EXTENDED REPORT

Fish oil in knee osteoarthritis: a randomised clinical trial of low dose versus high dose

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ABSTRACT

Objectives To determine whether high-dose fish oil is superior to low-dose supplementation for symptomatic and structural outcomes in knee osteoarthritis (OA).

Methods A randomised, double-blind, multicentre trial enrolled 202 patients with knee OA and regular knee pain. They were randomised 1:1 to high-dose fish oil (4.5 g omega-3 fatty acids) 15 mL/day or (2) low-dose fish oil (blend of fish oil and sunola oil; ratio of 1:9, 0.45 g omega-3 fatty acids) 15 mL/day. The primary endpoints were Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain score at 3, 6, 12 and 24 months, and change in cartilage volume at 24 months. Secondary outcomes included WOMAC function, quality of life, analgesic and non-steroidal anti-inflammatory drug use and bone marrow lesion score.

Results Although there was improvement in both groups, the low-dose fish oil group had greater improvement in WOMAC pain and function scores at 2 years compared with the high-dose group, whereas between-group differences at 1 year did not reach statistical significance. There was no difference between the two groups in cartilage volume loss at 2 years. For other secondary endpoints, there was no difference between the two groups at 2 years.

Conclusions In people with symptomatic knee OA, there was no additional benefit of a high-dose fish oil compared with low-dose fish oil. The combination comparator oil appeared to have better efficacy in reducing pain at 2 years, suggesting that this requires further investigation.

Trial registration number Australian New Zealand Clinical Trials Registry (ACTRN 12607000415404).

INTRODUCTION

Osteoarthritis (OA) is a major cause of disability in older persons.[1] Current medical treatment is confined to symptom control with paracetamol and/or non-steroidal anti-inflammatory drugs (NSAIDs), as well as physical therapy and weight loss.[2] Although NSAIDs transiently reduce knee OA pain, due to the adverse effects, American College of Rheumatology (ACR) guidelines recommend intermittent use only.[2] A systematic review of fish oil use in rheumatoid arthritis (RA) reported decreased NSAID use with fish oil,[3] and a randomised controlled trial (RCT) of high-dose fish oil in recent-onset RA demonstrated a higher remission rate.[4] Synovial inflammation is associated with severity of pain in knee OA[5–7] and has been variably associated with cartilage loss.[7 8] Since synovitis and cartilage degradation are common to both RA and OA, it is possible that fish oil may be useful in OA.

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the main omega-3 fatty acids in fish oil, decrease synthesis of the cyclooxygenase omega-6 fatty acid metabolite, prostaglandin E2 also a target of NSAID action. EPA and DHA are also precursors of the E-resolvins and D-resolvins that suppress inflammatory cytokine production and act to resolve inflammation.[9] In vitro experiments and animal OA models suggest potential benefit of EPA/DHA in OA, although few studies have been undertaken.[10–13] In healthy adults, higher baseline dietary intake of monounsaturated fats and n-6 fatty acids has been associated with increased bone marrow lesions (BMLs) on MRI 10 years later, but no significant effect on cartilage volume.[14] Data from the MOST study (n=472) showed a negative association between total n-3 fatty acid levels and patellofemoral cartilage loss, but no association with synovitis or tibiofemoral cartilage loss.[15] Neither study included n-3 fatty acids supplementation.

Community use of omega-3 supplements is widespread. An Australian study of 260 000 people reported 32.6% had taken omega-3 supplements within the past four weeks with presence of OA being positively correlated with use.[16] However, most people are taking a low median daily dose of 1 mL of fish oil, which contains approximately 30% (0.3 g) EPA+DHA.[17] Studies in RA and other inflammatory diseases have indicated that the anti-inflammatory dose of fish oil requires delivery of ≥2.7 g of EPA+DHA daily,[10] requiring approximately 10 mL of standard fish oil per day. Therefore, most people who self-medicate with fish oil are generally taking much less than the anti-inflammatory dose.

The aim of this study was to compare the effects of an anti-inflammatory dose of fish oil with a lower dose of fish oil (not considered to be in the anti-inflammatory range), in a double-blind RCT of knee OA. The comparator of low-dose fish oil was chosen for masking of high-dose fish oil and to allow compliance with recommendations on EPA +DHA intake for cardiovascular prevention.[18] The study hypothesis was that high-dose fish oil would have superior efficacy to low-dose fish oil for symptomatic and structural outcomes in people with knee OA.

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METHODS

Study design

We undertook a double-blind, randomised trial. Participants were recruited from the community through general media advertising and rheumatology databases at three Australian centres (August 2007–September 2009). Further details of the study protocol are available in online supplementary file.

Participants

Participants were >40 years with clinical knee OA defined using ACR criteria[19] and visual analogue scale knee pain score >20 mm (0–100 mm scale). Exclusion criteria included severe radiographic knee OA in index knee (grade 3 radiographic joint space narrowing using Osteoarthritis Research Society International atlas[20]), dementia or inability to give informed consent, pregnancy or lactation, planned knee replacement surgery, long-term use (≥6 months) of high-dose fish oil (equivalent to 15 mL of oil) and contraindications to MRI.

Run-in, randomisation and masking

Prior to randomisation, a 4-week run-in period with similarly flavoured oil (citrus-flavoured sunola oil), 15 mL/day, was performed to exclude participants intolerant of liquid oil. Participants who tolerated oil during the run-in period were randomly allocated to one of two treatment arms: high-dose or low-dose fish oil, 15 mL per day. High-dose fish oil contained EPA 18% and DHA 12%, supplying 4.5 g EPA+DHA per day. The comparator oil was a blend of low-dose fish oil and high-oleic sunola oil in a ratio of 1:9, supplying 0.45 g EPA+DHA per day, equivalent to 1.5 standard 1 g fish oil capsule daily. Both oils were flavoured with citrus oils and provided in identical dark 500 mL bottles. The oils, blending, masking and bottling were provided by Melrose Health, Victoria, Australia. Study oil bottles were returned at each study visit and volume of unconsumed oil was measured to assess compliance. Participants were provided with paracetamol (500 mg) tablets with instructions that they could safely use up to 8/day.

The computer-generated random allocation sequence and subsequent allocation was performed centrally at one pharmacy with stratification for study site. Participants and staff involved in patient care and assessment of MRI remained blinded throughout the study.

