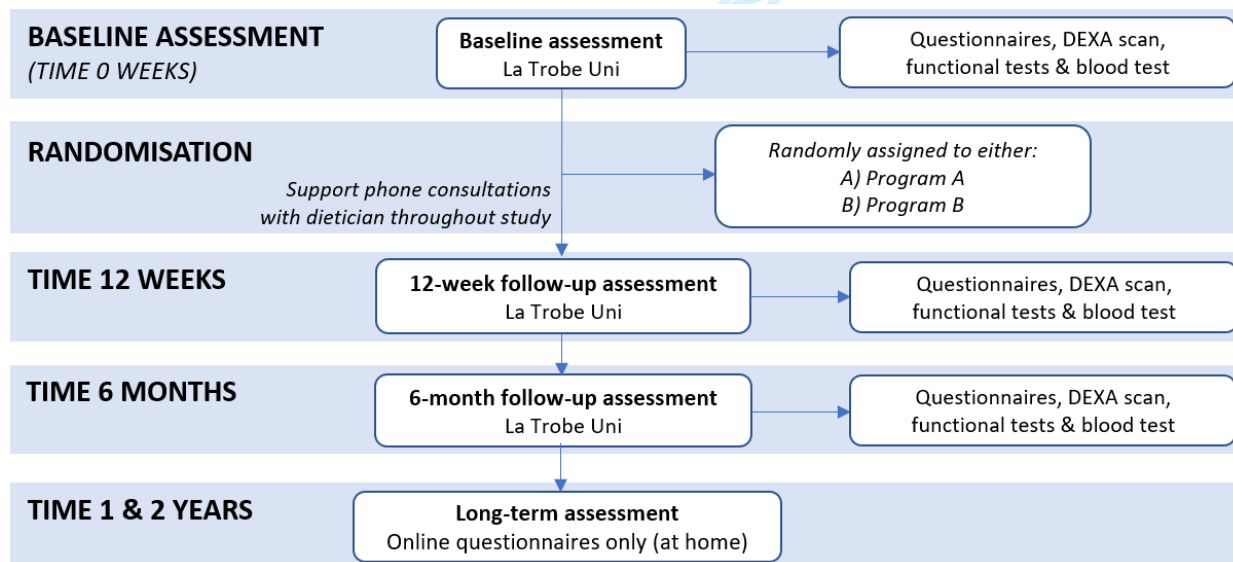


Figure 1. Flowchart of study assessments

Follow-up appointments

So that we can assess the results of the program you have been assigned, we will ask you to return for face-to-face appointments at La Trobe University at **12 weeks and 6 months after your first appointment.** These follow-up appointments will be like the first appointment where

1 we will do all the same tests and questionnaires. You will need to fast (not eat/drink anything) the
2 morning of your appointment for the blood test. You will have another dietary consultation with
3 the study dietitian who will provide support for you to continue with the program you have been
4 assigned. You should allow about 2 hours for these appointments. To assess longer-term results,
5 we will ask you to complete the same online questionnaires at 1 and 2 years after your first
6 appointment. The total time commitment for participating will be approximately 6-8 hours.
7

8
9 There are no additional costs associated with participating in this research project. All medical
10 care and tests (i.e., dietitian consultations, DEXA scan, blood tests) required as part of the
11 research project will be provided free of charge. The results of the DEXA scan and blood tests
12 will not be used to diagnose health conditions, but only to evaluate the effects of the intervention.
13 We will provide you with your individual results when the DEXA and blood analyses are completed
14 at the end of the study. Your travel costs to attend the assessments will be reimbursed up to \$100.
15

16
17 At the end of the first 12 weeks, or after 6-12 months, we may also ask if you are willing to have
18 a separate interview with one of the study researchers (this interview is optional and you can take
19 part in the study without needing to complete the interview). The purpose of this interview is to
20 seek feedback on the study treatments, satisfaction with the process received and whether there
21 are any suggestions for improvement. The interview will take approximately 30 minutes, but you
22 can cease the interview at any time. To ensure responses are correctly interpreted, responses to
23 questions will be audio recorded and transcribed. Audio recording transcriptions will be completed
24 by 'Transcription Australia' on their secure, encrypted Australian-based software. Although voice
25 in your audio recording could lead to your identification, this file will not be used during analysis.
26 Instead, a re-identifiable transcription, which you will have the opportunity to check for accuracy,
27 will be used for analysis. Re-identifiable means that we will use a code number and not your name
28 on data collected to ensure your anonymity. Following the completion of analysis of this
29 transcription, the audio file associated with your interview will be deleted. After analysis, overall
30 findings and conclusions from all interviews will also be sent to you, to allow an opportunity to
31 make any further comments. We will seek around 40 participants to be interviewed. It is your
32 decision or not whether you wish to be interviewed.
33

34 35 **5 What are the alternatives to participation?**

36
37 You do not have to take part in this research project to receive treatment for your knee. Other
38 options are available; these include seeing a physiotherapist or dietitian (e.g., private or public
39 health centre). The research team will discuss these options with you before you decide to take
40 part in this project. You can also discuss the options with your doctor, dietitian or physiotherapist.
41

42 43 **6 What are the possible benefits of taking part?**

44
45 We cannot guarantee or promise that you will receive any benefits from this research. However,
46 possible benefits may include improvement of pain, function, quality of life, physical activity, and
47 confidence in your knee. You may gain valuable insight into how to manage your food intake and
48 specific anti-inflammatory and low-fat foods, nutrients and eating habits. The expected benefit to
49 society is the development of a drug-free and non-invasive treatment option to help manage pain
50 and disability associated with osteoarthritis. This will give doctors and patients alternative ways
51 to manage knee pain, which in turn may lead to improvements in the quality of life for patients.
52
53

54 55 **7 What are the possible risks and disadvantages of taking part?**

56
57 With any medical treatment there are: (i) risks we know about; (ii) risks we don't know about; and
58 (iii) risks we don't expect. We have listed the risks we know about below. You may have none,
59 some or all the effects listed below, and they may be mild, moderate or severe. If you have any
60 of these side effects, or are worried about them, talk with the study coordinator.

Possible Side Effect	How often is it likely to occur?	How severe might it be?	How long might it last?
Emotional distress due to involvement in research and completion of questionnaires	Rarely; although can occur when completing study questionnaires	Minimal	While completing the study questionnaires
Emotional distress due to diet assessment	Rarely; although can occur when assessing food intake prior to, or during, appointments	Minimal	While completing the food diary or assessment
Discomfort due to body measurements	Can occur while measurements are done by your dietitian or researcher	Minimal Mild	During appointment only
Discomfort due to blood test	Rarely; while blood is being collected	Mild	Bruising or swelling may last 1-3 days
Exposure to ionising radiation	1x 7-minute scan at initial, 12-week and 6-month appointment	Minimal	Effect too small to measure
Tiredness/change in bowel patterns with change in diet	Any change in diet can make you feel tired or have different bowel patterns	Minimal	1-2 weeks
Contraction of COVID-19	Can occur during the face-to-face assessments	Minimal Moderate	1-2 weeks

If you become upset or distressed because of your participation in the research, the study coordinator together with the qualified dietitian will assist you with appropriate support. We can also provide you information about services you can access to seek help for emotional distress.

Risks associated with completing study questionnaires and diet assessment

Completing questionnaires about your knee pain, function, quality of life and dietary intake may cause emotional distress. If you begin to feel upset or distressed when completing your questionnaires or dietary assessment, please let a member of the research team know. We will provide you with the appropriate support, including a document outlining services you can access to help with your emotional distress.

Risks associated with blood test

Having a blood sample taken may cause some discomfort or bruising. On very rare occasions, the blood vessel may swell, or blood may clot in the blood vessel, or the spot from which blood is taken could become inflamed. Some people may feel light-headed when having blood taken and may occasionally faint. Very rarely, there could be a minor infection or bleeding. A qualified person will take a very small amount of your blood (max 30mL each appointment (normal blood donation is 500mL)) using stringent infection control procedures. If you notice increased redness, swelling or other signs of infection in the days following your assessment, tell us immediately.

Risks associated with eating low-inflammatory foods or low-fat foods

As you adjust to the eating program you are assigned to, you may experience feelings of tiredness and/or changes in bowel habits and patterns. The researchers will assess your diet and ensure you are meeting your energy and nutrient needs throughout the study intervention. This eating program may be different than your normal diet and therefore influence your usual weekly shopping bill and expenses. As part of the consultations, you will be provided with some advice on how to follow the diet on a budget if required to ensure there is minimal financial burden.

Exposure to ionising radiation

If you choose to take part in this research, you will undergo three 7-minute DEXA scans (first, 12-week and 6-month assessments). DEXA scans are a non-invasive, fast and simple procedure. This research study involves exposure to a very small amount of radiation from a DEXA scan that you would not normally receive. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose you will receive from all of these DEXA scans is approximately 0.03 mSv. At these

1 dose levels, no harmful effects of radiation have been demonstrated as any effect is too small to
2 measure. The risk is believed to be minimal.
3

4
5 The scans we are taking are for research purposes and are not intended to be used like scans
6 taken for a full clinical examination or to be used to help diagnose, treat or manage a particular
7 condition. The whole-body DEXA scan may identify participants with a low bone mineral density.
8 However, a whole body DEXA scan is not the established method for detecting low bone mineral
9 density. Therefore, as a precaution if you are identified as having a low bone mineral density you
10 will be encouraged to make an appointment with your General Practitioner to discuss the results.
11

12 Have you been involved in any other research studies that involve radiation? If so, please tell us.
13 Please keep information contained within this Patient Information Sheet about your exposure to
14 radiation in this study, including the radiation dose, for at least 5 years. You will be required to
15 provide this dose to researchers of any future research projects involving exposure to radiation.
16

17 **Contraction of COVID-19**

18 You may be at risk of contracting COVID-19 during one of the face-to-face appointments at La
19 Trobe University. Prior to attending La Trobe University, you will be screened for signs and
20 symptoms of COVID-19 by a member of the research team. You will also need to be fully
21 vaccinated (or hold a valid medical exemption) to be able to attend La Trobe University for your
22 assessments. The research team will put in place the appropriate control measures to reduce the
23 risk of COVID 19 transmission. The risk is believed to be minimal.
24

25 **8 What if I withdraw from this research project?**

26
27 You are under no obligation to continue with the research study. You may change your mind at
28 any time about participating in the research. People withdraw from studies for various reasons,
29 and you do not need to provide a reason.
30

31
32 You can withdraw from the study at any time by completing and signing the 'Participant
33 Withdrawal of Consent Form'. This form is provided at the end of this document and is to be
34 completed by you and supplied to the research team if you choose to withdraw at a later date.
35

36
37 If you withdraw from the study, you will be able to choose whether the study will destroy or retain
38 the information it has collected about you. Information about you that has already been analysed
39 (i.e., once you have been allocated to either program), may not be able to be destroyed to ensure
40 accurate and unbiased study reporting. Personal details collected, such as your name and contact
41 details, can be destroyed at any time upon study withdrawal.
42

43 **9 What happens when the research project ends?**

44
45 At the completion of the research project, you may continue to use the resources provided and to
46 follow the eating program principles if you choose to. If requested, we will provide you with your
47 individual results including your body composition (DEXA) assessment and whole study results.
48 We, or other researchers, may also use coded information (so that you cannot be identified)
49 collected for this research study in future related studies. If you consent (tick the box on the
50 consent form) to be contacted for future related research, we will store your contact details (name,
51 address, phone number, email) on the secure La Trobe University research drive, only accessible
52 to members of the research team, and may contact you about future related research projects.
53
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56 **Part 2 How is the research project being conducted?**

57 **10 What will happen to information about me?**

1 By signing the consent form you agree to the relevant research staff collecting and using personal
2 information about you for the research project. Any information obtained in connection with this
3 research project that can identify you will remain confidential and securely stored. It will be
4 disclosed only with your permission, or in compliance with the law.
5

6 **Storage, retention and destruction**

7 The anonymity of your participation is assured with our procedure, in which a code number (not
8 your name) will identify you. Data will be kept securely at La Trobe University in a locked filing
9 cabinet and password protected research computer. Identifiable data will be stored for 15 years,
10 then destroyed (electronic records deleted, paper-files shredded). Data will be strictly handled
11 confidentially under guidelines set out by the National Health and Medical Research Council. The
12 principal investigator (Dr Adam Culvenor) is responsible for maintaining this confidentiality.
13

14
15 In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have
16 the right to request access to your information collected and stored by the research team. You
17 also have the right to request that any information with which you disagree be corrected.
18

19 The results of this project may be published and/or presented in a variety of forums and used by
20 research students to obtain a research degree. In any publication, presentation or data files
21 shared with other researchers, information will be provided in such a way that you cannot be
22 identified, except with your permission.
23

24 **11 Who is organising and funding the research?**

25 This research project is being conducted by Dr Adam Culvenor and a team of researchers. It has
26 been funded by the NHMRC (GNT2008523) and Dr Peter Brukner. Dr Peter Brukner is also an
27 investigator on the project and has written a book and developed an app that will be used as part
28 of the study. He will not be involved in data collection, analysis or the decision to publish results.
29 No member of the research team will receive a personal financial benefit from your involvement
30 in this research project (other than their ordinary wages).
31

32 **12 Who has reviewed the research project?**

33 All research in Australia involving humans is reviewed by an independent group of people called
34 a Human Research Ethics Committee (HREC). The ethical aspects of this research project have
35 been approved by the HREC of La Trobe University Human Ethics Committee.
36

37 This project will be carried out according to the *National Statement on Ethical Conduct in Human
38 Research (2018)*. This statement has been developed to protect the interests of people who agree
39 to participate in human research studies.
40

41 **13 Further information and who to contact**

42 For all enquiries, you can contact the Clinical Trial Manager, during business hours:
43 Dr Adam Culvenor, Senior Research Fellow in Physiotherapy, La Trobe University
44 Telephone: 03 9479 5116; E-mail: a.culvenor@latrobe.edu.au
45

46 If you have any complaints about any aspect of the project, the way it is being conducted or any
47 questions about being a research participant in general, then you may contact:
48

49 Reviewing HREC: La Trobe University Human Research Ethics Committee
50 Complaints Contact: Senior Human Ethics Officer, Ethics and Integrity, Research Office
51 Telephone: 03 9479 1443 E-mail: humanethics@latrobe.edu.au
52

53 * Please quote the application reference number HEC22044
54



Consent Form - *Adult providing own consent*

Title	Optimising outcomes for people with knee pain through food: FEAST randomised controlled trial
Short Title	The FEAST trial
Ethics Reference Number	HEC22044
Project Sponsor	La Trobe University
Coordinating Principal Investigator/ Principal Investigator	Dr Adam Culvenor (La Trobe University)
Associate Investigator(s)	Dr Brooke Devlin (University of Queensland) Prof. Peter Brukner (La Trobe University) Ass. Prof. Joanne Kemp (La Trobe University) Prof. Kay Crossley (La Trobe University) Dr Andrea Mosler (La Trobe University) Dr Josh Heerey (La Trobe University) Ms Lynette Law (PhD student, La Trobe University) Ms Amanda Attanayake (SAHSS, La Trobe University)
Location	La Trobe University

Consent Agreement

I have read the Participant Information Sheet and I understand the purposes, procedures and risks of the research described in the project.

I understand that data files may be shared with other researchers, and that information will be provided in such a way that I cannot be identified, except with my permission.

I have had an opportunity to ask questions and I am satisfied with the answers I have received. I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. I agree that data gathered for the study may be published provided my name or other identifying information is not used.

- I wish... / do not wish... to receive results of the study
- I consent... / do not consent... to be contacted for future related research
- I consent... / do not consent... to have my interview responses audio-recorded/transcribed.
- I consent... / do not consent... to have my samples/data used in future research

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Researcher[†]

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Researcher[†] (please print) _____

Signature _____ Date _____

[†] An appropriately qualified member of the research team must provide the explanation of, and information concerning, the research project.

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3 FEAST Project
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6 **Standard Operating Procedure**
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9 **Blood collection, processing, handling, and storage procedures**
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For peer review only

1.1 Purpose

The purpose of the current SOP is to provide step-by-step instructions on the exact procedures that the research team needs to follow for conducting venous blood collection for biochemical analysis at baseline and follow-up examination.

1.2 General procedures for venous blood collection

Venous blood samples will be obtained from each participant for biochemical analysis following a 12-hour overnight fast, at baseline (T1), 12 weeks (T2) and 6 months (T3) (figure 1)

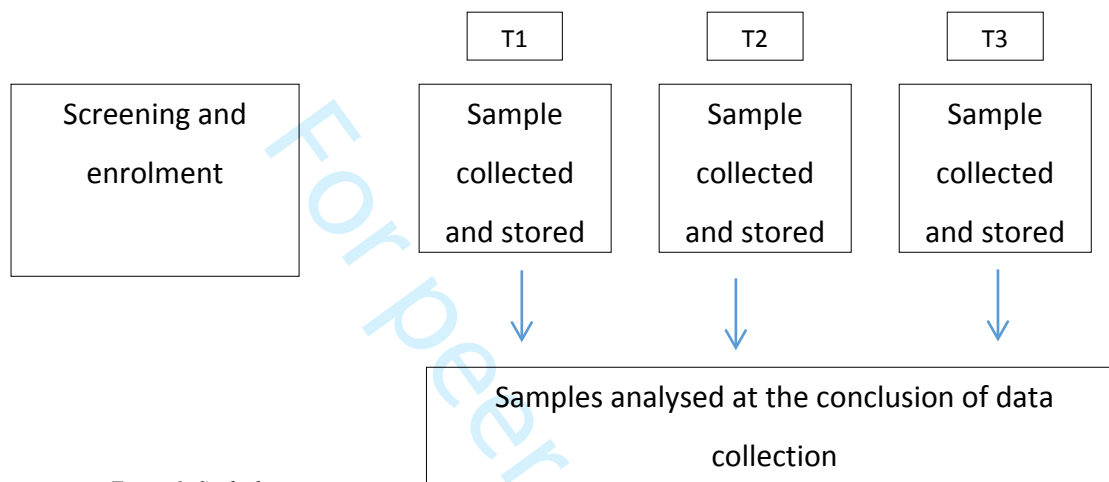


Figure 1: Study design

The researcher will perform venepuncture to obtain no more than 30mL of blood.

1.2.1 Consumables and supplies required for performing venepuncture

The consumables and supplies that will be used for performing the venepuncture in the study are the following:

- Disposable Latex gloves must be worn by the researcher and anyone else assisting with blood collection.
- Alcohol swab will be used to clean the venepuncture site.
- Winged steel needles appropriate for adults with an extension tube (a butterfly) will be used. The butterfly will have either a syringe or an evacuated tube with an adaptor. Sterile gauze pads will.....
- Adhesive hypo allergic bandages (plasters or Band-Aids) will be applied to the puncture site to minimize the risk of infection.
- Plastic Bag for Waste will be used to dispose all of the biohazardous waste generated as well as a sharps biocontainer to dispose of all needles.

1.2.2 Steps in obtaining venous blood from the participant

The steps for obtaining venous blood samples from the study participants are provided below:

Step 1: Complete general preparation.

- Find an indoor site to encourage privacy during blood collection. The site should have a table or other piece of furniture with a flat surface where you can lay out all consumables/ supplies. An examination bed should be readily available if the respondent feels faint and needs to lie down.
- Ensure that each subject has completed a 10-hour fast.

- Wash and dry hands, put on gloves before initiating blood collection from the participant.
- Take out a clean absorbent paper sheet and spread it over a flat surface to lay out consumable and supplies.

Step 2: Prepare the participant for the venepuncture.

- The individual should be seated comfortably in a chair with arm extended on the slanting armrest to form a straight line from the shoulder to the wrist. The arm and elbow should be supported firmly by the armrest and should not be bent at the elbow.
- Ask each volunteer if they have a history of fainting. If so, ensure that the blood sample is only drawn whilst the subject is lying down on a bed.
- Describe to the participant exactly what will be done during the collection of the blood sample.

Step 3: Prepare the venepuncture site.

- Apply (tighten) tourniquet.
- Ask the participant to close his/her hand so that the veins will become more prominent and thus easier to enter. Vigorous hand exercise or "pumping" should be avoided.
- Select the vein site. Palpate and trace the path of veins several times with the index finger. If superficial veins are not readily apparent, blood can be forced into the vein by gently massaging the arm from wrist to elbow. Several sharp taps at the vein site with index and second finger will cause the vein to dilate.
- Loosen tourniquet.
- The venepuncture site must be cleansed once with an alcohol swab to prevent any chemical or microbiologic contamination of either the patient or the specimen.
- Check equipment, tube selection and thread needle (or butterfly) securely onto tube holder (barrel).
- Re-apply the tourniquet and relocated vein position and direction. A tourniquet allows the veins to fill with blood, thus making the veins more prominent and easier to enter. Do not leave the tourniquet on for longer than 1 minute otherwise it may result in either hemoconcentration or variation in blood test values.
- Remove needle cover and check bevel is orientated uppermost.

Step 4: Blood drawing

- Puncture the skin 3–5 mm away from the vein; this allows good access without pushing the vein away.
- If the needle enters alongside the vein rather than into it, withdraw the needle slightly without removing it completely, and angle it into the vessel.
- Insert the tube into the holder and commence filling the tubes.
- Draw blood slowly and steadily.
- Release the tourniquet as soon as blood flow is established. Tourniquet release allows the blood circulation to return to normal and also reduces bleeding at the venipuncture site.
- Remove the tube from the holder and invert (8-10 times) to mix the blood with tube additives. Place blood samples on ice if required..
- Place a cotton wool above the venepuncture site, withdraw the needle and apply pressure.
- Dispose of needle in a sharps container.
- Check site and apply an adhesive bandage.
- Label all tubes immediately.



1.3 Blood processing and handling

1.3.1 Centrifuge procedure

Collected venous blood will be centrifuged and the extracted plasma and/or serum will be pipetted into aliquots according to the blood collection protocol.

- Set up in a well-ventilated environment, on a horizontally levelled and rigid surface with adequate load-bearing capacity.
- As safety zone maintain a clear radius of at least 30 cm around the centrifuge. Do not place any dangerous substances within this security zone.
- Open the centrifuge door by pressing the open button.
- Place the remaining tubes containing blood into appropriate sized adapters.
- Place the tubes containing water in opposite adapters, where they should mirror the placement of the tubes holding blood.
- Never place both tubes housing water and blood into the same adapters but should be placed in different adapters for even weight distribution.
- Place the adapters carefully and gently into the rotor buckets
- Seal the buckets with the lids and close the centrifuge.
- Use only with rotors which have been loaded properly.
- Make sure the rotor is locked properly into place before operating the centrifuge.
- Never overload the rotor.
- Never start the centrifuge when the centrifuge door is open.
- Do not lean on the centrifuge.
- Do not place anything on top of the centrifuge during a run.
- Gently close the centrifuge door. The centrifuge door mechanism will click and lock in place.
- Turn on the centrifuge by pressing the start button.
- Select the required speed and time from preprogrammed setting or manually using the arrow keys (3000xg for 10 mins for each tube).

Once the centrifuge has completely stopped spinning wait for an audible sound and then open the centrifuge. Remove the tubes from the centrifuge and place them in a tube rack.

1.3.2 Handling of collected blood

Three different types of test tubes will be used per study participant to collect venous blood. The collected blood will be designated for whole blood, or plasma and serum separation. One 8ml EDTA tube (with added anticoagulant) will be used to collect whole blood for analysis, one 6ml heparin tube will be used for plasma extraction, and one 8.5ml SST tube will be used for serum extraction. Tubes will be labelled with study timepoint (T1, T2 or T3), participant ID, and type of sample. All information regarding blood collection tubes is presented in Table 1.

Table 1. Volume of blood in different test tubes

Test tube	Blood volume	Designated for:
EDTA tube	6 ml	Whole blood
Heparin gel tube	6 ml	Heparin plasma extraction
SST tube	8.5 ml	Serum extraction
Total blood:	22.5ml	

- The whole blood sample (6ml) collected in the EDTA tube will be stored at -80°C, as indicated in Table 2.

Table 2. Volumes and use of EDTA whole blood sample.

Whole blood aliquot no.	EDTA volume	Designated for the analysis of:
1	6 ml	HbA1c

- The blood (8.5ml) collected in the SST tube will be left to separate at room temperature for 20 mins and then centrifuged at 3000 rpm for 10 min. The extracted (heparin) plasma will be pipetted into 4 aliquots of 1 ml (considering a 50% efficiency of centrifugation in plasma extraction). One aliquot of 1ml will be used for determining glucose, insulin, lipids, LFT and hsCRP, while the 3 aliquots of 1ml each will be stored at -80°C, as indicated in Table 3.

Table 3. Volumes and use of SST plasma aliquots.

Plasma aliquot no.	EDTA plasma volume	Designated for the analysis of:
1	1000 µl	Glucose, insulin, lipids, LFT, hsCRP
		Designated for:
2	1000 µl	Storage at -80°C
3	1000 µl	Storage at -80°C
4	1000 µl	Storage at -80°C

- The blood (6 ml) collected in the heparin tube will be centrifuged at 3000 rpm for 10 min and the extracted plasma will be pipetted into 3 aliquots of 600 µl (considering a 50% efficiency of centrifugation in plasma extraction). One aliquot of 600 µl will be used for determining cytokine concentrations, while the remaining 3 aliquots of 500 µl each will be stored at -80°C, as indicated in Table 4.

Table 4. Volumes and use of heparin plasma aliquots.

Plasma aliquot no.	Heparin plasma volume	Designated for the analysis of:
1	1ml	Cytokines (IL-1β, IL-6, IL-8, IL-10, and TNF)
		Designated for:
2	1ml	Storage at -80°C
3	1ml	Storage at -80°C
4	1ml	Storage at -80°C

NOTE: It is essential that ONLY NON-HAZARDOUS waste be placed in the wastepaper/ general rubbish bins. Pipette tips should be disposed in sharps containers, whereas laboratory and associated waste directly involved in specimen processing (i.e blood collection tubes, gloves etc) must be disposed in biological waste bags.

1.4 Blood storage

Eppendorf tubes or screw cap tubes must be clearly labelled with identification, media used and date, placed in a freezer well rack and should not be stored for long periods on a bench, but must be transferred with an ice esky box to a dedicated storage area (i.e. refrigerator, cold room or cupboard) as soon as possible.

Laboratory coats must be removed and hung up before leaving laboratory areas and should be laundered once a week. Hands must be washed with an antibacterial agent BEFORE leaving laboratory (Hibiclens/Microshield or equivalent, followed by extensive rinsing).

