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

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**ABSTRACT**

**Introduction:** Chronic inflammation plays a key role in knee osteoarthritis pathophysiology and increases risk of comorbidities, yet most interventions do not typically target inflammation. Our study will investigate if an anti-inflammatory dietary program is superior to a standard care low-fat dietary program for improving knee pain, function and quality-of-life in people with knee osteoarthritis.

**Methods and analysis:** The FEAST (eFEct of an Anti-inflammatory diet for knee oSTeoarthritis) Study is a parallel-group, assessor-blinded, superiority randomised controlled trial. Following baseline assessment, 140 participants aged 45-85 years with symptomatic knee osteoarthritis will be randomly allocated to one of two treatment groups (1:1 ratio). Participants randomised to the anti-inflammatory dietary program will receive six dietary consultations over 12 weeks (2 in-person, 4 phone/videoconference) and additional educational and behaviour change resources. The consultations and resources emphasise nutrient-dense minimally processed anti-inflammatory foods and discourage pro-inflammatory processed foods. Participants randomised to the standard care low-fat dietary program will receive three dietary consultations over 12 weeks (2 in-person, 1 phone/videoconference) consisting of healthy eating advice and education based on the Australian Dietary Guidelines, reflecting usual care in Australia. Adherence will be assessed with 3-day food diaries. Outcomes are assessed at 12 weeks and 6 months. The primary outcome will be change from baseline to 12 weeks in the mean score on four Knee injury and Osteoarthritis Outcome Score ($KOOS_4$) subscales: knee pain, symptoms, function in daily activities and knee-related quality-of-life. Secondary outcomes include change in individual KOOS subscale scores, patient-perceived improvement, health-related quality-of-life, body mass and composition using dual-energy X-ray absorptiometry, inflammatory (high-sensitivity C-Reactive Protein, Interleukins, Tumour Necrosis Factor-α) and metabolic blood biomarkers (glucose, HbA1c, insulin, liver function, lipids), lower-limb function and physical activity.

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

**Trial registration:** ACTRN12622000440729

**Keywords:** Inflammation, Low-carbohydrate, Anti-inflammatory, Pain, Osteoarthritis, Knee, Chronic disease, Rehabilitation, Diet

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- The anti-inflammatory dietary program was codeveloped and piloted with patients and clinicians, with the comparison low-fat dietary program representing usual care.
- Sufficiently powered trial evaluating change from baseline to 12 weeks (primary endpoint) and 6 months facilitating longer-term effectiveness evaluation of the anti-inflammatory dietary program.
- This trial will evaluate both self-reported and objective outcomes to understand potential mechanisms of symptomatic changes.
- While outcome assessors are blinded to group allocation, the health professionals delivering the interventions and participants are unable to be blinded to group allocation due to the type of interventions.

## INTRODUCTION

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

Clinical guidelines for knee OA recommend exercise-therapy and weight-loss as first-line management strategies due to their excellent safety profile and therapeutic effects similar to commonly used analgesics[2 6]. However, the effectiveness of exercise-therapy has recently been questioned due to its lack of benefit over an open-label placebo[7], and findings that one-third of people completing an exercise program do not achieve a clinically meaningful improvement in pain[8 9]. Weight-loss programs in those who are overweight or obese typically consist of caloric restrictive diets, which are challenging to adhere to and sustain[10]. A meta-analysis highlighted that, within two years of a calorie-restrictive program, over half of initial weight lost was regained, and by 5 years, this figure jumped to >80%[11].

Anti-inflammatory diets provide an alternative to calorie-restrictive approaches by targeting local and systemic inflammation, both contributors to OA disease onset, progression and symptom burden[12-14]. Anti-inflammatory diets are typically high in minimally processed, nutrient rich foods such as fruit, vegetables, spices and extra virgin olive oil, which are dense in nutrients such as polyphenols, carotenoids, fibre, monounsaturated and polyunsaturated fatty acids[15-18]. These nutrients can significantly reduce inflammation even in the absence of weight loss[19] via antioxidant and anti-inflammatory properties by neutralising free radicals and associated cell damage, as well as improved lipid profiles[15 16 20]. Due to their focus on real foods and consumption to satiety, anti-inflammatory diets are likely more sustainable than traditional calorie-restrictive approaches[16].

Anti-inflammatory diets have garnered much interest in recent years due to their effectiveness in alleviating symptoms and improving biomarkers for a variety of chronic diseases, including diabetes[17], cardiovascular disease[21], epilepsy[22] and rheumatoid arthritis[23]. Small studies investigating anti-inflammatory diets for knee OA have demonstrated feasibility and effectiveness in reducing symptoms and inflammation over 12-16 weeks[14 24 25]. To date, no fully powered randomised controlled trial (RCT) has evaluated the effectiveness of an anti-inflammatory diet in knee OA.

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

## METHODS AND ANALYSIS

### Study Design

This protocol describes a pragmatic, 2-arm, parallel-group assessor-blinded superiority RCT conforming to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement[26]. Reporting of the completed RCT will conform to the Consolidated Standards of Reporting Trials (CONSORT) statement[27]. The FEAST trial will be conducted at a single site (La Trobe University) in Melbourne, Australia with enrolment anticipated to occur over 24 months (2022-2024) and 6-month follow-up completed in 2024. The primary endpoint will be at 12 weeks, with additional follow-up at 6 months (further longer-term follow-up dependent on funding). The study was prospectively registered on the Australian and New Zealand Clinical Trial Registry (ACTRN 12622000440729).

**Participants**

One hundred and forty adults 45-85 years old with chronic knee pain consistent with a clinical OA diagnosis using criteria from the National Institute for Health and Care Excellence, which does not require radiographic evidence[28], will be enrolled (table 1).

**Table 1.** Eligibility criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| Fulfil National Institute for Health and Care Excellence[28] clinical criteria for osteoarthritis:<br>• 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;<br>• No morning stiffness or morning stiffness ≤30 min; and<br>• 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, >200kg body weight) |

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| | >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 |

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

**Recruitment and screening procedure**

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

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

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

*Randomisation procedure, concealment of allocation and blinding*

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

To ensure concealed allocation, the randomisation schedule will be stored electronically in the secure Research Electronic Data Capture (REDCap®) system and only accessible to an unblinded researcher once baseline measures have been obtained, who will communicate treatment allocation to the participant. Investigators conducting the follow-up assessments will be blinded to group allocation. As the primary outcome is self-reported, participants are considered assessors; therefore, participants (and thus assessors) will be blinded to previous scores. Health professionals delivering the interventions and participants cannot be blinded to group allocation owing to the type of interventions. An independent statistician, blinded to group allocation, will perform the primary RCT analysis.

**Interventions**

The anti-inflammatory dietary program and standard care low-fat dietary program are summarised aligning to Template for Intervention Description and Replication (TIDieR) guidelines[31] (table 2). The same health professionals will deliver the intervention for both groups.

*Anti-inflammatory dietary program*

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

Participants will be encouraged to follow a diet containing minimal processed foods and high amounts of healthy fats and nutrient-dense wholefoods known to fight inflammation (e.g., fresh fruits low in natural sugar such as berries, non-starchy vegetables, nuts and seeds, seafood, poultry, red meat, eggs, full-fat dairy). Healthy fats include monounsaturated and polyunsaturated fats with optimal omega-3: omega-6 ratios as found in seafood, nuts, and extra-virgin olive oil. Participants will be advised to limit processed foods, refined carbohydrates (e.g., pasta, bread, rice), confectionary and foods with added sugar.

Participants will be encouraged to consume a normocaloric diet and to eat to satiety, with no specific percentage of total energy intake targets for carbohydrate, fat or protein.

An initial in-person consultation (~45 minutes) will occur immediately following group allocation to constructively review participant's current dietary intake (using baseline 3-day food diary) and develop an individualised meal plan. Participants will be provided with a comprehensive explanation of anti-inflammatory dietary principles, its rationale (e.g., the role of inflammation in OA, link between foods and inflammation) and its potential benefits and side-effects, and address questions and/or concerns. The following educational and behaviour change resources will also be provided at the initial consultation to support adherence: i) bespoke information booklet providing anti-inflammatory eating information, example meal plans, and foods that are encouraged and foods to avoid; ii) complimentary subscription to an anti-inflammatory program (Defeat Diabetes phone app/website), providing anti-inflammatory recipes, masterclasses, meal plans and educational articles; iii) complimentary links to recommended documentaries exploring the benefits of anti-inflammatory nutrition (i.e., Fat Fiction, Cereal Killers, That Sugar Film); and iv) complimentary copy of a book exploring benefits of anti-inflammatory approach (A Fat Lot of Good[32]).

Follow-up phone/videoconference consultations (~30 minutes) will be scheduled in weeks 2, 4, 6, and 9, with timing to be negotiated between each participant and the health professional delivering the intervention. A final in-person consultation will be delivered immediately following the completion of the 12-week assessment. These follow-up consultations will provide participants with ongoing support, education and accountability. A 3-day food diary, completed prior to each consultation (see outcomes/adherence section), will guide individualised feedback and support to adapt meal plans to optimise adherence.

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].<br><br>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)<br>Four phone/videoconference follow-up consultations (~30 mins) in week 2, 4, 6, and 9.<br>***Total active intervention delivery time:*** ~3.5 hours<br><br>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)<br>One phone/videoconference follow-up consultation (30 mins) in week 6.<br>***Total active control delivery time:*** ~1.5 hours<br><br>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

*Standard care low-fat dietary program*

Participants allocated to the standard care low-fat dietary program will receive advice and education regarding healthy eating based on the Australian Dietary Guidelines[35]. These government-endorsed guidelines aim to optimise nutrition intake through adequate consumption of foods from the five core food groups (grains and cereals; fruit; vegetables and legumes; lean meats and poultry, fish, eggs, and tofu; reduced fat diary or alternatives), while limiting intake of foods containing saturated fat, added salt, added sugars and alcohol. They are high-carbohydrate and low-fat focused – participants will be encouraged to include at least four serves of wholegrains daily (e.g., brown rice, pasta, bread, quinoa, oats) and to choose low-fat protein and dairy foods where possible.

The program will be delivered through individual consultations with the treating dietitian or other specially trained health professional – the first in-person consultation immediately following baseline assessment (~45 minutes), the second via phone/videoconference at 6 weeks (~30 minutes) and the third in-person at 12-week follow-up with timing individualised as required. Two to three consultations represents usual care for patients referred for dietary management in Australia through the current public healthcare (Medicare) rebate system[34 36]. During the initial in-person consultation, participants will be provided with a bespoke educational booklet and advice and education emphasising the Australian Dietary Guideline principles (https://www.eatforhealth.gov.au/guidelines) and informed of complementary and publicly available online resources from the Eat for Health website (https://www.eatforhealth.gov.au/).

The follow-up phone/videoconference consultation in week-6 and in-person follow-up in week-12 will provide participants with ongoing support, education and accountability. The 3-day food diary, completed prior to each consultation (see outcomes/adherence section), will guide feedback and support to adapt meal plans to optimise adherence. The treating health professionals delivering the two dietary programs will be based centrally at La Trobe University and will be trained by the senior study dietitian (BLD) until deemed competent in intervention delivery.

Irrespective of group allocation, participants can continue usual medical care and consult with their treating health professionals as necessary (e.g., general practitioner regarding medication changes).

**Data collection procedure**

Data will be collected at baseline and 6 weeks, 12 weeks and 6 months after randomisation, with 12 weeks the *a priori* primary endpoint as this coincides with completion of supported interventions (table 3). Where possible, data will be collected and managed using a secure web-based software platform (REDCap®) hosted at La Trobe University[37], which has equivalent measurement properties to paper-based completion[38]. This strategy was used in our pilot study[25] and other trials of musculoskeletal conditions[39]. Paper versions will also be available if preferred.

## OUTCOMES

**Baseline characteristics**

Participant characteristics including age, sex, ethnicity, knee pain/surgery details, socioeconomic details (e.g., education level, employment status, living status), medical history and health literacy (assessed with the Rapid Estimate of Adult Literacy in Medicine (REALM)[40]) will be collected (table 3).

**Primary Outcome**

The primary outcome is the change from baseline to 12 weeks in the mean score on four Knee injury and Osteoarthritis Outcome Score ($KOOS_4$) subscales covering knee pain, symptoms, function in daily activities and knee-related quality of life. The KOOS is a 42-item patient-reported outcome measure assessing five separately scored subscales: Pain, Symptoms, Function in Sport and Recreation (Sport/Rec), Activities of Daily Living (ADL), and Quality of Life. The $KOOS_4$ and all KOOS subscale scores range from 0 (extreme problems) to 100 (no problems). The KOOS is a valid, responsive and reliable questionnaire, with $KOOS_4$ a primary outcome for other knee OA trials[30 41 42].