Outcome measures

Primary outcomes were knee-specific pain scales (Western Ontario and McMaster Universities Arthritis (WOMAC) index) at 3, 6, 12 and 24 months and change in cartilage volume on MRI at 24 months. Secondary outcome measures were WOMAC function, quality of life, analgesic and NSAID use, change in BML score and safety outcomes.

The WOMAC numerical rating scale (NRS) 3.1 index for knee pain and function, measured on a 10-point numerical scale,[21] and the Assessment of Quality of Life utility instrument, which has been validated in both the general population and patients with OA,[22] were measured 3 monthly. Analgesic use was measured using pill counts for paracetamol and daily diary for NSAIDs, using NSAID equivalence scores.[23]

MRIs of the study knee were performed at baseline and 2 years with 1.5 T whole-body MR unit using a commercial receive-only extremity coil. The MRI sequence was a T1-weighted, fat-suppressed, three-dimensional (3D) gradient recall acquisition in the steady state; flip angle 55°; repetition time 58 ms; echo time 12 ms; field of view 16 cm; 60 partitions; 512×192 matrix; one acquisition time 11 min, 56 s. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31×0.83 mm (512×192 pixels).

Individual cartilage plate volumes (medial tibia, lateral tibia and patella) were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section-by-section basis. Data were then resampled by means of bilinear and cubic interpolation (area of 312 and 1.5 mm thickness, continuous sections) for the final 3D rendering. There was one trained reader, blinded to treatment allocation and clinical data, with coefficient of variation of 2.1–2.6%.[24]

BMLs were assessed on a proton density-weighted fat saturation 2D fast spin echo sequence in the sagittal plane. They were defined as areas of increased signal adjacent to the subcortical bone at the medial tibial, medial femoral, lateral tibial, lateral femoral, superior patella and inferior patella sites. BMLs were scored by measuring the maximum area of the lesion (mm^2) at baseline and follow-up.[25] There was one trained reader, blinded to treatment allocation and clinical data, with intraclass correlation coefficient of 0.97.[25] BML size at all six sites was summed to create total BML size at each time point. A meaningful BML change was considered to be 140 mm^2 change in either direction, which corresponds to a one-unit change in WOMAC pain score.[25 26]

MRI scans at both baseline and end of study were available for cartilage reading (n=116), and BML reading (n=110) as only participants with readable scans at baseline and 24 months were included. All participants from one site were excluded from MRI analysis due to inconsistent MRI sequencing from baseline to 24 months (n=51). Further participants were excluded due to loss to follow-up, non-readable MRI, screws in the knee, incorrect sequence at one time point or incorrect knee scanned at one time point.

Serum fatty acid analysis

Fasting serum phospholipid fatty acid from two sites (Adelaide and Sydney; n=150) were measured at each clinic visit by capillary gas chromatography.[27]

Sample size

Sample sizes of 100 per treatment group were selected based on power calculations for longitudinal data with six treatment visits, $\alpha=0.05$, $\beta=0.2$, an attrition rate of 5% per visit and a standardised treatment effect at the end of the study of 0.4 (ie, a medium effect).

Statistical analysis

Primary hypotheses were tested using intention-to-treat (ITT) analysis, with secondary per protocol (PP) analysis of those who finished the 24-month visit taking study oil.

Analysis of outcomes at each visit was performed by constrained longitudinal data analysis,[28] using R statistical software.[29] Mixed effects models were estimated, with both patient and centre as random effects, and an autocorrelation error structure using the nlme library.[30] WOMAC scores were analysed from 20 multiply imputed data sets, imputed using the Amelia library.[31] Treatment effects for normally distributed variables were expressed as mean differences. Non-normally distributed variables were log-transformed as appropriate, and treatment effects for these variables were expressed as ratios. Relative risks were estimated for dichotomous outcomes. Causal mediation analysis, for the influence of weight gain on WOMAC outcomes, was performed using the R library mediation.[32]

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RESULTS

Participants

A total of 351 participants were screened (figure 1). A further 49 participants failed to complete the run-in period. Two-hundred and two participants were randomised to either arm. There was one protocol violation following randomisation. Although 54 (26.7%) discontinued the intervention, follow-up was 84% at 24 months as consenting participants were evaluated at 12 and 24 months irrespective of continuing the intervention. At baseline, participants in each group were well-matched, except for gender (table 1). There were more female participants randomised to the high-dose fish oil group (59%) compared with low-dose fish oil group (40%, p<0.01). The majority had evidence of radiographic OA (194/202; 96%).

Withdrawal from therapy was higher in the high-dose compared with the low-dose group (35% vs 20%) and occurred earlier (median time to cessation 3 vs 7.5 months). Reasons for withdrawals are shown in figure 1.

Pain and function

The low-dose fish oil group had lower pain scores at 18 and 24 months and better functional limitation scores at 24 months compared with the high-dose group (figure 2D, E and table 2). These differences were demonstrated in both ITT and PP analyses (table 2). Adjustment for gender had little or no effect on the outcomes (table 2).

There was no difference between the two groups in the use of paracetamol or NSAIDs (see online supplementary table S1, figure S1 and supplementary data) during the study, nor any difference in quality of at any time point (figure 2F).

MRI results

There was no statistically significant change in total cartilage volume from baseline to 24 months and no difference between the groups in the changes over 24 months (table 3). There was no difference in the proportion of participants who had a clinically significant change in BML over 24 months (table 3).

Other outcomes

There was no change in serum C reactive protein levels over time and no difference between groups (data not shown).