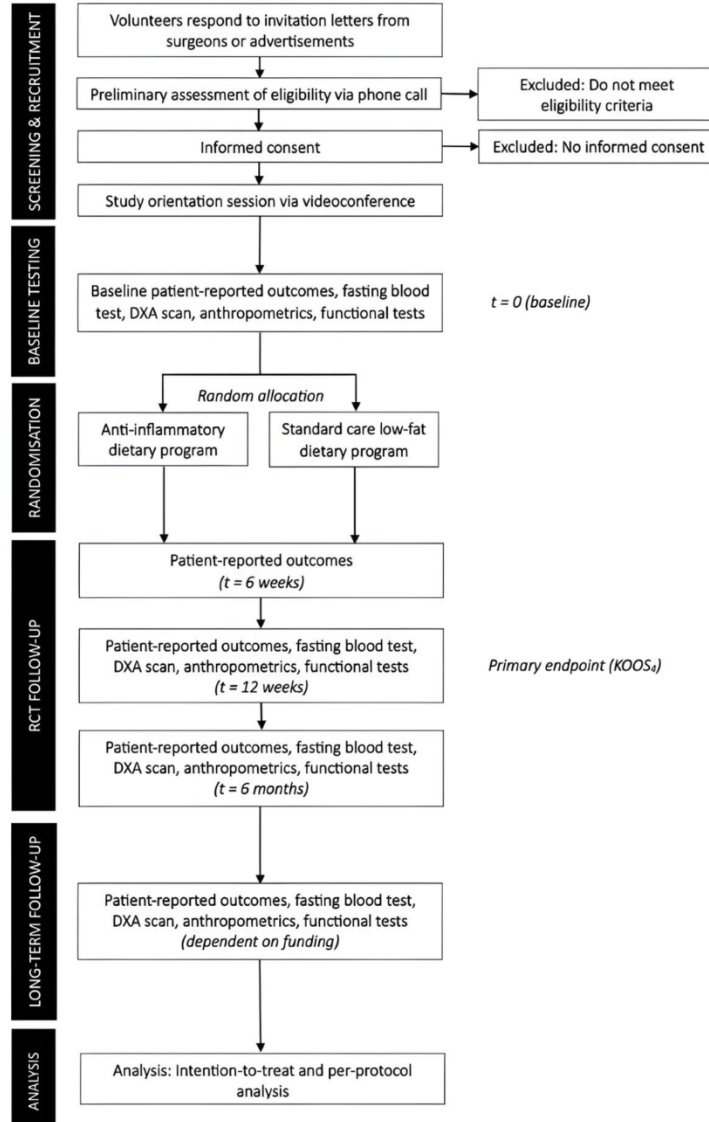


Figure 1. Flow of participants through the trial. DXA, Dual X-ray Absorptiometry; KOOS, Knee injury and Osteoarthritis Outcome Score

*Optional qualitative interview for process evaluation at 6 months

529x695mm (96 x 96 DPI)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	ACTRN1262200 0440729
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			

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4	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
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7	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
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11	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-13, Table 2, Supplementary File 1
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14		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Table 2
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18		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8-13, Table 2
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21		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
22				
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24	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-18, Table 3
25				
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30	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
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34	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19
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38	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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44	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8
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50	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7-8
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55	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
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57	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7-8
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	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
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Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
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	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
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Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
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	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
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	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
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Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
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	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19-20
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Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
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Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
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Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
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4	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20
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8	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20
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11		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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13				
14	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
15				
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18	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
19				
20	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Supplementary File 1
21				
22				
23				
24	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
25				
26	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
27				
28		31b	Authorship eligibility guidelines and any intended use of professional writers	NA
29				
30		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
31				
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38	Appendices			
39	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary File 1
40				
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43	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Supplementary File 2
44				
45				

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-Non Commercial-No Derivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

The effectiveness of an anti-inflammatory diet versus low-fat diet for knee osteoarthritis: the FEAST randomised controlled trial protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-079374.R1
Article Type:	Protocol
Date Submitted by the Author:	22-Jan-2024
Complete List of Authors:	Law, Lynette; La Trobe University, La Trobe Sport and Exercise Medicine Research Centre Heerey, Joshua; La Trobe University, La Trobe Sport and Exercise Medicine Research Centre Devlin, Brooke; University of Queensland, School of Human Movement and Nutrition Sciences Brukner, Peter; La Trobe University, La Trobe Sport and Exercise Medicine Research Centre Kemp, Joanne; La Trobe University, La Trobe Sport and Exercise Medicine Research Centre Attanayake, Amanda; La Trobe University, La Trobe Sport and Exercise Medicine Research Centre Hulett, Mark; La Trobe University, Department of Biochemistry and Chemistry, La Trobe Institute for Molecular Science De Livera, Alysha; La Trobe University, Department of Mathematics and Statistics; The University of Melbourne, School of Population and Global Health Mosler, Andrea; La Trobe University, La Trobe Sport and Exercise Medicine Research Centre Morris, Hayden; Melbourne Knee Centre White, Nathan; Melbourne Knee Centre Culvenor, Adam; La Trobe University, La Trobe Sport and Exercise Medicine Research Centre
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Chronic Disease, REHABILITATION MEDICINE, NUTRITION & DIETETICS

SCHOLARONE™
Manuscripts

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4 1 **The effectiveness of an anti-inflammatory diet versus low-**
5
6 2 **fat diet for knee osteoarthritis: the FEAST randomised**
7
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9 3 **controlled trial protocol**
10
11 4

13 5 Lynette Law¹, Joshua J Heerey¹, Brooke L Devlin², Peter Brukner¹, Joanne L Kemp¹, Amanda
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29 **Word count:** 3,998

1
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4 30 **ABSTRACT**

5
6 31 **Introduction:** Chronic inflammation plays a key role in knee osteoarthritis pathophysiology
7
8 32 and increases risk of comorbidities, yet most interventions do not typically target
9
10 33 inflammation. Our study will investigate if an anti-inflammatory dietary program is superior
11
12 34 to a standard care low-fat dietary program for improving knee pain, function and quality-of-
13
14 35 life in people with knee osteoarthritis.

15 36 **Methods and analysis:** The FEAST (eFEct of an Anti-inflammatory diet for knee oSTeoarthritis)
16
17 37 Study is a parallel-group, assessor-blinded, superiority randomised controlled trial. Following
18
19 38 baseline assessment, 144 participants aged 45-85 years with symptomatic knee osteoarthritis
20
21 39 will be randomly allocated to one of two treatment groups (1:1 ratio). Participants
22
23 40 randomised to the anti-inflammatory dietary program will receive six dietary consultations
24
25 41 over 12 weeks (2 in-person, 4 phone/videoconference) and additional educational and
26
27 42 behaviour change resources. The consultations and resources emphasise nutrient-dense
28
29 43 minimally processed anti-inflammatory foods and discourage pro-inflammatory processed
30
31 44 foods. Participants randomised to the standard care low-fat dietary program will receive
32
33 45 three dietary consultations over 12 weeks (2 in-person, 1 phone/videoconference) consisting
34
35 46 of healthy eating advice and education based on the Australian Dietary Guidelines, reflecting
36
37 47 usual care in Australia. Adherence will be assessed with 3-day food diaries. Outcomes are
38
39 48 assessed at 12 weeks and 6 months. The primary outcome will be change from baseline to 12
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41 49 weeks in the mean score on four Knee injury and Osteoarthritis Outcome Score (KOOS₄)
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43 50 subscales: knee pain, symptoms, function in daily activities and knee-related quality-of-life.
44
45 51 Secondary outcomes include change in individual KOOS subscale scores, patient-perceived
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47 52 improvement, health-related quality-of-life, body mass and composition using dual-energy X-
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49 53 ray absorptiometry, inflammatory (high-sensitivity C-Reactive Protein, Interleukins, Tumour
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51 54 Necrosis Factor- α) and metabolic blood biomarkers (glucose, HbA1c, insulin, liver function,
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53 55 lipids), lower-limb function and physical activity.

54
55 56 **Ethics and Dissemination:** Approved by La Trobe University Human Ethics Committee. Results
56
57 57 will be presented in peer-reviewed journals and at international conferences.

58 58 **Trial registration:** ACTRN12622000440729
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3 59 **Keywords:** Inflammation, Low-carbohydrate, Anti-inflammatory, Pain, Osteoarthritis, Knee,
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5 60 Chronic disease, Rehabilitation, Diet
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11 62 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
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- 13
14 63 • The anti-inflammatory dietary program was codeveloped and piloted with patients and
15 64 clinicians, with the comparison low-fat dietary program representing usual care.
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18 65 • Sufficiently powered trial evaluating change from baseline to 12 weeks (primary endpoint)
19 66 and 6 months facilitating longer-term effectiveness evaluation of the anti-inflammatory
20 67 dietary program.
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24 68 • This trial will evaluate both self-reported and objective outcomes to understand potential
25 69 mechanisms of symptomatic changes.
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29 70 • While outcome assessors are blinded to group allocation, the health professionals
30 71 delivering the interventions and participants are unable to be blinded to group allocation
31 72 due to the type of interventions.
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73 INTRODUCTION

74 Osteoarthritis (OA) is the most common rheumatic disease affecting approximately 15% of
75 the population, with OA of the knee being most prevalent.(1, 2) Knee OA and its associated
76 symptoms can be disabling and lead to substantial societal and healthcare costs.(3) In
77 Australia alone, annual OA-related healthcare expenditure exceeds \$2.1 billion.(4) Although
78 the main symptom of knee OA is pain, individuals with knee OA have an increased risk of
79 other chronic diseases, including cardiovascular disease and diabetes.(5) As many as two-
80 thirds of older adults with knee OA have more than one comorbidity.(6)

81
82 Clinical guidelines for knee OA recommend exercise-therapy and weight-loss as first-line
83 management strategies due to their excellent safety profile and therapeutic effects similar to
84 commonly used analgesics.(3, 7) However, the effectiveness of exercise-therapy has recently
85 been questioned due to its lack of benefit over an open-label placebo,(8) and findings that
86 one-third of people completing an exercise program do not achieve a clinically meaningful
87 improvement in pain.(9, 10) Weight-loss programs in those who are overweight or obese
88 typically consist of caloric restrictive diets, which are challenging to adhere to and sustain.(11)
89 A meta-analysis highlighted that, within two years of a calorie-restrictive program, over half
90 of initial weight lost was regained, and by 5 years, this figure jumped to >80%.(12)

91
92 Anti-inflammatory diets provide an alternative to calorie-restrictive approaches by targeting
93 local and systemic inflammation, both contributors to OA disease onset, progression and
94 symptom burden.(13-15) Anti-inflammatory diets are typically high in minimally processed,
95 nutrient rich foods such as fruit, vegetables, spices and extra virgin olive oil, which are dense
96 in nutrients such as polyphenols, carotenoids, fibre, monounsaturated and polyunsaturated
97 fatty acids.(16-19) These nutrients can significantly reduce inflammation even in the absence
98 of weight loss(20) via antioxidant and anti-inflammatory properties by neutralising free
99 radicals and associated cell damage, as well as improved lipid profiles.(16, 17, 21) Omega-3
100 fatty acids, abundant in nuts, seeds and fish, are also a key part of anti-inflammatory dietary
101 approaches and help to achieve a more desirable omega-6 to omega-3 ratio.(22) In contrast,
102 omega-6 fatty acids can be converted into arachidonic acid, a precursor for proinflammatory
103 eicosanoids.(23) An elevated omega-6:omega-3 ratio exacerbates oxidative stress, which

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3 104 increases the risk and severity of chronic disease, including OA.(15) Due to their focus on real
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5 105 foods and consumption to satiety, anti-inflammatory diets are likely more sustainable than
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7 106 traditional calorie-restrictive approaches.(17)
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10
11 108 Anti-inflammatory diets have garnered much interest in recent years due to their
12
13 109 effectiveness in alleviating symptoms and improving biomarkers for a variety of chronic
14
15 110 diseases, including diabetes,(18) cardiovascular disease,(24) epilepsy(25) and rheumatoid
16
17 111 arthritis.(26) Small studies investigating anti-inflammatory diets for knee OA have
18
19 112 demonstrated feasibility and effectiveness in reducing symptoms and inflammation over 12-
20
21 113 16 weeks.(15, 27, 28) To date, no fully powered randomised controlled trial (RCT) has
22
23 114 evaluated the effectiveness of an anti-inflammatory diet in knee OA.
24

25 115
26 116 The primary aim of this RCT is to estimate the average effect of an anti-inflammatory dietary
27
28 117 program compared to a standard care low-fat dietary program on knee-related pain, function
29
30 118 and quality of life in individuals with knee OA. We hypothesise that the anti-inflammatory
31
32 119 dietary program will result in greater improvements in knee-related pain, function and quality
33
34 120 of life after 12 weeks (primary endpoint) and 6 months (secondary endpoint) compared to
35
36 121 the standard care low-fat dietary program. Secondary aims are to assess 12-week and 6-
37
38 122 month effectiveness of the anti-inflammatory dietary program on: i) self-reported global
39
40 123 rating of change and achievement of acceptable symptoms; ii) health-related quality of life;
41
42 124 iii) body mass and composition using dual-energy X-ray absorptiometry (DXA); iv)
43
44 125 inflammatory and metabolic blood biomarkers, global lower-limb function and physical
45
46 126 activity.
47

48 128 **METHODS AND ANALYSIS**

49 129 **Study Design**

50
51
52 130 This protocol describes a pragmatic, 2-arm, parallel-group assessor-blinded superiority RCT
53
54 131 and will be reported according to the Standard Protocol Items: Recommendations for
55
56 132 Interventional Trials (SPIRIT) statement.(29) Reporting of the completed RCT will conform to
57
58 133 the Consolidated Standards of Reporting Trials (CONSORT) statement.(30) The FEAST trial will
59
60 134 be conducted at a single site (La Trobe University) in Melbourne, Australia with the first

1
2
3 135 participant randomised on August 31, 2022 and the final participant anticipated to be
4
5 136 randomised in June 2024. The primary endpoint will be at 12 weeks, with additional follow-
6
7 137 up at 6 months (further longer-term follow-up dependent on funding). The study was
8
9 138 prospectively registered on the Australian and New Zealand Clinical Trial Registry (ACTRN
10
11 139 12622000440729).

12
13 140

14 141 **Patient and public involvement**

16 142 Participants and clinicians co-designed the anti-inflammatory intervention, research
17
18 143 questions and study methods. This input was gained from: i) qualitative interviews with
19
20 144 participants from the pilot study as part of formal process evaluation strategies;(28) ii)
21
22 145 participant and clinician focus groups providing feedback on study recruitment material and
23
24 146 participant handbooks; and iii) discussion with experienced clinicians managing knee OA and
25
26 147 dietary intervention strategies as part of FEAST development. Patients and clinicians will
27
28 148 provide input into the dissemination of study results by assisting with the decision on what
29
30 149 information to share and in what format.

31 150

33 151 **Participants**

35 152 One hundred and forty adults 45-85 years old with chronic knee pain consistent with a clinical
36
37 153 OA diagnosis using criteria from the National Institute for Health and Care Excellence, which
38
39 154 does not require radiographic evidence,(31) will be enrolled (table 1).

40 155

42 156 **Table 1.** Eligibility criteria

Inclusion criteria	Exclusion criteria
Fulfil National Institute for Health and Care Excellence(31) clinical criteria for osteoarthritis:	Knee injection, injury or surgery in the past 3 months
<ul style="list-style-type: none"> • Activity-related joint pain with average knee pain severity ≥ 4 on 11-point numeric rating scale (NRS, where 0 = no pain, 10 = worst pain possible) in the past week; • No morning stiffness or morning stiffness ≤ 30 min; and • Age ≥ 45 years 	

Age \leq 85 years – due to potential safety reasons and additional co-morbidities that may hinder capacity for dietary adherence	Had all eligible knee joints replaced by arthroplasty
History of knee pain on most days of the past month	Planning to have knee surgery in next six months
History of knee pain for at least 3 months	Already strictly following an anti-inflammatory diet (e.g., low carbohydrate, high-fat, paleo, Mediterranean) or strict exclusion diet (e.g., vegan)
Be willing and able to attend 3-4 phone consults and 12-week and 6-month follow-up assessments	Unable to follow anti-inflammatory diet (e.g., medically contraindicated, history of food allergy/hypersensitivity, family reasons)
Able to understand written and spoken English, and to give informed consent	Taking the following diabetic medication that affects blood sugar levels (i.e., insulin, SGLT 2 inhibitors, sulfonylureas) to mitigate the risk of hypoglycaemia/ketoacidosis
	Contraindications for DXA scans (e.g., pregnant, breastfeeding, planning pregnancy in next 6 months, >200kg body weight)
	>5kg weight fluctuation in past 3 months (i.e., unstable weight)
	Dietary intervention (by a qualified dietitian) in past 3 months
	A diagnosed psychiatric disorder (excluding anxiety and depression), eating disorder or past bariatric surgery

157 NRS, numeric rating scale; SGLT, sodium glucose co-transporter; DXA, dual-energy X-ray

158 absorptiometry

159

160 **Recruitment and screening procedure**

161 Trial flow is outlined in figure 1. Participants will be recruited from our network of
 162 collaborating orthopaedic surgeons in Victoria, Australia. Consistent with our prior work in
 163 other musculoskeletal conditions,(32, 33) potentially eligible participants (i.e., individuals
 164 aged 45-85 years with a history of knee pain for which medical care was sought) will be sent
 165 a study information letter inviting them to contact the research team. Additional recruitment
 166 strategies will include advertisements in local newspapers, community/university
 167 magazines/posters, community market stalls and social media.

1
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3 168
45 169 *****FIGURE ONE HERE*****
6

7 170

8 171 Potential participants will be screened for eligibility via telephone. Once eligibility is
9 172 confirmed, participants will attend a study orientation session via videoconference to explain
10 173 further study details (e.g., fasting requirements) and be orientated to the dietary assessment
11 174 tool (3-day food diary). If both knees meet the inclusion criteria, the most symptomatic knee
12 175 will be considered as the index knee.
13
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18 176

19
20 177 *Randomisation procedure, concealment of allocation and blinding*

21
22 178 Upon completion of baseline assessment, participants will be randomised to either the anti-
23 179 inflammatory dietary program or standard care low-fat dietary program. Study treatments,
24 180 but not study hypotheses, will be revealed to participants. A computer-generated
25 181 randomisation schedule has been developed *a priori* by an independent statistician in random
26 182 permuted blocks of 4-8 and stratified by sex and body mass index ($\geq 30\text{kg.m}^{-2}$ vs $<30\text{kg.m}^{-2}$).
27 183 To ensure concealed allocation, the randomisation schedule will be stored electronically in
28 184 the secure Research Electronic Data Capture (REDCap®) system and only accessible to an
29 185 unblinded researcher once baseline measures have been obtained, who will communicate
30 186 treatment allocation to the participant. Investigators conducting the follow-up assessments
31 187 will be blinded to group allocation. As the primary outcome is self-reported, participants are
32 188 considered assessors; therefore, they will be blinded to previous scores. The health
33 189 professionals delivering the interventions will deliver the intervention for both groups.
34 190 Specific protocols for both interventions (including consultation contents and format, and
35 191 accompanying resources) have been developed, and the health professionals have received
36 192 training to ensure equal credibility. Random observations of intervention delivery will be
37 193 conducted by the principal investigators to ensure treatment delivery credibility and fidelity.
38 194 An independent statistician, blinded to group allocation, will perform the primary RCT
39 195 analysis.
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197 **Interventions**

198 The anti-inflammatory dietary program and standard care low-fat dietary program are
199 summarised aligning to Template for Intervention Description and Replication (TIDieR)
200 guidelines(34) (table 2). Participants in both intervention groups were not actively
201 discouraged to lose weight, but weight loss was described as a potential outcome of the
202 interventions. The same health professionals will deliver the intervention for both groups.

204 *Anti-inflammatory dietary program*

205 Participants allocated to the anti-inflammatory dietary program will receive specific anti-
206 inflammatory dietary education and an individualised eating plan, as well as a suite of
207 resources to support behaviour change. The anti-inflammatory dietary program will be
208 delivered over 12 weeks by a qualified dietitian or by another health professional specially
209 trained to deliver the intervention (e.g., physiotherapist).

210
211 Participants will be encouraged to follow a diet containing minimally-processed foods and
212 vegetable oils, and higher amounts of healthy fats and nutrient-dense wholefoods known to
213 fight inflammation (e.g., fresh fruits low in natural sugar such as berries, non-starchy
214 vegetables, nuts and seeds, seafood, poultry, red meat, eggs, full-fat dairy). Healthy fats
215 include monounsaturated and polyunsaturated fats with optimal omega-3: omega-6 ratios as
216 found in seafood, nuts, and extra-virgin olive oil. Participants will be advised to limit processed
217 foods, refined carbohydrates (e.g., pasta, bread, rice), confectionary and foods with added
218 sugar. Participants will be encouraged to consume a normocaloric diet and to eat to satiety,
219 with no specific percentage of total energy intake targets for carbohydrate, fat or protein.

220
221 An initial in-person consultation (~45 minutes) will occur immediately following group
222 allocation to constructively review participant's current dietary intake (using baseline 3-day
223 food diary) and develop an individualised meal plan. Participants will be provided with a
224 comprehensive explanation of anti-inflammatory dietary principles, its rationale (e.g., the role
225 of inflammation in OA, link between foods and inflammation) and its potential benefits and
226 side-effects, and address questions and/or concerns. The following educational and
227 behaviour change resources will also be provided at the initial consultation to support

1
2
3 228 adherence: i) bespoke information booklet providing anti-inflammatory eating information,
4 229 example meal plans, and foods that are encouraged and foods to avoid (Supplementary file 1
5 230 and 2); ii) complimentary subscription to an anti-inflammatory program (Defeat Diabetes
6 231 phone app/website), providing anti-inflammatory recipes, masterclasses, meal plans and
7 232 educational articles; iii) complimentary links to recommended documentaries exploring the
8 233 benefits of anti-inflammatory nutrition (i.e., Fat Fiction, Cereal Killers, That Sugar Film); and
9 234 iv) complimentary copy of a book exploring benefits of anti-inflammatory approach (A Fat Lot
10 235 of Good(35)).
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20 237 Follow-up phone/videoconference consultations (~30 minutes) will be scheduled in weeks 2,
21 238 4, 6, and 9, with timing to be negotiated between each participant and the health professional
22 239 delivering the intervention. A final in-person consultation will be delivered immediately
23 240 following the completion of the 12-week assessment. These follow-up consultations will
24 241 provide participants with ongoing support, education and accountability. A 3-day food diary,
25 242 completed prior to each consultation (see outcomes/adherence section), will guide
26 243 individualised feedback and support to adapt meal plans to optimise adherence.
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244 **Table 2:** Overview of intervention delivery described according to the TIDieR guidelines

1. BRIEF NAME	Anti-inflammatory dietary program	Standard care low-fat dietary program
2. WHY	Anti-inflammatory diets targeting systemic inflammation assist in the prevention and management of various chronic diseases.(16) Small pilot studies have shown a positive effect of anti-inflammatory diets to improve knee-related symptoms in people with knee osteoarthritis.(28)	Healthy eating guidelines and dietary advice described in the standard care program booklet was based on Australian Dietary Guidelines (ADGs).(36, 37) Two-three dietetic consultations represent usual care for patients referred for dietary management in Australia.(37, 38)
3. WHAT (MATERIALS)	Participants receive an intervention handbook containing all study details, key anti-inflammatory eating principles, example meal plans, traffic light system of foods encouraged and discouraged, and education (e.g., common myths, tips for eating out, shopping tips); complimentary access to the Defeat Diabetes program app/website; complimentary links to three movies; and a complimentary copy of the book “A Fat Lot of Good”.(35)	Participants receive an educational handbook emphasising ADGs healthy eating principles and are provided links to the online resources from the Eat for Health website (https://www.eatforhealth.gov.au/).
4. WHAT (PROCEDURES)	Six consultations providing individualised guidance and support to follow an anti-inflammatory eating pattern, emphasising the consumption of fruits, non-starchy vegetables, fish, poultry, red meat, eggs, full-fat dairy, nuts, seeds, and extra virgin olive oil. Participants will be encouraged to avoid highly processed foods, refined carbohydrates, added sugar, and processed meats.	Three consultations providing general advice and education regarding healthy eating based on the ADGs. The principles focus on consumption of foods from the five food groups, while limiting intake of foods containing saturated fat, added salt, added sugars and alcohol.
5. WHO PROVIDED	A qualified dietitian or health professional specially trained to deliver all components.	A qualified dietitian or health professional specially trained to deliver all components.
6. HOW	Delivered with individual support for 12 weeks, after which, participants will be encouraged to sustain the anti-inflammatory diet unsupported up to 6 months. Consultations are one-to-one.	Delivered with standard healthy eating advice for 12 weeks, after which, participants will be encouraged to sustain the program unsupported up to 6 months. Consultations are one-to-one.
7. WHERE	In-person consultations will occur at La Trobe University Nutrition and Dietetics research laboratory. Additional	In-person consultations will occur at the La Trobe University Nutrition and Dietetics research

	consultations will occur via telephone/videoconference (e.g., Zoom). Participants will integrate the diet principles into their daily consumption of foods and beverages.	laboratory. Additional consultations will occur via telephone/videoconference (e.g., Zoom). Participants will integrate the diet principles into their daily consumption of foods and beverages.
8. WHEN AND HOW MUCH	<p>Two in-person consultations at baseline (~45 mins) and week 12 (~30 mins)</p> <p>Four phone/videoconference follow-up consultations (~30 mins) in week 2, 4, 6, and 9.</p> <p>Total active intervention delivery time: ~3.5 hours</p> <p>Participants are provided with self-management resources to optimise adherence to the anti-inflammatory diet up to the 6-month follow-up.</p>	<p>Two in-person consultations at baseline (~45 mins) and week 12 (~30 mins)</p> <p>One phone/videoconference follow-up consultation (30 mins) in week 6.</p> <p>Total active control delivery time: ~1.5 hours</p> <p>Participants encouraged to sustain their diet up to 6-month follow-up.</p>
9. TAILORING	Individualised anti-inflammatory dietary advice, education, and support aligning with participant preferences and goals.	Advice based on the ADGs.
10. MODIFICATIONS	Any modifications will be reported.	
11. HOW WELL (planned)	Two-three professionals (qualified dietitian and other health professional) receive prior training in how to deliver and supervise the program. Fidelity is assessed through random auditing by members of the principal investigator team (AC or BD). Participant adherence to the anti-inflammatory diet is assessed through consultation attendance, regular 3-day food diaries and self-report.	Two-three professionals (qualified dietitian and health professional) receive prior training in how to deliver and supervise the program. Fidelity is assessed through random auditing by members of the principal investigator team (AC or BD). Participant adherence to the standard care low-fat diet is assessed through consultation attendance, regular 3-day food diaries and self-report.
12. HOW WELL (actual)	This will be reported in the primary paper.	

245 TIDieR, Template for Intervention Description and Replication; ADG, Australian Dietary Guidelines

1
2 246 *Standard care low-fat dietary program*
3
4

5 247 Participants allocated to the standard care low-fat dietary program will receive advice and
6
7 248 education regarding healthy eating based on the Australian Dietary Guidelines.(39) These
8
9 249 government-endorsed guidelines aim to optimise nutrition intake through adequate
10
11 250 consumption of foods from the five core food groups (grains and cereals; fruit; vegetables and
12
13 251 legumes; lean meats and poultry, fish, eggs, and tofu; reduced fat dairy or alternatives), while
14
15 252 limiting intake of foods containing saturated fat, added salt, added sugars and alcohol. They are
16
17 253 high-carbohydrate and low-fat focused – participants will be encouraged to include at least four
18
19 254 serves of wholegrains daily (e.g., brown rice, pasta, bread, quinoa, oats) and to choose low-fat
20
21 255 protein and dairy foods where possible.
22

23
24
25 257 The program will be delivered through individual consultations with the treating dietitian or other
26
27 258 specially trained health professional – the first in-person consultation immediately following
28
29 259 baseline assessment (~45 minutes), the second via phone/videoconference at 6 weeks (~30
30
31 260 minutes) and the third in-person at 12-week follow-up with timing individualised as required.
32
33 261 Two to three consultations represents usual care for patients referred for dietary management
34
35 262 in Australia through the current public healthcare (Medicare) rebate system.(37, 38) During the
36
37 263 initial in-person consultation, participants will be provided with a bespoke educational booklet
38
39 264 and advice and education emphasising the Australian Dietary Guideline principles
40
41 265 (<https://www.eatforhealth.gov.au/guidelines>) and informed of complementary and publicly
42
43 266 available online resources from the Eat for Health website (<https://www.eatforhealth.gov.au/>).
44

45
46 268 The follow-up phone/videoconference consultation in week-6 and in-person follow-up in week-
47
48 269 12 will provide participants with ongoing support, education and accountability. The 3-day food
49
50 270 diary, completed prior to each consultation (see outcomes/adherence section), will guide
51
52 271 feedback and support to adapt meal plans to optimise adherence. The treating health
53
54 272 professionals delivering the two dietary programs will be based centrally at La Trobe University
55
56 273 and will be trained by the senior study dietitian (BLD) until deemed competent in intervention
57
58 274 delivery.
59

60 275

1
2 276 Irrespective of group allocation, participants can continue usual medical care and consult with
3
4 277 their treating health professionals as necessary (e.g., general practitioner regarding medication
5
6 278 changes).