**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 |

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

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

**Secondary effectiveness outcomes**

*KOOS subscales*

To allow for clinical in-depth interpretation, scores for the five KOOS subscales will be reported individually (i.e., pain, symptoms, function in sports and recreational activities, activities of daily living, quality of life)[9 42].

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

Self-perceived change in pain and function will be assessed using a 7-point Likert scale ranging from 'much worse' to 'much better' in response to the questions: "Overall, how has your knee pain changed since the start of the study?" and "Overall, how has your knee function changed since the start of the study?", respectively. Treatment success will be defined as a response of either 'better' or 'much better'. Satisfaction with current knee function using the self-reported Patient Acceptable Symptom State (PASS) question[43]. Participants not satisfied with current knee function at follow-up assessments will be asked a second question to determine if they considered the treatment to have failed[43].

*Anthropometrics*

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

*Global lower-limb function*

Two performance-based tests of lower-limb function recommended by the OA Research Society International (OARSI) will be conducted: the 30-second chair-stand test (number of chair-stands from a standardised height chair in 20 seconds) and 40-metre walk test (time to walk 40 metres safely, using walking aids if required)[44].

### *Body composition*

A whole-body DXA scan will be acquired using a Hologic Horizon® DXA scanner (Bedford, MA, United States) to assess adiposity (visceral, peripheral) and lean mass[45].

### *Inflammatory and metabolic biomarkers*

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

## Secondary safety outcomes

### *Adverse events*

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

## Exploratory outcomes

### *Dietary Analysis*

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

Premium Edition nutrient analysis software (Version 10, Brisbane, Australia 2019) and Australian food composition databases. Paper-based 3-day food diaries will be manually entered into FoodWorks®. Total energy intake, macronutrients, micronutrients and core food group analysis will be reported. Dietary analysis data will also be used to calculate the inflammatory potential of participants' diets (e.g., Dietary Inflammatory Index)[47].

### *Quality of life*

Health-related quality of life will be assessed with the EQ-5D-5L generic health index, which comprises five dimensions of health (mobility, self-care, usual activities, pain or discomfort, anxiety or depression) and a Visual Analogue Scale (VAS) of current overall health status[48]. Both validity and reliability has been demonstrated in arthritic populations[49].

### *Knee pain and interference*

Self-reported knee pain (current, worst over past week, average over past week) will be assessed using a 100mm VAS (0=no pain, 100=worst pain imaginable). The degree to which knee pain interferes with participant's daily functioning will be assessed using the Brief Pain Inventory[50], a tool with reliability and validity demonstrated in knee pain populations[51 52].

### *Change in analgesic medication use*

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

### *Physical activity*

Physical activity will be assessed using the International Physical Activity Questionnaire (IPAQ)[53], a standardised and valid questionnaire providing an estimate of physical activity and sedentary behaviour, which has been widely validated[53 54 55]. Respondents are asked to report time spent in physical activity across three intensities (walking, moderate, vigorous). Using the IPAQ scoring protocol[56], total weekly physical activity can be estimated by weighting time spent in each activity intensity with its estimated metabolic equivalent (MET) energy expenditure[57].

*Blood pressure*

A pair of seated blood pressure measurements will be obtained using an automated monitor (Omron Model HEM-7121). The blood pressure cuff is placed over the mid-upper arm with the participant seated.

*Self-perceived wellness*

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

*Intervention adherence*

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

**DATA MANAGEMENT**

Most outcome data will be collected and managed electronically via REDCap© web-based software hosted at La Trobe University. Other data (e.g., DXA reports) will be stored electronically on the La Trobe University secure research drive. All electronic data will be de-identified (participant code) and exported for data analysis and saved in a password protected database on the La Trobe University research drive only accessible to the research team. Paper-based identifying documents (e.g., consent forms) will be securely stored in a locked filing cabinet accessible only to members of the research team and separately from re-identifiable (i.e., coded) data.

Due to the minimal known risks associated with the interventions being evaluated, our study will not have a formal data monitoring committee and does not require an interim analysis. Any unexpected serious adverse events or outcomes will be discussed by the trial management committee (authors of this protocol) and reported to the approving human research ethics committee for monitoring.

**Sample size calculation**

This trial has been powered to detect a clinically significant between-group difference for the primary outcome of $KOOS_4$. The estimated effect size for low-inflammatory diets on self-reported pain and function in individuals with arthritis is at least moderate (Cohen's d 0.62)[58]. Recruiting 112 participants (equally distributed between two arms) would yield 90% power to observe such an effect or larger at a two-tailed Type I error of 0.05. This sample size estimation is conservative since it is based on independent samples t-test. Using an ANCOVA model that includes the baseline value as a covariate and is pre-specified for the analysis should provide higher power for the same sample size. To account for a potential 20% drop-out, we will recruit 140 participants. This sample size will be sufficient to detect a minimal important change (MIC) in $KOOS_4$ estimated at 10 points in patients with knee OA (with a common between-subject standard deviation of 15). Including 140 participants will also provide ≥90% power to detect a statistically significant between-group difference (two-tailed $\alpha$=0.05) on the secondary outcome of inflammatory biomarkers (anticipated effect size: Cohen's d 2.33 for hsCRP/IL-6)[58].

**Statistical analyses**

Analysis will be performed according to the Estimands Framework[59] with a statistical analyst blinded to group allocation. All outcomes and analyses are prospectively categorised as primary, secondary or exploratory. For the primary hypothesis, a linear model with baseline value, sex and BMI (≥30 vs <30kg.m$^{-2}$) as covariates and treatment condition as a fixed factor will evaluate the treatment effect on $KOOS_4$ at 12 weeks. A linear mixed model utilising repeated measures at all time-points for secondary hypotheses will allow non-biased estimates of treatment effect in the presence of any potential missing cases, providing data are missing at random. A sensitivity analysis using pattern-mixture model to investigate the deviation from the missingness-at-random assumption will be carried out[60]. For secondary binary outcomes (e.g., treatment success), mixed-effect logistic regression models will be used to assess the effect of treatment. A subsequent analysis of participants classified as adherent to the protocol will be performed.

**Healthcare resource use**

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

**Process Evaluation**

Semi-structured interviews will be conducted on a subset of consenting participants (until data saturation reached) at 6 months. Interviews will explore experiences, knowledge and understanding of interventions received including potential benefits; acceptability and perceived effectiveness of the intervention; and reasons for adhering (or not) to the allocated diet. Purposive sampling will be used to recruit interview participants who will then be stratified based upon characteristics and outcomes of the trial (good outcome; poor outcome). Interviews will be audio recorded, transcribed and analysed using Framework Analysis[61]. Data will be coded and an inductive thematic analysis will be applied until no new themes emerge.

*Patient and public involvement*

Participants and clinicians co-designed the anti-inflammatory intervention, research questions and study methods. This input was gained from: i) qualitative interviews with participants from the pilot study as part of formal process evaluation strategies[25]; ii) participant and clinician focus groups providing feedback on study recruitment material and participant handbooks; and iii) discussion with experienced clinicians managing knee OA and dietary intervention strategies as part of FEAST development. Patients and clinicians will provide input into the dissemination of study results by assisting with the decision on what information to share and in what format.

**ETHICS AND DISSEMINATION**

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

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

## 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-morbidities[62]. 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 and read and approved the final manuscript.

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## COMPETING INTERESTS STATEMENT

PB is the founder of Defeat Diabetes and author of "A Fat Lot of Good". PB contributed to study design but has no role in study execution, data management, analysis or the decision to publish. The NHMRC has no role in study design and will not have any role in its execution, data management, analysis and interpretation or on the decision to submit the results for publication. JLK is an editor of the British Journal of Sports Medicine (British Medical Journal Group). AGC is an associate editor of British Journal of Sports Medicine (British Medical Journal Group). All other authors have no competing interests.

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**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.** Patient information and consent form

**Supplementary File 2.** Standard Operating Procedures for blood collection, processing and storage

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LA TROBE UNIVERSITY

# 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)<br>Prof. Peter Brukner (SAHHSS, La Trobe University)<br>Ass. Prof. Joanne Kemp (SAHHSS, La Trobe University)<br>Prof. Kay Crossley (SAHHSS, La Trobe University)<br>Dr Andrea Mosler (SAHHSS, La Trobe University)<br>Dr Josh Heerey (SAHHSS, La Trobe University)<br>Ms Lynette Law (PhD student, SAHHSS, La Trobe University)<br>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 ≥5kg weight loss in the past 3 months or body weight ≥200kg
- 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:

i) minimise processed foods that are known to promote inflammation and optimise foods shown to reduce inflammation; or

ii) 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).

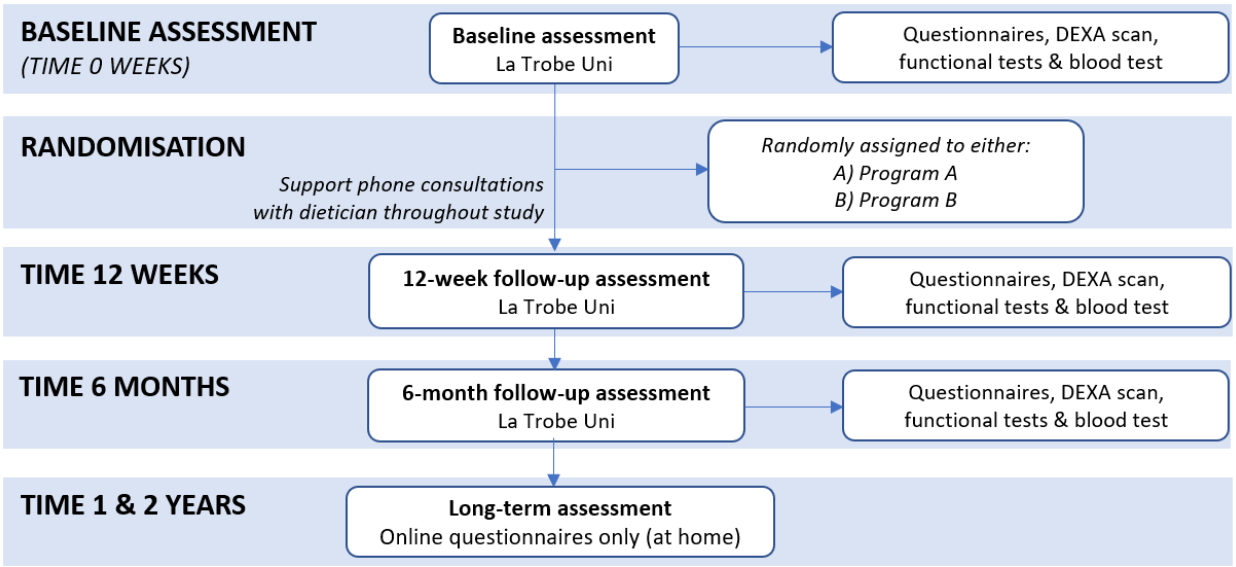


***Figure 1. Flowchart of study assessments***

***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

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

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

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

## 5 What are the alternatives to participation?

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

## 6 What are the possible benefits of taking part?

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

## 7 What are the possible risks and disadvantages of taking part?

With any medical treatment there are: (i) risks we know about; (ii) risks we don't know about; and (iii) risks we don't expect. We have listed the risks we know about below. You may have none, some or all the effects listed below, and they may be mild, moderate or severe. If you have any 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<br>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<br>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

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

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

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

**Contraction of COVID-19**

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

### 8 What if I withdraw from this research project?

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

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

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

### 9 What happens when the research project ends?

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

## Part 2 How is the research project being conducted?

### 10 What will happen to information about me?

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

***Storage, retention and destruction***

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

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

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

## 11 Who is organising and funding the research?

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

## 12 Who has reviewed the research project?

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

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

## 13 Further information and who to contact

For all enquiries, you can contact the Clinical Trial Manager, during business hours:

Dr Adam Culvenor, Senior Research Fellow in Physiotherapy, La Trobe University
Telephone: 03 9479 5116; E-mail: a.culvenor@latrobe.edu.au

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

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

* Please quote the application reference number HEC22044

LA TROBE UNIVERSITY

# 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)<br>Prof. Peter Brukner (La Trobe University)<br>Ass. Prof. Joanne Kemp (La Trobe University)<br>Prof. Kay Crossley (La Trobe University)<br>Dr Andrea Mosler (La Trobe University)<br>Dr Josh Heerey (La Trobe University)<br>Ms Lynette Law (PhD student, La Trobe University)<br>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.