Both treatment groups, on average, gained a small amount of weight (see online supplementary table S2 and supplementary data), with significantly greater weight gain in the high-dose group (p<0.05). As weight gain is a potential mediator of effects on pain and function in knee OA,[34–36] it is plausible that the increased weight gain observed in the high-dose group may have contributed to their poorer WOMAC scores. A post hoc causal

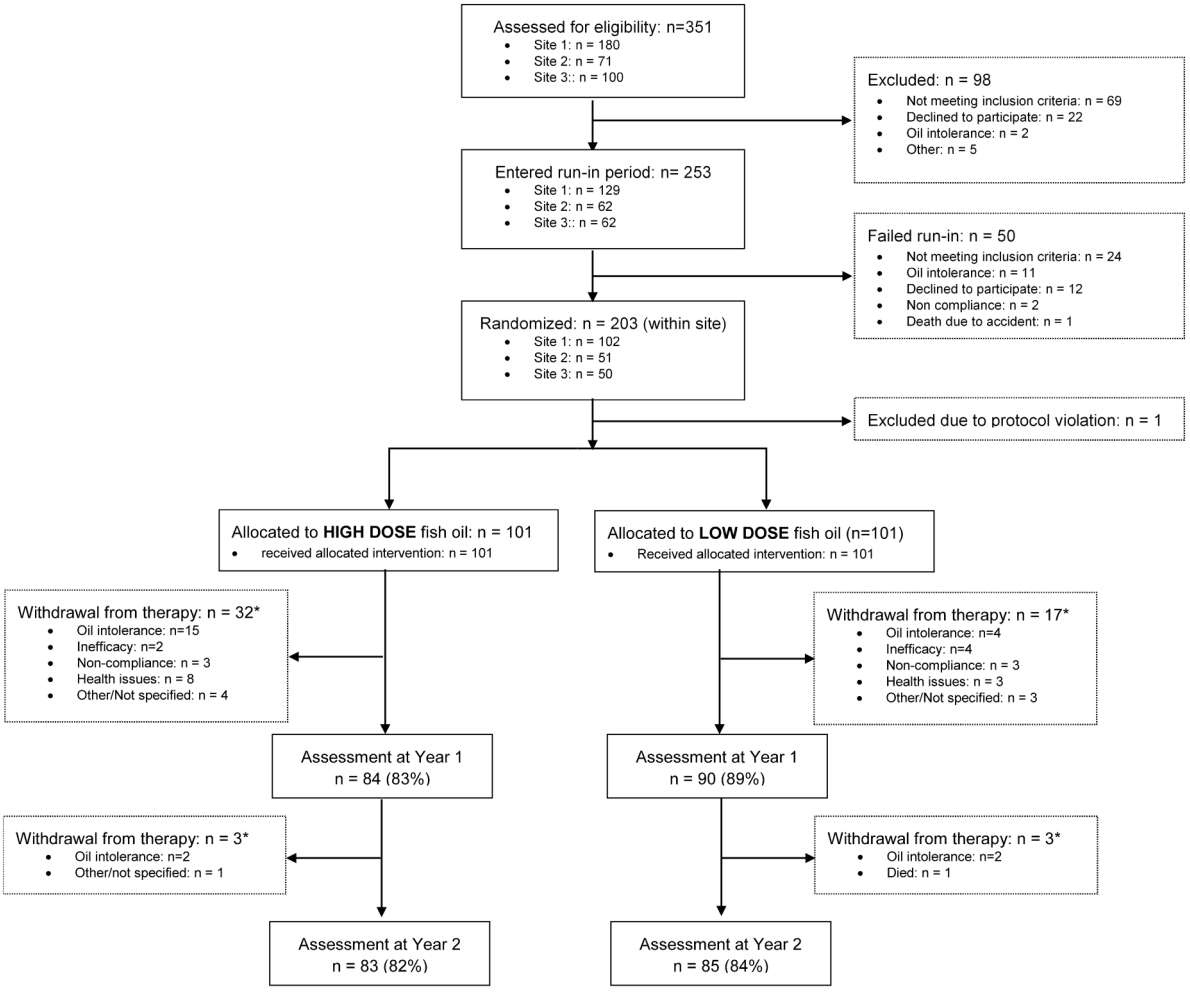

Figure 1 Flow diagram of participant recruitment and completion.

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Table 1 Demographic and baseline characteristics

Characteristic	Low-dose fish oil	High-dose fish oil	p Value
N	101	101	
Age (years): mean (SD)	61 (10)	61 (10)	0.84
Gender (% female)	40	59	<0.01
BMI (kg/m^2): mean (SD)	29 (4)	29 (5)	0.67
WOMAC* pain: mean (SD)	15 (9)	16 (9)	0.35
WOMAC* function: mean (SD)	49 (29)	54 (34)	0.28
Quality of life (AQoL-4D): mean (SD)	0.77 (0.27)	0.74 (0.25)	0.50
NSAID use (%)	34	30	0.54
Radiographic knee OA (OARSI%)[20]	96/101 (95%)	98/101 (97%)	0.47
Total OARSI joint space narrowing :mean (SD)	1.7 (0.1)	1.8 (0.1)	0.62
Total OARSI osteophyte score: mean (SD)	2.0 (0.3)	2.3 (0.2)	0.42
MRI Total cartilage volume (μL): mean (SD)	7.46 (2.09) (n=56)	6.60 (1.73) (n=60)	0.02†
MRI BML			
Any BML (%)	44/55 (82%)	47/55 (85%)	0.61
BML size (mm^2): median (IQR)	118 (209)	122 (219)	0.70
CRP: median (IQR)	1.5 (2.2)	1.7 (2.3)	0.43
Plasma omega-3 fatty acids			
Plasma EPA (20:5n-3): mean (SD)	1.3 (0.7) (n=95)	1.5 (1.1) (n=94)	0.17
Plasma DHA (22:6n-3): mean (SD)	3.4 (1.0) (n=95)	3.5 (1.2) (n=94)	0.75

*Western Ontario and McMaster Universities Arthritis Index, scored on the NRS 3.1 10-point numerical scale.[21] Pain scores range (0,50) and function scores range (0,170).
†p=0.26 after gender adjustment.
BMI, body mass index; BML, bone marrow lesion; CRP, C reactive protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; NRS, numerical rating scale; NSAID, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

mediation analysis determined that weight, as a mediator variable, contributed <1% to the average difference between the high-dose and low-dose treatments (over the six treatment visits) for either pain (p=0.88) or function (p=0.89). It is therefore unlikely that the between-group differences in WOMAC outcomes can be attributed to differences in weight gain.

Compliance

Assessed by measuring the oil volume in returned bottles, compliance was >80% in both groups. Both groups had increases from baseline in plasma EPA and DHA with the high-dose group having substantially larger increases, consistent with compliance with study oil (figure 2A–C).

Success of blinding

At the end of the study, 52% of participants were unsure which group to which they had been allocated (50% high dose, 50% low dose). Of the remaining who thought they knew which group they were allocated, only 57% answered correctly, suggesting that blinding had been well maintained.