7 279

9 280 **Data collection procedure**

11 281 Data will be collected at baseline and 6 weeks, 12 weeks and 6 months after randomisation, with
12
13 282 12 weeks the *a priori* primary endpoint as this coincides with completion of supported
14
15 283 interventions (table 3). Where possible, data will be collected and managed using a secure web-
16
17 284 based software platform (REDCap®) hosted at La Trobe University,(40) which has equivalent
18
19 285 measurement properties to paper-based completion.(41) This strategy was used in our pilot
20
21 286 study(28) and other trials of musculoskeletal conditions.(42) Paper versions will also be available
22
23 287 if preferred.

24 288

26 289 **OUTCOMES**

28 290 **Baseline characteristics**

30 291 Participant characteristics including age, sex, ethnicity, knee pain/surgery details, socioeconomic
31
32 292 details (e.g., education level, employment status, living status), medical history and health
33
34 293 literacy (assessed with the Rapid Estimate of Adult Literacy in Medicine (REALM)(43)) will be
35
36 294 collected (table 3).

37 295

39 296 **Primary Outcome**

41 297 The primary outcome is the change from baseline to 12 weeks in the mean score on four Knee
42
43 298 injury and Osteoarthritis Outcome Score (KOOS₄) subscales covering knee pain, symptoms,
44
45 299 function in daily activities and knee-related quality of life. The KOOS is a 42-item patient-reported
46
47 300 outcome measure assessing five separately scored subscales: Pain, Symptoms, Function in Sport
48
49 301 and Recreation (Sport/Rec), Activities of Daily Living (ADL), and Quality of Life. The KOOS₄ and all
50
51 302 KOOS subscale scores range from 0 (extreme problems) to 100 (no problems). The KOOS is a
52
53 303 valid, responsive and reliable questionnaire, with KOOS₄ a primary outcome for other knee OA
54
55 304 trials.(33, 44, 45)

56 305

57 306

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309

310 **Table 3.** Overview of data collection

Variable	Baseline	6 weeks	12 weeks	6 months
Participant characteristics				
Age	X			
Sex	X			
Ethnicity	X			
Education level	X			
Health literacy (REALM)	X			
Employment status	X			
Smoking status	X			
Civil status, living situation	X			
Medical history, comorbidities	X			
Knee pain/injury/surgery history	X			
Objective Clinical Outcomes				
Height, weight, waist girth	X		X	X
30-second chair stand test	X		X	X
40 metre walk test	X		X	X
Body composition (DXA)	X		X	X
Blood inflammatory and metabolic biomarkers	X		X	X
Blood pressure	X		X	X
Patient-reported Outcomes				
KOOS subscales	X	X	X	X
Global rating of change		X	X	X
Desire for knee surgery	X	X	X	X
Medication use	X	X	X	X
Knee pain (current and worst in past week)	X	X	X	X
EQ-5D-5L [^]	X	X	X	X
Patient acceptable symptom state	X	X	X	X
Brief Pain Inventory	X		X	X
International Physical Activity Questionnaire	X		X	X
Kessler Psychological Distress Scale (K10)	X		X	X
3-day Food Diaries*	X	X	X	X
Adverse events		X	X	X

311 REALM, Rapid Estimate of Adult Literacy in Medicine; KOOS, Knee injury and Osteoarthritis Outcome
 312 Score; DXA, Dual-Energy X-ray absorptiometry

1
2 313 *3-day food diaries are also assessed prior to anti-inflammatory dietary program consultations at 2, 4 and
3 314 9 weeks
4

5 315 ^Assesses health-related quality of life across 5 dimensions of health (mobility, self-care, usual activities,
6 316 pain/discomfort, anxiety/depression) and a visual analogue scale (0-100) of current overall health status.
7 317
8

9 318
10

11 319 **Secondary effectiveness outcomes**

12 13 320 *KOOS subscales*

14
15 321 To allow for clinical in-depth interpretation, scores for the five KOOS subscales will be reported
16 322 individually (i.e., pain, symptoms, function in sports and recreational activities, activities of daily
17 323 living, quality of life).(10, 45)
18
19
20
21 324

22 23 325 *Global Rating of Change (GROC) and patient-acceptable state*

24
25 326 Self-perceived change in pain and function will be assessed using a 7-point Likert scale ranging
26 327 from 'much worse' to 'much better' in response to the questions: "Overall, how has your knee
27 328 pain changed since the start of the study?" and "Overall, how has your knee function changed
28 329 since the start of the study?", respectively. Treatment success will be defined as a response of
29 330 either 'better' or 'much better'. Satisfaction with current knee function using the self-reported
30 331 Patient Acceptable Symptom State (PASS) question(46). Participants not satisfied with current
31 332 knee function at follow-up assessments will be asked a second question to determine if they
32 333 considered the treatment to have failed.(46)
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40 334

41 42 335 *Anthropometrics*

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44 336 Height and weight will be assessed using a seca 217 stadiometer and seca 703 EMR-validated
45 337 column scale (Hammer Steindamm, Hamburg, Germany), respectively. Waist circumference will
46 338 be measured using a metal tape measure (Lufkin W606PM ¼ inch x 2m Executive Thinline Pocket
47 339 Tape).
48
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51 340

52 53 341 *Global lower-limb function*

54
55 342 Two performance-based tests of lower-limb function recommended by the OA Research Society
56 343 International (OARSI) will be conducted: the 30-second chair-stand test (number of chair-stands
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2 344 from a standardised height chair in 30 seconds) and 40-metre walk test (time to walk 40 metres
3
4 345 safely, using walking aids if required).(47)

5 346

7
8 347 *Body composition*

9
10 348 A whole-body DXA scan will be acquired using a Hologic Horizon® DXA scanner (Bedford, MA,
11
12 349 United States) to assess adiposity (visceral, peripheral) and lean mass.(48)

13
14 350

16
17 351 *Inflammatory and metabolic biomarkers*

18
19 352 An array of blood inflammatory and metabolic biomarkers will be analysed from samples of blood
20
21 353 collected, including high sensitivity C-Reactive Protein (hsCRP), cytokines (IL-1 β , IL-6, IL-8, IL-10,
22
23 354 TNF- α), blood glucose, HbA1c, serum insulin, liver function tests (including albumin), and lipids
24
25 355 (e.g., high density lipoprotein, triglycerides). Participants will be instructed to fast for at least 10
26
27 356 hours prior to blood collection and a single forearm venepuncture will take place to collect a total
28
29 357 of ≤ 30 mL blood. Plasma and serum samples will be centrifuged (3000ms, 10 minutes), and all
30
31 358 samples (plasma, serum, and whole blood) frozen at -80°C for later analysis (Supplementary File
32
33 359 3).

34 360

35
36 361 **Secondary safety outcomes**

37
38 362 *Adverse events*

39
40 363 Adverse events and serious adverse events will be recorded at 6-week, 12-week and 6-month
41
42 364 follow-up via open probe questioning to optimise collection of sufficient detail. Under the
43
44 365 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) harms
45
46 366 statement, an adverse event is defined as any undesirable experience causing participants to
47
48 367 seek medical treatment (e.g., general practitioner).(49) A serious adverse event is defined as any
49
50 368 undesirable event/illness/injury classified as having the potential to significantly compromise
51
52 369 clinical outcome or result in significant disability or incapacity, those requiring inpatient or
53
54 370 outpatient hospital care, to be life-threatening or result in death.

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372 **Exploratory outcomes**

373 *Dietary Analysis*

374 Participants will record food and beverage intake over three days via the smartphone application
375 *Australia Calorie Counter - Easy Diet Diary* (Xyris Software Pty Ltd) or on paper (personal
376 preference). Easy Diet Diary is a commercial calorie counter and food diary that allows users to
377 email recorded diaries to treating professionals. Once received by the treating health
378 professional, the 3-day food diaries will be imported into, and analysed using, Foodworks®
379 Premium Edition nutrient analysis software (Version 10, Brisbane, Australia 2019) and Australian
380 food composition databases. Paper-based 3-day food diaries will be manually entered into
381 FoodWorks®. Total energy intake, macronutrients, micronutrients and core food group analysis
382 will be reported. Dietary analysis data will also be used to calculate the inflammatory potential
383 of participants' diets (e.g., Dietary Inflammatory Index).(50)

384

385 *Quality of life*

386 Health-related quality of life will be assessed with the EQ-5D-5L generic health index, which
387 comprises five dimensions of health (mobility, self-care, usual activities, pain or discomfort,
388 anxiety or depression) and a Visual Analogue Scale (VAS) of current overall health status.(51)
389 Both validity and reliability has been demonstrated in arthritic populations.(52)

390

391 *Knee pain and interference*

392 Self-reported knee pain (current, worst over past week, average over past week) will be assessed
393 using a 100mm VAS (0=no pain, 100=worst pain imaginable). The degree to which knee pain
394 interferes with participant's daily functioning will be assessed using the Brief Pain Inventory,(53)
395 a tool with reliability and validity demonstrated in knee pain populations.(54, 55)

396

397 *Change in analgesic medication use*

398 Change in analgesic medication use from baseline to 12-week and 6-month follow-up will be
399 assessed with a 7-point Likert scale (much less to much more).

400

1
2 401 *Physical activity*
3

4 402 Physical activity will be assessed using the International Physical Activity Questionnaire
5
6 403 (IPAQ),(56) a standardised and valid questionnaire providing an estimate of physical activity and
7
8 404 sedentary behaviour, which has been widely validated.(56-58) Respondents are asked to report
9
10 405 time spent in physical activity across three intensities (walking, moderate, vigorous). Using the
11
12 406 IPAQ scoring protocol,(59) total weekly physical activity can be estimated by weighting time
13
14 407 spent in each activity intensity with its estimated metabolic equivalent (MET) energy
15
16 408 expenditure.(60)
17

18
19 410 *Blood pressure*
20

21
22 411 A pair of seated blood pressure measurements will be obtained using an automated monitor
23
24 412 (Omron Model HEM-7121). The blood pressure cuff is placed over the mid-upper arm with the
25
26 413 participant seated.
27

28
29 415 *Self-perceived wellness*
30

31
32 416 Self-reported sleep quality, hunger, fatigue and energy levels will be assessed using a 100mm
33
34 417 VAS (0=worst outcome, 100=best outcome).
35

36 418
37
38 419 *Intervention adherence*
39

40 420 Adherence will be assessed by a self-reported VAS (0=not at all adherent, 100=extremely
41
42 421 adherent) and 5-point Likert scale at 6 weeks, 12 weeks and 6 months and evaluation of 3-day
43
44 422 food diaries by consulting health professionals. Satisfactory adherence is defined as a self-report
45
46 423 of both ≥ 80 on the VAS and 'Most days' or 'Every day' on the Likert scale, at both the 6-week and
47
48 424 12-week timepoints.
49

50 425 **DATA MANAGEMENT**
51

52 426 Most outcome data will be collected and managed electronically via REDCap© web-based
53
54 427 software hosted at La Trobe University. Other data (e.g., DXA reports) will be stored electronically
55
56 428 on the La Trobe University secure research drive. All electronic data will be de-identified
57
58 429 (participant code) and exported for data analysis and saved in a password protected database on
59
60 430 the La Trobe University research drive only accessible to the research team. Paper-based
431 identifying documents (e.g., consent forms) will be securely stored in a locked filing cabinet

1
2 432 accessible only to members of the research team and separately from re-identifiable (i.e., coded)
3
4 433 data.

5 434
6
7 435 Due to the minimal known risks associated with the interventions being evaluated, our study will
8
9 436 not have a formal data monitoring committee and does not require an interim analysis. This is
10
11 437 the same approach we have taken with other low risk RCTs.(42) Any unexpected serious adverse
12
13 438 events or outcomes will be discussed by the trial management committee (authors of this
14
15 439 protocol) and reported to the approving human research ethics committee for monitoring.

16 440

18 441 **Sample size calculation**

20 442 This trial has been powered to detect a clinically significant between-group difference for the
21
22 443 primary outcome of KOOS₄. A recent RCT comparing an anti-inflammatory diet vs low-caloric diet
23
24 444 in overweight women with knee OA observed an effect size (standardised mean difference) on
25
26 445 self-reported pain and function of 1.0 (95% confidence interval 0.5 to 1.6).(61) Given inherent
27
28 446 differences in the FEAST RCT (e.g., Australian Dietary Guideline control group, not specifically
29
30 447 targeting overweight participants, inclusion of both women and men), we used the lower bound
31
32 448 95% confidence interval to provide a conservative estimate of the anticipated effect size (0.5).
33
34 449 This estimated effect size is also a conservative estimate based on our single-arm anti-
35
36 450 inflammatory diet pilot trial, which had an effect size of 0.68.(28) Recruiting 128 participants
37
38 451 (equally distributed between two arms) would yield 80% power to observe such an effect or
39
40 452 larger at a two-tailed Type I error of 0.05. This sample size estimation is also conservative since
41
42 453 it is based on independent samples t-test. Using an ANCOVA model that includes the baseline
43
44 454 value as a covariate and is pre-specified for the analysis should provide higher power for the
45
46 455 same sample size.(62) To account for a potential 10% drop-out, we will recruit 144 participants.
47
48 456 This sample size will also be sufficient to detect a minimal important change (MIC) in KOOS₄
49
50 457 estimated at 10 points in patients with knee OA (with a common between-subject standard
51
52 458 deviation of 15).(63)

51 459

53 460 **Statistical analyses**

55 461 Analysis will be performed according to the Estimands Framework(64) with a statistical analyst
56
57 462 blinded to group allocation. All outcomes and analyses are prospectively categorised as primary,
58
59 463 secondary or exploratory. For the primary hypothesis, a linear model with baseline value, sex and
60
61 464 BMI (≥ 30 vs < 30 kg.m⁻²) as covariates and treatment condition as a fixed factor will evaluate the

1
2 465 treatment effect on the primary outcome of KOOS₄ (mean score of four of the five subscales of
3
4 466 the KOOS) at 12 weeks. A linear mixed model utilising repeated measures at all time-points for
5
6 467 secondary hypotheses will allow non-biased estimates of treatment effect in the presence of any
7
8 468 potential missing cases, providing data are missing at random. A sensitivity analysis using pattern-
9
10 469 mixture model to investigate the deviation from the missingness-at-random assumption will be
11
12 470 carried out.(65) For secondary binary outcomes (e.g., treatment success), mixed-effect logistic
13
14 471 regression models will be used to assess the effect of treatment. A subsequent analysis of
15
16 472 participants classified as adherent to the protocol will be performed.

17 473 18 474 **Healthcare resource use**

19
20 475 Healthcare resource utilisation (e.g., hospitalisations, medical imaging, healthcare visits,
21
22 476 medication use) will be assessed by participant self-report to estimate costs associated with the
23
24 477 trial programs (e.g., hospital admissions, medication use, clinician visits, imaging tests, out-of-
25
26 478 pocket expenses).

27 479 28 29 480 **Process Evaluation**

30
31 481 Semi-structured interviews will be conducted on a subset of consenting participants (until data
32
33 482 saturation reached) at 6 months. Interviews will explore experiences, knowledge and
34
35 483 understanding of interventions received including potential benefits; acceptability and perceived
36
37 484 effectiveness of the intervention; and reasons for adhering (or not) to the allocated diet.
38
39 485 Purposive sampling will be used to recruit interview participants based upon characteristics (anti-
40
41 486 inflammatory dietary program vs standard care low-fat dietary program, men vs women) and
42
43 487 outcomes of the trial (good outcome vs poor outcome). Interviews will be audio recorded,
44
45 488 transcribed and analysed using Framework Analysis,(66) a flexible technique allowing
46
47 489 researchers to identify, compare and contrast data according to inductively- and deductively-
48
49 490 derived themes. Data will be coded and an inductive thematic analysis will be applied until no
50
51 491 new themes emerge.

52 492 53 54 493 **ETHICS AND DISSEMINATION**

55
56 494 This study complies with the Declaration of Helsinki and has received approval from La Trobe
57
58 495 University Human Ethics Committee (HEC-22044). Written informed consent will be obtained
59
60 496 from participants prior to enrolment (Supplementary File 4). Anti-inflammatory diets are
497 associated with minimal and transient adverse events, thus there are minimal safety

1
2 498 considerations associated with this trial.

3
4 499

5 500 Study outcomes will be widely disseminated through a variety of sources. Results will be reported
6
7 501 in peer-reviewed publications and presented at key national and international conferences. Only
8
9 502 aggregate data will be reported. A lay summary report will be available for study participants.
10
11 503 Any important protocol amendments will be reported to the approving ethics committee,
12
13 504 registered at ANZCTR and communicated in the primary RCT paper. Any serious adverse events
14
15 505 will be recorded and reported to the approving ethics committee.

16 506

17
18 507 Deidentified data will be made available upon reasonable request to the principal investigator
19
20 508 (AGC) after publication (except where the sharing of data is prevented by privacy, confidentiality,
21
22 509 or other ethical matters, or other contractual or legal obligations) according to La Trobe
23
24 510 University Research Data Management Policy.

25 511

26 512 **DISCUSSION**

27
28
29 513 The current RCT will be the first full-scale trial to evaluate the symptomatic, inflammatory,
30
31 514 functional and body composition benefits of an anti-inflammatory dietary program compared to
32
33 515 a standard care low-fat dietary program based on Australian Dietary Guidelines. While outcome
34
35 516 assessors are blinded to group allocation, owing to the type of interventions (i.e., dietary advice)
36
37 517 blinding of participants will not be possible. We also acknowledge that, like most RCTs, there is a
38
39 518 risk that our recruitment strategy may result in a selected sample not representative of the
40
41 519 general population. However, using similar recruitment strategies, our prior RCTs have resulted
42
43 520 in a representative sample of the culturally and sociodemographically diverse Australian
44
45 521 population that has similar characteristics to other international cohorts with the index
46
47 522 musculoskeletal condition.(67)

48 523

49 524 The evaluation of a non-pharmacological anti-inflammatory dietary program to improve pain,
50
51 525 symptoms, and quality of life for individuals with OA could have important individual and socio-
52
53 526 economic benefits – decreased healthcare dollars spent on managing OA and reduced surgery
54
55 527 waiting lists. Another benefit is that anti-inflammatory diets are also effective at combating
56
57 528 metabolic syndrome, a key risk factor for chronic diseases, and thus the benefits from treating
58
59 529 OA could stretch further to improving other medical co-morbidities.(68) This fully-powered RCT
60
60 530 represents a crucial step towards the development of a sustainable and cost-effective therapy

1
2 531 that can both supplement and complement existing treatment strategies to optimise OA
3
4 532 outcomes.

5 533

6
7 534

8 9 535 **AUTHOR CONTRIBUTIONS**

10 536 AGC, BLD, PB and JLK conceived the study and obtained funding. AGC, BLD, PB, and JLK designed
11
12 537 the study protocol with input from LL, JJH and ABM. ADL provided statistical expertise and will
13
14 538 conduct primary statistical analysis. MDH provided blood analysis expertise and will lead
15
16 539 inflammatory and metabolic marker analyses. HGM and NPW assisted with participant
17
18 540 recruitment from their clinical population with knee osteoarthritis. LL drafted the manuscript
19
20 541 with input from AGC, JJH, BLD, PB, JLK, AA, MDH, ADL, ABM, HGM and NPW. All authors read
21
22 542 and approved the final manuscript.

23 543

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28
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30
31 547 (APP2017844), and a philanthropic donation from PB.

32 548

33 34 549 **COMPETING INTERESTS STATEMENT**

35
36 550 PB is the founder of Defeat Diabetes and author of "A Fat Lot of Good". PB contributed to study
37
38 551 design but has no role in study execution, data management, analysis or the decision to publish.
39
40 552 The NHMRC has no role in study design and will not have any role in its execution, data
41
42 553 management, analysis and interpretation or on the decision to submit the results for publication.
43
44 554 JLK is an editor of the British Journal of Sports Medicine (British Medical Journal Group). AGC is
45
46 555 an associate editor of British Journal of Sports Medicine (British Medical Journal Group). All other
47
48 556 authors have no competing interests.

49 557

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53
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55
56 561 Melbourne Pathology for providing pathology collection kits and analysis of biomarkers from
57
58 562 blood specimens.

59
60 563

564 **FIGURE LEGENDS**

1
2 565 **Figure 1.** Flow of participants through the trial. DXA, Dual X-ray Absorptiometry; KOOS, Knee
3
4 566 injury and Osteoarthritis Outcome Score

5 567 *Optional qualitative interview for process evaluation at 6 months
6
7 568
8
9 569

10 570 SUPPLEMENTARY FILES

11 571 **Supplementary File 1.** Sample of the standard care low fat dietary program participant booklet

12
13 572 **Supplementary File 2.** Sample of the anti-inflammatory dietary program participant booklet

14
15 573 **Supplementary File 3.** Standard Operating Procedures for blood collection, processing and
16
17 574 storage

18
19
20 575 **Supplementary File 4.** Patient information and consent form
21
22 576

23 24 25 577 REFERENCES

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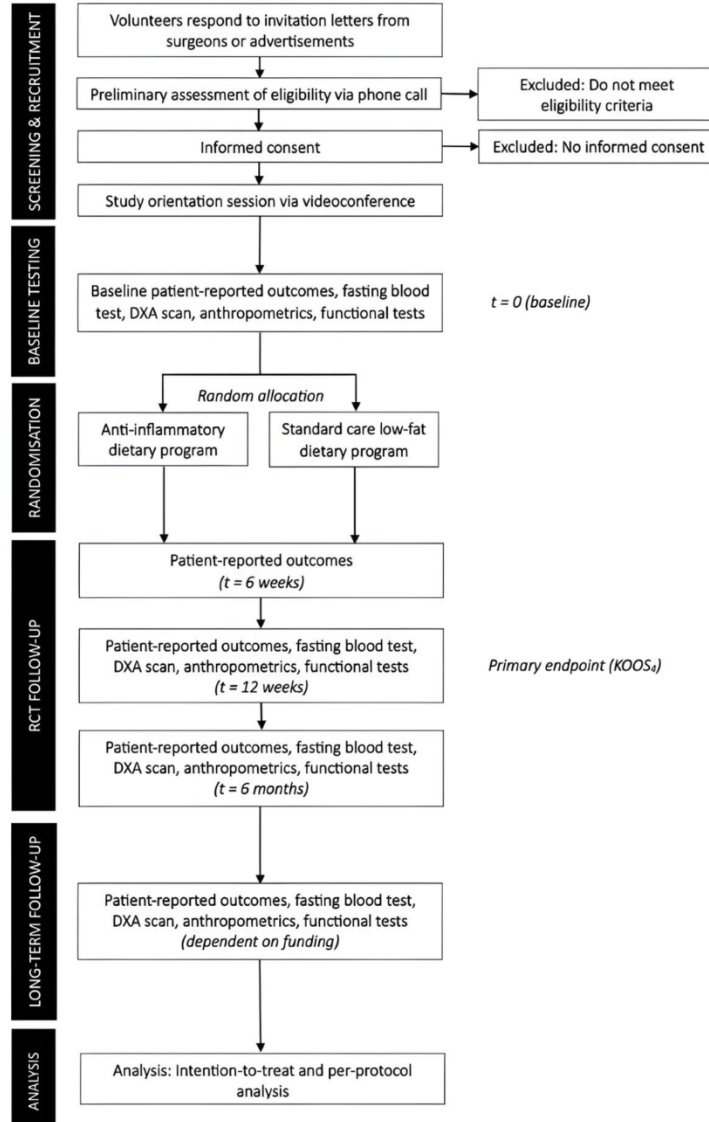


Figure 1. Flow of participants through the trial. DXA, Dual X-ray Absorptiometry; KOOS, Knee injury and Osteoarthritis Outcome Score

*Optional qualitative interview for process evaluation at 6 months

529x695mm (96 x 96 DPI)

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FEAST

SAMPLE FROM LOW-FAT PARTICIPANT BOOKLET





Australian Government
National Health and Medical Research Council
Department of Health and Ageing

www.eatforhealth.gov.au

Australian Guide to Healthy Eating

Enjoy a wide variety of nutritious foods from these five food groups every day.

Drink plenty of water.



Grain (cereal) foods, mostly wholegrain and/or high cereal fibre varieties



Vegetables and legumes/beans



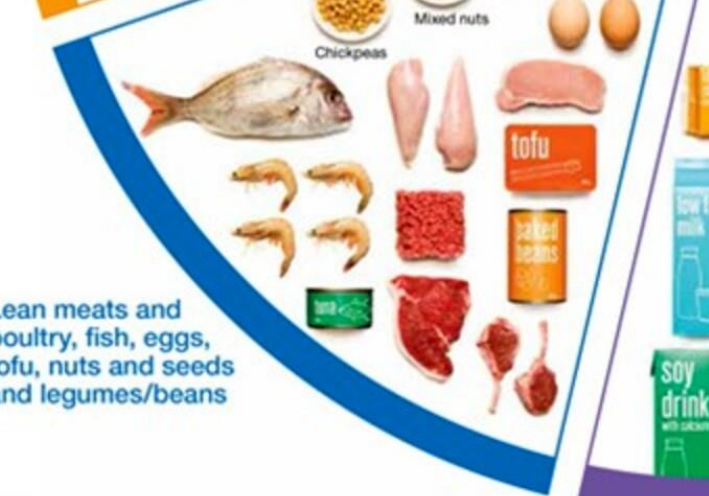
Lean meats and poultry, fish, eggs, tofu, nuts and seeds and legumes/beans



Fruit



Milk, yoghurt, cheese and/or alternatives, mostly reduced fat



Use small amounts



Only sometimes and in small amounts



Vegetables and legumes

Vegetables, including legumes/beans are nutrient dense, low in kilojoules, and are a good source of minerals and vitamins (such as magnesium, vitamin C and folate), dietary fibre and a range of natural plant chemicals such as carotenoids. Legumes include chickpeas, kidney beans, and peas. **Aim for 5 serves a day.**

What is a serve of vegetables*?

A standard serve is about 75g (100–350kJ) or:

½ cup	cooked green or orange vegetables (for example, broccoli, spinach, carrots or pumpkin)
½ cup	cooked dried or canned beans, peas or lentils
1 cup	green leafy or raw salad vegetables
½ cup	sweet corn
½ medium	potato or other starchy vegetables (sweet potato, taro or cassava)
1 medium	tomato



*With canned varieties, choose those with no added salt

Fruit

A wide variety of fruit is grown and available in Australia. Choosing fruits in season provides **better value and better quality**. And just like with veggies, choosing different coloured fruits increases the variety of nutrients, which can enhance your health! Aim for **two serves** of fruit a day.

Try eating fruits from these different fruit categories:

- citrus fruit such as oranges, mandarins, and grapefruit
- pome fruits such as apples and pears
- stone fruit such as apricots, cherries, peaches, nectarines, and plums
- tropical fruit such as bananas, papaya, mangoes, pineapple, and melons
- berries

What is a serve of fruit?