FEAST Project

# Standard Operating Procedure

# Blood collection, processing, handling, and storage procedures

### 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)

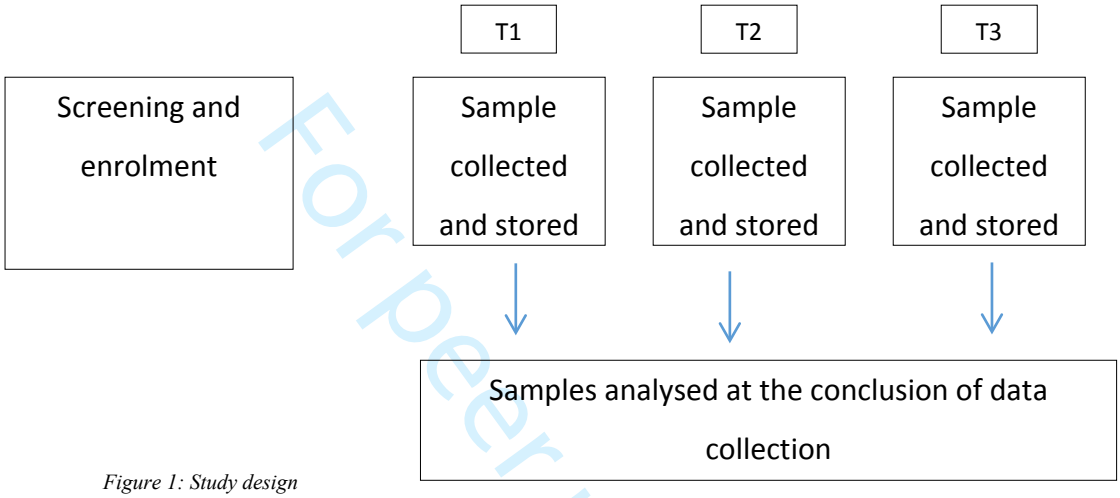


*Figure 1: Study design*

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 adaptorSterile 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 biocan 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.

FEAST v 2.0
17.08.2023

## 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 preprogramed 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).

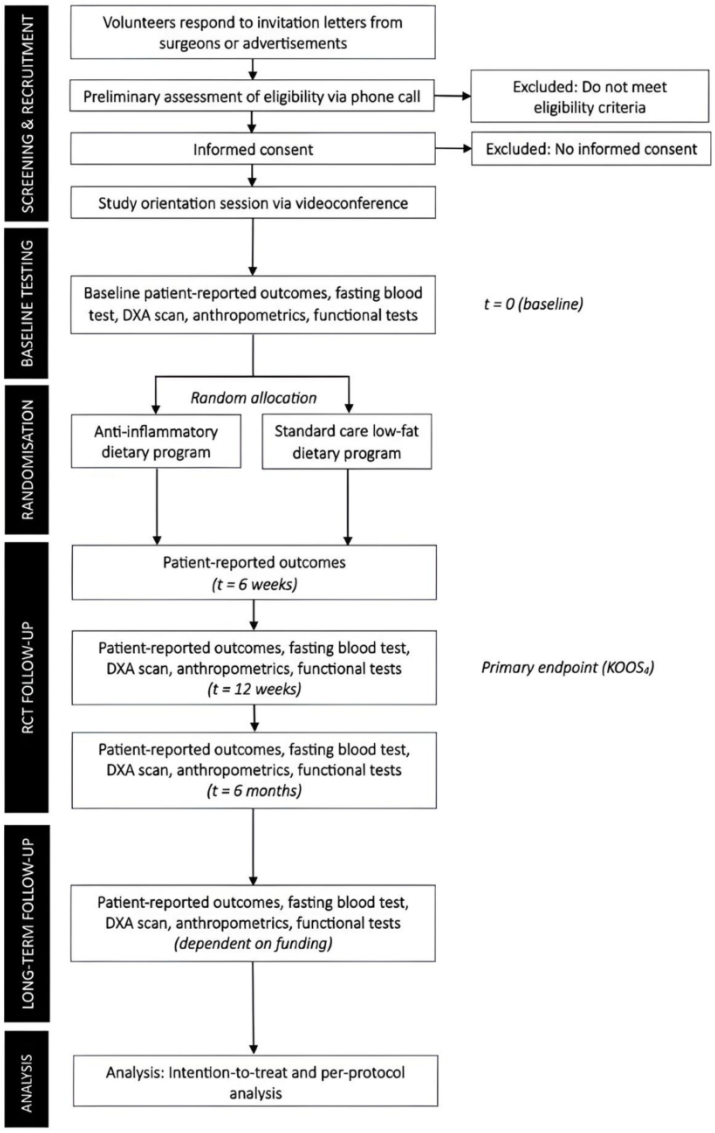


Figure 1. Flow of participants through the trial. DXA, Dual X-ray Absorptiometry; KOOS, Knee injury and Osteoarthritis Outcome Score
*Optional qualitative interview for process evaluation at 6 months

529x695mm (96 x 96 DPI)


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 | ACTRN12622000440729 |
| 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 |

| | | | |
|---|---|---|---|
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | NA |
| **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 |
| | 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 |
| 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 |
| | 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 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | NA |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 20 |

| | | | |
|---|---|---|---|
| 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 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 20 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| 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 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 21 |
| 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 |
| 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 |
| 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 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | NA |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | NA |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Supplementary File 1 |
| 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 |

*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" license.

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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| | |

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

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**ABSTRACT**

**Introduction:** Chronic inflammation plays a key role in knee osteoarthritis pathophysiology and increases risk of comorbidities, yet most interventions do not typically target inflammation. Our study will investigate if an anti-inflammatory dietary program is superior to a standard care low-fat dietary program for improving knee pain, function and quality-of-life in people with knee osteoarthritis.

**Methods and analysis:** The FEAST (eFEct of an Anti-inflammatory diet for knee oSTeoarthritis) Study is a parallel-group, assessor-blinded, superiority randomised controlled trial. Following baseline assessment, 144 participants aged 45-85 years with symptomatic knee osteoarthritis will be randomly allocated to one of two treatment groups (1:1 ratio). Participants randomised to the anti-inflammatory dietary program will receive six dietary consultations over 12 weeks (2 in-person, 4 phone/videoconference) and additional educational and behaviour change resources. The consultations and resources emphasise nutrient-dense minimally processed anti-inflammatory foods and discourage pro-inflammatory processed foods. Participants randomised to the standard care low-fat dietary program will receive three dietary consultations over 12 weeks (2 in-person, 1 phone/videoconference) consisting of healthy eating advice and education based on the Australian Dietary Guidelines, reflecting usual care in Australia. Adherence will be assessed with 3-day food diaries. Outcomes are assessed at 12 weeks and 6 months. The primary outcome will be change from baseline to 12 weeks in the mean score on four Knee injury and Osteoarthritis Outcome Score ($KOOS_4$) subscales: knee pain, symptoms, function in daily activities and knee-related quality-of-life. Secondary outcomes include change in individual KOOS subscale scores, patient-perceived improvement, health-related quality-of-life, body mass and composition using dual-energy X-ray absorptiometry, inflammatory (high-sensitivity C-Reactive Protein, Interleukins, Tumour Necrosis Factor-α) and metabolic blood biomarkers (glucose, HbA1c, insulin, liver function, lipids), lower-limb function and physical activity.

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

**Trial registration:** ACTRN12622000440729

**Keywords:** Inflammation, Low-carbohydrate, Anti-inflammatory, Pain, Osteoarthritis, Knee, Chronic disease, Rehabilitation, Diet

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- The anti-inflammatory dietary program was codeveloped and piloted with patients and clinicians, with the comparison low-fat dietary program representing usual care.
- Sufficiently powered trial evaluating change from baseline to 12 weeks (primary endpoint) and 6 months facilitating longer-term effectiveness evaluation of the anti-inflammatory dietary program.
- This trial will evaluate both self-reported and objective outcomes to understand potential mechanisms of symptomatic changes.
- While outcome assessors are blinded to group allocation, the health professionals delivering the interventions and participants are unable to be blinded to group allocation due to the type of interventions.

## INTRODUCTION

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

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

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

increases the risk and severity of chronic disease, including OA.(15) Due to their focus on real foods and consumption to satiety, anti-inflammatory diets are likely more sustainable than traditional calorie-restrictive approaches.(17)

Anti-inflammatory diets have garnered much interest in recent years due to their effectiveness in alleviating symptoms and improving biomarkers for a variety of chronic diseases, including diabetes,(18) cardiovascular disease,(24) epilepsy(25) and rheumatoid arthritis.(26) Small studies investigating anti-inflammatory diets for knee OA have demonstrated feasibility and effectiveness in reducing symptoms and inflammation over 12-16 weeks.(15, 27, 28) To date, no fully powered randomised controlled trial (RCT) has evaluated the effectiveness of an anti-inflammatory diet in knee OA.

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

## METHODS AND ANALYSIS

### Study Design

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

participant randomised on August 31, 2022 and the final participant anticipated to be randomised in June 2024. The primary endpoint will be at 12 weeks, with additional follow-up at 6 months (further longer-term follow-up dependent on funding). The study was prospectively registered on the Australian and New Zealand Clinical Trial Registry (ACTRN 12622000440729).

## Patient and public involvement

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

## Participants

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

**Table 1.** Eligibility criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| Fulfil National Institute for Health and Care Excellence(31) clinical criteria for osteoarthritis:<br>• 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;<br>• No morning stiffness or morning stiffness ≤30 min; and<br>• 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 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 |

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

**Recruitment and screening procedure**

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

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

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

### *Randomisation procedure, concealment of allocation and blinding*

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

**Interventions**

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

*Anti-inflammatory dietary program*

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

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

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

adherence: i) bespoke information booklet providing anti-inflammatory eating information, example meal plans, and foods that are encouraged and foods to avoid (Supplementary file 1 and 2); ii) complimentary subscription to an anti-inflammatory program (Defeat Diabetes phone app/website), providing anti-inflammatory recipes, masterclasses, meal plans and educational articles; iii) complimentary links to recommended documentaries exploring the benefits of anti-inflammatory nutrition (i.e., Fat Fiction, Cereal Killers, That Sugar Film); and iv) complimentary copy of a book exploring benefits of anti-inflammatory approach (A Fat Lot of Good(35)).

Follow-up phone/videoconference consultations (~30 minutes) will be scheduled in weeks 2, 4, 6, and 9, with timing to be negotiated between each participant and the health professional delivering the intervention. A final in-person consultation will be delivered immediately following the completion of the 12-week assessment. These follow-up consultations will provide participants with ongoing support, education and accountability. A 3-day food diary, completed prior to each consultation (see outcomes/adherence section), will guide individualised feedback and support to adapt meal plans to optimise adherence.

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)<br><br>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** | Two in-person consultations at baseline (~45 mins) and week 12 (~30 mins)<br>Four phone/videoconference follow-up consultations (~30 mins) in week 2, 4, 6, and 9.<br>***Total active intervention delivery time:*** ~3.5 hours<br><br>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)<br>One phone/videoconference follow-up consultation (30 mins) in week 6.<br>***Total active control delivery time:*** ~1.5 hours<br><br>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 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

*Standard care low-fat dietary program*

Participants allocated to the standard care low-fat dietary program will receive advice and education regarding healthy eating based on the Australian Dietary Guidelines.(39) These government-endorsed guidelines aim to optimise nutrition intake through adequate consumption of foods from the five core food groups (grains and cereals; fruit; vegetables and legumes; lean meats and poultry, fish, eggs, and tofu; reduced fat diary or alternatives), while limiting intake of foods containing saturated fat, added salt, added sugars and alcohol. They are high-carbohydrate and low-fat focused – participants will be encouraged to include at least four serves of wholegrains daily (e.g., brown rice, pasta, bread, quinoa, oats) and to choose low-fat protein and dairy foods where possible.

The program will be delivered through individual consultations with the treating dietitian or other specially trained health professional – the first in-person consultation immediately following baseline assessment (~45 minutes), the second via phone/videoconference at 6 weeks (~30 minutes) and the third in-person at 12-week follow-up with timing individualised as required. Two to three consultations represents usual care for patients referred for dietary management in Australia through the current public healthcare (Medicare) rebate system.(37, 38) During the initial in-person consultation, participants will be provided with a bespoke educational booklet and advice and education emphasising the Australian Dietary Guideline principles (https://www.eatforhealth.gov.au/guidelines) and informed of complementary and publicly available online resources from the Eat for Health website (https://www.eatforhealth.gov.au/).