Adverse events

Adverse events were common and did not occur more frequently in either group (table 4). Serious adverse events were primarily non-elective hospital admissions. There was a sudden cardiac death in the low-dose group, considered unrelated to the intervention. There were no significant bleeding or thrombosis complications in either group. Although gastrointestinal adverse events were equally common in each group, this led to greater discontinuation of treatment in the high-dose compared with the low-dose group (16.8% vs 5.9%; p<0.015).

DISCUSSION

This double-blinded randomised clinical trial demonstrated that ingestion of low-dose fish oil (in combination with sunola oil) resulted in better pain and function scores at 18 and 24 months compared with high-dose fish oil. This difference occurred with no change in the use of analgesics or NSAIDs over 24 months. There was no difference in structural outcomes of cartilage volumes and BMLs over 24 months. The study showed no benefit of high-dose fish oil over low-dose fish oil, which was the primary hypothesis of the study. Unexpectedly, the lower dose fish oil group had less pain and better function than the high-dose group. The reasons for this unanticipated result remain unclear. There was greater weight gain in the high-dose group compared with the low–dose group, which may contribute to higher pain scores. However, a post hoc mediator analysis demonstrated this differential weight gain did not influence the difference in pain and function seen between the two groups. The small difference in weight gain is itself difficult to explain, as both groups consumed equivalent volumes of oil, with similar caloric intake.

There was no group difference at 24 months in change in cartilage volume or BMLs. Although MRI data from one site could not be used due to inconsistent MRI sequences, there was no imbalance in the groups due to stratification of randomisation by study site, and there was good follow-up (84%) for MRI data from the other two sites. However, there was loss of power for these endpoints, so it is not possible to make firm conclusions regarding structure modification from our findings.

The comparator oil, which contained predominantly sunola oil, was not expected to have any therapeutic effect. It is low in saturated fatty acids, n-6 fatty acids and n-3 fatty acids, and is predominantly non-essential, monounsaturated oleic acid (n-9). A previous 6-month RCT in OA comparing cod liver oil (rich in omega-3 fatty acids) and olive oil (rich in n-9 fatty acids) demonstrated no difference between the groups after 6 months.[37] However, in contrast to olive oil, sunola oil is not rich in polyphenols with which anti-inflammatory actions have been associated.[38 39] One possible explanation could be that

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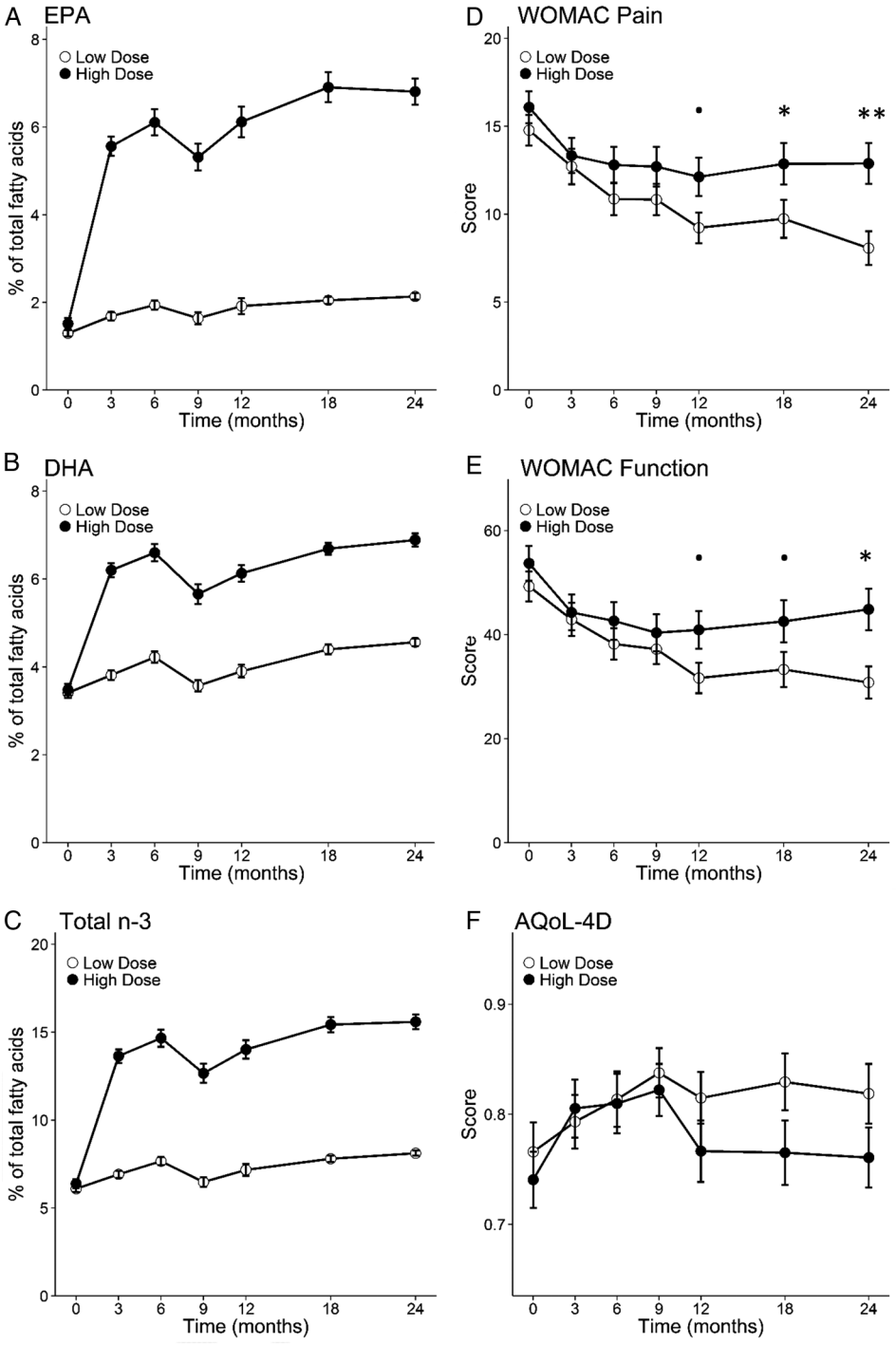

Figure 2 Mean n-3 fatty acids and osteoarthritis outcomes over the study duration (intention-to-treat patients) for high-dose compared with low-dose fish oil treatment. Vertical error bars represent the SE of the mean. n-3 fatty acids ((A) eicosapentaenoic acid (EPA); (B) docosahexaenoic acid (DHA); and (C) total n-3)) were expressed as a percentage of total fatty acids, and were significantly increased in high-dose compared with low-dose patients at all treatment visits. Western Ontario and McMaster Universities Arthritis Index (WOMAC) outcomes were (D). Pain (numerical rating scale (NRS) 3.1 0–50 scale) and (E) function (NRS 3.1 0–170 scale). Both were significantly higher in the high-dose patients at the end of study (<0.10, *p<0.05, **p<0.01). There were no significant differences between the two treatment groups for quality of life scores ((F) AQoL-4D).