A standard serve is about 150g (350kJ) or:

1 medium	apple, banana, orange or pear
2 small	apricots, kiwi fruits or plums
1 cup	diced or canned fruit (no added sugar)

Or only occasionally:

125ml (½ cup)	fruit juice (no added sugar)
30g	dried fruit (for example, 4 dried apricot halves, 1½ tablespoons of sultanas)



- other fruits such as grapes and passionfruit

Enjoy more fruit by trying:

- chopped fruit to cereal, porridge, salad, or toast
- fruit as a convenient snack while out and about
- fruit-based desserts (baked apples, fruit crumbles, stewed/ poached fruit)
- adding fruit to pancakes, scones, pikelets, and low-fat muffins.



Wholegrains

All types of grains are good sources of complex carbohydrates and some key vitamins and minerals. Grain foods are mostly made from wheat, oats, rice, rye, barley, millet, quinoa and corn.

Wholegrains are naturally high in fibre, helping you feel full and satisfied — which makes it easier to maintain a healthy body weight. Nutritionally, wholegrain and wholemeal foods are very similar.

What is a serve of grain* (cereal) food?

A standard serve is (500kJ) or:

1 slice (40g)	bread
½ medium (40g)	roll or flat bread
½ cup (75-120g)	cooked rice, pasta, noodles, barley, buckwheat, semolina, polenta, bulgur or quinoa
½ cup (120g)	cooked porridge
⅔ cup (30g)	wheat cereal flakes
¼ cup (30g)	muesli
3 (35g)	crispbreads
1 (60g)	crumpet
1 small (35g)	English muffin or scone



*Grain (cereal) foods, mostly wholegrain and/or high cereal fibre varieties

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Aim for 4-6 serves of grain foods a day. Additional serves can be eaten depending on your activity level.

Enjoy more wholegrains by having:

- breakfasts that include whole-grain cereals, like oatmeal.
- wholemeal toast or wholemeal bagels for white-flour versions.
- low-fat muffins made with whole-grain flours.
- sandwiches using whole-grain breads or rolls.
- quinoa, brown rice, wild rice, barley or bulgur instead of white rice.
- wild rice or barley in soups, stews, casseroles and salads.
- rolled oats or crushed whole-wheat bran cereal in recipes instead of dry breadcrumbs.

Lean meat and poultry, fish, eggs, tofu, nuts and seeds

These are a critical part of having enough protein each day. They also provide other nutrients such as: iodine, iron, zinc, vitamins, especially B12, and essential fatty acids.


There's a lot to choose from:

- Lean meats - Beef, lamb, veal, pork, kangaroo
- Poultry - Chicken, turkey, duck, emu, goose, bush birds
- Fish and seafood - Fish, prawns, crab, lobster, mussels, oysters, scallops, clams
- Eggs
- Nuts and seeds - Almonds, pine nuts, walnut, macadamia, hazelnut, cashew, peanut, nut spreads, and pumpkin seeds
- Legumes/beans - All beans, lentils, chickpeas, split peas, tofu.

How much is a serve of lean meat and poultry, fish, eggs, nuts and seeds, and legumes/beans*?

A standard serve is (500–600kJ):

65g	cooked lean red meats such as beef, lamb, veal, pork, goat or kangaroo (about 90-100g raw)
80g	cooked lean poultry such as chicken or turkey (100g raw)
100g	cooked fish fillet (about 115g raw) or one small can of fish
2 large (120g)	eggs
1 cup (150g)	cooked or canned legumes/beans such as lentils, chick peas or split peas
170g	tofu
30g	nuts, seeds, peanut or almond butter or tahini or other nut or seed paste



*Choose those with no added salt

Milk, yoghurt, cheese, and/or alternatives

Dairy products (and dairy alternatives) are rich in calcium, protein, and lots of nutrients. Dairy foods contribute to strong bones. Aim for **at least 2-3 serves daily**.

Examples of milk, yoghurt, cheese and/or alternatives include:

- Milks - All reduced fat or full cream milks, plain and flavoured, long life milks, fortified soy beverages
- Yoghurt - All yoghurts including reduced fat or full cream, plain and flavoured, soy yoghurt (calcium fortified)
- Cheese - All hard cheeses, reduced or full fat for example cheddar, Gouda, Swiss

How much is a serve of milk*, yoghurt*, cheese* and/or alternatives?

A standard serve is (500–600kJ):

1 cup (250ml)	fresh, UHT long life, reconstituted powdered milk or buttermilk
½ cup (120ml)	evaporated milk
2 slices (40g)	or 4 x 3 x 2cm cube (40g) of hard cheese, such as cheddar
½ cup (120g)	ricotta cheese
¾ cup (200g)	yoghurt
1 cup (250ml)	soy, rice or other cereal drink with at least 100mg of added calcium per 100ml

The following foods contain about the same amount of calcium as a serve of milk, yoghurt or cheese:

100g	almonds with skin
60g	sardines, canned in water
½ cup (100g)	canned pink salmon with bones
100g	firm tofu (check the label as calcium levels vary)

*Choose mostly reduced fat

FEAST

SAMPLE OF ANTI-INFLAMMATORY PARTICIPANT BOOKLET



EXAMPLE WEEKLY MEAL PLANS

Here are examples of what a week might look like. Consider these plans as a guide to give you ideas, not something written in stone! Most of the recipes below can be found on the **Defeat Diabetes** app, or by simply searching on Google online.

Lots of other anti-inflammatory/low-carbohydrate ideas online at: <https://www.eatthebutter.org/dinner-ideas/>

Week 1

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Breakfast	Raspberrry chia pot	Yoghurt with berries	Raspberrry chia pot	Coconut crunch granola	Berry yoghurt smoothie	Scrambled eggs with spinach and avocado	Zucchini and feta fritters
Snack	Apple with peanut butter	Hummus and veggies	Apple with peanut butter	Handful of almonds with piece of dark chocolate	Hummus and veggies	Apple with peanut butter	Handful of walnuts
Lunch	Roast vegetable salad	Salad with can of tuna	Leftover prawn pad thai	Leftover burrito bowl	Salad with can of tuna	Salmon with cauliflower rice bowl	One pan spiced halloumi and eggplant
Snack	Handful of almonds with piece of dark chocolate	Almond meal blueberry muffin	Zucchini and feta fritter	Almond meal blueberry muffin	Handful of almonds with piece of dark chocolate	Yoghurt with berries	Almond meal blueberry muffin
Dinner	Garlic prawns with zoodles	Beef pad thai	15-minute burrito bowl	Miso barramundi with vegetables	Swedish meatballs	Baked portobello mushrooms with feta	Grilled lamb chops with roasted vegetables

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Week 2

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Breakfast	Coconut crunch granola	Berry smoothie	Scrambled eggs with spinach and avocado	Berry smoothie	Coconut crunch granola	Scrambled eggs with spinach and avocado	Shakshuka
Snack	Mini frittata	Pear	Apple with handful of almonds	Pear	Mini frittata	Handful of walnuts with piece of dark chocolate	Yoghurt with berries
Lunch	Salad with sliced steak	Easy Tuna Niçoise	Leftover stuffed capsicum	Leftover burger patty with salad	Leftover green curry with cauliflower rice	Caesar salad	Warm veggie salad with almonds
Snack	Slice of orange almond meal cake	Handful of walnuts with piece of dark chocolate	Mini frittata	Slice of orange almond meal cake	Apple with handful of almonds	Yoghurt with berries	Pear
Dinner	Salmon poke bowl	Stuffed capsicums	Smoky beef burger on mushroom buns	Green vegetable and prawn curry with cauliflower rice	Easy mushroom, lemon, and garlic chicken	Cauliflower pizza with pesto, sausage, and herbs	Grilled steak and roasted vegetables

Week 3

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Breakfast	Breakfast egg muffins	Berry yoghurt smoothie	Breakfast egg muffins	Chia pudding pot	Berry yoghurt smoothie	Bacon and eggs with roasted tomatoes	Mexican breakfast scramble
Snack	Chia pudding pot	Beef jerky	Greek yoghurt with berries	Breakfast egg muffins	Handful of almonds with cheese stick	Apple with peanut butter	Strawberry power balls
Lunch	Zucchini and walnut salad	Leftover beef burrito bowl	Leftover salmon patties with salad	Greek salad	Leftover tagine	Kale, broccoli and almond salad	Mushroom soup with crispy cheese croutons
Snack	Strawberry power balls	Handful of almonds with square of dark chocolate	Strawberry power balls	Handful of almonds with apple	Dark chocolate (avocado) mousse	Beef jerky	Dark chocolate (avocado) mousse
Dinner	15-minute beef burrito bowl	Salmon patties with feta sauce and beet salad	Chicken curry with cauliflower rice	Lamb and apricot tagine	Pan-seared barramundi with cauliflower mash	Zucchini lasagne	Grilled lamb chops with roasted vegetables

Week 4

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Breakfast	Coconut granola with milk	Blueberry almond protein smoothie	Vegetable cheese frittata	Blueberry almond protein smoothie	Coconut granola with milk	Tofu scramble	Almond flour pancakes

1	Snack	Roasted chickpeas	Slice of almond flour banana bread	Greek yoghurt with berries	Peanut butter balls	Beef jerky	Roasted chickpeas	Handful of walnuts
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5	Lunch	Vegetable cheese frittata	Leftover roast vegetable salad with halloumi	Leftover broccoli and leek soup	Vegetable cheese frittata	Kale Caesar salad	Leftover stuffed capsicums	Creamy Tuscan soup
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9	Snack	Slice of almond flour banana bread	Handful of almonds with dark chocolate	Roasted chickpeas	Slice of almond flour banana bread	Handful of almonds with dark chocolate	Greek yoghurt with berries	Peanut butter balls
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13	Dinner	Roast vegetable salad with halloumi	Cheesy broccoli soup	Spicy tofu san choi bao	Vegetarian stuffed zucchini boats	Stuffed capsicums	Beetroot & halloumi salad with pomegranate	Spiced eggplant curry with cauliflower rice
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6 **Standard Operating Procedure**
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9 **Blood collection, processing, handling, and storage procedures**
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For peer review only

1.1 Purpose

The purpose of the current SOP is to provide step-by-step instructions on the exact procedures that the research team needs to follow for conducting venous blood collection for biochemical analysis at baseline and follow-up examination.

1.2 General procedures for venous blood collection

Venous blood samples will be obtained from each participant for biochemical analysis following a 12-hour overnight fast, at baseline (T1), 12 weeks (T2) and 6 months (T3) (figure 1)

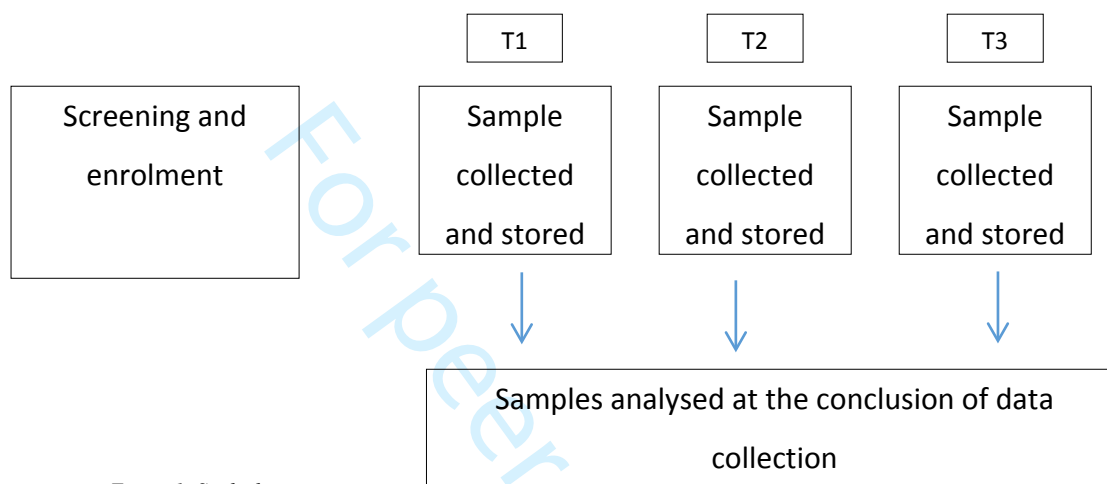


Figure 1: Study design

The researcher will perform venepuncture to obtain no more than 30mL of blood.

1.2.1 Consumables and supplies required for performing venepuncture

The consumables and supplies that will be used for performing the venepuncture in the study are the following:

- Disposable Latex gloves must be worn by the researcher and anyone else assisting with blood collection.
- Alcohol swab will be used to clean the venepuncture site.
- Winged steel needles appropriate for adults with an extension tube (a butterfly) will be used. The butterfly will have either a syringe or an evacuated tube with an adaptor. Sterile gauze pads will.....
- Adhesive hypo allergic bandages (plasters or Band-Aids) will be applied to the puncture site to minimize the risk of infection.
- Plastic Bag for Waste will be used to dispose all of the biohazardous waste generated as well as a sharps biocontainer to dispose of all needles.

1.2.2 Steps in obtaining venous blood from the participant

The steps for obtaining venous blood samples from the study participants are provided below:

Step 1: Complete general preparation.

- Find an indoor site to encourage privacy during blood collection. The site should have a table or other piece of furniture with a flat surface where you can lay out all consumables/ supplies. An examination bed should be readily available if the respondent feels faint and needs to lie down.
- Ensure that each subject has completed a 10-hour fast.

- Wash and dry hands, put on gloves before initiating blood collection from the participant.
- Take out a clean absorbent paper sheet and spread it over a flat surface to lay out consumable and supplies.

Step 2: Prepare the participant for the venepuncture.

- The individual should be seated comfortably in a chair with arm extended on the slanting armrest to form a straight line from the shoulder to the wrist. The arm and elbow should be supported firmly by the armrest and should not be bent at the elbow.
- Ask each volunteer if they have a history of fainting. If so, ensure that the blood sample is only drawn whilst the subject is lying down on a bed.
- Describe to the participant exactly what will be done during the collection of the blood sample.

Step 3: Prepare the venepuncture site.

- Apply (tighten) tourniquet.
- Ask the participant to close his/her hand so that the veins will become more prominent and thus easier to enter. Vigorous hand exercise or "pumping" should be avoided.
- Select the vein site. Palpate and trace the path of veins several times with the index finger. If superficial veins are not readily apparent, blood can be forced into the vein by gently massaging the arm from wrist to elbow. Several sharp taps at the vein site with index and second finger will cause the vein to dilate.
- Loosen tourniquet.
- The venepuncture site must be cleansed once with an alcohol swab to prevent any chemical or microbiologic contamination of either the patient or the specimen.
- Check equipment, tube selection and thread needle (or butterfly) securely onto tube holder (barrel).
- Re-apply the tourniquet and relocated vein position and direction. A tourniquet allows the veins to fill with blood, thus making the veins more prominent and easier to enter. Do not leave the tourniquet on for longer than 1 minute otherwise it may result in either hemoconcentration or variation in blood test values.
- Remove needle cover and check bevel is orientated uppermost.

Step 4: Blood drawing

- Puncture the skin 3–5 mm away from the vein; this allows good access without pushing the vein away.
- If the needle enters alongside the vein rather than into it, withdraw the needle slightly without removing it completely, and angle it into the vessel.
- Insert the tube into the holder and commence filling the tubes.
- Draw blood slowly and steadily.
- Release the tourniquet as soon as blood flow is established. Tourniquet release allows the blood circulation to return to normal and also reduces bleeding at the venipuncture site.
- Remove the tube from the holder and invert (8-10 times) to mix the blood with tube additives. Place blood samples on ice if required..
- Place a cotton wool above the venepuncture site, withdraw the needle and apply pressure.
- Dispose of needle in a sharps container.
- Check site and apply an adhesive bandage.
- Label all tubes immediately.



1.3 Blood processing and handling

1.3.1 Centrifuge procedure

Collected venous blood will be centrifuged and the extracted plasma and/or serum will be pipetted into aliquots according to the blood collection protocol.

- Set up in a well-ventilated environment, on a horizontally levelled and rigid surface with adequate load-bearing capacity.
- As safety zone maintain a clear radius of at least 30 cm around the centrifuge. Do not place any dangerous substances within this security zone.
- Open the centrifuge door by pressing the open button.
- Place the remaining tubes containing blood into appropriate sized adapters.
- Place the tubes containing water in opposite adapters, where they should mirror the placement of the tubes holding blood.
- Never place both tubes housing water and blood into the same adapters but should be placed in different adapters for even weight distribution.
- Place the adapters carefully and gently into the rotor buckets
- Seal the buckets with the lids and close the centrifuge.
- Use only with rotors which have been loaded properly.
- Make sure the rotor is locked properly into place before operating the centrifuge.
- Never overload the rotor.
- Never start the centrifuge when the centrifuge door is open.
- Do not lean on the centrifuge.
- Do not place anything on top of the centrifuge during a run.
- Gently close the centrifuge door. The centrifuge door mechanism will click and lock in place.
- Turn on the centrifuge by pressing the start button.
- Select the required speed and time from preprogrammed setting or manually using the arrow keys (3000xg for 10 mins for each tube).

Once the centrifuge has completely stopped spinning wait for an audible sound and then open the centrifuge. Remove the tubes from the centrifuge and place them in a tube rack.

1.3.2 Handling of collected blood

Three different types of test tubes will be used per study participant to collect venous blood. The collected blood will be designated for whole blood, or plasma and serum separation. One 8ml EDTA tube (with added anticoagulant) will be used to collect whole blood for analysis, one 6ml heparin tube will be used for plasma extraction, and one 8.5ml SST tube will be used for serum extraction. Tubes will be labelled with study timepoint (T1, T2 or T3), participant ID, and type of sample. All information regarding blood collection tubes is presented in Table 1.

Table 1. Volume of blood in different test tubes

Test tube	Blood volume	Designated for:
EDTA tube	6 ml	Whole blood
Heparin gel tube	6 ml	Heparin plasma extraction
SST tube	8.5 ml	Serum extraction
Total blood:	22.5ml	

- The whole blood sample (6ml) collected in the EDTA tube will be stored at -80°C, as indicated in Table 2.

Table 2. Volumes and use of EDTA whole blood sample.

Whole blood aliquot no.	EDTA volume	Designated for the analysis of:
1	6 ml	HbA1c

- The blood (8.5ml) collected in the SST tube will be left to separate at room temperature for 20 mins and then centrifuged at 3000 rpm for 10 min. The extracted (heparin) plasma will be pipetted into 4 aliquots of 1 ml (considering a 50% efficiency of centrifugation in plasma extraction). One aliquot of 1ml will be used for determining glucose, insulin, lipids, LFT and hsCRP, while the 3 aliquots of 1ml each will be stored at -80°C, as indicated in Table 3.

Table 3. Volumes and use of SST plasma aliquots.

Plasma aliquot no.	EDTA plasma volume	Designated for the analysis of:
1	1000 µl	Glucose, insulin, lipids, LFT, hsCRP
		Designated for:
2	1000 µl	Storage at -80°C
3	1000 µl	Storage at -80°C
4	1000 µl	Storage at -80°C

- The blood (6 ml) collected in the heparin tube will be centrifuged at 3000 rpm for 10 min and the extracted plasma will be pipetted into 3 aliquots of 600 µl (considering a 50% efficiency of centrifugation in plasma extraction). One aliquot of 600 µl will be used for determining cytokine concentrations, while the remaining 3 aliquots of 500 µl each will be stored at -80°C, as indicated in Table 4.

Table 4. Volumes and use of heparin plasma aliquots.

Plasma aliquot no.	Heparin plasma volume	Designated for the analysis of:
1	1ml	Cytokines (IL-1 β , IL-6, IL-8, IL-10, and TNF)
		Designated for:
2	1ml	Storage at -80°C
3	1ml	Storage at -80°C
4	1ml	Storage at -80°C

NOTE: It is essential that ONLY NON-HAZARDOUS waste be placed in the wastepaper/ general rubbish bins. Pipette tips should be disposed in sharps containers, whereas laboratory and associated waste directly involved in specimen processing (i.e blood collection tubes, gloves etc) must be disposed in biological waste bags.

1.4 Blood storage

Eppendorf tubes or screw cap tubes must be clearly labelled with identification, media used and date, placed in a freezer well rack and should not be stored for long periods on a bench, but must be transferred with an ice esky box to a dedicated storage area (i.e. refrigerator, cold room or cupboard) as soon as possible.

Laboratory coats must be removed and hung up before leaving laboratory areas and should be laundered once a week. Hands must be washed with an antibacterial agent BEFORE leaving laboratory (Hibiclens/Microshield or equivalent, followed by extensive rinsing).



Participant Information Sheet/Consent Form

Interventional study - Adult providing own consent

Title	Optimising outcomes for people with knee pain through food: FEAST randomised controlled trial
Short Title	The FEAST trial
Ethics Reference Number	HEC22044
Project Sponsor	La Trobe University
Coordinating Principal Investigator/ Principal Investigator	Dr Adam Culvenor (School of Allied Health, Human Services and Sport (SAHHSS), La Trobe University)
Associate Investigator(s)	Dr Brooke Devlin (School of Human Movement and Nutrition Sciences, University of Queensland) Prof. Peter Brukner (SAHHSS, La Trobe University) Ass. Prof. Joanne Kemp (SAHHSS, La Trobe University) Prof. Kay Crossley (SAHHSS, La Trobe University) Dr Andrea Mosler (SAHHSS, La Trobe University) Dr Josh Heerey (SAHHSS, La Trobe University) Ms Lynette Law (PhD student, SAHHSS, La Trobe University) Ms Amanda Attanayake (SAHHSS, La Trobe University)
Location	La Trobe University

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project because you have knee pain. This research project aims to assess the effectiveness of two different programs provided through advice and education by a qualified dietitian to improve your knee pain, function and quality of life.

This information sheet tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the project. Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Your participation is voluntary

Participation in this research is completely voluntary and there will be no cost to you. If you don't wish to take part, you don't have to. If you decide you want to take part, you will be given a copy of this Participant Information Sheet and asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participation Information Sheet and Consent Form to keep.

2 What is the purpose of this research?

As you may be aware, knee pain is very common and is often associated with knee osteoarthritis. Osteoarthritis is the most common form of arthritis and is a leading cause of disability in Australia. Currently, there is no cure for osteoarthritis, therefore it is important to investigate treatments that can improve the main symptoms associated with osteoarthritis: pain, swelling, stiffness and movement difficulties. We will recruit 140 adults who have knee pain.

This study is being conducted by researchers at La Trobe University and is partly funded by the National Health and Medical Research Council (NHMRC) of Australia and Dr Peter Brukner. All assessments and consultations will be at **no cost** to you.

3 Who can participate?

You can participate in this study if you meet all the following:

- Between 45-85 years of age and understand written and spoken English
- Activity-related knee pain on most days of the past month
- Knee pain for at least 3 months
- No morning knee stiffness, or morning stiffness that lasts less than 30mins
- Willing to complete the assigned 12-week eating program and attend all appointments (detailed below)

You are not eligible and cannot participate in this study if you meet any of the following:

- Knee pain not primarily due to osteoarthritis (e.g., fibromyalgia, referred pain)
- Bilateral knee replacement
- Already strictly following a specific diet (e.g., low-carb, paleo, Mediterranean, Vegan)
- Received treatment from a dietitian, or knee injection, in the past 3 months
- Experienced ≥ 5 kg weight loss in the past 3 months or body weight ≥ 200 kg
- Planning to have knee surgery in the next 6 months
- Pregnant or breastfeeding
- History of psychiatric or eating disorder (excluding anxiety/depression) or bariatric surgery

4 What does participation in this research involve?

This study will be conducted over 6 months in total (see flowchart on next page).

Pre-baseline (online/phone) appointment

You will be asked to attend a 30-minute Zoom/telephone appointment prior to your first face-to-face appointment. At this appointment, we will discuss the consent form, outline the fasting process needed to complete your blood test and DEXA scan, and answer any questions you might have. We will also explain how to complete a 3-day food diary, which will be done using a smart phone application or paper-based food diary (personal preference).

Baseline (first) appointment

This appointment will be arranged at a convenient time for you at La Trobe University, Bundoora and will take approximately 2 hours. You will be asked to not eat/drink anything or conduct any exercise in the morning of your appointment (i.e., fasting for 12-hours) for the purpose of a blood test. At the appointment, we will assess your:

- Height, weight, waist circumference and blood pressure
- Body composition measured via a Dual-energy X-ray Absorptiometry Scan (DEXA).
This involves laying on the scanner bed for ~7 mins. The machine uses small doses (<1% yearly dose) of radiation to assess tissue density (how much muscle and adipose tissue you have). The total effective dose of radiation has been calculated by a Medical Physicist (see risks below). Light clothing with no metal (e.g., zips, clips, underwire) should be worn (gown provided if needed). All measures will be taken by trained

researchers who hold Victorian Government radiation licenses and comply to the Code of Practice set out by the Australian Radiation Protection and Nuclear Safety Agency.

- Blood test: A trained researcher qualified to take blood will collect a small amount of blood (~25 mL, equivalent to ~4 teaspoons) from a forearm vein to assess inflammation levels.
- Questionnaires assessing your pain, activity level and quality of life and food intake
- Functional tests: i) how many times you can stand from a chair in 30 secs; and ii) how fast you can walk 40 metres.

We will provide a snack/drink as soon as you complete the DEXA and blood tests.

Random assignment to one of two different treatments

At the end of the first appointment at La Trobe University, you will be randomly assigned (50:50 chance, like a coin toss) to receive a program (from qualified dietitians) to either:

- minimise processed foods that are known to promote inflammation and optimise foods shown to reduce inflammation; or
- minimise foods that are known to be high in fat content.

This means neither you nor the researchers will be able to choose which group you are assigned to. We do not know which treatment is best; to find out we need to compare the two programs. Although the two programs involve modifying some types of food that you eat, you can eat as much as you like of these foods. **You do not need to restrict the amount of food that you eat.**

Irrespective of which group you are assigned to, you will receive specific education and advice from an Accredited Practising Dietitian (APD) in a dietary consultation at the start of the study (at the end of your first appointment at La Trobe University). Your dietitian will also work with you to develop a personalised management plan to support you throughout the study. You will be asked to follow the program for 12 weeks (but you can continue for as long as you like). We will ask you to record your food intake for 3 days at up to six different times throughout the study.

Support phone calls

To support you throughout the study and answer any questions you have, we will arrange up to four follow-up consultations to be conducted over the phone/online during the 12 weeks. This phone call will take approximately 15-20 minutes. At these times, we will also ask you to complete some of the same questionnaires online (via a secure link provided by e-mail).