The follow-up phone/videoconference consultation in week-6 and in-person follow-up in week-12 will provide participants with ongoing support, education and accountability. The 3-day food diary, completed prior to each consultation (see outcomes/adherence section), will guide feedback and support to adapt meal plans to optimise adherence. The treating health professionals delivering the two dietary programs will be based centrally at La Trobe University and will be trained by the senior study dietitian (BLD) until deemed competent in intervention delivery.

Irrespective of group allocation, participants can continue usual medical care and consult with their treating health professionals as necessary (e.g., general practitioner regarding medication changes).

**Data collection procedure**

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

## OUTCOMES

**Baseline characteristics**

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

**Primary Outcome**

The primary outcome is the change from baseline to 12 weeks in the mean score on four Knee injury and Osteoarthritis Outcome Score ($KOOS_4$) subscales covering knee pain, symptoms, function in daily activities and knee-related quality of life. The KOOS is a 42-item patient-reported outcome measure assessing five separately scored subscales: Pain, Symptoms, Function in Sport and Recreation (Sport/Rec), Activities of Daily Living (ADL), and Quality of Life. The $KOOS_4$ and all KOOS subscale scores range from 0 (extreme problems) to 100 (no problems). The KOOS is a valid, responsive and reliable questionnaire, with $KOOS_4$ a primary outcome for other knee OA 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

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

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

**Secondary effectiveness outcomes**

*KOOS subscales*

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

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

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

*Anthropometrics*

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

*Global lower-limb function*

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

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

### *Body composition*

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

### *Inflammatory and metabolic biomarkers*

An array of blood inflammatory and metabolic biomarkers will be analysed from samples of blood collected, including high sensitivity C-Reactive Protein (hsCRP), cytokines (IL-1β, IL-6, IL-8, IL-10, TNF-α), blood glucose, HbA1c, serum insulin, liver function tests (including albumin), and lipids (e.g., high density lipoprotein, triglycerides). Participants will be instructed to fast for at least 10 hours prior to blood collection and a single forearm venepuncture will take place to collect a total of ≤30 mL blood. Plasma and serum samples will be centrifuged (3000ms, 10 minutes), and all samples (plasma, serum, and whole blood) frozen at -80°C for later analysis (Supplementary File 3).

## **Secondary safety outcomes**

### *Adverse events*

Adverse events and serious adverse events will be recorded at 6-week, 12-week and 6-month follow-up via open probe questioning to optimise collection of sufficient detail. Under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) harms statement, an adverse event is defined as any undesirable experience causing participants to seek medical treatment (e.g., general practitioner).(49) A serious adverse event is defined as any undesirable event/illness/injury classified as having the potential to significantly compromise clinical outcome or result in significant disability or incapacity, those requiring inpatient or outpatient hospital care, to be life-threatening or result in death.

**Exploratory outcomes**

*Dietary Analysis*

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

*Quality of life*

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

*Knee pain and interference*

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

*Change in analgesic medication use*

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

### *Physical activity*

Physical activity will be assessed using the International Physical Activity Questionnaire (IPAQ),(56) a standardised and valid questionnaire providing an estimate of physical activity and sedentary behaviour, which has been widely validated.(56-58) Respondents are asked to report time spent in physical activity across three intensities (walking, moderate, vigorous). Using the IPAQ scoring protocol,(59) total weekly physical activity can be estimated by weighting time spent in each activity intensity with its estimated metabolic equivalent (MET) energy expenditure.(60)

### *Blood pressure*

A pair of seated blood pressure measurements will be obtained using an automated monitor (Omron Model HEM-7121). The blood pressure cuff is placed over the mid-upper arm with the participant seated.

### *Self-perceived wellness*

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

### *Intervention adherence*

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

## DATA MANAGEMENT

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

accessible only to members of the research team and separately from re-identifiable (i.e., coded) data.

Due to the minimal known risks associated with the interventions being evaluated, our study will not have a formal data monitoring committee and does not require an interim analysis. This is the same approach we have taken with other low risk RCTs.(42) Any unexpected serious adverse events or outcomes will be discussed by the trial management committee (authors of this protocol) and reported to the approving human research ethics committee for monitoring.

**Sample size calculation**

This trial has been powered to detect a clinically significant between-group difference for the primary outcome of $KOOS_4$. A recent RCT comparing an anti-inflammatory diet vs low-caloric diet in overweight women with knee OA observed an effect size (standardised mean difference) on self-reported pain and function of 1.0 (95% confidence interval 0.5 to 1.6).(61) Given inherent differences in the FEAST RCT (e.g., Australian Dietary Guideline control group, not specifically targeting overweight participants, inclusion of both women and men), we used the lower bound 95% confidence interval to provide a conservative estimate of the anticipated effect size (0.5). This estimated effect size is also a conservative estimate based on our single-arm anti-inflammatory diet pilot trial, which had an effect size of 0.68.(28) Recruiting 128 participants (equally distributed between two arms) would yield 80% power to observe such an effect or larger at a two-tailed Type I error of 0.05. This sample size estimation is also conservative since it is based on independent samples t-test. Using an ANCOVA model that includes the baseline value as a covariate and is pre-specified for the analysis should provide higher power for the same sample size.(62) To account for a potential 10% drop-out, we will recruit 144 participants. This sample size will also be sufficient to detect a minimal important change (MIC) in $KOOS_4$ estimated at 10 points in patients with knee OA (with a common between-subject standard deviation of 15).(63)

**Statistical analyses**

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

treatment effect on the primary outcome of $KOOS_4$ (mean score of four of the five subscales of the KOOS) at 12 weeks. A linear mixed model utilising repeated measures at all time-points for secondary hypotheses will allow non-biased estimates of treatment effect in the presence of any potential missing cases, providing data are missing at random. A sensitivity analysis using pattern-mixture model to investigate the deviation from the missingness-at-random assumption will be carried out.(65) For secondary binary outcomes (e.g., treatment success), mixed-effect logistic regression models will be used to assess the effect of treatment. A subsequent analysis of participants classified as adherent to the protocol will be performed.

**Healthcare resource use**

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

**Process Evaluation**

Semi-structured interviews will be conducted on a subset of consenting participants (until data saturation reached) at 6 months. Interviews will explore experiences, knowledge and understanding of interventions received including potential benefits; acceptability and perceived effectiveness of the intervention; and reasons for adhering (or not) to the allocated diet. Purposive sampling will be used to recruit interview participants based upon characteristics (anti-inflammatory dietary program vs standard care low-fat dietary program, men vs women) and outcomes of the trial (good outcome vs poor outcome). Interviews will be audio recorded, transcribed and analysed using Framework Analysis,(66) a flexible technique allowing researchers to identify, compare and contrast data according to inductively- and deductively-derived themes. Data will be coded and an inductive thematic analysis will be applied until no new themes emerge.

## ETHICS AND DISSEMINATION

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

considerations associated with this trial.

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

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

## 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. We also acknowledge that, like most RCTs, there is a risk that our recruitment strategy may result in a selected sample not representative of the general population. However, using similar recruitment strategies, our prior RCTs have resulted in a representative sample of the culturally and sociodemographically diverse Australian population that has similar characteristics to other international cohorts with the index musculoskeletal condition.(67)

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-morbidities.(68) 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 and read and approved the final manuscript.

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## COMPETING INTERESTS STATEMENT

PB is the founder of Defeat Diabetes and author of “A Fat Lot of Good”. PB contributed to study design but has no role in study execution, data management, analysis or the decision to publish. The NHMRC has no role in study design and will not have any role in its execution, data management, analysis and interpretation or on the decision to submit the results for publication. JLK is an editor of the British Journal of Sports Medicine (British Medical Journal Group). AGC is an associate editor of British Journal of Sports Medicine (British Medical Journal Group). All other authors have no competing interests.

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## 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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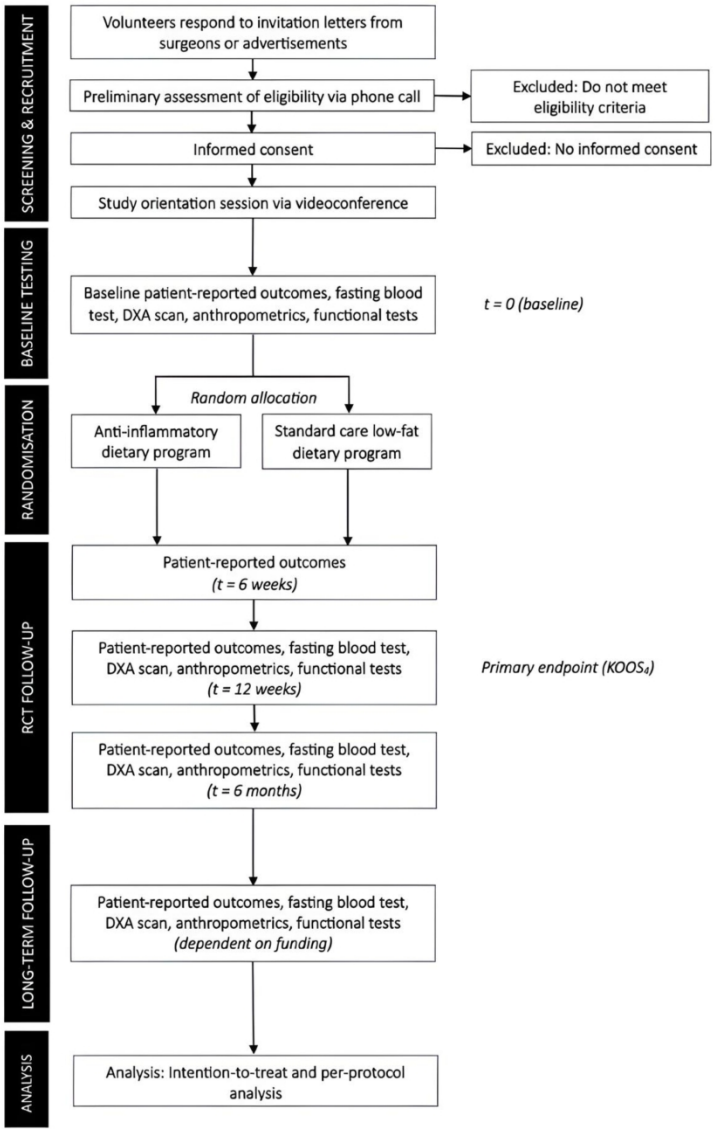



Figure 1. Flow of participants through the trial. DXA, Dual X-ray Absorptiometry; KOOS, Knee injury and Osteoarthritis Outcome Score
*Optional qualitative interview for process evaluation at 6 months

529x695mm (96 x 96 DPI)

# 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.**


**Use small amounts**

**Only sometimes and in small amounts**

## Vegetables and legumes

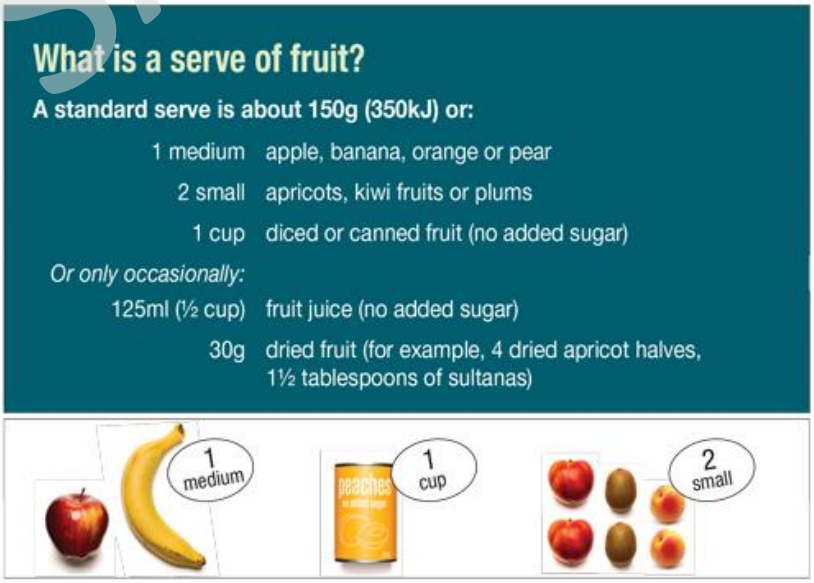
Vegetables, including legumes/beans are nutrient dense, low in kilojoules, and are a good source of minerals and vitamins (such as magnesium, vitamin C and folate), dietary fibre and a range of natural plant chemicals such as carotenoids. Legumes include chickpeas, kidney beans, and peas. **Aim for 5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