Table 2 Difference in Western Ontario and McMaster Universities Arthritis Index (WOMAC) outcomes between high-dose and low-dose fish oil at 1 and 2 years, respectively

	Intention-to-treat				Per protocol			
	High dose—low dose				High dose—low dose			
	1 year (n=101)		2 years (n=101)		1 year (n=80)		2 years (n=65)	
Outcome	Mean (SE)	p Value	Mean (SE)	p Value	Mean (SE)	p Value	Mean (SE)	p Value
WOMAC Pain	2.3 (1.2)	0.06	3.3 (1.3)	0.009	3.3 (1.2)	0.007	4.1 (1.2)	0.001
Gender adjusted	2.1 (1.2)	0.081	3.1 (1.3)	0.014	3.1 (1.2)	0.009	4.0 (1.2)	0.001
WOMAC function	6.5 (3.7)	0.08	8.5 (4.0)	0.032	8.4 (3.6)	0.019	11.6 (3.7)	0.002
Gender adjusted	5.9 (3.7)	0.11	7.9 (4.0)	0.046	8.0 (3.6)	0.026	11.2 (3.7)	0.003

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Table 3 Changes in MRI cartilage volume and bone marrow lesion area over 2 years of fish oil treatment

	Intention to treat			Per protocol		
	Low dose	High dose	p Value	Low dose	High dose	p Value
N	56	59		53	45	
Cartilage volume: proportion with a statistically significant change (least significant change) at 2 years†						
Decrease	3 (5%)	8 (14%)	0.21*	2 (4%)	5 (11%)	0.09*
No change	47 (84%)	42 (71%)		46 (87%)	31 (69%)	
Increase	6 (11%)	9 (15%)		5 (10%)	9 (20%)	
Bone marrow lesions: proportion with a clinically significant change at 2 years‡						
Decrease	5 (9%)	7 (13%)	0.23*	5 (10%)	6 (14%)	0.41*
No change	48 (87%)	42 (76%)		45 (87%)	33 (77%)	
Increase	2 (4%)	6 (11%)		2 (4%)	4 (9%)	

*p Values refer to comparisons between fish oil treatment groups.
†Least significant change[33] was considered a change of >8% in either direction.
‡Clinically significant was considered a change >140 mm^2 in either direction, which corresponds to a one-unit change in Western Ontario and McMaster Universities Arthritis Index score.[25]

Table 4 Number of participants with adverse events

	Low-dose fish oil	High-dose fish oil
Hospitalisations	37 (36.6%)	38 (37.6%)
Infection (all)	66 (65.3%)	71 (70.3%)
Respiratory	46 (45.5%)	51 (50.5%)
Ear	1 (1.0%)	4 (4.0%)
Other	19 (18.8%)	16 (15.8%)
Gastrointestinal (all)	62 (61.4%)	67 (66.3%)
Upset	26 (25.7%)	15 (14.9%)
Reflux	12 (11.9%)	17 (16.8%)
Nausea	13 (12.9%)	19 (18.8%)
Diarrhoea	5 (5.0%)	8 (7.9%)
Intolerance/other	6 (5.9%)	8 (7.9%)
Bleeding (all)	4 (4.0%)	1 (1.0%)
Epistaxis	1 (1.0%)	0 (0.0%)
Haemarthrosis	0 (0.0%)	1 (1.0%)
Postoperative	1 (1.0%)	0 (0.0%)
Rectal	1 (1.0%)	0 (0.0%)
Minor	1 (1.0%)	0 (0.0%)
Thrombosis (all)	1 (1.0%)	1 (1.0%)
Superficial leg vein	1 (1.0%)	0 (0.0%)
Deep vein thrombosis	0 (0.0%)	1 (1.0%)
Cancer (all)	9 (8.9%)	12 (11.9%)
Breast cancer	1 (1.0%)	1 (1.0%)
Prostate cancer	1 (1.0%)	0 (0.0%)
Non-melanotic skin Ca	6 (5.9%)	9 (8.9%)
Melanoma	1 (1.0%)	0 (0.0%)
Other cancer	0 (0.0%)	2 (2.0%)
Cardiovascular (all)	16 (15.8%)	18 (17.8%)
Sudden cardiac death	1 (1.0%)	0 (0.0%)
Acute coronary syndrome	10 (9.9%)	10 (9.9%)
Palpitations/atrial fibrillation	4 (4.0%)	4 (4.0%)
Uncontrolled hypo/hypertension	1 (1.0%)	3 (3.0%)
Pulmonary oedema	0 (0.0%)	1 (1.0%)
Knee surgery (all)	5 (5.0%)	6 (5.9%)
Study knee	2 (2.0%)	4 (4.0%)
Non-study knee	3 (3.0%)	2 (2.0%)

sunola oil with or without low-dose fish may confer a beneficial effect, but this unanticipated finding requires confirmation in further trials.

An alternative explanation is that both groups experienced a 'placebo effect'. Although the changes in pain scores in this study are comparable to those seen with 'placebo effect' for pain,[40] this is difficult to assess in the current study due to lack of control group. The GAIT study, which compared glucosamine, chondroitin, glucosamine/chondroitin, celecoxib and placebo, demonstrated similar improvement in pain in all groups over 2 years. WOMAC pain scores declined in the first 12 weeks with little or no change thereafter.[41] In our study, the WOMAC pain scores in both groups were similar at 3 months then began to diverge with participants in the low-dose group continuing to have reduction after 12 months. The initial reduction in WOMAC scores at 3 months is consistent with regression to the mean. However, it is unlikely that this phenomenon can fully explain the better outcome observed in the low-dose group during the second year of the study.