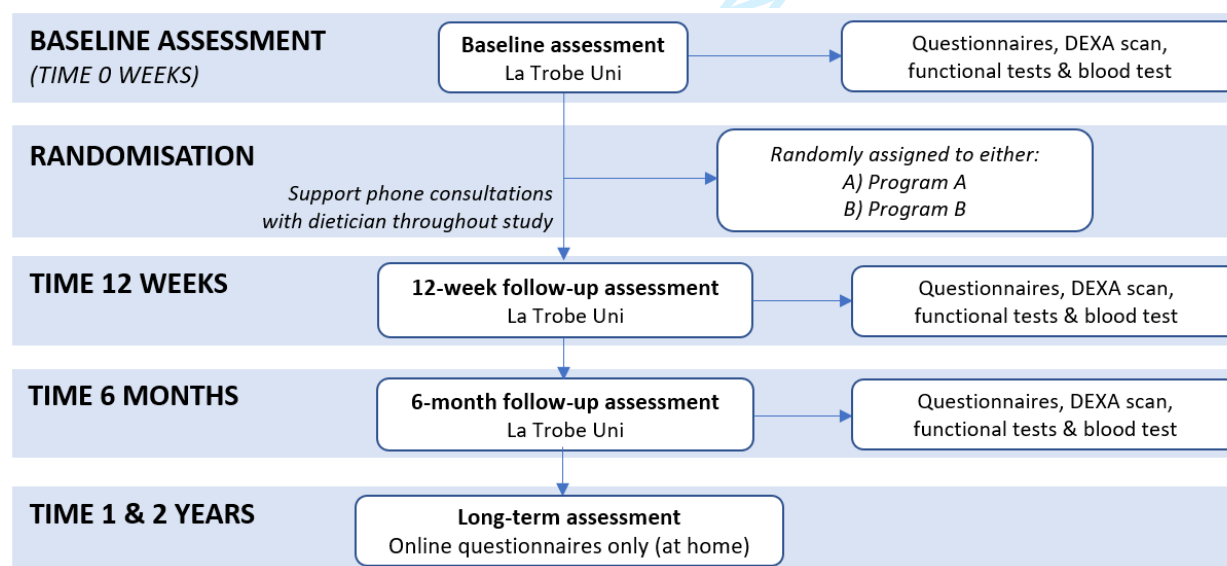


Figure 1. Flowchart of study assessments

Follow-up appointments

So that we can assess the results of the program you have been assigned, we will ask you to return for face-to-face appointments at La Trobe University at **12 weeks and 6 months after your first appointment.** These follow-up appointments will be like the first appointment where

1 we will do all the same tests and questionnaires. You will need to fast (not eat/drink anything) the
2 morning of your appointment for the blood test. You will have another dietary consultation with
3 the study dietitian who will provide support for you to continue with the program you have been
4 assigned. You should allow about 2 hours for these appointments. To assess longer-term results,
5 we will ask you to complete the same online questionnaires at 1 and 2 years after your first
6 appointment. The total time commitment for participating will be approximately 6-8 hours.
7

8
9 There are no additional costs associated with participating in this research project. All medical
10 care and tests (i.e., dietitian consultations, DEXA scan, blood tests) required as part of the
11 research project will be provided free of charge. The results of the DEXA scan and blood tests
12 will not be used to diagnose health conditions, but only to evaluate the effects of the intervention.
13 We will provide you with your individual results when the DEXA and blood analyses are completed
14 at the end of the study. Your travel costs to attend the assessments will be reimbursed up to \$100.
15

16
17 At the end of the first 12 weeks, or after 6-12 months, we may also ask if you are willing to have
18 a separate interview with one of the study researchers (this interview is optional and you can take
19 part in the study without needing to complete the interview). The purpose of this interview is to
20 seek feedback on the study treatments, satisfaction with the process received and whether there
21 are any suggestions for improvement. The interview will take approximately 30 minutes, but you
22 can cease the interview at any time. To ensure responses are correctly interpreted, responses to
23 questions will be audio recorded and transcribed. Audio recording transcriptions will be completed
24 by 'Transcription Australia' on their secure, encrypted Australian-based software. Although voice
25 in your audio recording could lead to your identification, this file will not be used during analysis.
26 Instead, a re-identifiable transcription, which you will have the opportunity to check for accuracy,
27 will be used for analysis. Re-identifiable means that we will use a code number and not your name
28 on data collected to ensure your anonymity. Following the completion of analysis of this
29 transcription, the audio file associated with your interview will be deleted. After analysis, overall
30 findings and conclusions from all interviews will also be sent to you, to allow an opportunity to
31 make any further comments. We will seek around 40 participants to be interviewed. It is your
32 decision or not whether you wish to be interviewed.
33

34 35 **5 What are the alternatives to participation?**

36
37 You do not have to take part in this research project to receive treatment for your knee. Other
38 options are available; these include seeing a physiotherapist or dietitian (e.g., private or public
39 health centre). The research team will discuss these options with you before you decide to take
40 part in this project. You can also discuss the options with your doctor, dietitian or physiotherapist.
41

42 43 **6 What are the possible benefits of taking part?**

44
45 We cannot guarantee or promise that you will receive any benefits from this research. However,
46 possible benefits may include improvement of pain, function, quality of life, physical activity, and
47 confidence in your knee. You may gain valuable insight into how to manage your food intake and
48 specific anti-inflammatory and low-fat foods, nutrients and eating habits. The expected benefit to
49 society is the development of a drug-free and non-invasive treatment option to help manage pain
50 and disability associated with osteoarthritis. This will give doctors and patients alternative ways
51 to manage knee pain, which in turn may lead to improvements in the quality of life for patients.
52
53

54 55 **7 What are the possible risks and disadvantages of taking part?**

56
57 With any medical treatment there are: (i) risks we know about; (ii) risks we don't know about; and
58 (iii) risks we don't expect. We have listed the risks we know about below. You may have none,
59 some or all the effects listed below, and they may be mild, moderate or severe. If you have any
60 of these side effects, or are worried about them, talk with the study coordinator.

Possible Side Effect	How often is it likely to occur?	How severe might it be?	How long might it last?
Emotional distress due to involvement in research and completion of questionnaires	Rarely; although can occur when completing study questionnaires	Minimal	While completing the study questionnaires
Emotional distress due to diet assessment	Rarely; although can occur when assessing food intake prior to, or during, appointments	Minimal	While completing the food diary or assessment
Discomfort due to body measurements	Can occur while measurements are done by your dietitian or researcher	Minimal Mild	During appointment only
Discomfort due to blood test	Rarely; while blood is being collected	Mild	Bruising or swelling may last 1-3 days
Exposure to ionising radiation	1x 7-minute scan at initial, 12-week and 6-month appointment	Minimal	Effect too small to measure
Tiredness/change in bowel patterns with change in diet	Any change in diet can make you feel tired or have different bowel patterns	Minimal	1-2 weeks
Contraction of COVID-19	Can occur during the face-to-face assessments	Minimal Moderate	1-2 weeks

If you become upset or distressed because of your participation in the research, the study coordinator together with the qualified dietitian will assist you with appropriate support. We can also provide you information about services you can access to seek help for emotional distress.

Risks associated with completing study questionnaires and diet assessment

Completing questionnaires about your knee pain, function, quality of life and dietary intake may cause emotional distress. If you begin to feel upset or distressed when completing your questionnaires or dietary assessment, please let a member of the research team know. We will provide you with the appropriate support, including a document outlining services you can access to help with your emotional distress.

Risks associated with blood test

Having a blood sample taken may cause some discomfort or bruising. On very rare occasions, the blood vessel may swell, or blood may clot in the blood vessel, or the spot from which blood is taken could become inflamed. Some people may feel light-headed when having blood taken and may occasionally faint. Very rarely, there could be a minor infection or bleeding. A qualified person will take a very small amount of your blood (max 30mL each appointment (normal blood donation is 500mL)) using stringent infection control procedures. If you notice increased redness, swelling or other signs of infection in the days following your assessment, tell us immediately.

Risks associated with eating low-inflammatory foods or low-fat foods

As you adjust to the eating program you are assigned to, you may experience feelings of tiredness and/or changes in bowel habits and patterns. The researchers will assess your diet and ensure you are meeting your energy and nutrient needs throughout the study intervention. This eating program may be different than your normal diet and therefore influence your usual weekly shopping bill and expenses. As part of the consultations, you will be provided with some advice on how to follow the diet on a budget if required to ensure there is minimal financial burden.

Exposure to ionising radiation

If you choose to take part in this research, you will undergo three 7-minute DEXA scans (first, 12-week and 6-month assessments). DEXA scans are a non-invasive, fast and simple procedure. This research study involves exposure to a very small amount of radiation from a DEXA scan that you would not normally receive. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose you will receive from all of these DEXA scans is approximately 0.03 mSv. At these

1 dose levels, no harmful effects of radiation have been demonstrated as any effect is too small to
2 measure. The risk is believed to be minimal.
3

4
5 The scans we are taking are for research purposes and are not intended to be used like scans
6 taken for a full clinical examination or to be used to help diagnose, treat or manage a particular
7 condition. The whole-body DEXA scan may identify participants with a low bone mineral density.
8 However, a whole body DEXA scan is not the established method for detecting low bone mineral
9 density. Therefore, as a precaution if you are identified as having a low bone mineral density you
10 will be encouraged to make an appointment with your General Practitioner to discuss the results.
11

12 Have you been involved in any other research studies that involve radiation? If so, please tell us.
13 Please keep information contained within this Patient Information Sheet about your exposure to
14 radiation in this study, including the radiation dose, for at least 5 years. You will be required to
15 provide this dose to researchers of any future research projects involving exposure to radiation.
16

17 **Contraction of COVID-19**

18 You may be at risk of contracting COVID-19 during one of the face-to-face appointments at La
19 Trobe University. Prior to attending La Trobe University, you will be screened for signs and
20 symptoms of COVID-19 by a member of the research team. You will also need to be fully
21 vaccinated (or hold a valid medical exemption) to be able to attend La Trobe University for your
22 assessments. The research team will put in place the appropriate control measures to reduce the
23 risk of COVID 19 transmission. The risk is believed to be minimal.
24

25 **8 What if I withdraw from this research project?**

26
27 You are under no obligation to continue with the research study. You may change your mind at
28 any time about participating in the research. People withdraw from studies for various reasons,
29 and you do not need to provide a reason.
30

31
32 You can withdraw from the study at any time by completing and signing the 'Participant
33 Withdrawal of Consent Form'. This form is provided at the end of this document and is to be
34 completed by you and supplied to the research team if you choose to withdraw at a later date.
35

36
37 If you withdraw from the study, you will be able to choose whether the study will destroy or retain
38 the information it has collected about you. Information about you that has already been analysed
39 (i.e., once you have been allocated to either program), may not be able to be destroyed to ensure
40 accurate and unbiased study reporting. Personal details collected, such as your name and contact
41 details, can be destroyed at any time upon study withdrawal.
42

43 **9 What happens when the research project ends?**

44
45 At the completion of the research project, you may continue to use the resources provided and to
46 follow the eating program principles if you choose to. If requested, we will provide you with your
47 individual results including your body composition (DEXA) assessment and whole study results.
48 We, or other researchers, may also use coded information (so that you cannot be identified)
49 collected for this research study in future related studies. If you consent (tick the box on the
50 consent form) to be contacted for future related research, we will store your contact details (name,
51 address, phone number, email) on the secure La Trobe University research drive, only accessible
52 to members of the research team, and may contact you about future related research projects.
53
54
55

56 **Part 2 How is the research project being conducted?**

57 **10 What will happen to information about me?**

1 By signing the consent form you agree to the relevant research staff collecting and using personal
2 information about you for the research project. Any information obtained in connection with this
3 research project that can identify you will remain confidential and securely stored. It will be
4 disclosed only with your permission, or in compliance with the law.
5

6 **Storage, retention and destruction**

7 The anonymity of your participation is assured with our procedure, in which a code number (not
8 your name) will identify you. Data will be kept securely at La Trobe University in a locked filing
9 cabinet and password protected research computer. Identifiable data will be stored for 15 years,
10 then destroyed (electronic records deleted, paper-files shredded). Data will be strictly handled
11 confidentially under guidelines set out by the National Health and Medical Research Council. The
12 principal investigator (Dr Adam Culvenor) is responsible for maintaining this confidentiality.
13

14
15 In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have
16 the right to request access to your information collected and stored by the research team. You
17 also have the right to request that any information with which you disagree be corrected.
18

19 The results of this project may be published and/or presented in a variety of forums and used by
20 research students to obtain a research degree. In any publication, presentation or data files
21 shared with other researchers, information will be provided in such a way that you cannot be
22 identified, except with your permission.
23

24 **11 Who is organising and funding the research?**

25
26 This research project is being conducted by Dr Adam Culvenor and a team of researchers. It has
27 been funded by the NHMRC (GNT2008523) and Dr Peter Brukner. Dr Peter Brukner is also an
28 investigator on the project and has written a book and developed an app that will be used as part
29 of the study. He will not be involved in data collection, analysis or the decision to publish results.
30 No member of the research team will receive a personal financial benefit from your involvement
31 in this research project (other than their ordinary wages).
32

33 **12 Who has reviewed the research project?**

34
35 All research in Australia involving humans is reviewed by an independent group of people called
36 a Human Research Ethics Committee (HREC). The ethical aspects of this research project have
37 been approved by the HREC of La Trobe University Human Ethics Committee.
38

39 This project will be carried out according to the *National Statement on Ethical Conduct in Human*
40 *Research (2018)*. This statement has been developed to protect the interests of people who agree
41 to participate in human research studies.
42

43 **13 Further information and who to contact**

44 For all enquiries, you can contact the Clinical Trial Manager, during business hours:
45 Dr Adam Culvenor, Senior Research Fellow in Physiotherapy, La Trobe University
46 Telephone: 03 9479 5116; E-mail: a.culvenor@latrobe.edu.au
47

48 If you have any complaints about any aspect of the project, the way it is being conducted or any
49 questions about being a research participant in general, then you may contact:
50

51 Reviewing HREC: La Trobe University Human Research Ethics Committee
52 Complaints Contact: Senior Human Ethics Officer, Ethics and Integrity, Research Office
53 Telephone: 03 9479 1443 E-mail: humanethics@latrobe.edu.au
54

55 * Please quote the application reference number HEC22044
56



Consent Form - *Adult providing own consent*

Title Optimising outcomes for people with knee pain through food: FEAST randomised controlled trial

Short Title The FEAST trial

Ethics Reference Number HEC22044

Project Sponsor La Trobe University

**Coordinating Principal Investigator/
Principal Investigator** Dr Adam Culvenor (La Trobe University)
Dr Brooke Devlin (University of Queensland)
Prof. Peter Brukner (La Trobe University)
Ass. Prof. Joanne Kemp (La Trobe University)

Associate Investigator(s) Prof. Kay Crossley (La Trobe University)
Dr Andrea Mosler (La Trobe University)
Dr Josh Heerey (La Trobe University)
Ms Lynette Law (PhD student, La Trobe University)
Ms Amanda Attanayake (SAHHSS, La Trobe University)

Location La Trobe University

Consent Agreement

I have read the Participant Information Sheet and I understand the purposes, procedures and risks of the research described in the project.

I understand that data files may be shared with other researchers, and that information will be provided in such a way that I cannot be identified, except with my permission.

I have had an opportunity to ask questions and I am satisfied with the answers I have received. I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. I agree that data gathered for the study may be published provided my name or other identifying information is not used.

- I wish... / do not wish... to receive results of the study
- I consent... / do not consent... to be contacted for future related research
- I consent... / do not consent... to have my interview responses audio-recorded/transcribed.
- I consent... / do not consent... to have my samples/data used in future research

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Researcher[†]

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Researcher[†] (please print) _____

Signature _____ Date _____

[†] An appropriately qualified member of the research team must provide the explanation of, and information concerning, the research project.



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	ACTRN1262200 0440729
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			

1				
2				
3				
4	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
5				
6				
7	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
8				
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10				
11	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-13, Table 2, Supplementary File 1
12				
13				
14		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Table 2
15				
16				
17				
18		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8-13, Table 2
19				
20				
21		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
22				
23				
24	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-18, Table 3
25				
26				
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30	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
31				
32				
33				
34	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19
35				
36				
37				
38	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
39				

Methods: Assignment of interventions (for controlled trials)

Allocation:

43				
44	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8
45				
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50	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7-8
51				
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55	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
56				
57	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7-8
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	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
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Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
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	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
-----------------	----	---	----

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
---------------------	-----	--	----

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
--	-----	--	----

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
--	-----	---	----

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
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	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19-20
--	-----	---	-------

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
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Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
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Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
--------------------------	----	---	----

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2				
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4	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20
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8	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20
9				
10				
11		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
12				
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14	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
15				
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18	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
19				
20	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Supplementary File 1
21				
22				
23				
24	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
25				
26	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
27				
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32		31b	Authorship eligibility guidelines and any intended use of professional writers	NA
33				
34				
35		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
36				
37				
38	Appendices			
39	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary File 1
40				
41				
42				
43	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Supplementary File 2
44				
45				

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-Non Commercial-No Derivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

The effectiveness of an anti-inflammatory diet versus low-fat diet for knee osteoarthritis: the FEAST randomised controlled trial protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-079374.R2
Article Type:	Protocol
Date Submitted by the Author:	04-Mar-2024
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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Chronic Disease, REHABILITATION MEDICINE, NUTRITION & DIETETICS

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Manuscripts

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4 1 **The effectiveness of an anti-inflammatory diet versus low-**
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6 2 **fat diet for knee osteoarthritis: the FEAST randomised**
7
8
9 3 **controlled trial protocol**
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11 4

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3
4 30 **ABSTRACT**

5
6 31 **Introduction:** Chronic inflammation plays a key role in knee osteoarthritis pathophysiology
7
8 32 and increases risk of comorbidities, yet most interventions do not typically target
9
10 33 inflammation. Our study will investigate if an anti-inflammatory dietary program is superior
11
12 34 to a standard care low-fat dietary program for improving knee pain, function and quality-of-
13
14 35 life in people with knee osteoarthritis.

15 36 **Methods and analysis:** The FEAST (eFEct of an Anti-inflammatory diet for knee oSTeoarthritis)
16
17 37 Study is a parallel-group, assessor-blinded, superiority randomised controlled trial. Following
18
19 38 baseline assessment, 144 participants aged 45-85 years with symptomatic knee osteoarthritis
20
21 39 will be randomly allocated to one of two treatment groups (1:1 ratio). Participants
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23 40 randomised to the anti-inflammatory dietary program will receive six dietary consultations
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25 41 over 12 weeks (2 in-person, 4 phone/videoconference) and additional educational and
26
27 42 behaviour change resources. The consultations and resources emphasise nutrient-dense
28
29 43 minimally processed anti-inflammatory foods and discourage pro-inflammatory processed
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31 44 foods. Participants randomised to the standard care low-fat dietary program will receive
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33 45 three dietary consultations over 12 weeks (2 in-person, 1 phone/videoconference) consisting
34
35 46 of healthy eating advice and education based on the Australian Dietary Guidelines, reflecting
36
37 47 usual care in Australia. Adherence will be assessed with 3-day food diaries. Outcomes are
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39 48 assessed at 12 weeks and 6 months. The primary outcome will be change from baseline to 12
40
41 49 weeks in the mean score on four Knee injury and Osteoarthritis Outcome Score (KOOS₄)
42
43 50 subscales: knee pain, symptoms, function in daily activities and knee-related quality-of-life.
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45 51 Secondary outcomes include change in individual KOOS subscale scores, patient-perceived
46
47 52 improvement, health-related quality-of-life, body mass and composition using dual-energy X-
48
49 53 ray absorptiometry, inflammatory (high-sensitivity C-Reactive Protein, Interleukins, Tumour
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51 54 Necrosis Factor- α) and metabolic blood biomarkers (glucose, HbA1c, insulin, liver function,
52
53 55 lipids), lower-limb function and physical activity.

54
55 56 **Ethics and Dissemination:** Approved by La Trobe University Human Ethics Committee. Results
56
57 57 will be presented in peer-reviewed journals and at international conferences.

58 58 **Trial registration:** ACTRN12622000440729
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3 59 **Keywords:** Inflammation, Low-carbohydrate, Anti-inflammatory, Pain, Osteoarthritis, Knee,
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5 60 Chronic disease, Rehabilitation, Diet
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11 62 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
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14 63 • The anti-inflammatory dietary program was codeveloped and piloted with patients and
15 64 clinicians, with the comparison low-fat dietary program representing usual care.
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17
18 65 • Sufficiently powered trial evaluating change from baseline to 12 weeks (primary endpoint)
19 66 and 6 months facilitating longer-term effectiveness evaluation of the anti-inflammatory
20 67 dietary program.
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24 68 • This trial will evaluate both self-reported and objective outcomes to understand potential
25 69 mechanisms of symptomatic changes.
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29 70 • While outcome assessors are blinded to group allocation, the health professionals
30 71 delivering the interventions and participants are unable to be blinded to group allocation
31 72 due to the type of interventions.
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73 INTRODUCTION

74 Osteoarthritis (OA) is the most common rheumatic disease affecting approximately 15% of
75 the population, with OA of the knee being most prevalent.(1, 2) Knee OA and its associated
76 symptoms can be disabling and lead to substantial societal and healthcare costs.(3) In
77 Australia alone, annual OA-related healthcare expenditure exceeds \$2.1 billion.(4) Although
78 the main symptom of knee OA is pain, individuals with knee OA have an increased risk of
79 other chronic diseases, including cardiovascular disease and diabetes.(5) As many as two-
80 thirds of older adults with knee OA have more than one comorbidity.(6)

81
82 Clinical guidelines for knee OA recommend exercise-therapy and weight-loss as first-line
83 management strategies due to their excellent safety profile and therapeutic effects similar to
84 commonly used analgesics.(3, 7) However, the effectiveness of exercise-therapy has recently
85 been questioned due to its lack of benefit over an open-label placebo,(8) and findings that
86 one-third of people completing an exercise program do not achieve a clinically meaningful
87 improvement in pain.(9, 10) Weight-loss programs in those who are overweight or obese
88 typically consist of caloric restrictive diets, which are challenging to adhere to and sustain.(11)
89 A meta-analysis highlighted that, within two years of a calorie-restrictive program, over half
90 of initial weight lost was regained, and by 5 years, this figure jumped to >80%.(12)

91
92 Anti-inflammatory diets provide an alternative to calorie-restrictive approaches by targeting
93 local and systemic inflammation, both contributors to OA disease onset, progression and
94 symptom burden.(13-15) Anti-inflammatory diets are typically high in minimally processed,
95 nutrient rich foods such as fruit, vegetables, spices and extra virgin olive oil, which are dense
96 in nutrients such as polyphenols, carotenoids, fibre, monounsaturated and polyunsaturated
97 fatty acids.(16-19) These nutrients can significantly reduce inflammation even in the absence
98 of weight loss(20) via antioxidant and anti-inflammatory properties by neutralising free
99 radicals and associated cell damage, as well as improved lipid profiles.(16, 17, 21) Omega-3
100 fatty acids, abundant in nuts, seeds and fish, are also a key part of anti-inflammatory dietary
101 approaches and help to achieve a more desirable omega-6 to omega-3 ratio.(22) In contrast,
102 omega-6 fatty acids can be converted into arachidonic acid, a precursor for proinflammatory
103 eicosanoids.(23) An elevated omega-6:omega-3 ratio exacerbates oxidative stress, which

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3 104 increases the risk and severity of chronic disease, including OA.(15) Due to their focus on real
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5 105 foods and consumption to satiety, anti-inflammatory diets are likely more sustainable than
6
7 106 traditional calorie-restrictive approaches.(17)
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11 108 Anti-inflammatory diets have garnered much interest in recent years due to their
12
13 109 effectiveness in alleviating symptoms and improving biomarkers for a variety of chronic
14
15 110 diseases, including diabetes,(18) cardiovascular disease,(24) epilepsy(25) and rheumatoid
16
17 111 arthritis.(26) Small studies investigating anti-inflammatory diets for knee OA have
18
19 112 demonstrated feasibility and effectiveness in reducing symptoms and inflammation over 12-
20
21 113 16 weeks.(15, 27, 28) To date, no fully powered randomised controlled trial (RCT) has
22
23 114 evaluated the effectiveness of an anti-inflammatory diet in knee OA.
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25 115
26 116 The primary aim of this RCT is to estimate the average effect of an anti-inflammatory dietary
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28 117 program compared to a standard care low-fat dietary program on knee-related pain, function
29
30 118 and quality of life in individuals with knee OA. We hypothesise that the anti-inflammatory
31
32 119 dietary program will result in greater improvements in knee-related pain, function and quality
33
34 120 of life after 12 weeks (primary endpoint) and 6 months (secondary endpoint) compared to
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36 121 the standard care low-fat dietary program. Secondary aims are to assess 12-week and 6-
37
38 122 month effectiveness of the anti-inflammatory dietary program on: i) self-reported global
39
40 123 rating of change and achievement of acceptable symptoms; ii) health-related quality of life;
41
42 124 iii) body mass and composition using dual-energy X-ray absorptiometry (DXA); iv)
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44 125 inflammatory and metabolic blood biomarkers, global lower-limb function and physical
45
46 126 activity.
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48 128 **METHODS AND ANALYSIS**

49 129 **Study Design**

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51
52 130 This protocol describes a pragmatic, 2-arm, parallel-group assessor-blinded superiority RCT
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54 131 and will be reported according to the Standard Protocol Items: Recommendations for
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56 132 Interventional Trials (SPIRIT) statement.(29) Reporting of the completed RCT will conform to
57
58 133 the Consolidated Standards of Reporting Trials (CONSORT) statement.(30) The FEAST trial will
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60 134 be conducted at a single site (La Trobe University) in Melbourne, Australia with the first

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2
3 135 participant randomised on August 31, 2022 and the final participant anticipated to be
4
5 136 randomised in June 2024. The primary endpoint will be at 12 weeks, with additional follow-
6
7 137 up at 6 months (further longer-term follow-up dependent on funding). The study was
8
9 138 prospectively registered on the Australian and New Zealand Clinical Trial Registry (ACTRN
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11 139 12622000440729).

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141 **Patient and public involvement**

142 Participants and clinicians co-designed the anti-inflammatory intervention, research
143 questions and study methods. This input was gained from: i) qualitative interviews with
144 participants from the pilot study as part of formal process evaluation strategies;(28) ii)
145 participant and clinician focus groups providing feedback on study recruitment material and
146 participant handbooks; and iii) discussion with experienced clinicians managing knee OA and
147 dietary intervention strategies as part of FEAST development. Patients and clinicians will
148 provide input into the dissemination of study results by assisting with the decision on what
149 information to share and in what format.

150

151 **Participants**

152 One hundred and forty adults 45-85 years old with chronic knee pain consistent with a clinical
153 OA diagnosis using criteria from the National Institute for Health and Care Excellence, which
154 does not require radiographic evidence,(31) will be enrolled (table 1).

155

156 **Table 1.** Eligibility criteria

Inclusion criteria	Exclusion criteria
Fulfil National Institute for Health and Care Excellence(31) clinical criteria for osteoarthritis:	Another reason than OA for knee symptoms (e.g., tumour, fibromyalgia)
<ul style="list-style-type: none"> • Activity-related joint pain with average knee pain severity ≥ 4 on 11-point numeric rating scale (NRS, where 0 = no pain, 10 = worst pain possible) in the past week; • No morning stiffness or morning stiffness ≤ 30 min; and • Age ≥ 45 years 	

Age ≤85 years – due to potential safety reasons and additional co-morbidities that may hinder capacity for dietary adherence	Planning to have knee surgery in next 6 months
History of knee pain on most days of the past month	Already strictly following an anti-inflammatory diet (e.g., low carbohydrate, high-fat, paleo, Mediterranean)
History of knee pain for at least 3 months	Following a habitual diet that excludes animal products (e.g., vegan)
Be willing and able to attend 3-4 phone consults and 12-week and 6-month follow-up assessments	Unable to follow anti-inflammatory diet (e.g., medically contraindicated, history of food allergy/hypersensitivity, family reasons)
Able to understand written and spoken English, and to give informed consent	Taking the following diabetic medication that affects blood sugar levels (i.e., insulin, SGLT 2 inhibitors, sulfonylureas) to mitigate the risk of hypoglycaemia/ketoacidosis
	Contraindications for DXA scans (e.g., pregnant, breastfeeding, planning pregnancy in next 6 months, >200kg body weight)
	>5kg weight fluctuation in past 3 months (i.e., unstable weight)
	Unable to understand written and spoken English
	Knee injection, injury or surgery in the past 3 months
	A diagnosed psychiatric disorder (excluding anxiety and depression)
	History of eating disorder or bariatric surgery
	Had all eligible knee joints replaced by arthroplasty

157 NRS, numeric rating scale; SGLT, sodium glucose co-transporter; DXA, dual-energy X-ray

158 absorptiometry

159

160 **Recruitment and screening procedure**

161 Trial flow is outlined in figure 1. Participants will be recruited from our network of
 162 collaborating orthopaedic surgeons in Victoria, Australia. Consistent with our prior work in
 163 other musculoskeletal conditions,(32, 33) potentially eligible participants (i.e., individuals
 164 aged 45-85 years with a history of knee pain for which medical care was sought) will be sent
 165 a study information letter inviting them to contact the research team. Additional recruitment

166 strategies will include advertisements in local newspapers, community/university
167 magazines/posters, community market stalls and social media.