*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

- other fruits such as grapes and passionfruit

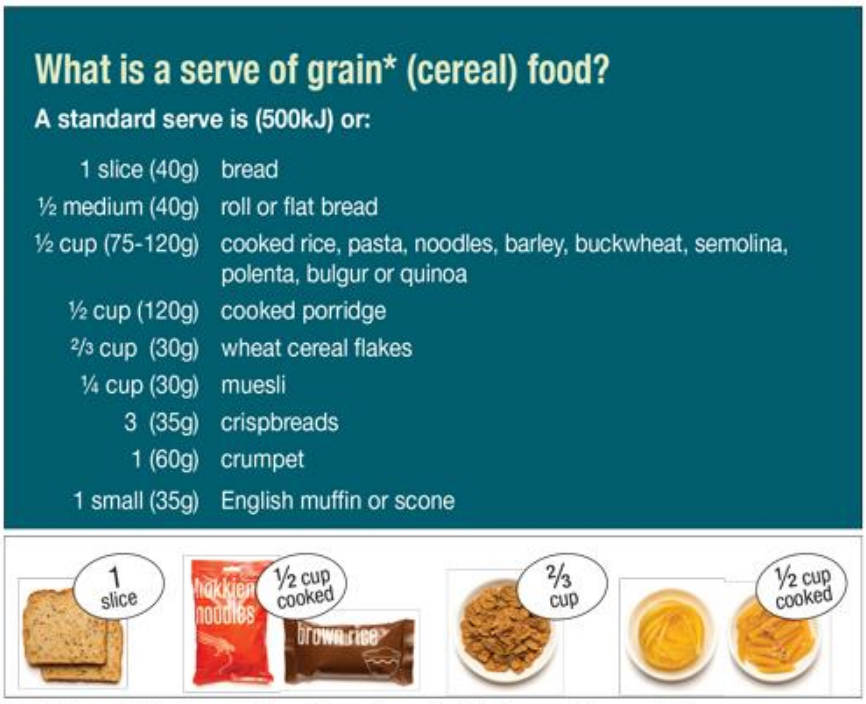
Enjoy more fruit by trying:

- 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.




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

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

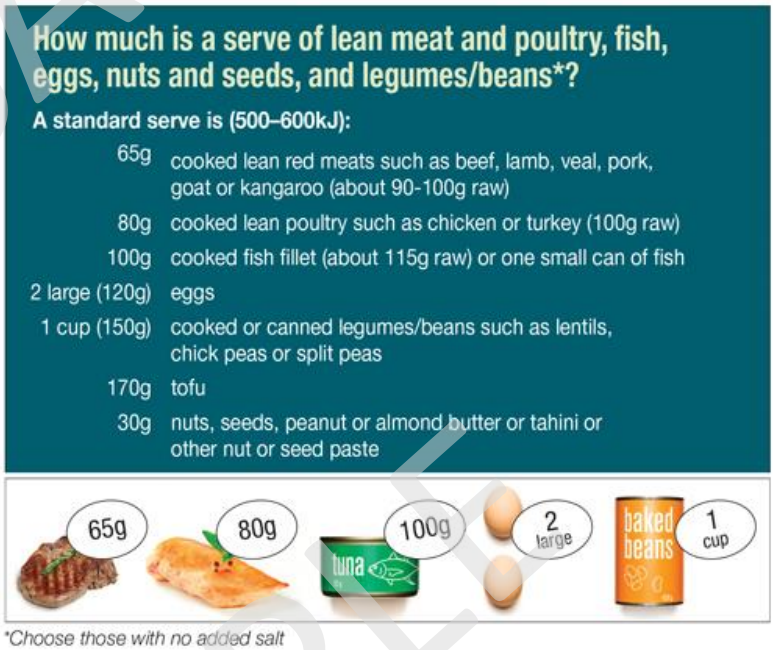
Enjoy more wholegrains by having:

- 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:



*Choose those with no added salt

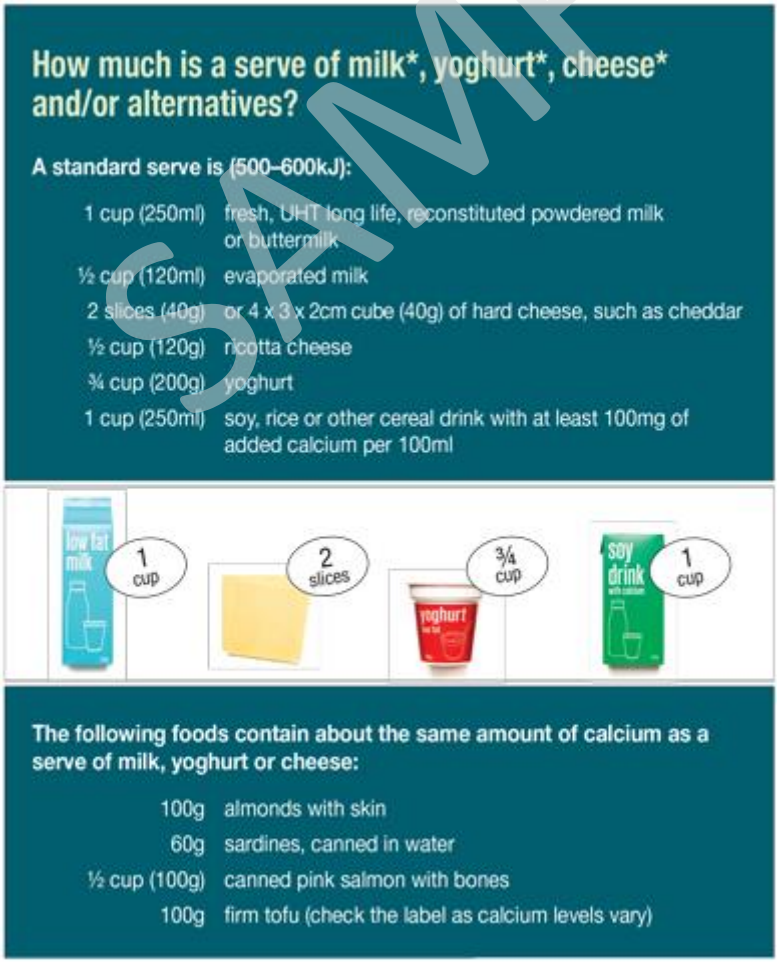
- Lean meats - Beef, lamb, veal, pork, kangaroo
- Poultry - Chicken, turkey, duck, emu, goose, bush birds
- Fish and seafood - Fish, prawns, crab, lobster, mussels, oysters, scallops, clams
- Eggs
- Nuts and seeds - Almonds, pine nuts, walnut, macadamia, hazelnut, cashew, peanut, nut spreads, and pumpkin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

## 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




*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** | Raspberry chia pot | Yoghurt with berries | Raspberry 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 |

# 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 cauli 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 cauli 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 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Snack** | Roasted chickpeas | Slice of almond flour banana bread | Greek yoghurt with berries | Peanut butter balls | Beef jerky | Roasted chickpeas | Handful of walnuts |
| **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 |
| **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 |
| **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 |

FEAST Project

# Standard Operating Procedure

# Blood collection, processing, handling, and storage procedures

### 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)

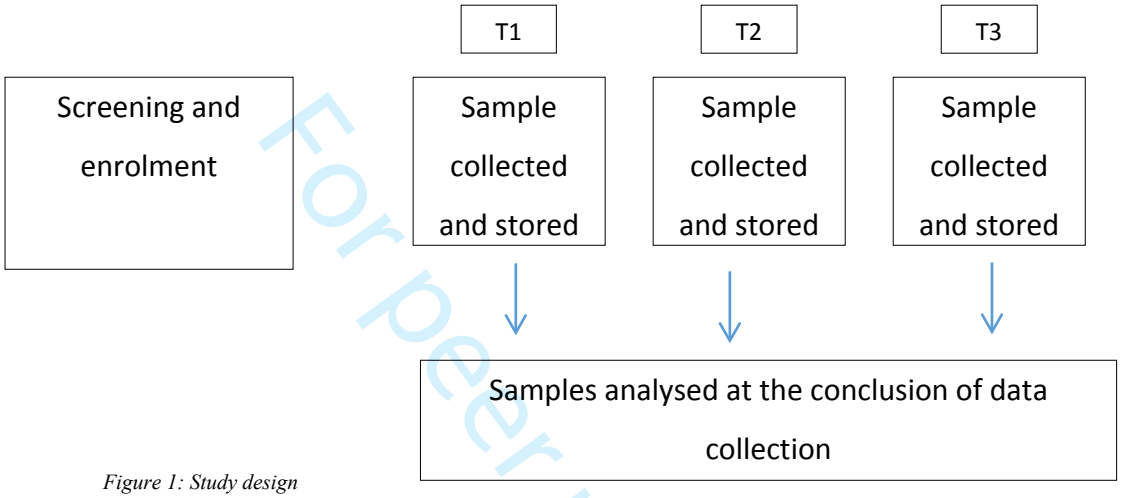



*Figure 1: Study design*

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 adaptorSterile 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 biocan 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 preprogramed 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).

LA TROBE UNIVERSITY

# 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)<br>Prof. Peter Brukner (SAHHSS, La Trobe University)<br>Ass. Prof. Joanne Kemp (SAHHSS, La Trobe University)<br>Prof. Kay Crossley (SAHHSS, La Trobe University)<br>Dr Andrea Mosler (SAHHSS, La Trobe University)<br>Dr Josh Heerey (SAHHSS, La Trobe University)<br>Ms Lynette Law (PhD student, SAHHSS, La Trobe University)<br>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 ≥5kg weight loss in the past 3 months or body weight ≥200kg
- 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:

i) minimise processed foods that are known to promote inflammation and optimise foods shown to reduce inflammation; or

ii) 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).

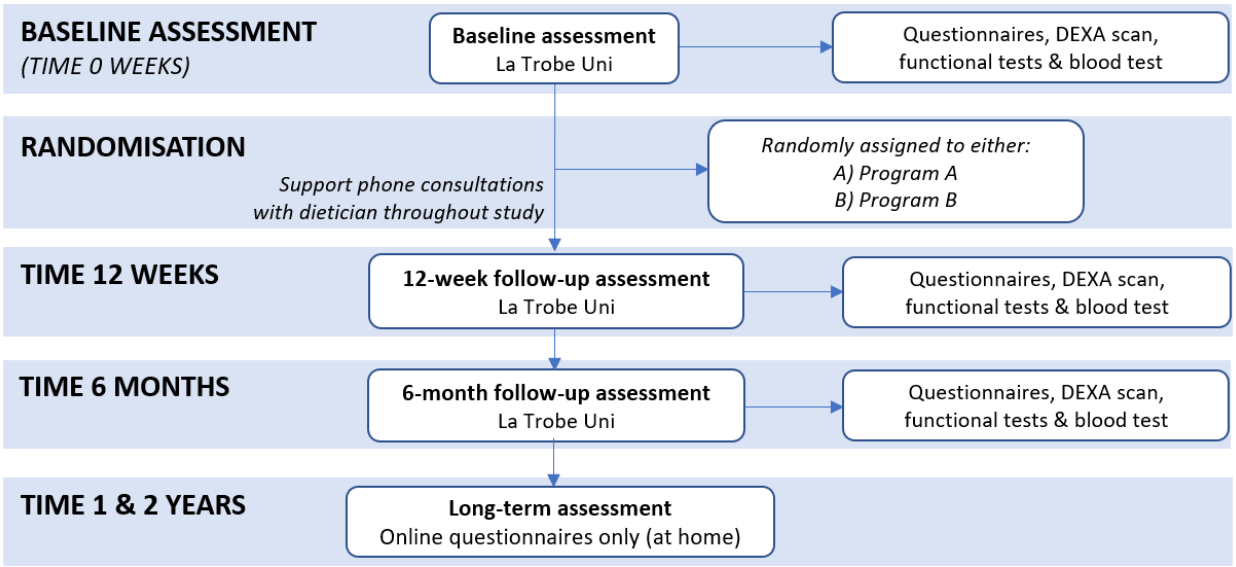



***Figure 1. Flowchart of study assessments***

***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

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

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

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

## 5 What are the alternatives to participation?

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

## 6 What are the possible benefits of taking part?

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

## 7 What are the possible risks and disadvantages of taking part?

With any medical treatment there are: (i) risks we know about; (ii) risks we don't know about; and (iii) risks we don't expect. We have listed the risks we know about below. You may have none, some or all the effects listed below, and they may be mild, moderate or severe. If you have any 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<br>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<br>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

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

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

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

**Contraction of COVID-19**

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

### 8 What if I withdraw from this research project?

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

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

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

### 9 What happens when the research project ends?

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

## Part 2 How is the research project being conducted?

### 10 What will happen to information about me?

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

***Storage, retention and destruction***

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

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

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

## 11 Who is organising and funding the research?

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

## 12 Who has reviewed the research project?

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

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

## 13 Further information and who to contact

For all enquiries, you can contact the Clinical Trial Manager, during business hours:

Dr Adam Culvenor, Senior Research Fellow in Physiotherapy, La Trobe University
Telephone: 03 9479 5116; E-mail: a.culvenor@latrobe.edu.au

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

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

* Please quote the application reference number HEC22044

LA TROBE UNIVERSITY

# 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)<br>Prof. Peter Brukner (La Trobe University)<br>Ass. Prof. Joanne Kemp (La Trobe University)<br>Prof. Kay Crossley (La Trobe University)<br>Dr Andrea Mosler (La Trobe University)<br>Dr Josh Heerey (La Trobe University)<br>Ms Lynette Law (PhD student, La Trobe University)<br>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.