A study limitation is the lack of a control group. Inclusion of a small amount of fish oil allowed appropriate masking of the oils. This was successful as participants were not able to accurately detect the oil to which they had been randomised. The greater intolerance and greater withdrawal in the high-dose group was unexpected given the run-in period with daily ingestion of liquid oil and the additives of citrus oils, which gave both oils a similar taste. It was considered unethical to prevent fish oil supplements for 2 years in these older, more overweight participants and the 450 mg EPA+DHA daily intake in the low-dose group complies with recommendations aimed at reducing cardiac mortality, which are based on the antiarrhythmic effect of these fatty acids.[42] Anti-inflammatory effects have not been seen at doses this low.[43]

The question arises whether sunola oil may have some efficacy in OA. With hindsight, we believe that the most appropriate control group would have been no oil at all, which would of course sacrifice the ability to perform a blinded study. However, given the study we performed, it is a reasonable conclusion that it is still unknown whether low-dose fish oil and/or sunola oil are beneficial for knee OA.

This was an investigator-initiated rigorously conducted study with excellent 2-year follow-up. The strengths of the study

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include adequate masking of fish oil, repeated symptom measures and MRI imaging. There was a low overall dropout rate for the study despite significant withdrawal due to oil intolerance.

We found no benefit of high-dose fish oil supplementation compared with low-dose fish oil supplementation in knee OA. The unanticipated finding of better pain and function in the low-dose fish oil/sunola group requires further investigation.

Correction notice This article has been corrected since it was published Online First. The first name of the sixth author has been corrected and the affiliations for the sixth and last authors have been corrected.

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Contributors CLH, LMM, LGC and GJ designed the study and obtained funding. RB, KH and TF recruited participants. CLH, LMM, GJ, RB, KH and TF screened participants. DA read and interpreted MR images. SEL provided statistical analysis and advice. CLH and MJ wrote the draft manuscript. CLH, GJ, LMM, SMP, LGC and MJ participated in data interpretation. All authors critically reviewed and edited the manuscript and approved the final version.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The Queen Elizabeth Hospital Human Research Ethics Committee, Royal North Shore Hospital Human Research Ethics Committee, Tasmanian Human Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data is available for sharing on request to authors.

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SUPPLEMENTARY FILE 1: Study Protocol for Fish oil in knee osteoarthritis: A randomised clinical trial of low dose versus high dose (also known as the FOSTAR study).

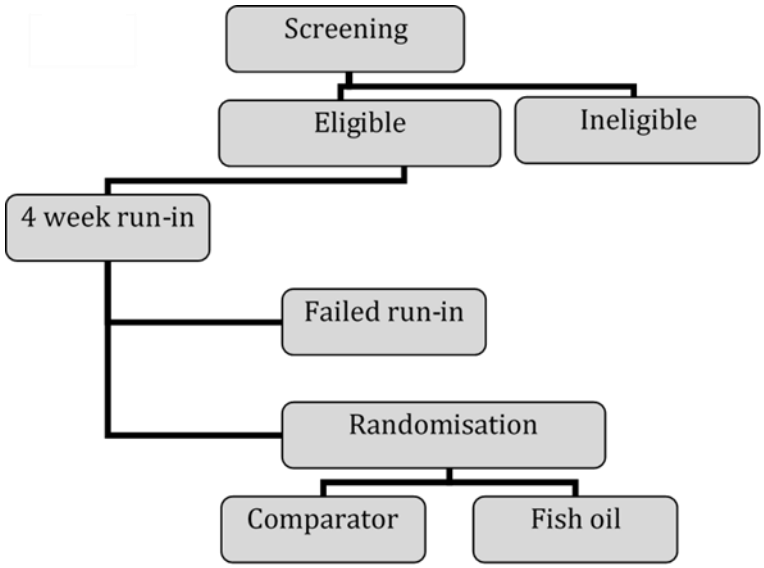
STUDY DESIGN

The FOSTAR study is a randomised double-blind controlled clinical trial of 200 subjects with symptomatic knee osteoarthritis from three Australian centres (The Queen Elizabeth Hospital, Adelaide, South Australia; Menzies Research Institute, Hobart, Tasmania and Royal North Shore Hospital, Sydney, New South Wales). Participants will be recruited and randomly allocated to either high or low dose fish oil, following completion of a one month run-in period.

All participants will provide written informed consent. The study has been approved by The Queen Elizabeth Hospital, Royal North Shore Hospital and Tasmanian Human Research Ethics Committees. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12607000415404) on 19th August 2007.

The proposed flow of subjects through the study is shown in Figure 1.

Figure 1. Flow of subjects through the FOSTAR study



RECRUITMENT

Subjects will be recruited at three centres through patient databases currently held by study

Investigators and direct advertising in local newspapers and Arthritis Australia newsletters.

INCLUSION CRITERIA

The inclusion criteria required (i) age greater than 40 years (ii) clinical knee OA defined using American College of Rheumatology criteria [1] and (iii) VAS knee specific pain score greater than 20mm (0-100mm scale). The knee which is most symptomatic knee, as determined by the participant, will represent the 'index' knee for the remainder of the study.

EXCLUSION CRITERIA

Exclusion criteria included (i) dementia or inability to give informed consent, (ii) pregnancy or lactation, (iii) severe knee OA (Grade 3 radiographic joint space narrowing using the Osteoarthritis Research Society International atlas), (iv) planned knee replacement surgery, (v) long-term use ($\geq$6 months) of anti-inflammatory dose of fish oil (15mL of oil or $\geq$9 capsules), (vi) presence of inflammatory arthritis and (vii) contra-indications to MRI.

RUN-IN PERIOD

Once volunteers have been screened, they will enter a 4-week pre-randomisation run-in period to exclude participants intolerant to taking liquid oil. All subjects will be instructed to take 15 ml daily of a similarly flavoured oil (citrus flavoured Sunola oil). While the exact contents of this preparation will not be revealed, it will be explained to participants that this preparation is designed to test common aspects of the interventions, but differs from the actual test oil preparations. A standardized instructional video demonstrating a method of taking liquid oil that enhanced tolerability by 'layering' on juice will be shown to all participants prior to run-in. Participants will be instructed to take the test oil on juice using the two glass technique [2]. Briefly, one of two shot glasses is filled with fruit juice and the other half filled with juice. The required dose of oil is then measured and layered onto the juice in the half filled glass. Without stirring, the contents are then swallowed in a single gulp. Immediately thereafter, the glass of juice alone is sipped slowly over a period of about 15 seconds. The oil and juice is taken with a meal and not on an empty stomach. Carbonated drinks are avoided. The oil can be taken in divided doses. This method has generally been effective in avoiding a 'repeating' fish oil taste.