168

169 *****FIGURE ONE HERE*******

170

171 Potential participants will be screened for eligibility via telephone. Once eligibility is
172 confirmed, participants will attend a study orientation session via videoconference to explain
173 further study details (e.g., fasting requirements) and be orientated to the dietary assessment
174 tool (3-day food diary). If both knees meet the inclusion criteria, the most symptomatic knee
175 will be considered as the index knee.

176

177 *Randomisation procedure, concealment of allocation and blinding*

178 Upon completion of baseline assessment, participants will be randomised to either the anti-
179 inflammatory dietary program or standard care low-fat dietary program. Study treatments,
180 but not study hypotheses, will be revealed to participants. A computer-generated
181 randomisation schedule has been developed *a priori* by an independent statistician in random
182 permuted blocks of 4-8 and stratified by sex and body mass index ($\geq 30\text{kg}\cdot\text{m}^{-2}$ vs $< 30\text{kg}\cdot\text{m}^{-2}$).
183 To ensure concealed allocation, the randomisation schedule will be stored electronically in
184 the secure Research Electronic Data Capture (REDCap®) system and only accessible to an
185 unblinded researcher once baseline measures have been obtained, who will communicate
186 treatment allocation to the participant. Investigators conducting the follow-up assessments
187 will be blinded to group allocation. As the primary outcome is self-reported, participants are
188 considered assessors; therefore, they will be blinded to previous scores. The health
189 professionals delivering the interventions will deliver the intervention for both groups.
190 Specific protocols for both interventions (including consultation contents and format, and
191 accompanying resources) have been developed, and the health professionals have received
192 training to ensure equal credibility. Random observations of intervention delivery will be
193 conducted by the principal investigators to ensure treatment delivery credibility and fidelity.
194 An independent statistician, blinded to group allocation, will perform the primary RCT
195 analysis.

196

197 **Interventions**

198 The anti-inflammatory dietary program and standard care low-fat dietary program are
199 summarised aligning to Template for Intervention Description and Replication (TIDieR)
200 guidelines(34) (table 2). Participants in both intervention groups were not actively
201 discouraged to lose weight, but weight loss was described as a potential outcome of the
202 interventions. The same health professionals will deliver the intervention for both groups.

204 *Anti-inflammatory dietary program*

205 Participants allocated to the anti-inflammatory dietary program will receive specific anti-
206 inflammatory dietary education and an individualised eating plan, as well as a suite of
207 resources to support behaviour change. The anti-inflammatory dietary program will be
208 delivered over 12 weeks by a qualified dietitian or by another health professional specially
209 trained to deliver the intervention (e.g., physiotherapist).

210
211 Participants will be encouraged to follow a diet containing minimally-processed foods and
212 vegetable oils, and higher amounts of healthy fats and nutrient-dense wholefoods known to
213 fight inflammation (e.g., fresh fruits low in natural sugar such as berries, non-starchy
214 vegetables, nuts and seeds, seafood, poultry, red meat, eggs, full-fat dairy). Healthy fats
215 include monounsaturated and polyunsaturated fats with optimal omega-3: omega-6 ratios as
216 found in seafood, nuts, and extra-virgin olive oil. Participants will be advised to limit processed
217 foods, refined carbohydrates (e.g., pasta, bread, rice), confectionary and foods with added
218 sugar. Participants will be encouraged to consume a normocaloric diet and to eat to satiety,
219 with no specific percentage of total energy intake targets for carbohydrate, fat or protein.

220
221 An initial in-person consultation (~45 minutes) will occur immediately following group
222 allocation to constructively review participant's current dietary intake (using baseline 3-day
223 food diary) and develop an individualised meal plan. Participants will be provided with a
224 comprehensive explanation of anti-inflammatory dietary principles, its rationale (e.g., the role
225 of inflammation in OA, link between foods and inflammation) and its potential benefits and
226 side-effects, and address questions and/or concerns. The following educational and
227 behaviour change resources will also be provided at the initial consultation to support

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3 228 adherence: i) bespoke information booklet providing anti-inflammatory eating information,
4 229 example meal plans, and foods that are encouraged and foods to avoid (Supplementary file 1
5 230 and 2); ii) complimentary subscription to an anti-inflammatory program (Defeat Diabetes
6 231 phone app/website), providing anti-inflammatory recipes, masterclasses, meal plans and
7 232 educational articles; iii) complimentary links to recommended documentaries exploring the
8 233 benefits of anti-inflammatory nutrition (i.e., Fat Fiction, Cereal Killers, That Sugar Film); and
9 234 iv) complimentary copy of a book exploring benefits of anti-inflammatory approach (A Fat Lot
10 235 of Good(35)).
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20 237 Follow-up phone/videoconference consultations (~30 minutes) will be scheduled in weeks 2,
21 238 4, 6, and 9, with timing to be negotiated between each participant and the health professional
22 239 delivering the intervention. A final in-person consultation will be delivered immediately
23 240 following the completion of the 12-week assessment. These follow-up consultations will
24 241 provide participants with ongoing support, education and accountability. A 3-day food diary,
25 242 completed prior to each consultation (see outcomes/adherence section), will guide
26 243 individualised feedback and support to adapt meal plans to optimise adherence.
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244 **Table 2:** Overview of intervention delivery described according to the TIDieR guidelines

1. BRIEF NAME	Anti-inflammatory dietary program	Standard care low-fat dietary program
2. WHY	Anti-inflammatory diets targeting systemic inflammation assist in the prevention and management of various chronic diseases.(16) Small pilot studies have shown a positive effect of anti-inflammatory diets to improve knee-related symptoms in people with knee osteoarthritis.(28)	Healthy eating guidelines and dietary advice described in the standard care program booklet was based on Australian Dietary Guidelines (ADGs).(36, 37) Two-three dietetic consultations represent usual care for patients referred for dietary management in Australia.(37, 38)
3. WHAT (MATERIALS)	Participants receive an intervention handbook containing all study details, key anti-inflammatory eating principles, example meal plans, traffic light system of foods encouraged and discouraged, and education (e.g., common myths, tips for eating out, shopping tips); complimentary access to the Defeat Diabetes program app/website; complimentary links to three movies; and a complimentary copy of the book “A Fat Lot of Good”.(35)	Participants receive an educational handbook emphasising ADGs healthy eating principles and are provided links to the online resources from the Eat for Health website (https://www.eatforhealth.gov.au/).
4. WHAT (PROCEDURES)	Six consultations providing individualised guidance and support to follow an anti-inflammatory eating pattern, emphasising the consumption of fruits, non-starchy vegetables, fish, poultry, red meat, eggs, full-fat dairy, nuts, seeds, and extra virgin olive oil. Participants will be encouraged to avoid highly processed foods, refined carbohydrates, added sugar, and processed meats.	Three consultations providing general advice and education regarding healthy eating based on the ADGs. The principles focus on consumption of foods from the five food groups, while limiting intake of foods containing saturated fat, added salt, added sugars and alcohol.
5. WHO PROVIDED	A qualified dietitian or health professional specially trained to deliver all components.	A qualified dietitian or health professional specially trained to deliver all components.
6. HOW	Delivered with individual support for 12 weeks, after which, participants will be encouraged to sustain the anti-inflammatory diet unsupported up to 6 months. Consultations are one-to-one.	Delivered with standard healthy eating advice for 12 weeks, after which, participants will be encouraged to sustain the program unsupported up to 6 months. Consultations are one-to-one.
7. WHERE	In-person consultations will occur at La Trobe University Nutrition and Dietetics research laboratory. Additional	In-person consultations will occur at the La Trobe University Nutrition and Dietetics research

	consultations will occur via telephone/videoconference (e.g., Zoom). Participants will integrate the diet principles into their daily consumption of foods and beverages.	laboratory. Additional consultations will occur via telephone/videoconference (e.g., Zoom). Participants will integrate the diet principles into their daily consumption of foods and beverages.
8. WHEN AND HOW MUCH	<p>Two in-person consultations at baseline (~45 mins) and week 12 (~30 mins)</p> <p>Four phone/videoconference follow-up consultations (~30 mins) in week 2, 4, 6, and 9.</p> <p>Total active intervention delivery time: ~3.5 hours</p> <p>Participants are provided with self-management resources to optimise adherence to the anti-inflammatory diet up to the 6-month follow-up.</p>	<p>Two in-person consultations at baseline (~45 mins) and week 12 (~30 mins)</p> <p>One phone/videoconference follow-up consultation (30 mins) in week 6.</p> <p>Total active control delivery time: ~1.5 hours</p> <p>Participants encouraged to sustain their diet up to 6-month follow-up.</p>
9. TAILORING	Individualised anti-inflammatory dietary advice, education, and support aligning with participant preferences and goals.	Advice based on the ADGs.
10. MODIFICATIONS	Any modifications will be reported.	
11. HOW WELL (planned)	Two-three professionals (qualified dietitian and other health professional) receive prior training in how to deliver and supervise the program. Fidelity is assessed through random auditing by members of the principal investigator team (AC or BD). Participant adherence to the anti-inflammatory diet is assessed through consultation attendance, regular 3-day food diaries and self-report.	Two-three professionals (qualified dietitian and health professional) receive prior training in how to deliver and supervise the program. Fidelity is assessed through random auditing by members of the principal investigator team (AC or BD). Participant adherence to the standard care low-fat diet is assessed through consultation attendance, regular 3-day food diaries and self-report.
12. HOW WELL (actual)	This will be reported in the primary paper.	

245 TIDieR, Template for Intervention Description and Replication; ADG, Australian Dietary Guidelines

1
2 246 *Standard care low-fat dietary program*
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5 247 Participants allocated to the standard care low-fat dietary program will receive advice and
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7 248 education regarding healthy eating based on the Australian Dietary Guidelines.(39) These
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9 249 government-endorsed guidelines aim to optimise nutrition intake through adequate
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11 250 consumption of foods from the five core food groups (grains and cereals; fruit; vegetables and
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13 251 legumes; lean meats and poultry, fish, eggs, and tofu; reduced fat dairy or alternatives), while
14
15 252 limiting intake of foods containing saturated fat, added salt, added sugars and alcohol. They are
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17 253 high-carbohydrate and low-fat focused – participants will be encouraged to include at least four
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19 254 serves of wholegrains daily (e.g., brown rice, pasta, bread, quinoa, oats) and to choose low-fat
20
21 255 protein and dairy foods where possible.
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25 257 The program will be delivered through individual consultations with the treating dietitian or other
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27 258 specially trained health professional – the first in-person consultation immediately following
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29 259 baseline assessment (~45 minutes), the second via phone/videoconference at 6 weeks (~30
30
31 260 minutes) and the third in-person at 12-week follow-up with timing individualised as required.
32
33 261 Two to three consultations represents usual care for patients referred for dietary management
34
35 262 in Australia through the current public healthcare (Medicare) rebate system.(37, 38) During the
36
37 263 initial in-person consultation, participants will be provided with a bespoke educational booklet
38
39 264 and advice and education emphasising the Australian Dietary Guideline principles
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41 265 (<https://www.eatforhealth.gov.au/guidelines>) and informed of complementary and publicly
42
43 266 available online resources from the Eat for Health website (<https://www.eatforhealth.gov.au/>).
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46 268 The follow-up phone/videoconference consultation in week-6 and in-person follow-up in week-
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48 269 12 will provide participants with ongoing support, education and accountability. The 3-day food
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50 270 diary, completed prior to each consultation (see outcomes/adherence section), will guide
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52 271 feedback and support to adapt meal plans to optimise adherence. The treating health
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54 272 professionals delivering the two dietary programs will be based centrally at La Trobe University
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56 273 and will be trained by the senior study dietitian (BLD) until deemed competent in intervention
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58 274 delivery.
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2 276 Irrespective of group allocation, participants can continue usual medical care and consult with
3
4 277 their treating health professionals as necessary (e.g., general practitioner regarding medication
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6 278 changes).

7 279

9 280 **Data collection procedure**

11 281 Data will be collected at baseline and 6 weeks, 12 weeks and 6 months after randomisation, with
12
13 282 12 weeks the *a priori* primary endpoint as this coincides with completion of supported
14
15 283 interventions (table 3). Where possible, data will be collected and managed using a secure web-
16
17 284 based software platform (REDCap®) hosted at La Trobe University,(40) which has equivalent
18
19 285 measurement properties to paper-based completion.(41) This strategy was used in our pilot
20
21 286 study(28) and other trials of musculoskeletal conditions.(42) Paper versions will also be available
22
23 287 if preferred.

24 288

26 289 **OUTCOMES**

28 290 **Baseline characteristics**

30 291 Participant characteristics including age, sex, ethnicity, knee pain/surgery details, socioeconomic
31
32 292 details (e.g., education level, employment status, living status), medical history and health
33
34 293 literacy (assessed with the Rapid Estimate of Adult Literacy in Medicine (REALM)(43)) will be
35
36 294 collected (table 3).

37 295

39 296 **Primary Outcome**

41 297 The primary outcome is the change from baseline to 12 weeks in the mean score on four Knee
42
43 298 injury and Osteoarthritis Outcome Score (KOOS₄) subscales covering knee pain, symptoms,
44
45 299 function in daily activities and knee-related quality of life. The KOOS is a 42-item patient-reported
46
47 300 outcome measure assessing five separately scored subscales: Pain, Symptoms, Function in Sport
48
49 301 and Recreation (Sport/Rec), Activities of Daily Living (ADL), and Quality of Life. The KOOS₄ and all
50
51 302 KOOS subscale scores range from 0 (extreme problems) to 100 (no problems). The KOOS is a
52
53 303 valid, responsive and reliable questionnaire, with KOOS₄ a primary outcome for other knee OA
54
55 304 trials.(33, 44, 45)

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310 **Table 3.** Overview of data collection

Variable	Baseline	6 weeks	12 weeks	6 months
Participant characteristics				
Age	X			
Sex	X			
Ethnicity	X			
Education level	X			
Health literacy (REALM)	X			
Employment status	X			
Smoking status	X			
Civil status, living situation	X			
Medical history, comorbidities	X			
Knee pain/injury/surgery history	X			
Objective Clinical Outcomes				
Height, weight, waist girth	X		X	X
30-second chair stand test	X		X	X
40 metre walk test	X		X	X
Body composition (DXA)	X		X	X
Blood inflammatory and metabolic biomarkers	X		X	X
Blood pressure	X		X	X
Patient-reported Outcomes				
KOOS subscales	X	X	X	X
Global rating of change		X	X	X
Desire for knee surgery	X	X	X	X
Medication use	X	X	X	X
Knee pain (current and worst in past week)	X	X	X	X
EQ-5D-5L [^]	X	X	X	X
Patient acceptable symptom state	X	X	X	X
Brief Pain Inventory	X		X	X
International Physical Activity Questionnaire	X		X	X
Kessler Psychological Distress Scale (K10)	X		X	X
3-day Food Diaries*	X	X	X	X
Adverse events		X	X	X

311 REALM, Rapid Estimate of Adult Literacy in Medicine; KOOS, Knee injury and Osteoarthritis Outcome
 312 Score; DXA, Dual-Energy X-ray absorptiometry

1
2 313 *3-day food diaries are also assessed prior to anti-inflammatory dietary program consultations at 2, 4 and
3 314 9 weeks

4
5 315 ^Assesses health-related quality of life across 5 dimensions of health (mobility, self-care, usual activities,
6 316 pain/discomfort, anxiety/depression) and a visual analogue scale (0-100) of current overall health status.

7 317

8

9 318

10

11 319 **Secondary effectiveness outcomes**

12

13 320 *KOOS subscales*

14

15 321 To allow for clinical in-depth interpretation, scores for the five KOOS subscales will be reported
16 322 individually (i.e., pain, symptoms, function in sports and recreational activities, activities of daily
17 323 living, quality of life).(10, 45)

18

19 324

20

21 325 *Global Rating of Change (GROC) and patient-acceptable state*

22

23 326 Self-perceived change in pain and function will be assessed using a 7-point Likert scale ranging
24 327 from 'much worse' to 'much better' in response to the questions: "Overall, how has your knee
25 328 pain changed since the start of the study?" and "Overall, how has your knee function changed
26 329 since the start of the study?", respectively. Treatment success will be defined as a response of
27 330 either 'better' or 'much better'. Satisfaction with current knee function using the self-reported
28 331 Patient Acceptable Symptom State (PASS) question(46). Participants not satisfied with current
29 332 knee function at follow-up assessments will be asked a second question to determine if they
30 333 considered the treatment to have failed.(46)

31 334

32

33

34 335 *Anthropometrics*

35

36 336 Height and weight will be assessed using a seca 217 stadiometer and seca 703 EMR-validated
37 337 column scale (Hammer Steindamm, Hamburg, Germany), respectively. Waist circumference will
38 338 be measured using a metal tape measure (Lufkin W606PM ¼ inch x 2m Executive Thinline Pocket
39 339 Tape).

40 340

41

42

43 341 *Global lower-limb function*

44

45 342 Two performance-based tests of lower-limb function recommended by the OA Research Society
46 343 International (OARSI) will be conducted: the 30-second chair-stand test (number of chair-stands

47

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1
2 344 from a standardised height chair in 30 seconds) and 40-metre walk test (time to walk 40 metres
3
4 345 safely, using walking aids if required).(47)

5 346

7
8 347 *Body composition*

9
10 348 A whole-body DXA scan will be acquired using a Hologic Horizon® DXA scanner (Bedford, MA,
11
12 349 United States) to assess adiposity (visceral, peripheral) and lean mass.(48)

13
14 350

16
17 351 *Inflammatory and metabolic biomarkers*

18
19 352 An array of blood inflammatory and metabolic biomarkers will be analysed from samples of blood
20
21 353 collected, including high sensitivity C-Reactive Protein (hsCRP), cytokines (IL-1 β , IL-6, IL-8, IL-10,
22
23 354 TNF- α), blood glucose, HbA1c, serum insulin, liver function tests (including albumin), and lipids
24
25 355 (e.g., high density lipoprotein, triglycerides). Participants will be instructed to fast for at least 10
26
27 356 hours prior to blood collection and a single forearm venepuncture will take place to collect a total
28
29 357 of ≤ 30 mL blood. Plasma and serum samples will be centrifuged (3000ms, 10 minutes), and all
30
31 358 samples (plasma, serum, and whole blood) frozen at -80°C for later analysis (Supplementary File
32
33 359 3).

34 360

35
36 361 **Secondary safety outcomes**

37
38 362 *Adverse events*

39
40 363 Adverse events and serious adverse events will be recorded at 6-week, 12-week and 6-month
41
42 364 follow-up via open probe questioning to optimise collection of sufficient detail. Under the
43
44 365 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) harms
45
46 366 statement, an adverse event is defined as any undesirable experience causing participants to
47
48 367 seek medical treatment (e.g., general practitioner).(49) A serious adverse event is defined as any
49
50 368 undesirable event/illness/injury classified as having the potential to significantly compromise
51
52 369 clinical outcome or result in significant disability or incapacity, those requiring inpatient or
53
54 370 outpatient hospital care, to be life-threatening or result in death.

55 371

56

57

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60

372 **Exploratory outcomes**

373 *Dietary Analysis*

374 Participants will record food and beverage intake over three days via the smartphone application
375 *Australia Calorie Counter - Easy Diet Diary* (Xyris Software Pty Ltd) or on paper (personal
376 preference). Easy Diet Diary is a commercial calorie counter and food diary that allows users to
377 email recorded diaries to treating professionals. Once received by the treating health
378 professional, the 3-day food diaries will be imported into, and analysed using, Foodworks®
379 Premium Edition nutrient analysis software (Version 10, Brisbane, Australia 2019) and Australian
380 food composition databases. Paper-based 3-day food diaries will be manually entered into
381 FoodWorks®. Total energy intake, macronutrients, micronutrients and core food group analysis
382 will be reported. Dietary analysis data will also be used to calculate the inflammatory potential
383 of participants' diets (e.g., Dietary Inflammatory Index).(50)

384

385 *Quality of life*

386 Health-related quality of life will be assessed with the EQ-5D-5L generic health index, which
387 comprises five dimensions of health (mobility, self-care, usual activities, pain or discomfort,
388 anxiety or depression) and a Visual Analogue Scale (VAS) of current overall health status.(51)
389 Both validity and reliability has been demonstrated in arthritic populations.(52)

390

391 *Knee pain and interference*

392 Self-reported knee pain (current, worst over past week, average over past week) will be assessed
393 using a 100mm VAS (0=no pain, 100=worst pain imaginable). The degree to which knee pain
394 interferes with participant's daily functioning will be assessed using the Brief Pain Inventory,(53)
395 a tool with reliability and validity demonstrated in knee pain populations.(54, 55)

396

397 *Change in analgesic medication use*

398 Change in analgesic medication use from baseline to 12-week and 6-month follow-up will be
399 assessed with a 7-point Likert scale (much less to much more).

400

1
2 401 *Physical activity*
3

4 402 Physical activity will be assessed using the International Physical Activity Questionnaire
5
6 403 (IPAQ),(56) a standardised and valid questionnaire providing an estimate of physical activity and
7
8 404 sedentary behaviour, which has been widely validated.(56-58) Respondents are asked to report
9
10 405 time spent in physical activity across three intensities (walking, moderate, vigorous). Using the
11
12 406 IPAQ scoring protocol,(59) total weekly physical activity can be estimated by weighting time
13
14 407 spent in each activity intensity with its estimated metabolic equivalent (MET) energy
15
16 408 expenditure.(60)
17

18
19 410 *Blood pressure*
20

21
22 411 A pair of seated blood pressure measurements will be obtained using an automated monitor
23
24 412 (Omron Model HEM-7121). The blood pressure cuff is placed over the mid-upper arm with the
25
26 413 participant seated.
27

28 414
29 415 *Self-perceived wellness*
30

31
32 416 Self-reported sleep quality, hunger, fatigue and energy levels will be assessed using a 100mm
33
34 417 VAS (0=worst outcome, 100=best outcome).
35

36 418
37
38 419 *Intervention adherence*
39

40 420 Adherence will be assessed by a self-reported VAS (0=not at all adherent, 100=extremely
41
42 421 adherent) and 5-point Likert scale at 6 weeks, 12 weeks and 6 months and evaluation of 3-day
43
44 422 food diaries by consulting health professionals. Satisfactory adherence is defined as a self-report
45
46 423 of both ≥ 80 on the VAS and 'Most days' or 'Every day' on the Likert scale, at both the 6-week and
47
48 424 12-week timepoints.
49

50 425 **DATA MANAGEMENT**
51

52 426 Most outcome data will be collected and managed electronically via REDCap© web-based
53
54 427 software hosted at La Trobe University. Other data (e.g., DXA reports) will be stored electronically
55
56 428 on the La Trobe University secure research drive. All electronic data will be de-identified
57
58 429 (participant code) and exported for data analysis and saved in a password protected database on
59
60 430 the La Trobe University research drive only accessible to the research team. Paper-based
431 identifying documents (e.g., consent forms) will be securely stored in a locked filing cabinet

1
2 432 accessible only to members of the research team and separately from re-identifiable (i.e., coded)
3
4 433 data.

5 434
6
7 435 Due to the minimal known risks associated with the interventions being evaluated, our study will
8
9 436 not have a formal data monitoring committee and does not require an interim analysis. This is
10
11 437 the same approach we have taken with other low risk RCTs.(42) Any unexpected serious adverse
12
13 438 events or outcomes will be discussed by the trial management committee (authors of this
14
15 439 protocol) and reported to the approving human research ethics committee for monitoring.

16 440

18 441 **Sample size calculation**

20 442 This trial has been powered to detect a clinically significant between-group difference for the
21
22 443 primary outcome of KOOS₄. A recent RCT comparing an anti-inflammatory diet vs low-caloric diet
23
24 444 in overweight women with knee OA observed an effect size (standardised mean difference) on
25
26 445 self-reported pain and function of 1.0 (95% confidence interval 0.5 to 1.6).(61) Given inherent
27
28 446 differences in the FEAST RCT (e.g., Australian Dietary Guideline control group, not specifically
29
30 447 targeting overweight participants, inclusion of both women and men), we used the lower bound
31
32 448 95% confidence interval to provide a conservative estimate of the anticipated effect size (0.5).
33
34 449 This estimated effect size is also a conservative estimate based on our single-arm anti-
35
36 450 inflammatory diet pilot trial, which had an effect size of 0.68.(28) Recruiting 128 participants
37
38 451 (equally distributed between two arms) would yield 80% power to observe such an effect or
39
40 452 larger at a two-tailed Type I error of 0.05. This sample size estimation is also conservative since
41
42 453 it is based on independent samples t-test. Using an ANCOVA model that includes the baseline
43
44 454 value as a covariate and is pre-specified for the analysis should provide higher power for the
45
46 455 same sample size.(62) To account for a potential 10% drop-out, we will recruit 144 participants.
47
48 456 This sample size will also be sufficient to detect a minimal important change (MIC) in KOOS₄
49
50 457 estimated at 10 points in patients with knee OA (with a common between-subject standard
51
52 458 deviation of 15).(63)

51 459

53 460 **Statistical analyses**

55 461 Analysis will be performed according to the Estimands Framework(64) with a statistical analyst
56
57 462 blinded to group allocation. All outcomes and analyses are prospectively categorised as primary,
58
59 463 secondary or exploratory. For the primary hypothesis, a linear model with baseline value, sex and
60
61 464 BMI (≥ 30 vs $< 30 \text{ kg.m}^{-2}$) as covariates and treatment condition as a fixed factor will evaluate the

1
2 465 treatment effect on the primary outcome of KOOS₄ (mean score of four of the five subscales of
3
4 466 the KOOS) at 12 weeks. A linear mixed model utilising repeated measures at all time-points for
5
6 467 secondary hypotheses will allow non-biased estimates of treatment effect in the presence of any
7
8 468 potential missing cases, providing data are missing at random. A sensitivity analysis using pattern-
9
10 469 mixture model to investigate the deviation from the missingness-at-random assumption will be
11
12 470 carried out.⁽⁶⁵⁾ For secondary binary outcomes (e.g., treatment success), mixed-effect logistic
13
14 471 regression models will be used to assess the effect of treatment. A subsequent analysis of
15
16 472 participants classified as adherent to the protocol will be performed. Following publication of the
17
18 473 primary trial results, we will also perform a formal mediation analysis to estimate direct and
19
20 474 indirect (e.g., through weight and inflammation change) effects.

21 475

22 476 **Healthcare resource use**

23
24 477 Healthcare resource utilisation (e.g., hospitalisations, medical imaging, healthcare visits,
25
26 478 medication use) will be assessed by participant self-report to estimate costs associated with the
27
28 479 trial programs (e.g., hospital admissions, medication use, clinician visits, imaging tests, out-of-
29
30 480 pocket expenses).