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 | ACTRN12622000440729 |
| 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 |

| | | | |
|---|---|---|---|
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | NA |
| **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 |
| | 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 |
| 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 |
| | 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 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | NA |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 20 |

| | | | |
|---|---|---|---|
| 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 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 20 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| 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 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 21 |
| 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 |
| 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 |
| 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 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | NA |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | NA |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Supplementary File 1 |
| 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 |

*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" license.

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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| Date Submitted by the Author: | 04-Mar-2024 |
| Complete List of Authors: | Law, Lynette; La Trobe University, La Trobe Sport and Exercise Medicine Research Centre<br>Heerey, Joshua; La Trobe University, La Trobe Sport and Exercise Medicine Research Centre<br>Devlin, Brooke; University of Queensland, School of Human Movement and Nutrition Sciences<br>Brukner, Peter; La Trobe University, La Trobe Sport and Exercise Medicine Research Centre<br>Kemp, Joanne; La Trobe University, La Trobe Sport and Exercise Medicine Research Centre<br>Attanayake, Amanda; La Trobe University, La Trobe Sport and Exercise Medicine Research Centre<br>Hullet, Mark; La Trobe University, Department of Biochemistry and Chemistry, La Trobe Institute for Molecular Science<br>De Livera, Alysha; La Trobe University, Department of Mathematics and Statistics; The University of Melbourne, School of Population and Global Health<br>Mosler, Andrea; La Trobe University, La Trobe Sport and Exercise Medicine Research Centre<br>Morris, Hayden; Melbourne Knee Centre<br>White, Nathan; Melbourne Knee Centre<br>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 |
| | |

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

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**Word count:** 3,998

**ABSTRACT**

**Introduction:** Chronic inflammation plays a key role in knee osteoarthritis pathophysiology and increases risk of comorbidities, yet most interventions do not typically target inflammation. Our study will investigate if an anti-inflammatory dietary program is superior to a standard care low-fat dietary program for improving knee pain, function and quality-of-life in people with knee osteoarthritis.

**Methods and analysis:** The FEAST (eFEct of an Anti-inflammatory diet for knee oSTeoarthritis) Study is a parallel-group, assessor-blinded, superiority randomised controlled trial. Following baseline assessment, 144 participants aged 45-85 years with symptomatic knee osteoarthritis will be randomly allocated to one of two treatment groups (1:1 ratio). Participants randomised to the anti-inflammatory dietary program will receive six dietary consultations over 12 weeks (2 in-person, 4 phone/videoconference) and additional educational and behaviour change resources. The consultations and resources emphasise nutrient-dense minimally processed anti-inflammatory foods and discourage pro-inflammatory processed foods. Participants randomised to the standard care low-fat dietary program will receive three dietary consultations over 12 weeks (2 in-person, 1 phone/videoconference) consisting of healthy eating advice and education based on the Australian Dietary Guidelines, reflecting usual care in Australia. Adherence will be assessed with 3-day food diaries. Outcomes are assessed at 12 weeks and 6 months. The primary outcome will be change from baseline to 12 weeks in the mean score on four Knee injury and Osteoarthritis Outcome Score ($KOOS_4$) subscales: knee pain, symptoms, function in daily activities and knee-related quality-of-life. Secondary outcomes include change in individual KOOS subscale scores, patient-perceived improvement, health-related quality-of-life, body mass and composition using dual-energy X-ray absorptiometry, inflammatory (high-sensitivity C-Reactive Protein, Interleukins, Tumour Necrosis Factor-α) and metabolic blood biomarkers (glucose, HbA1c, insulin, liver function, lipids), lower-limb function and physical activity.

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

**Trial registration:** ACTRN12622000440729

**Keywords:** Inflammation, Low-carbohydrate, Anti-inflammatory, Pain, Osteoarthritis, Knee, Chronic disease, Rehabilitation, Diet

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- The anti-inflammatory dietary program was codeveloped and piloted with patients and clinicians, with the comparison low-fat dietary program representing usual care.
- Sufficiently powered trial evaluating change from baseline to 12 weeks (primary endpoint) and 6 months facilitating longer-term effectiveness evaluation of the anti-inflammatory dietary program.
- This trial will evaluate both self-reported and objective outcomes to understand potential mechanisms of symptomatic changes.
- While outcome assessors are blinded to group allocation, the health professionals delivering the interventions and participants are unable to be blinded to group allocation due to the type of interventions.

## INTRODUCTION

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

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

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

increases the risk and severity of chronic disease, including OA.(15) Due to their focus on real foods and consumption to satiety, anti-inflammatory diets are likely more sustainable than traditional calorie-restrictive approaches.(17)

Anti-inflammatory diets have garnered much interest in recent years due to their effectiveness in alleviating symptoms and improving biomarkers for a variety of chronic diseases, including diabetes,(18) cardiovascular disease,(24) epilepsy(25) and rheumatoid arthritis.(26) Small studies investigating anti-inflammatory diets for knee OA have demonstrated feasibility and effectiveness in reducing symptoms and inflammation over 12-16 weeks.(15, 27, 28) To date, no fully powered randomised controlled trial (RCT) has evaluated the effectiveness of an anti-inflammatory diet in knee OA.

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

## METHODS AND ANALYSIS

### Study Design

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

participant randomised on August 31, 2022 and the final participant anticipated to be randomised in June 2024. The primary endpoint will be at 12 weeks, with additional follow-up at 6 months (further longer-term follow-up dependent on funding). The study was prospectively registered on the Australian and New Zealand Clinical Trial Registry (ACTRN 12622000440729).

## Patient and public involvement

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

## Participants

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

**Table 1.** Eligibility criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| Fulfil National Institute for Health and Care Excellence(31) clinical criteria for osteoarthritis:<br>• 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;<br>• No morning stiffness or morning stiffness ≤30 min; and<br>• Age ≥45 years | Another reason than OA for knee symptoms (e.g., tumour, fibromyalgia) |

| | |
|---|---|
| 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 |

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

**Recruitment and screening procedure**

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

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

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

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

*Randomisation procedure, concealment of allocation and blinding*

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

**Interventions**

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

*Anti-inflammatory dietary program*

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

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

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

adherence: i) bespoke information booklet providing anti-inflammatory eating information, example meal plans, and foods that are encouraged and foods to avoid (Supplementary file 1 and 2); ii) complimentary subscription to an anti-inflammatory program (Defeat Diabetes phone app/website), providing anti-inflammatory recipes, masterclasses, meal plans and educational articles; iii) complimentary links to recommended documentaries exploring the benefits of anti-inflammatory nutrition (i.e., Fat Fiction, Cereal Killers, That Sugar Film); and iv) complimentary copy of a book exploring benefits of anti-inflammatory approach (A Fat Lot of Good(35)).

Follow-up phone/videoconference consultations (~30 minutes) will be scheduled in weeks 2, 4, 6, and 9, with timing to be negotiated between each participant and the health professional delivering the intervention. A final in-person consultation will be delivered immediately following the completion of the 12-week assessment. These follow-up consultations will provide participants with ongoing support, education and accountability. A 3-day food diary, completed prior to each consultation (see outcomes/adherence section), will guide individualised feedback and support to adapt meal plans to optimise adherence.

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)<br><br>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** | Two in-person consultations at baseline (~45 mins) and week 12 (~30 mins)<br>Four phone/videoconference follow-up consultations (~30 mins) in week 2, 4, 6, and 9.<br>***Total active intervention delivery time:*** ~3.5 hours<br><br>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)<br>One phone/videoconference follow-up consultation (30 mins) in week 6.<br>***Total active control delivery time:*** ~1.5 hours<br><br>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 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

*Standard care low-fat dietary program*

Participants allocated to the standard care low-fat dietary program will receive advice and education regarding healthy eating based on the Australian Dietary Guidelines.(39) These government-endorsed guidelines aim to optimise nutrition intake through adequate consumption of foods from the five core food groups (grains and cereals; fruit; vegetables and legumes; lean meats and poultry, fish, eggs, and tofu; reduced fat diary or alternatives), while limiting intake of foods containing saturated fat, added salt, added sugars and alcohol. They are high-carbohydrate and low-fat focused – participants will be encouraged to include at least four serves of wholegrains daily (e.g., brown rice, pasta, bread, quinoa, oats) and to choose low-fat protein and dairy foods where possible.

The program will be delivered through individual consultations with the treating dietitian or other specially trained health professional – the first in-person consultation immediately following baseline assessment (~45 minutes), the second via phone/videoconference at 6 weeks (~30 minutes) and the third in-person at 12-week follow-up with timing individualised as required. Two to three consultations represents usual care for patients referred for dietary management in Australia through the current public healthcare (Medicare) rebate system.(37, 38) During the initial in-person consultation, participants will be provided with a bespoke educational booklet and advice and education emphasising the Australian Dietary Guideline principles (https://www.eatforhealth.gov.au/guidelines) and informed of complementary and publicly available online resources from the Eat for Health website (https://www.eatforhealth.gov.au/).

The follow-up phone/videoconference consultation in week-6 and in-person follow-up in week-12 will provide participants with ongoing support, education and accountability. The 3-day food diary, completed prior to each consultation (see outcomes/adherence section), will guide feedback and support to adapt meal plans to optimise adherence. The treating health professionals delivering the two dietary programs will be based centrally at La Trobe University and will be trained by the senior study dietitian (BLD) until deemed competent in intervention delivery.

Irrespective of group allocation, participants can continue usual medical care and consult with their treating health professionals as necessary (e.g., general practitioner regarding medication changes).

**Data collection procedure**

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

## OUTCOMES

**Baseline characteristics**

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

**Primary Outcome**

The primary outcome is the change from baseline to 12 weeks in the mean score on four Knee injury and Osteoarthritis Outcome Score ($KOOS_4$) subscales covering knee pain, symptoms, function in daily activities and knee-related quality of life. The KOOS is a 42-item patient-reported outcome measure assessing five separately scored subscales: Pain, Symptoms, Function in Sport and Recreation (Sport/Rec), Activities of Daily Living (ADL), and Quality of Life. The $KOOS_4$ and all KOOS subscale scores range from 0 (extreme problems) to 100 (no problems). The KOOS is a valid, responsive and reliable questionnaire, with $KOOS_4$ a primary outcome for other knee OA trials.(33, 44, 45)

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

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

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

**Secondary effectiveness outcomes**

*KOOS subscales*

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

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

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

*Anthropometrics*

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

*Global lower-limb function*

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

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

### *Body composition*

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

### *Inflammatory and metabolic biomarkers*

An array of blood inflammatory and metabolic biomarkers will be analysed from samples of blood collected, including high sensitivity C-Reactive Protein (hsCRP), cytokines (IL-1β, IL-6, IL-8, IL-10, TNF-α), blood glucose, HbA1c, serum insulin, liver function tests (including albumin), and lipids (e.g., high density lipoprotein, triglycerides). Participants will be instructed to fast for at least 10 hours prior to blood collection and a single forearm venepuncture will take place to collect a total of ≤30 mL blood. Plasma and serum samples will be centrifuged (3000ms, 10 minutes), and all samples (plasma, serum, and whole blood) frozen at -80°C for later analysis (Supplementary File 3).