Patients will be reviewed in the 3rd week after commencing the run-in oil. Subjects who do not attend the appointments or are non-compliant (who consume less than 75% of the oil as assessed by volume) or are intolerant of the oil will not be randomised. The requirements

for the run-in test (and the consequences of failing) will be disclosed to the subjects prior to screening. During this run-in period, subjects will be asked to cease fish oil and glucosamine but will be permitted to take paracetamol for first line analgesia and NSAID (ibuprofen up to 400mg QID if required) for second line analgesia. In our experience about 20% of subjects recommended fish oil fail to establish a pattern of daily ingestion. This period will establish the patient's ability to take a test oil preparation using the recommended oil on juice technique as well as tolerance to and adequacy of rescue analgesia, including, if required, the selected NSAIDs. None of these medications, including the 'run-in' oil will be taken in the week prior to the baseline assessment, when randomisation and commencement of the allocated test preparation will take place. The use of a run-in has been used to improve compliance and retention in RCTs [3]

RANDOMIZATION BY CENTRE

Subjects who satisfy compliance criteria and VAS pain score criteria during the run-in period will be randomised (1:1) to one of the two arms of the RCT. The randomisation will be done centrally at The Queen Elizabeth Hospital in Adelaide by computer generated random numbers and will be stratified by centre.

INTERVENTION

Participants will be randomly allocated to one of two treatment arms:

1. Anti-inflammatory dose of fish oil, 15 ml/day (high dose fish oil)
2. Comparator oil comprising 10% fish oil in sunola oil, 15 ml/day (low dose fish oil)

High dose fish oil contains EPA 18% and DHA 12%, supplying 4.5g EPA+DHA per day. The low dose comparator oil, a blend of fish oil and high oleic sunola oil in a ratio of 1:9, supplies 0.45g EPA + DHA per day, which is equivalent to 1.5 standard 1g fish oil capsule daily. Both oils are flavoured with citrus oils and will be provided in identical dark 500mL bottles. Fish oil is sourced from Berg LipidTech Aalesund, Norway. The oils, blending, masking and bottling is performed by Melrose Health, Victoria, Australia. Study oil bottles will be returned at each study visit and volume of unconsumed oil measured to assess compliance. The presence of fish oil in the comparator will obviate the ethical problem of denying patients n-3 fatty acids that are recommended for cardiovascular health and will also add 'fishy' sensate properties that will militate against unmasking. We have previously shown addition of citrus flavouring to fish oils and vegetable oils achieves masking. The EPA and

DHA dose in the undiluted test fish oil has been shown to have anti-inflammatory effects in a variety of clinical settings, whereas the comparator oil will deliver a dose of fish oil that is well below the minimum amount (10ml/d) that has been associated with anti-inflammatory effects in RCTs. Participants will be provided with paracetamol (500mg) tablets with instructions that they could safely use up to 8 per day.

Participants will undergo assessments at baseline, 6 weeks, 3, 6, 9, 12, 18 and 24 months with interim phone calls to participants to encourage continuing compliance and participation

Dietary and general advice:

Subjects will be instructed to use olive oil based products (spreads, cooking oils, dressings etc), where possible, to minimise variation in consumption of n6 polyunsaturated fatty acids which compete with dietary n3 fatty acids. Written instructions regarding technique for taking the oil and directions for the background diet will be provided. All participants will also be given written information on knee osteoarthritis and generic instructions regarding exercises appropriate for maintaining knee function in OA and general fitness. The package of informed consent and written advice will include information regarding potential unwanted effects of fish oil and paracetamol.

COMPLIANCE

The degree of compliance with test oils will be measured in two ways: (i) calculation of consumed fish oil by count of bottles provided and measurement of oil remaining in returned partly used bottles and (ii) fasting plasma omega-3 fatty acid analysis. These assessments will be undertaken at 3, 6, 12, 18 and 24 months. The plasma fatty acid analysis results will not be available to subjects or investigators till the completion of the study.

OUTCOME MEASURES

Primary outcomes:

1. Pain (WOMAC NRS 3.1 index [4], 10 point numerical scale) at 3, 6, 9, 12 and 24 months (knee specific)
2. Change in knee MRI cartilage volume at 2 yrs.

Secondary outcomes:

1. Disability (WOMAC NRS 3.1 index [4], 10 point numerical scale) at 3,6, 9,12 and 24 months (knee specific)

2. Quality of life (AQOL) [5]
3. Analgesic use, measured using a daily diary (NSAID) and paracetamol (pill count at each visit)
4. Change in MRI scores of bone marrow lesions at 2 years
5. Safety assessments/adverse events

In addition to the designated outcome measures, blood pressure, full blood count and electrolytes and liver function testing, presence of comorbidities (eg renal disease, cardiovascular disease, peptic ulcer disease) and a diet questionnaire, DQES V2[6], used to assess n-3 and n-6 fatty acid intake in usual diet, will be assessed at baseline.

As the study will extend over two years in a population at an age at risk for cardiovascular disease and declining bone density, routine investigations will be undertaken at baseline and two years to monitor collateral health effects and risks including:

1. fasting blood lipids
2. low titre c-reactive protein
3. bone mineral density of hip and spine
4. lung spirometry (The Queen Elizabeth Hospital participants only)

The assessment schedule is summarized in Table 1, and data collection forms are presented in Appendix 1.