31 481

32 482 **Process Evaluation**

33
34 483 Semi-structured interviews will be conducted on a subset of consenting participants (until data
35
36 484 saturation reached) at 6 months. Interviews will explore experiences, knowledge and
37
38 485 understanding of interventions received including potential benefits; acceptability and perceived
39
40 486 effectiveness of the intervention; and reasons for adhering (or not) to the allocated diet.
41
42 487 Purposive sampling will be used to recruit interview participants based upon characteristics (anti-
43
44 488 inflammatory dietary program vs standard care low-fat dietary program, men vs women) and
45
46 489 outcomes of the trial (good outcome vs poor outcome). Interviews will be audio recorded,
47
48 490 transcribed and analysed using Framework Analysis,⁽⁶⁶⁾ a flexible technique allowing
49
50 491 researchers to identify, compare and contrast data according to inductively- and deductively-
51
52 492 derived themes. Data will be coded and an inductive thematic analysis will be applied until no
53
54 493 new themes emerge.

55 494

56 495 **ETHICS AND DISSEMINATION**

57
58 496 This study complies with the Declaration of Helsinki and has received approval from La Trobe
59
60 497 University Human Ethics Committee (HEC-22044). Written informed consent will be obtained

1
2 498 from participants prior to enrolment (Supplementary File 4). Anti-inflammatory diets are
3
4 499 associated with minimal and transient adverse events, thus there are minimal safety
5
6 500 considerations associated with this trial.

7 501
8
9 502 Study outcomes will be widely disseminated through a variety of sources. Results will be reported
10
11 503 in peer-reviewed publications and presented at key national and international conferences. Only
12
13 504 aggregate data will be reported. A lay summary report will be available for study participants.
14
15 505 Any important protocol amendments will be reported to the approving ethics committee,
16
17 506 registered at ANZCTR and communicated in the primary RCT paper. Any serious adverse events
18
19 507 will be recorded and reported to the approving ethics committee.

20 508
21
22 509 Deidentified data will be made available upon reasonable request to the principal investigator
23
24 510 (AGC) after publication (except where the sharing of data is prevented by privacy, confidentiality,
25
26 511 or other ethical matters, or other contractual or legal obligations) according to La Trobe
27
28 512 University Research Data Management Policy.

29 513

30 31 514 **DISCUSSION**

32
33 515 The current RCT will be the first full-scale trial to evaluate the symptomatic, inflammatory,
34
35 516 functional and body composition benefits of an anti-inflammatory dietary program compared to
36
37 517 a standard care low-fat dietary program based on Australian Dietary Guidelines. While outcome
38
39 518 assessors are blinded to group allocation, owing to the type of interventions (i.e., dietary advice)
40
41 519 blinding of participants will not be possible. We also acknowledge that, like most RCTs, there is a
42
43 520 risk that our recruitment strategy may result in a selected sample not representative of the
44
45 521 general population. However, using similar recruitment strategies, our prior RCTs have resulted
46
47 522 in a representative sample of the culturally and sociodemographically diverse Australian
48
49 523 population that has similar characteristics to other international cohorts with the index
50
51 524 musculoskeletal condition.(67)

51 525

52
53 526 The evaluation of a non-pharmacological anti-inflammatory dietary program to improve pain,
54
55 527 symptoms, and quality of life for individuals with OA could have important individual and socio-
56
57 528 economic benefits – decreased healthcare dollars spent on managing OA and reduced surgery
58
59 529 waiting lists. Another benefit is that anti-inflammatory diets are also effective at combating
60
530 metabolic syndrome, a key risk factor for chronic diseases, and thus the benefits from treating
531
532 531 OA could stretch further to improving other medical co-morbidities.(68) This fully-powered RCT

1
2 532 represents a crucial step towards the development of a sustainable and cost-effective therapy
3
4 533 that can both supplement and complement existing treatment strategies to optimise OA
5
6 534 outcomes.

7 535 8 9 536 10 **AUTHOR CONTRIBUTIONS**

11 537
12 538 AGC, BLD, PB and JLK conceived the study and obtained funding. AGC, BLD, PB, and JLK designed
13
14 539 the study protocol with input from LL, JJH and ABM. ADL provided statistical expertise and will
15
16 540 conduct primary statistical analysis. MDH provided blood analysis expertise and will lead
17
18 541 inflammatory and metabolic marker analyses. HGM and NPW assisted with participant
19
20 542 recruitment from their clinical population with knee osteoarthritis. LL drafted the manuscript
21
22 543 with input from AGC, JJH, BLD, PB, JLK, AA, MDH, ADL, ABM, HGM and NPW. All authors and read
23
24 544 and approved the final manuscript.

25 545 26 27 **FUNDING**

28
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30
31 548 through an Investigator Grant held by AGC (GNT2008523), an Investigator Grant held by JLK
32
33 549 (APP2017844), and a philanthropic donation from PB.

34 550 35 36 **COMPETING INTERESTS STATEMENT**

37
38 552 PB is the founder of Defeat Diabetes and author of "A Fat Lot of Good". PB contributed to study
39
40 553 design but has no role in study execution, data management, analysis or the decision to publish.
41
42 554 The NHMRC has no role in study design and will not have any role in its execution, data
43
44 555 management, analysis and interpretation or on the decision to submit the results for publication.
45
46 556 JLK is an editor of the British Journal of Sports Medicine (British Medical Journal Group). AGC is
47
48 557 an associate editor of British Journal of Sports Medicine (British Medical Journal Group). All other
49
50 558 authors have no competing interests.

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55
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57
58 563 Melbourne Pathology for providing pathology collection kits and analysis of biomarkers from
59
60 564 blood specimens.

565

FIGURE LEGENDS

Figure 1. Flow of participants through the trial. DXA, Dual X-ray Absorptiometry; KOOS, Knee injury and Osteoarthritis Outcome Score

*Optional qualitative interview for process evaluation at 6 months

SUPPLEMENTARY FILES

Supplementary File 1. Sample of the standard care low fat dietary program participant booklet

Supplementary File 2. Sample of the anti-inflammatory dietary program participant booklet

Supplementary File 3. Standard Operating Procedures for blood collection, processing and storage

Supplementary File 4. Patient information and consent form

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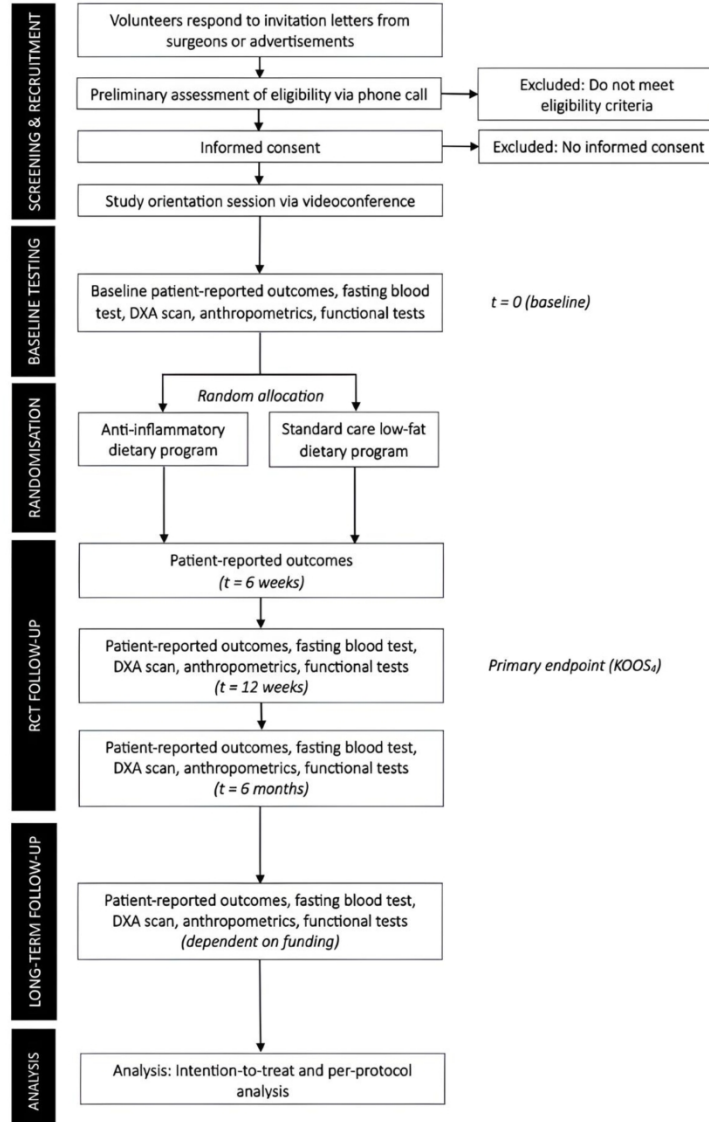


Figure 1. Flow of participants through the trial. DXA, Dual X-ray Absorptiometry; KOOS, Knee injury and Osteoarthritis Outcome Score

*Optional qualitative interview for process evaluation at 6 months

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FEAST

SAMPLE FROM LOW-FAT PARTICIPANT BOOKLET





Australian Government
National Health and Medical Research Council
Department of Health and Ageing

www.eatforhealth.gov.au

Australian Guide to Healthy Eating

Enjoy a wide variety of nutritious foods from these five food groups every day.

Drink plenty of water.



Grain (cereal) foods, mostly wholegrain and/or high cereal fibre varieties



Vegetables and legumes/beans



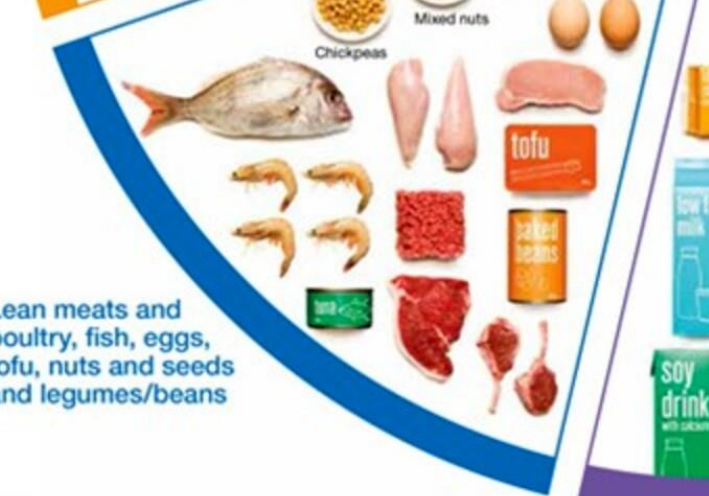
Lean meats and poultry, fish, eggs, tofu, nuts and seeds and legumes/beans



Fruit



Milk, yoghurt, cheese and/or alternatives, mostly reduced fat



Use small amounts



Only sometimes and in small amounts



Vegetables and legumes

Vegetables, including legumes/beans are nutrient dense, low in kilojoules, and are a good source of minerals and vitamins (such as magnesium, vitamin C and folate), dietary fibre and a range of natural plant chemicals such as carotenoids. Legumes include chickpeas, kidney beans, and peas. **Aim for 5 serves a day.**

What is a serve of vegetables*?

A standard serve is about 75g (100–350kJ) or:

½ cup	cooked green or orange vegetables (for example, broccoli, spinach, carrots or pumpkin)
½ cup	cooked dried or canned beans, peas or lentils
1 cup	green leafy or raw salad vegetables
½ cup	sweet corn
½ medium	potato or other starchy vegetables (sweet potato, taro or cassava)
1 medium	tomato



*With canned varieties, choose those with no added salt

Fruit

A wide variety of fruit is grown and available in Australia. Choosing fruits in season provides **better value and better quality**. And just like with veggies, choosing different coloured fruits increases the variety of nutrients, which can enhance your health! Aim for **two serves** of fruit a day.

Try eating fruits from these different fruit categories:

- citrus fruit such as oranges, mandarins, and grapefruit
- pome fruits such as apples and pears
- stone fruit such as apricots, cherries, peaches, nectarines, and plums
- tropical fruit such as bananas, papaya, mangoes, pineapple, and melons
- berries

What is a serve of fruit?

A standard serve is about 150g (350kJ) or:

1 medium	apple, banana, orange or pear
2 small	apricots, kiwi fruits or plums
1 cup	diced or canned fruit (no added sugar)

Or only occasionally:

125ml (½ cup)	fruit juice (no added sugar)
30g	dried fruit (for example, 4 dried apricot halves, 1½ tablespoons of sultanas)



- other fruits such as grapes and passionfruit

Enjoy more fruit by trying:

- chopped fruit to cereal, porridge, salad, or toast
- fruit as a convenient snack while out and about
- fruit-based desserts (baked apples, fruit crumbles, stewed/ poached fruit)
- adding fruit to pancakes, scones, pikelets, and low-fat muffins.



Wholegrains

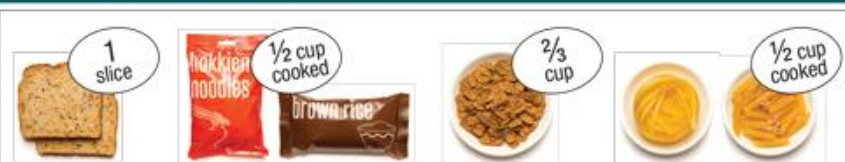
All types of grains are good sources of complex carbohydrates and some key vitamins and minerals. Grain foods are mostly made from wheat, oats, rice, rye, barley, millet, quinoa and corn.

Wholegrains are naturally high in fibre, helping you feel full and satisfied — which makes it easier to maintain a healthy body weight. Nutritionally, wholegrain and wholemeal foods are very similar.

What is a serve of grain* (cereal) food?

A standard serve is (500kJ) or:

1 slice (40g)	bread
½ medium (40g)	roll or flat bread
½ cup (75-120g)	cooked rice, pasta, noodles, barley, buckwheat, semolina, polenta, bulgur or quinoa
½ cup (120g)	cooked porridge
⅔ cup (30g)	wheat cereal flakes
¼ cup (30g)	muesli
3 (35g)	crispbreads
1 (60g)	crumpet
1 small (35g)	English muffin or scone



*Grain (cereal) foods, mostly wholegrain and/or high cereal fibre varieties

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Aim for 4-6 serves of grain foods a day. Additional serves can be eaten depending on your activity level.

Enjoy more wholegrains by having:

- breakfasts that include whole-grain cereals, like oatmeal.
- wholemeal toast or wholemeal bagels for white-flour versions.
- low-fat muffins made with whole-grain flours.
- sandwiches using whole-grain breads or rolls.
- quinoa, brown rice, wild rice, barley or bulgur instead of white rice.
- wild rice or barley in soups, stews, casseroles and salads.
- rolled oats or crushed whole-wheat bran cereal in recipes instead of dry breadcrumbs.

Lean meat and poultry, fish, eggs, tofu, nuts and seeds

These are a critical part of having enough protein each day. They also provide other nutrients such as: iodine, iron, zinc, vitamins, especially B12, and essential fatty acids.


There's a lot to choose from:

- Lean meats - Beef, lamb, veal, pork, kangaroo
- Poultry - Chicken, turkey, duck, emu, goose, bush birds
- Fish and seafood - Fish, prawns, crab, lobster, mussels, oysters, scallops, clams
- Eggs
- Nuts and seeds - Almonds, pine nuts, walnut, macadamia, hazelnut, cashew, peanut, nut spreads, and pumpkin seeds
- Legumes/beans - All beans, lentils, chickpeas, split peas, tofu.

How much is a serve of lean meat and poultry, fish, eggs, nuts and seeds, and legumes/beans*?

A standard serve is (500–600kJ):

65g	cooked lean red meats such as beef, lamb, veal, pork, goat or kangaroo (about 90-100g raw)
80g	cooked lean poultry such as chicken or turkey (100g raw)
100g	cooked fish fillet (about 115g raw) or one small can of fish
2 large (120g)	eggs
1 cup (150g)	cooked or canned legumes/beans such as lentils, chick peas or split peas
170g	tofu
30g	nuts, seeds, peanut or almond butter or tahini or other nut or seed paste



*Choose those with no added salt

Milk, yoghurt, cheese, and/or alternatives

Dairy products (and dairy alternatives) are rich in calcium, protein, and lots of nutrients. Dairy foods contribute to strong bones. Aim for **at least 2-3 serves daily**.

Examples of milk, yoghurt, cheese and/or alternatives include:

- Milks - All reduced fat or full cream milks, plain and flavoured, long life milks, fortified soy beverages
- Yoghurt - All yoghurts including reduced fat or full cream, plain and flavoured, soy yoghurt (calcium fortified)
- Cheese - All hard cheeses, reduced or full fat for example cheddar, Gouda, Swiss

How much is a serve of milk*, yoghurt*, cheese* and/or alternatives?

A standard serve is (500–600kJ):

1 cup (250ml)	fresh, UHT long life, reconstituted powdered milk or buttermilk
½ cup (120ml)	evaporated milk
2 slices (40g)	or 4 x 3 x 2cm cube (40g) of hard cheese, such as cheddar
½ cup (120g)	ricotta cheese
¾ cup (200g)	yoghurt
1 cup (250ml)	soy, rice or other cereal drink with at least 100mg of added calcium per 100ml

The following foods contain about the same amount of calcium as a serve of milk, yoghurt or cheese:

100g	almonds with skin
60g	sardines, canned in water
½ cup (100g)	canned pink salmon with bones
100g	firm tofu (check the label as calcium levels vary)

*Choose mostly reduced fat

EXAMPLE WEEKLY MEAL PLANS

Here are examples of what a week might look like. Consider these plans as a guide to give you ideas, not something written in stone! Most of the recipes below can be found on the **Defeat Diabetes** app, or by simply searching on Google online.

Lots of other anti-inflammatory/low-carbohydrate ideas online at: <https://www.eatthebutter.org/dinner-ideas/>

Week 1

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Breakfast	Raspberrry chia pot	Yoghurt with berries	Raspberrry chia pot	Coconut crunch granola	Berry yoghurt smoothie	Scrambled eggs with spinach and avocado	Zucchini and feta fritters
Snack	Apple with peanut butter	Hummus and veggies	Apple with peanut butter	Handful of almonds with piece of dark chocolate	Hummus and veggies	Apple with peanut butter	Handful of walnuts
Lunch	Roast vegetable salad	Salad with can of tuna	Leftover prawn pad thai	Leftover burrito bowl	Salad with can of tuna	Salmon with cauliflower rice bowl	One pan spiced halloumi and eggplant
Snack	Handful of almonds with piece of dark chocolate	Almond meal blueberry muffin	Zucchini and feta fritter	Almond meal blueberry muffin	Handful of almonds with piece of dark chocolate	Yoghurt with berries	Almond meal blueberry muffin
Dinner	Garlic prawns with zoodles	Beef pad thai	15-minute burrito bowl	Miso barramundi with vegetables	Swedish meatballs	Baked portobello mushrooms with feta	Grilled lamb chops with roasted vegetables

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Week 2

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Breakfast	Coconut crunch granola	Berry smoothie	Scrambled eggs with spinach and avocado	Berry smoothie	Coconut crunch granola	Scrambled eggs with spinach and avocado	Shakshuka
Snack	Mini frittata	Pear	Apple with handful of almonds	Pear	Mini frittata	Handful of walnuts with piece of dark chocolate	Yoghurt with berries
Lunch	Salad with sliced steak	Easy Tuna Niçoise	Leftover stuffed capsicum	Leftover burger patty with salad	Leftover green curry with cauliflower rice	Caesar salad	Warm veggie salad with almonds
Snack	Slice of orange almond meal cake	Handful of walnuts with piece of dark chocolate	Mini frittata	Slice of orange almond meal cake	Apple with handful of almonds	Yoghurt with berries	Pear
Dinner	Salmon poke bowl	Stuffed capsicums	Smoky beef burger on mushroom buns	Green vegetable and prawn curry with cauliflower rice	Easy mushroom, lemon, and garlic chicken	Cauliflower pizza with pesto, sausage, and herbs	Grilled steak and roasted vegetables

Week 3

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Breakfast	Breakfast egg muffins	Berry yoghurt smoothie	Breakfast egg muffins	Chia pudding pot	Berry yoghurt smoothie	Bacon and eggs with roasted tomatoes	Mexican breakfast scramble
Snack	Chia pudding pot	Beef jerky	Greek yoghurt with berries	Breakfast egg muffins	Handful of almonds with cheese stick	Apple with peanut butter	Strawberry power balls
Lunch	Zucchini and walnut salad	Leftover beef burrito bowl	Leftover salmon patties with salad	Greek salad	Leftover tagine	Kale, broccoli and almond salad	Mushroom soup with crispy cheese croutons
Snack	Strawberry power balls	Handful of almonds with square of dark chocolate	Strawberry power balls	Handful of almonds with apple	Dark chocolate (avocado) mousse	Beef jerky	Dark chocolate (avocado) mousse
Dinner	15-minute beef burrito bowl	Salmon patties with feta sauce and beet salad	Chicken curry with cauliflower rice	Lamb and apricot tagine	Pan-seared barramundi with cauliflower mash	Zucchini lasagne	Grilled lamb chops with roasted vegetables

Week 4

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Breakfast	Coconut granola with milk	Blueberry almond protein smoothie	Vegetable cheese frittata	Blueberry almond protein smoothie	Coconut granola with milk	Tofu scramble	Almond flour pancakes

1	Snack	Roasted chickpeas	Slice of almond flour banana bread	Greek yoghurt with berries	Peanut butter balls	Beef jerky	Roasted chickpeas	Handful of walnuts
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5	Lunch	Vegetable cheese frittata	Leftover roast vegetable salad with halloumi	Leftover broccoli and leek soup	Vegetable cheese frittata	Kale Caesar salad	Leftover stuffed capsicums	Creamy Tuscan soup
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9	Snack	Slice of almond flour banana bread	Handful of almonds with dark chocolate	Roasted chickpeas	Slice of almond flour banana bread	Handful of almonds with dark chocolate	Greek yoghurt with berries	Peanut butter balls
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13	Dinner	Roast vegetable salad with halloumi	Cheesy broccoli soup	Spicy tofu san choi bao	Vegetarian stuffed zucchini boats	Stuffed capsicums	Beetroot & halloumi salad with pomegranate	Spiced eggplant curry with cauliflower rice
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6 **Standard Operating Procedure**
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9 **Blood collection, processing, handling, and storage procedures**
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1.1 Purpose

The purpose of the current SOP is to provide step-by-step instructions on the exact procedures that the research team needs to follow for conducting venous blood collection for biochemical analysis at baseline and follow-up examination.

1.2 General procedures for venous blood collection

Venous blood samples will be obtained from each participant for biochemical analysis following a 12-hour overnight fast, at baseline (T1), 12 weeks (T2) and 6 months (T3) (figure 1)

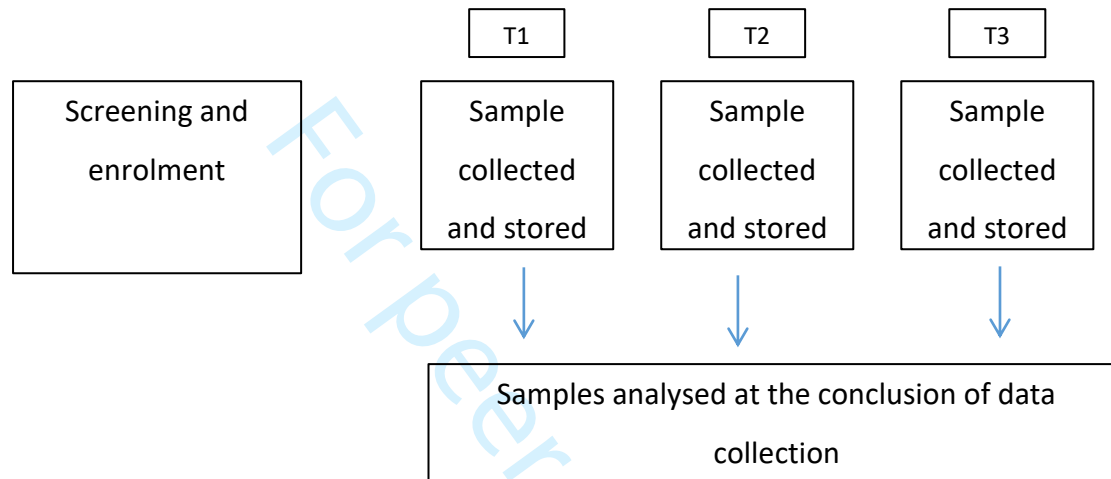


Figure 1: Study design

The researcher will perform venepuncture to obtain no more than 30mL of blood.

1.2.1 Consumables and supplies required for performing venepuncture

The consumables and supplies that will be used for performing the venepuncture in the study are the following:

- Disposable Latex gloves must be worn by the researcher and anyone else assisting with blood collection.
- Alcohol swab will be used to clean the venepuncture site.
- Winged steel needles appropriate for adults with an extension tube (a butterfly) will be used. The butterfly will have either a syringe or an evacuated tube with an adaptor. Sterile gauze pads will....
- Adhesive hypo allergic bandages (plasters or Band-Aids) will be applied to the puncture site to minimize the risk of infection.
- Plastic Bag for Waste will be used to dispose all of the biohazardous waste generated as well as a sharps biocontainer to dispose of all needles.

1.2.2 Steps in obtaining venous blood from the participant

The steps for obtaining venous blood samples from the study participants are provided below:

Step 1: Complete general preparation.

- Find an indoor site to encourage privacy during blood collection. The site should have a table or other piece of furniture with a flat surface where you can lay out all consumables/ supplies. An examination bed should be readily available if the respondent feels faint and needs to lie down.
- Ensure that each subject has completed a 10-hour fast.

- Wash and dry hands, put on gloves before initiating blood collection from the participant.
- Take out a clean absorbent paper sheet and spread it over a flat surface to lay out consumable and supplies.

Step 2: Prepare the participant for the venepuncture.

- The individual should be seated comfortably in a chair with arm extended on the slanting armrest to form a straight line from the shoulder to the wrist. The arm and elbow should be supported firmly by the armrest and should not be bent at the elbow.
- Ask each volunteer if they have a history of fainting. If so, ensure that the blood sample is only drawn whilst the subject is lying down on a bed.
- Describe to the participant exactly what will be done during the collection of the blood sample.

Step 3: Prepare the venepuncture site.

- Apply (tighten) tourniquet.
- Ask the participant to close his/her hand so that the veins will become more prominent and thus easier to enter. Vigorous hand exercise or "pumping" should be avoided.
- Select the vein site. Palpate and trace the path of veins several times with the index finger. If superficial veins are not readily apparent, blood can be forced into the vein by gently massaging the arm from wrist to elbow. Several sharp taps at the vein site with index and second finger will cause the vein to dilate.
- Loosen tourniquet.
- The venepuncture site must be cleansed once with an alcohol swab to prevent any chemical or microbiologic contamination of either the patient or the specimen.
- Check equipment, tube selection and thread needle (or butterfly) securely onto tube holder (barrel).
- Re-apply the tourniquet and relocated vein position and direction. A tourniquet allows the veins to fill with blood, thus making the veins more prominent and easier to enter. Do not leave the tourniquet on for longer than 1 minute otherwise it may result in either hemoconcentration or variation in blood test values.
- Remove needle cover and check bevel is orientated uppermost.

Step 4: Blood drawing

- Puncture the skin 3–5 mm away from the vein; this allows good access without pushing the vein away.
- If the needle enters alongside the vein rather than into it, withdraw the needle slightly without removing it completely, and angle it into the vessel.
- Insert the tube into the holder and commence filling the tubes.
- Draw blood slowly and steadily.
- Release the tourniquet as soon as blood flow is established. Tourniquet release allows the blood circulation to return to normal and also reduces bleeding at the venipuncture site.
- Remove the tube from the holder and invert (8-10 times) to mix the blood with tube additives. Place blood samples on ice if required..
- Place a cotton wool above the venepuncture site, withdraw the needle and apply pressure.
- Dispose of needle in a sharps container.
- Check site and apply an adhesive bandage.
- Label all tubes immediately.