## **Secondary safety outcomes**

### *Adverse events*

Adverse events and serious adverse events will be recorded at 6-week, 12-week and 6-month follow-up via open probe questioning to optimise collection of sufficient detail. Under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) harms statement, an adverse event is defined as any undesirable experience causing participants to seek medical treatment (e.g., general practitioner).(49) A serious adverse event is defined as any undesirable event/illness/injury classified as having the potential to significantly compromise clinical outcome or result in significant disability or incapacity, those requiring inpatient or outpatient hospital care, to be life-threatening or result in death.

**Exploratory outcomes**

*Dietary Analysis*

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

*Quality of life*

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

*Knee pain and interference*

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

*Change in analgesic medication use*

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

*Physical activity*

Physical activity will be assessed using the International Physical Activity Questionnaire (IPAQ),(56) a standardised and valid questionnaire providing an estimate of physical activity and sedentary behaviour, which has been widely validated.(56-58) Respondents are asked to report time spent in physical activity across three intensities (walking, moderate, vigorous). Using the IPAQ scoring protocol,(59) total weekly physical activity can be estimated by weighting time spent in each activity intensity with its estimated metabolic equivalent (MET) energy expenditure.(60)

*Blood pressure*

A pair of seated blood pressure measurements will be obtained using an automated monitor (Omron Model HEM-7121). The blood pressure cuff is placed over the mid-upper arm with the participant seated.

*Self-perceived wellness*

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

*Intervention adherence*

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

**DATA MANAGEMENT**

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

accessible only to members of the research team and separately from re-identifiable (i.e., coded) data.

Due to the minimal known risks associated with the interventions being evaluated, our study will not have a formal data monitoring committee and does not require an interim analysis. This is the same approach we have taken with other low risk RCTs.(42) Any unexpected serious adverse events or outcomes will be discussed by the trial management committee (authors of this protocol) and reported to the approving human research ethics committee for monitoring.

**Sample size calculation**

This trial has been powered to detect a clinically significant between-group difference for the primary outcome of $KOOS_4$. A recent RCT comparing an anti-inflammatory diet vs low-caloric diet in overweight women with knee OA observed an effect size (standardised mean difference) on self-reported pain and function of 1.0 (95% confidence interval 0.5 to 1.6).(61) Given inherent differences in the FEAST RCT (e.g., Australian Dietary Guideline control group, not specifically targeting overweight participants, inclusion of both women and men), we used the lower bound 95% confidence interval to provide a conservative estimate of the anticipated effect size (0.5). This estimated effect size is also a conservative estimate based on our single-arm anti-inflammatory diet pilot trial, which had an effect size of 0.68.(28) Recruiting 128 participants (equally distributed between two arms) would yield 80% power to observe such an effect or larger at a two-tailed Type I error of 0.05. This sample size estimation is also conservative since it is based on independent samples t-test. Using an ANCOVA model that includes the baseline value as a covariate and is pre-specified for the analysis should provide higher power for the same sample size.(62) To account for a potential 10% drop-out, we will recruit 144 participants. This sample size will also be sufficient to detect a minimal important change (MIC) in $KOOS_4$ estimated at 10 points in patients with knee OA (with a common between-subject standard deviation of 15).(63)

**Statistical analyses**

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

treatment effect on the primary outcome of $KOOS_4$ (mean score of four of the five subscales of the KOOS) at 12 weeks. A linear mixed model utilising repeated measures at all time-points for secondary hypotheses will allow non-biased estimates of treatment effect in the presence of any potential missing cases, providing data are missing at random. A sensitivity analysis using pattern-mixture model to investigate the deviation from the missingness-at-random assumption will be carried out.(65) For secondary binary outcomes (e.g., treatment success), mixed-effect logistic regression models will be used to assess the effect of treatment. A subsequent analysis of participants classified as adherent to the protocol will be performed. Following publication of the primary trial results, we will also perform a formal mediation analysis to estimate direct and indirect (e.g., through weight and inflammation change) effects.

**Healthcare resource use**

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

**Process Evaluation**

Semi-structured interviews will be conducted on a subset of consenting participants (until data saturation reached) at 6 months. Interviews will explore experiences, knowledge and understanding of interventions received including potential benefits; acceptability and perceived effectiveness of the intervention; and reasons for adhering (or not) to the allocated diet. Purposive sampling will be used to recruit interview participants based upon characteristics (anti-inflammatory dietary program vs standard care low-fat dietary program, men vs women) and outcomes of the trial (good outcome vs poor outcome). Interviews will be audio recorded, transcribed and analysed using Framework Analysis,(66) a flexible technique allowing researchers to identify, compare and contrast data according to inductively- and deductively-derived themes. Data will be coded and an inductive thematic analysis will be applied until no new themes emerge.

## ETHICS AND DISSEMINATION

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

from participants prior to enrolment (Supplementary File 4). Anti-inflammatory diets are associated with minimal and transient adverse events, thus there are minimal safety considerations associated with this trial.

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

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

**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. We also acknowledge that, like most RCTs, there is a risk that our recruitment strategy may result in a selected sample not representative of the general population. However, using similar recruitment strategies, our prior RCTs have resulted in a representative sample of the culturally and sociodemographically diverse Australian population that has similar characteristics to other international cohorts with the index musculoskeletal condition.(67)

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-morbidities.(68) 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 and read and approved the final manuscript.

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## COMPETING INTERESTS STATEMENT

PB is the founder of Defeat Diabetes and author of “A Fat Lot of Good”. PB contributed to study design but has no role in study execution, data management, analysis or the decision to publish. The NHMRC has no role in study design and will not have any role in its execution, data management, analysis and interpretation or on the decision to submit the results for publication. JLK is an editor of the British Journal of Sports Medicine (British Medical Journal Group). AGC is an associate editor of British Journal of Sports Medicine (British Medical Journal Group). All other authors have no competing interests.

## ACKNOWLEDGEMENTS

We thank La Trobe University Medical Centre for assistance with blood collection, La Trobe Nutrition and Dietetics department for the use of the nutrition lab and DXA scanner, and Melbourne Pathology for providing pathology collection kits and analysis of biomarkers from blood specimens.

## 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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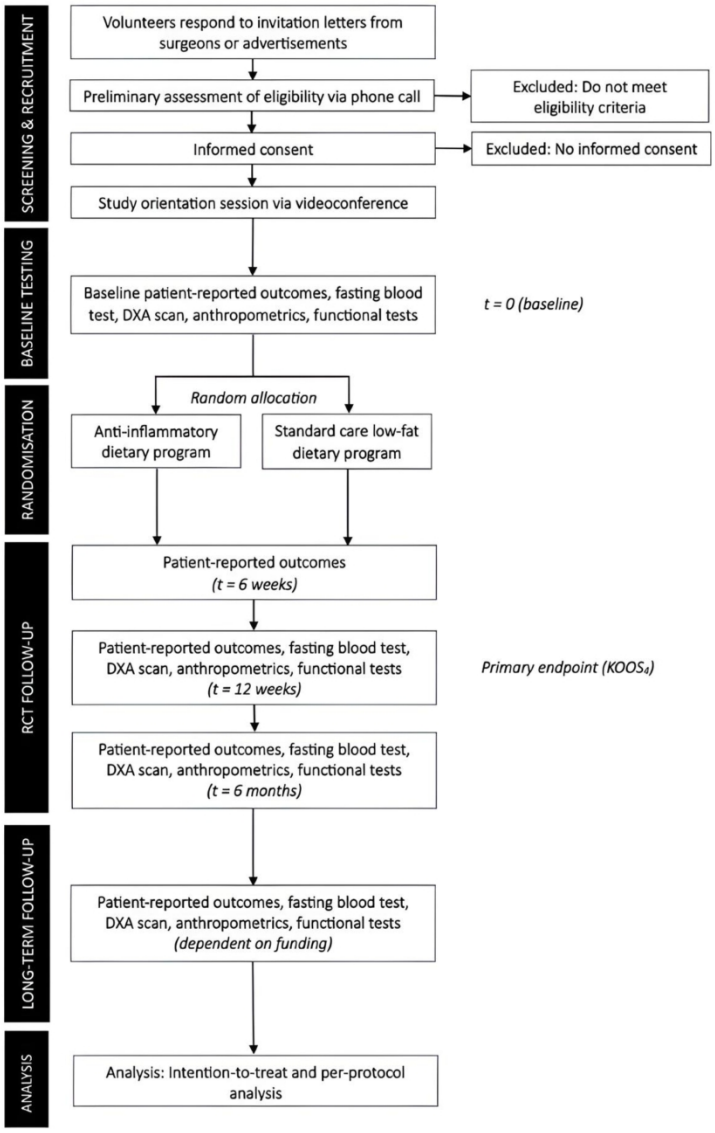


Figure 1. Flow of participants through the trial. DXA, Dual X-ray Absorptiometry; KOOS, Knee injury and Osteoarthritis Outcome Score
*Optional qualitative interview for process evaluation at 6 months

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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.**


**Use small amounts**

**Only sometimes and in small amounts**

## Vegetables and legumes

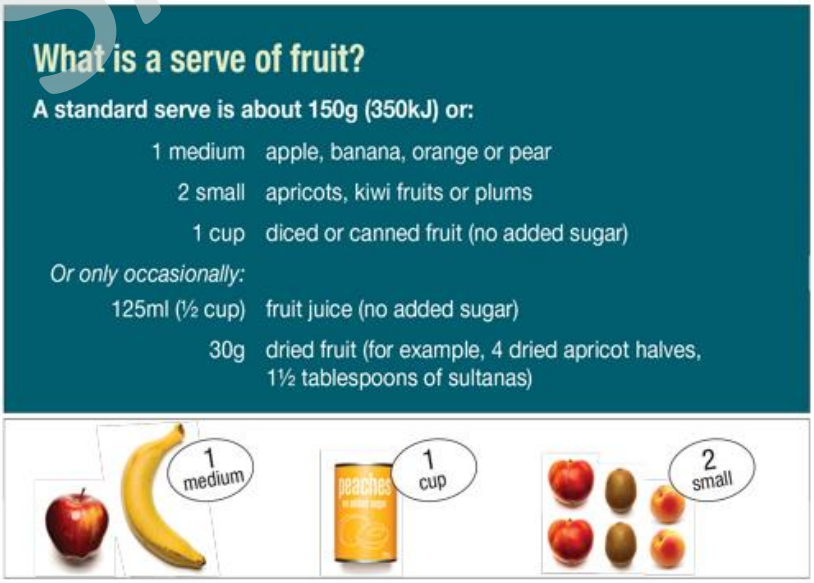
Vegetables, including legumes/beans are nutrient dense, low in kilojoules, and are a good source of minerals and vitamins (such as magnesium, vitamin C and folate), dietary fibre and a range of natural plant chemicals such as carotenoids. Legumes include chickpeas, kidney beans, and peas. **Aim for 5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


*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

- other fruits such as grapes and passionfruit

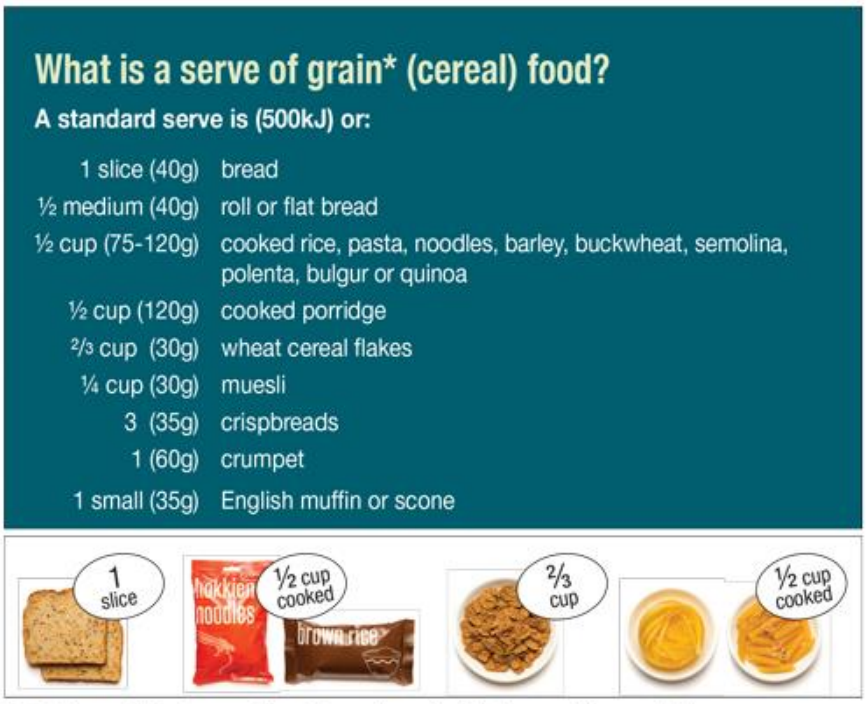
Enjoy more fruit by trying:

- 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.




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

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

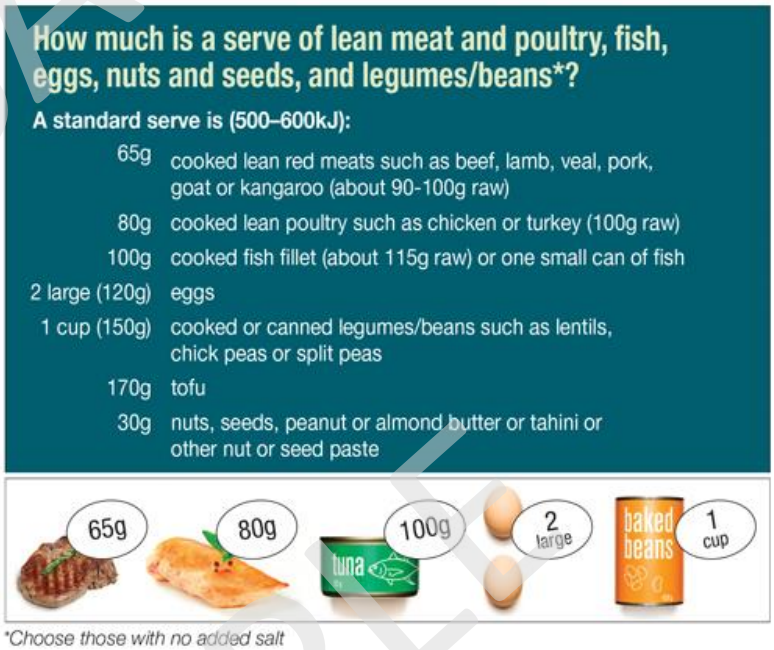
Enjoy more wholegrains by having:

- 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:



*Choose those with no added salt

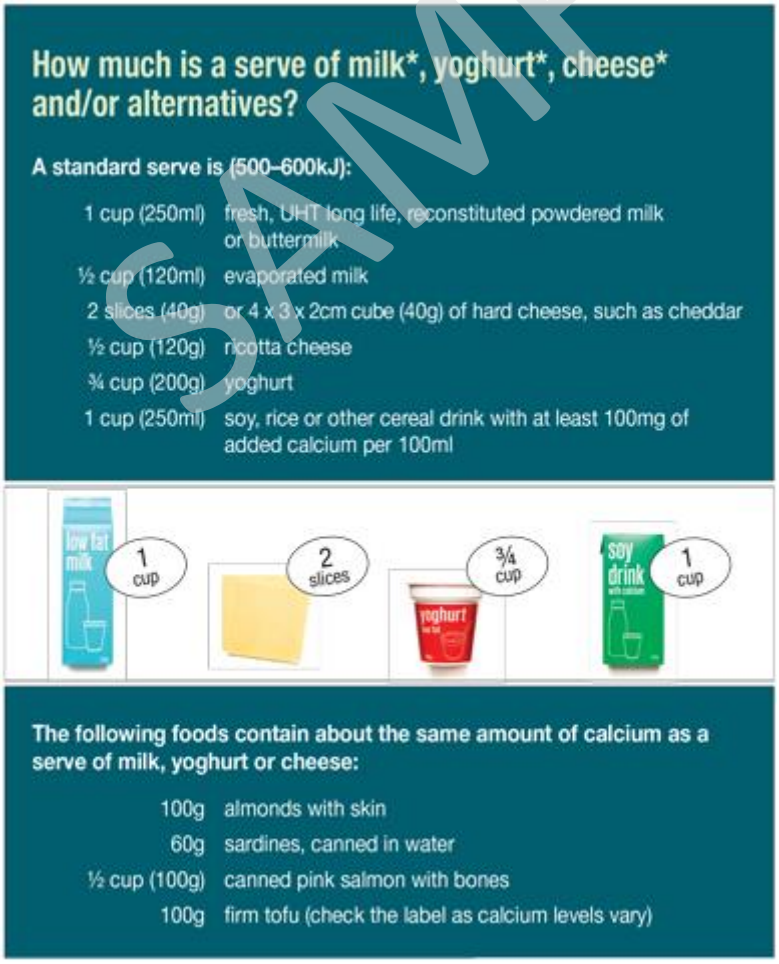
- Lean meats - Beef, lamb, veal, pork, kangaroo
- Poultry - Chicken, turkey, duck, emu, goose, bush birds
- Fish and seafood - Fish, prawns, crab, lobster, mussels, oysters, scallops, clams
- Eggs
- Nuts and seeds - Almonds, pine nuts, walnut, macadamia, hazelnut, cashew, peanut, nut spreads, and pumpkin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

## 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




*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** | Raspberry chia pot | Yoghurt with berries | Raspberry 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 |

# 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 cauli 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 cauli 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 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Snack** | Roasted chickpeas | Slice of almond flour banana bread | Greek yoghurt with berries | Peanut butter balls | Beef jerky | Roasted chickpeas | Handful of walnuts |
| **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 |
| **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 |
| **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 |

FEAST v 2.0
17.08.2023

FEAST Project

## Standard Operating Procedure

## Blood collection, processing, handling, and storage procedures

### 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)

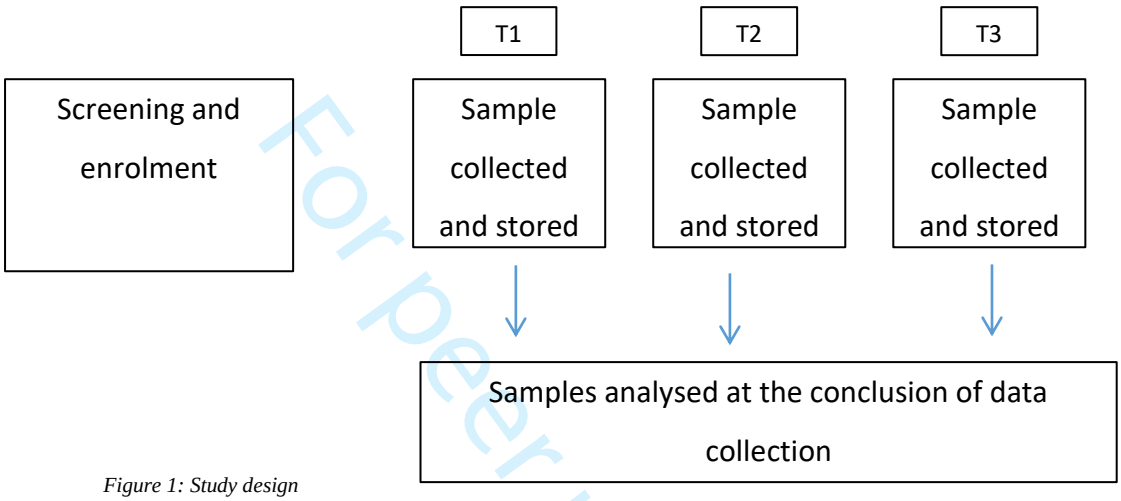



*Figure 1: Study design*

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 adaptorSterile 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 biocan 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 preprogramed 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 -80ºC, 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 -80ºC, 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 -80ºC |
| 3 | 1000 µl | Storage at -80ºC |
| 4 | 1000 µl | Storage at -80ºC |

- 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 -80ºC, 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 -80ºC |
| 3 | 1ml | Storage at -80ºC |
| 4 | 1ml | Storage at -80ºC |

**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).

LA TROBE UNIVERSITY

# 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)<br>Prof. Peter Brukner (SAHHSS, La Trobe University)<br>Ass. Prof. Joanne Kemp (SAHHSS, La Trobe University)<br>Prof. Kay Crossley (SAHHSS, La Trobe University)<br>Dr Andrea Mosler (SAHHSS, La Trobe University)<br>Dr Josh Heerey (SAHHSS, La Trobe University)<br>Ms Lynette Law (PhD student, SAHHSS, La Trobe University)<br>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 ≥5kg weight loss in the past 3 months or body weight ≥200kg
- 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:

i) minimise processed foods that are known to promote inflammation and optimise foods shown to reduce inflammation; or

ii) 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).

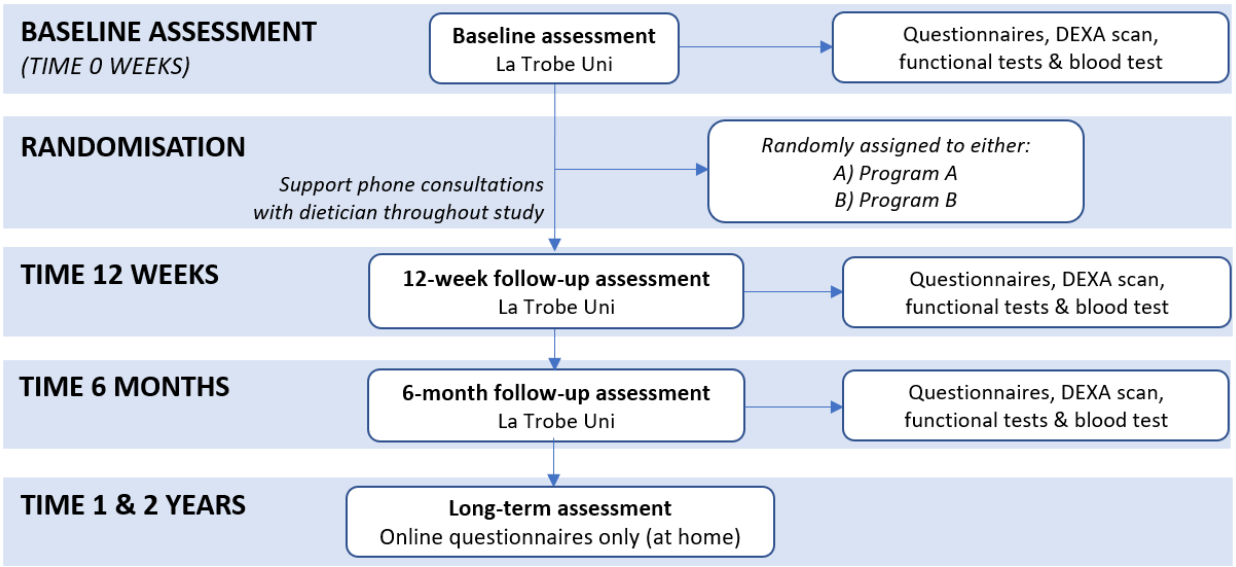



***Figure 1. Flowchart of study assessments***

***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

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

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

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

## 5 What are the alternatives to participation?

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

## 6 What are the possible benefits of taking part?

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

## 7 What are the possible risks and disadvantages of taking part?

With any medical treatment there are: (i) risks we know about; (ii) risks we don't know about; and (iii) risks we don't expect. We have listed the risks we know about below. You may have none, some or all the effects listed below, and they may be mild, moderate or severe. If you have any 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<br>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<br>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

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

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

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

**Contraction of COVID-19**

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

### 8 What if I withdraw from this research project?

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

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

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

### 9 What happens when the research project ends?

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

## Part 2 How is the research project being conducted?

### 10 What will happen to information about me?

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

***Storage, retention and destruction***

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

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

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

## 11 Who is organising and funding the research?

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

## 12 Who has reviewed the research project?

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

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

## 13 Further information and who to contact

For all enquiries, you can contact the Clinical Trial Manager, during business hours:

Dr Adam Culvenor, Senior Research Fellow in Physiotherapy, La Trobe University
Telephone: 03 9479 5116; E-mail: a.culvenor@latrobe.edu.au

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

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

* Please quote the application reference number HEC22044

LA TROBE UNIVERSITY

# 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)<br>Prof. Peter Brukner (La Trobe University)<br>Ass. Prof. Joanne Kemp (La Trobe University)<br>Prof. Kay Crossley (La Trobe University)<br>Dr Andrea Mosler (La Trobe University)<br>Dr Josh Heerey (La Trobe University)<br>Ms Lynette Law (PhD student, La Trobe University)<br>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.


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 | ACTRN12622000440729 |
| 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 |

| | | | |
|---|---|---|---|
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | NA |
| **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 |
| | 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 |
| 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 |
| | 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 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | NA |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 20 |

| | | | |
|---|---|---|---|
| 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 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 20 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| 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 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 21 |
| 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 |
| 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 |
| 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 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | NA |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | NA |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Supplementary File 1 |
| 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 |

*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" license.