1.3 Blood processing and handling

1.3.1 Centrifuge procedure

Collected venous blood will be centrifuged and the extracted plasma and/or serum will be pipetted into aliquots according to the blood collection protocol.

- Set up in a well-ventilated environment, on a horizontally levelled and rigid surface with adequate load-bearing capacity.
- As safety zone maintain a clear radius of at least 30 cm around the centrifuge. Do not place any dangerous substances within this security zone.
- Open the centrifuge door by pressing the open button.
- Place the remaining tubes containing blood into appropriate sized adapters.
- Place the tubes containing water in opposite adapters, where they should mirror the placement of the tubes holding blood.
- Never place both tubes housing water and blood into the same adapters but should be placed in different adapters for even weight distribution.
- Place the adapters carefully and gently into the rotor buckets
- Seal the buckets with the lids and close the centrifuge.
- Use only with rotors which have been loaded properly.
- Make sure the rotor is locked properly into place before operating the centrifuge.
- Never overload the rotor.
- Never start the centrifuge when the centrifuge door is open.
- Do not lean on the centrifuge.
- Do not place anything on top of the centrifuge during a run.
- Gently close the centrifuge door. The centrifuge door mechanism will click and lock in place.
- Turn on the centrifuge by pressing the start button.
- Select the required speed and time from preprogrammed setting or manually using the arrow keys (3000xg for 10 mins for each tube).

Once the centrifuge has completely stopped spinning wait for an audible sound and then open the centrifuge. Remove the tubes from the centrifuge and place them in a tube rack.

1.3.2 Handling of collected blood

Three different types of test tubes will be used per study participant to collect venous blood. The collected blood will be designated for whole blood, or plasma and serum separation. One 8ml EDTA tube (with added anticoagulant) will be used to collect whole blood for analysis, one 6ml heparin tube will be used for plasma extraction, and one 8.5ml SST tube will be used for serum extraction. Tubes will be labelled with study timepoint (T1, T2 or T3), participant ID, and type of sample. All information regarding blood collection tubes is presented in Table 1.

Table 1. Volume of blood in different test tubes

Test tube	Blood volume	Designated for:
EDTA tube	6 ml	Whole blood
Heparin gel tube	6 ml	Heparin plasma extraction
SST tube	8.5 ml	Serum extraction
Total blood:	22.5ml	

- The whole blood sample (6ml) collected in the EDTA tube will be stored at -80°C, as indicated in Table 2.

Table 2. Volumes and use of EDTA whole blood sample.

Whole blood aliquot no.	EDTA volume	Designated for the analysis of:
1	6 ml	HbA1c

- The blood (8.5ml) collected in the SST tube will be left to separate at room temperature for 20 mins and then centrifuged at 3000 rpm for 10 min. The extracted (heparin) plasma will be pipetted into 4 aliquots of 1 ml (considering a 50% efficiency of centrifugation in plasma extraction). One aliquot of 1ml will be used for determining glucose, insulin, lipids, LFT and hsCRP, while the 3 aliquots of 1ml each will be stored at -80°C, as indicated in Table 3.

Table 3. Volumes and use of SST plasma aliquots.

Plasma aliquot no.	EDTA plasma volume	Designated for the analysis of:
1	1000 µl	Glucose, insulin, lipids, LFT, hsCRP
		Designated for:
2	1000 µl	Storage at -80°C
3	1000 µl	Storage at -80°C
4	1000 µl	Storage at -80°C

- The blood (6 ml) collected in the heparin tube will be centrifuged at 3000 rpm for 10 min and the extracted plasma will be pipetted into 3 aliquots of 600 µl (considering a 50% efficiency of centrifugation in plasma extraction). One aliquot of 600 µl will be used for determining cytokine concentrations, while the remaining 3 aliquots of 500 µl each will be stored at -80°C, as indicated in Table 4.

Table 4. Volumes and use of heparin plasma aliquots.

Plasma aliquot no.	Heparin plasma volume	Designated for the analysis of:
1	1ml	Cytokines (IL-1β, IL-6, IL-8, IL-10, and TNF)
		Designated for:
2	1ml	Storage at -80°C
3	1ml	Storage at -80°C
4	1ml	Storage at -80°C

NOTE: It is essential that ONLY NON-HAZARDOUS waste be placed in the wastepaper/ general rubbish bins. Pipette tips should be disposed in sharps containers, whereas laboratory and associated waste directly involved in specimen processing (i.e blood collection tubes, gloves etc) must be disposed in biological waste bags.

1.4 Blood storage

Eppendorf tubes or screw cap tubes must be clearly labelled with identification, media used and date, placed in a freezer well rack and should not be stored for long periods on a bench, but must be transferred with an ice esky box to a dedicated storage area (i.e. refrigerator, cold room or cupboard) as soon as possible.

Laboratory coats must be removed and hung up before leaving laboratory areas and should be laundered once a week. Hands must be washed with an antibacterial agent BEFORE leaving laboratory (Hibiclens/Microshield or equivalent, followed by extensive rinsing).



Participant Information Sheet/Consent Form

Interventional study - *Adult providing own consent*

Title	Optimising outcomes for people with knee pain through food: FEAST randomised controlled trial
Short Title	The FEAST trial
Ethics Reference Number	HEC22044
Project Sponsor	La Trobe University
Coordinating Principal Investigator/ Principal Investigator	Dr Adam Culvenor (School of Allied Health, Human Services and Sport (SAHHSS), La Trobe University)
Associate Investigator(s)	Dr Brooke Devlin (School of Human Movement and Nutrition Sciences, University of Queensland) Prof. Peter Brukner (SAHHSS, La Trobe University) Ass. Prof. Joanne Kemp (SAHHSS, La Trobe University) Prof. Kay Crossley (SAHHSS, La Trobe University) Dr Andrea Mosler (SAHHSS, La Trobe University) Dr Josh Heerey (SAHHSS, La Trobe University) Ms Lynette Law (PhD student, SAHHSS, La Trobe University) Ms Amanda Attanayake (SAHHSS, La Trobe University)
Location	La Trobe University

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project because you have knee pain. This research project aims to assess the effectiveness of two different programs provided through advice and education by a qualified dietitian to improve your knee pain, function and quality of life.

This information sheet tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the project. Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Your participation is voluntary

Participation in this research is completely voluntary and there will be no cost to you. If you don't wish to take part, you don't have to. If you decide you want to take part, you will be given a copy of this Participant Information Sheet and asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participation Information Sheet and Consent Form to keep.

2 What is the purpose of this research?

As you may be aware, knee pain is very common and is often associated with knee osteoarthritis. Osteoarthritis is the most common form of arthritis and is a leading cause of disability in Australia. Currently, there is no cure for osteoarthritis, therefore it is important to investigate treatments that can improve the main symptoms associated with osteoarthritis: pain, swelling, stiffness and movement difficulties. We will recruit 140 adults who have knee pain.

This study is being conducted by researchers at La Trobe University and is partly funded by the National Health and Medical Research Council (NHMRC) of Australia and Dr Peter Brukner. All assessments and consultations will be at **no cost** to you.

3 Who can participate?

You can participate in this study if you meet all the following:

- Between 45-85 years of age and understand written and spoken English
- Activity-related knee pain on most days of the past month
- Knee pain for at least 3 months
- No morning knee stiffness, or morning stiffness that lasts less than 30mins
- Willing to complete the assigned 12-week eating program and attend all appointments (detailed below)

You are not eligible and cannot participate in this study if you meet any of the following:

- Knee pain not primarily due to osteoarthritis (e.g., fibromyalgia, referred pain)
- Bilateral knee replacement
- Already strictly following a specific diet (e.g., low-carb, paleo, Mediterranean, Vegan)
- Received treatment from a dietitian, or knee injection, in the past 3 months
- Experienced ≥ 5 kg weight loss in the past 3 months or body weight ≥ 200 kg
- Planning to have knee surgery in the next 6 months
- Pregnant or breastfeeding
- History of psychiatric or eating disorder (excluding anxiety/depression) or bariatric surgery

4 What does participation in this research involve?

This study will be conducted over 6 months in total (see flowchart on next page).

Pre-baseline (online/phone) appointment

You will be asked to attend a 30-minute Zoom/telephone appointment prior to your first face-to-face appointment. At this appointment, we will discuss the consent form, outline the fasting process needed to complete your blood test and DEXA scan, and answer any questions you might have. We will also explain how to complete a 3-day food diary, which will be done using a smart phone application or paper-based food diary (personal preference).

Baseline (first) appointment

This appointment will be arranged at a convenient time for you at La Trobe University, Bundoora and will take approximately 2 hours. You will be asked to not eat/drink anything or conduct any exercise in the morning of your appointment (i.e., fasting for 12-hours) for the purpose of a blood test. At the appointment, we will assess your:

- Height, weight, waist circumference and blood pressure
- Body composition measured via a Dual-energy X-ray Absorptiometry Scan (DEXA).
This involves laying on the scanner bed for ~7 mins. The machine uses small doses (<1% yearly dose) of radiation to assess tissue density (how much muscle and adipose tissue you have). The total effective dose of radiation has been calculated by a Medical Physicist (see risks below). Light clothing with no metal (e.g., zips, clips, underwire) should be worn (gown provided if needed). All measures will be taken by trained

researchers who hold Victorian Government radiation licenses and comply to the Code of Practice set out by the Australian Radiation Protection and Nuclear Safety Agency.

- Blood test: A trained researcher qualified to take blood will collect a small amount of blood (~25 mL, equivalent to ~4 teaspoons) from a forearm vein to assess inflammation levels.
- Questionnaires assessing your pain, activity level and quality of life and food intake
- Functional tests: i) how many times you can stand from a chair in 30 secs; and ii) how fast you can walk 40 metres.

We will provide a snack/drink as soon as you complete the DEXA and blood tests.

Random assignment to one of two different treatments

At the end of the first appointment at La Trobe University, you will be randomly assigned (50:50 chance, like a coin toss) to receive a program (from qualified dietitians) to either:

- minimise processed foods that are known to promote inflammation and optimise foods shown to reduce inflammation; or
- minimise foods that are known to be high in fat content.

This means neither you nor the researchers will be able to choose which group you are assigned to. We do not know which treatment is best; to find out we need to compare the two programs. Although the two programs involve modifying some types of food that you eat, you can eat as much as you like of these foods. **You do not need to restrict the amount of food that you eat.**

Irrespective of which group you are assigned to, you will receive specific education and advice from an Accredited Practising Dietitian (APD) in a dietary consultation at the start of the study (at the end of your first appointment at La Trobe University). Your dietitian will also work with you to develop a personalised management plan to support you throughout the study. You will be asked to follow the program for 12 weeks (but you can continue for as long as you like). We will ask you to record your food intake for 3 days at up to six different times throughout the study.

Support phone calls

To support you throughout the study and answer any questions you have, we will arrange up to four follow-up consultations to be conducted over the phone/online during the 12 weeks. This phone call will take approximately 15-20 minutes. At these times, we will also ask you to complete some of the same questionnaires online (via a secure link provided by e-mail).

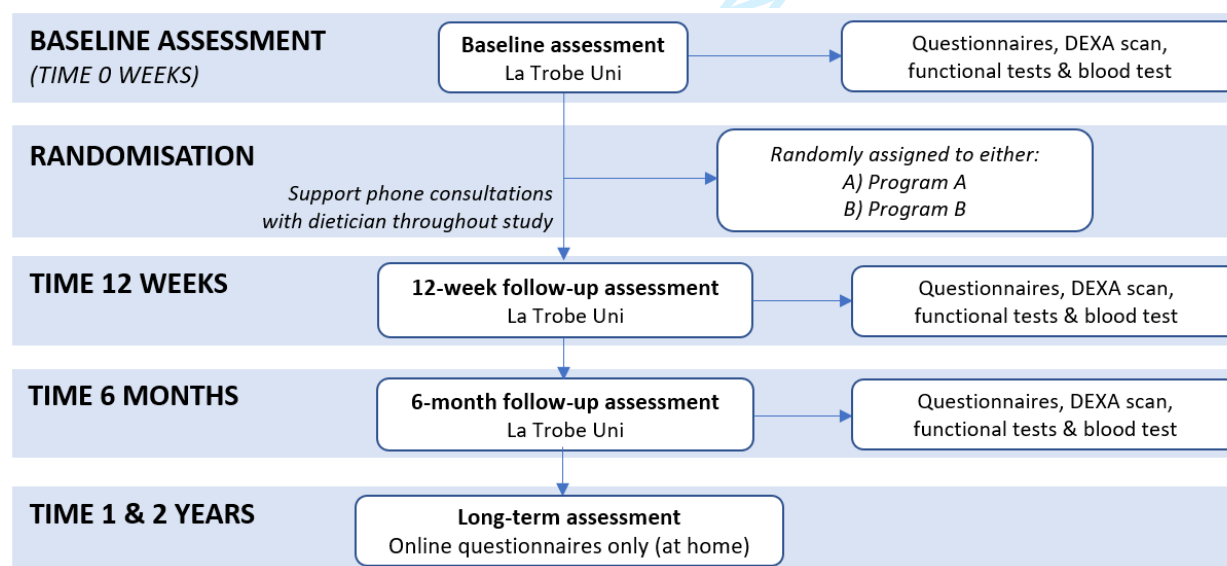


Figure 1. Flowchart of study assessments

Follow-up appointments

So that we can assess the results of the program you have been assigned to, we will ask you to return for face-to-face appointments at La Trobe University at **12 weeks and 6 months after your first appointment.** These follow-up appointments will be like the first appointment where

1 we will do all the same tests and questionnaires. You will need to fast (not eat/drink anything) the
2 morning of your appointment for the blood test. You will have another dietary consultation with
3 the study dietitian who will provide support for you to continue with the program you have been
4 assigned. You should allow about 2 hours for these appointments. To assess longer-term results,
5 we will ask you to complete the same online questionnaires at 1 and 2 years after your first
6 appointment. The total time commitment for participating will be approximately 6-8 hours.
7

8
9 There are no additional costs associated with participating in this research project. All medical
10 care and tests (i.e., dietitian consultations, DEXA scan, blood tests) required as part of the
11 research project will be provided free of charge. The results of the DEXA scan and blood tests
12 will not be used to diagnose health conditions, but only to evaluate the effects of the intervention.
13 We will provide you with your individual results when the DEXA and blood analyses are completed
14 at the end of the study. Your travel costs to attend the assessments will be reimbursed up to \$100.
15

16
17 At the end of the first 12 weeks, or after 6-12 months, we may also ask if you are willing to have
18 a separate interview with one of the study researchers (this interview is optional and you can take
19 part in the study without needing to complete the interview). The purpose of this interview is to
20 seek feedback on the study treatments, satisfaction with the process received and whether there
21 are any suggestions for improvement. The interview will take approximately 30 minutes, but you
22 can cease the interview at any time. To ensure responses are correctly interpreted, responses to
23 questions will be audio recorded and transcribed. Audio recording transcriptions will be completed
24 by 'Transcription Australia' on their secure, encrypted Australian-based software. Although voice
25 in your audio recording could lead to your identification, this file will not be used during analysis.
26 Instead, a re-identifiable transcription, which you will have the opportunity to check for accuracy,
27 will be used for analysis. Re-identifiable means that we will use a code number and not your name
28 on data collected to ensure your anonymity. Following the completion of analysis of this
29 transcription, the audio file associated with your interview will be deleted. After analysis, overall
30 findings and conclusions from all interviews will also be sent to you, to allow an opportunity to
31 make any further comments. We will seek around 40 participants to be interviewed. It is your
32 decision or not whether you wish to be interviewed.
33

34 35 **5 What are the alternatives to participation?**

36
37 You do not have to take part in this research project to receive treatment for your knee. Other
38 options are available; these include seeing a physiotherapist or dietitian (e.g., private or public
39 health centre). The research team will discuss these options with you before you decide to take
40 part in this project. You can also discuss the options with your doctor, dietitian or physiotherapist.
41

42 43 **6 What are the possible benefits of taking part?**

44
45 We cannot guarantee or promise that you will receive any benefits from this research. However,
46 possible benefits may include improvement of pain, function, quality of life, physical activity, and
47 confidence in your knee. You may gain valuable insight into how to manage your food intake and
48 specific anti-inflammatory and low-fat foods, nutrients and eating habits. The expected benefit to
49 society is the development of a drug-free and non-invasive treatment option to help manage pain
50 and disability associated with osteoarthritis. This will give doctors and patients alternative ways
51 to manage knee pain, which in turn may lead to improvements in the quality of life for patients.
52
53

54 55 **7 What are the possible risks and disadvantages of taking part?**

56
57 With any medical treatment there are: (i) risks we know about; (ii) risks we don't know about; and
58 (iii) risks we don't expect. We have listed the risks we know about below. You may have none,
59 some or all the effects listed below, and they may be mild, moderate or severe. If you have any
60 of these side effects, or are worried about them, talk with the study coordinator.

Possible Side Effect	How often is it likely to occur?	How severe might it be?	How long might it last?
Emotional distress due to involvement in research and completion of questionnaires	Rarely; although can occur when completing study questionnaires	Minimal	While completing the study questionnaires
Emotional distress due to diet assessment	Rarely; although can occur when assessing food intake prior to, or during, appointments	Minimal	While completing the food diary or assessment
Discomfort due to body measurements	Can occur while measurements are done by your dietitian or researcher	Minimal Mild	During appointment only
Discomfort due to blood test	Rarely; while blood is being collected	Mild	Bruising or swelling may last 1-3 days
Exposure to ionising radiation	1x 7-minute scan at initial, 12-week and 6-month appointment	Minimal	Effect too small to measure
Tiredness/change in bowel patterns with change in diet	Any change in diet can make you feel tired or have different bowel patterns	Minimal	1-2 weeks
Contraction of COVID-19	Can occur during the face-to-face assessments	Minimal Moderate	1-2 weeks

If you become upset or distressed because of your participation in the research, the study coordinator together with the qualified dietitian will assist you with appropriate support. We can also provide you information about services you can access to seek help for emotional distress.

Risks associated with completing study questionnaires and diet assessment

Completing questionnaires about your knee pain, function, quality of life and dietary intake may cause emotional distress. If you begin to feel upset or distressed when completing your questionnaires or dietary assessment, please let a member of the research team know. We will provide you with the appropriate support, including a document outlining services you can access to help with your emotional distress.

Risks associated with blood test

Having a blood sample taken may cause some discomfort or bruising. On very rare occasions, the blood vessel may swell, or blood may clot in the blood vessel, or the spot from which blood is taken could become inflamed. Some people may feel light-headed when having blood taken and may occasionally faint. Very rarely, there could be a minor infection or bleeding. A qualified person will take a very small amount of your blood (max 30mL each appointment (normal blood donation is 500mL)) using stringent infection control procedures. If you notice increased redness, swelling or other signs of infection in the days following your assessment, tell us immediately.

Risks associated with eating low-inflammatory foods or low-fat foods

As you adjust to the eating program you are assigned to, you may experience feelings of tiredness and/or changes in bowel habits and patterns. The researchers will assess your diet and ensure you are meeting your energy and nutrient needs throughout the study intervention. This eating program may be different than your normal diet and therefore influence your usual weekly shopping bill and expenses. As part of the consultations, you will be provided with some advice on how to follow the diet on a budget if required to ensure there is minimal financial burden.

Exposure to ionising radiation

If you choose to take part in this research, you will undergo three 7-minute DEXA scans (first, 12-week and 6-month assessments). DEXA scans are a non-invasive, fast and simple procedure. This research study involves exposure to a very small amount of radiation from a DEXA scan that you would not normally receive. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose you will receive from all of these DEXA scans is approximately 0.03 mSv. At these

1 dose levels, no harmful effects of radiation have been demonstrated as any effect is too small to
2 measure. The risk is believed to be minimal.
3

4
5 The scans we are taking are for research purposes and are not intended to be used like scans
6 taken for a full clinical examination or to be used to help diagnose, treat or manage a particular
7 condition. The whole-body DEXA scan may identify participants with a low bone mineral density.
8 However, a whole body DEXA scan is not the established method for detecting low bone mineral
9 density. Therefore, as a precaution if you are identified as having a low bone mineral density you
10 will be encouraged to make an appointment with your General Practitioner to discuss the results.
11

12 Have you been involved in any other research studies that involve radiation? If so, please tell us.
13 Please keep information contained within this Patient Information Sheet about your exposure to
14 radiation in this study, including the radiation dose, for at least 5 years. You will be required to
15 provide this dose to researchers of any future research projects involving exposure to radiation.
16

17 **Contraction of COVID-19**

18 You may be at risk of contracting COVID-19 during one of the face-to-face appointments at La
19 Trobe University. Prior to attending La Trobe University, you will be screened for signs and
20 symptoms of COVID-19 by a member of the research team. You will also need to be fully
21 vaccinated (or hold a valid medical exemption) to be able to attend La Trobe University for your
22 assessments. The research team will put in place the appropriate control measures to reduce the
23 risk of COVID 19 transmission. The risk is believed to be minimal.
24

25 **8 What if I withdraw from this research project?**

26
27 You are under no obligation to continue with the research study. You may change your mind at
28 any time about participating in the research. People withdraw from studies for various reasons,
29 and you do not need to provide a reason.
30

31
32 You can withdraw from the study at any time by completing and signing the 'Participant
33 Withdrawal of Consent Form'. This form is provided at the end of this document and is to be
34 completed by you and supplied to the research team if you choose to withdraw at a later date.
35

36
37 If you withdraw from the study, you will be able to choose whether the study will destroy or retain
38 the information it has collected about you. Information about you that has already been analysed
39 (i.e., once you have been allocated to either program), may not be able to be destroyed to ensure
40 accurate and unbiased study reporting. Personal details collected, such as your name and contact
41 details, can be destroyed at any time upon study withdrawal.
42

43 **9 What happens when the research project ends?**

44
45 At the completion of the research project, you may continue to use the resources provided and to
46 follow the eating program principles if you choose to. If requested, we will provide you with your
47 individual results including your body composition (DEXA) assessment and whole study results.
48 We, or other researchers, may also use coded information (so that you cannot be identified)
49 collected for this research study in future related studies. If you consent (tick the box on the
50 consent form) to be contacted for future related research, we will store your contact details (name,
51 address, phone number, email) on the secure La Trobe University research drive, only accessible
52 to members of the research team, and may contact you about future related research projects.
53
54
55
56
57

58 **Part 2 How is the research project being conducted?**

59 **10 What will happen to information about me?**

1 By signing the consent form you agree to the relevant research staff collecting and using personal
2 information about you for the research project. Any information obtained in connection with this
3 research project that can identify you will remain confidential and securely stored. It will be
4 disclosed only with your permission, or in compliance with the law.
5

6 **Storage, retention and destruction**

7 The anonymity of your participation is assured with our procedure, in which a code number (not
8 your name) will identify you. Data will be kept securely at La Trobe University in a locked filing
9 cabinet and password protected research computer. Identifiable data will be stored for 15 years,
10 then destroyed (electronic records deleted, paper-files shredded). Data will be strictly handled
11 confidentially under guidelines set out by the National Health and Medical Research Council. The
12 principal investigator (Dr Adam Culvenor) is responsible for maintaining this confidentiality.
13

14
15 In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have
16 the right to request access to your information collected and stored by the research team. You
17 also have the right to request that any information with which you disagree be corrected.
18

19 The results of this project may be published and/or presented in a variety of forums and used by
20 research students to obtain a research degree. In any publication, presentation or data files
21 shared with other researchers, information will be provided in such a way that you cannot be
22 identified, except with your permission.
23

24 **11 Who is organising and funding the research?**

25 This research project is being conducted by Dr Adam Culvenor and a team of researchers. It has
26 been funded by the NHMRC (GNT2008523) and Dr Peter Brukner. Dr Peter Brukner is also an
27 investigator on the project and has written a book and developed an app that will be used as part
28 of the study. He will not be involved in data collection, analysis or the decision to publish results.
29 No member of the research team will receive a personal financial benefit from your involvement
30 in this research project (other than their ordinary wages).
31

32 **12 Who has reviewed the research project?**

33 All research in Australia involving humans is reviewed by an independent group of people called
34 a Human Research Ethics Committee (HREC). The ethical aspects of this research project have
35 been approved by the HREC of La Trobe University Human Ethics Committee.
36

37 This project will be carried out according to the *National Statement on Ethical Conduct in Human
38 Research (2018)*. This statement has been developed to protect the interests of people who agree
39 to participate in human research studies.
40

41 **13 Further information and who to contact**

42 For all enquiries, you can contact the Clinical Trial Manager, during business hours:
43 Dr Adam Culvenor, Senior Research Fellow in Physiotherapy, La Trobe University
44 Telephone: 03 9479 5116; E-mail: a.culvenor@latrobe.edu.au
45

46 If you have any complaints about any aspect of the project, the way it is being conducted or any
47 questions about being a research participant in general, then you may contact:
48

49 Reviewing HREC: La Trobe University Human Research Ethics Committee
50 Complaints Contact: Senior Human Ethics Officer, Ethics and Integrity, Research Office
51 Telephone: 03 9479 1443 E-mail: humanethics@latrobe.edu.au
52

53 * Please quote the application reference number HEC22044
54



Consent Form - *Adult providing own consent*

Title Optimising outcomes for people with knee pain through food: FEAST randomised controlled trial

Short Title The FEAST trial

Ethics Reference Number HEC22044

Project Sponsor La Trobe University

**Coordinating Principal Investigator/
Principal Investigator** Dr Adam Culvenor (La Trobe University)
Dr Brooke Devlin (University of Queensland)
Prof. Peter Brukner (La Trobe University)
Ass. Prof. Joanne Kemp (La Trobe University)

Associate Investigator(s) Prof. Kay Crossley (La Trobe University)
Dr Andrea Mosler (La Trobe University)
Dr Josh Heerey (La Trobe University)
Ms Lynette Law (PhD student, La Trobe University)
Ms Amanda Attanayake (SAHHSS, La Trobe University)

Location La Trobe University

Consent Agreement

I have read the Participant Information Sheet and I understand the purposes, procedures and risks of the research described in the project.

I understand that data files may be shared with other researchers, and that information will be provided in such a way that I cannot be identified, except with my permission.

I have had an opportunity to ask questions and I am satisfied with the answers I have received. I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. I agree that data gathered for the study may be published provided my name or other identifying information is not used.

- I wish... / do not wish... to receive results of the study
- I consent... / do not consent... to be contacted for future related research
- I consent... / do not consent... to have my interview responses audio-recorded/transcribed.
- I consent... / do not consent... to have my samples/data used in future research

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Researcher[†]

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Researcher[†] (please print) _____

Signature _____ Date _____

[†] An appropriately qualified member of the research team must provide the explanation of, and information concerning, the research project.



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	ACTRN1262200 0440729
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-13, Table 2, Supplementary File 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Table 2
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8-13, Table 2
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-18, Table 3
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7-8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7-8

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	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
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Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
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	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
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Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
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	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
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	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
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Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
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	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19-20
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Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
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Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
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Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
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4	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20
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8	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20
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11		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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14	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
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18	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
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20	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Supplementary File 1
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24	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
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26	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
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28		31b	Authorship eligibility guidelines and any intended use of professional writers	NA
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30		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
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38	Appendices			
39	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary File 1
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43	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Supplementary File 2
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-Non Commercial-No Derivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.