Table 1. Schedule of assessment for primary and secondary outcome measures

FOSTAR STUDY ASSESSMENTS								
	Enrolment	Ransomisation	Treatment					Completion
	Visit 1 (-4 weeks)	Visit 2 (0 weeks)	Visit 3 (3 month)	Visit 4 (6 month)	Visit 5 (9 month)	Visit 6 (12 month)	Visit 7 (18 month)	Visit 8 (24 month)
Informed Consent for FOSTAR	X							
Medical History	X							
Surgical History	X	X	X	X	X	X	X	X
OA History		X						
Inclusion/Exclusion Criteria	X	X						
Concomitant medications	X	X	X	X	X	X	X	X
Physical Exam/Vital Signs	X	X	X	X	X	X	X	X
Fish Oil Dosing DVD	X	X						
Run-In Fish Oil	X							
Diet information sheet		X						
Exercise information sheet		X						
Osteoarthritis Information sheet		X						
Laboratory testing								
Blood sampling for FBC, CRP, LFT electrolytes and fasting lipids		X				X		X
Blood sampling for serum fatty acids		X	X	X	X	X	X	X
Imaging								
Knee X-ray	X							
MRI scan		X						X
DEXA scan		X						X
Questionnaires								
WOMAC Questionnaire	X	X	X	X	X	X	X	X
NRS pain Questionnaire	X	X	X	X	X	X	X	X
MAPT Questionnaire		X				X		X
AQoL Questionnaire		X	X	X	X	X	X	X
Diet Questionnaire		X						X
Analgesic Medication		X	X	X	X	X	X	
Take-Home Diary	X	X	X	X	X	X	X	
Randomisation		X						
Study Fish Oil		X	X	X	X	X	X	
Pedometer Readings		X						X

MRI scanning and scoring:

MRI scans will be performed at each of the study centres. MRI will be performed on the most symptomatic knee as determined by the participant, and will represent the 'index'

knee for the remainder of the study. Each participant will have an MRI performed on their 'index' knee at baseline and after 2 years. The 'index' knee will be imaged in the sagittal plane on the same model 1.5T whole-body MR unit using a commercial receive-only extremity coil. The following sequence and parameters will be used: a T1-weighted, fat-suppressed, 3-dimensional gradient recall acquisition in the steady state; flip angle 55 degrees; repetition time 58 msec; echo time 12 msec; field of view 16 cm; 60 partitions; 512 × 192 matrix; one acquisition time 11 minutes, 56 seconds. Sagittal images will be obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 × 0.83 mm (512 × 192 pixels).

The MRI scans will be assessed by a single trained observer. Each participant's baseline and follow-up MRI scans will be scored unpaired with blinding to subject identification and timing of MRI. The volumes of individual cartilage plates (medial tibia, lateral tibia and patella) will be isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section by section basis. These data will then be resampled by means of bilinear and cubic interpolation (area of 312 mm and 1.5 mm thickness, continuous sections) for the final 3D rendering. The coefficient of variation for this method in our hands is 2.1% to 2.6% [7].

Bone marrow lesions (BMLs) will be assessed on a proton density-weighted fat saturation 2D fast spin echo sequence in the sagittal plane. They will be defined as areas of increased signal adjacent to the subcortical bone at the medial tibial, medial femoral, lateral tibial, lateral femoral, superior patella and inferior patella sites. One trained and blinded observer will score BMLs by measuring the maximum area of the lesion (mm^2) at baseline and follow-up, as previously described [8]. The intraclass correlation coefficient (ICC) in our hands for this method of measurement is 0.97 [8].

Radiographic assessment:

Radiographs will only be used as a screening tool at participant recruitment, and not as an outcome measure. Radiographs of the index knee in the Buckland-Wright view will be taken at baseline, to allow comparison with MRI assessments and as this is putatively the most reproducible technique with regard to non-fluoroscopic positioning [9].

Radiographs will scored independently by 2 trained observers at each site using a published atlas to classify disease in the tibiofemoral joint. The radiographic features of tibiofemoral

OA will be graded in each compartment on a 4-point scale (0-3) for individual features of osteophytes and joint space narrowing [10]. We have shown previously high degrees of intra-observer and inter-observer reproducibility for agreement on features of OA in the knee with regard to both osteophytes and joint space narrowing [11].

Success of Blinding:

Success of blinding will be assessed by asking the participants the following question:
"If you were asked which oil you were taking during the FOSTAR study would you say? Possible responses: Low dose, comparison oil OR high dose fish oil OR I am not sure which oil I may have been taking". This will be asked at final visit.

ANALYSIS PLAN

Both intention-to-treat and per protocol analyses will be undertaken. Multiple imputation will be used for missing data. Analyses will be performed using longitudinal mixed model regression. The primary interpretation will be the comparison between the two treatment groups at the end of study.

SAMPLE SIZE CONSIDERATION

Sample sizes of 100 per treatment group were selected based on power calculations for longitudinal (ie repeated data) data with 6 treatment visits, $\alpha = 0.05$, $\beta = 0.2$, an attrition rate of 5% per visit, and a standardised treatment effect at the end of the study of 0.4 (i.e. a medium effect).

WITHDRAWALS

All participants will be followed for the duration of the two year study, irrespective of whether they discontinue the study oil (unless they decide to withdraw consent).

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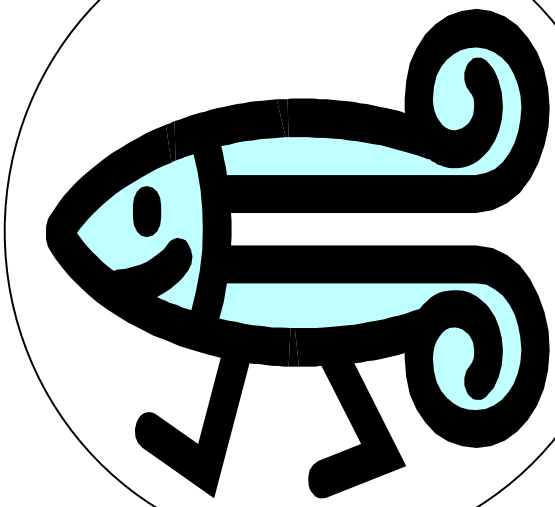
APPENDIX 1: FOSTAR STUDY DATA COLLECTION FORMS

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

FOSTAR



STUDY

A two year, multi-centre, double-blinded, randomised, controlled clinical trial to assess the benefits of high-dose oral fish oil in patients experiencing symptomatic knee osteoarthritis.

Site Number: ☐

Randomisation Number: ☐☐☐☐

Subject Initials: ☐☐☐

Study Selected Knee:

☐☐☐☐☐

FOSTAR STUDY ASSESSMENTS

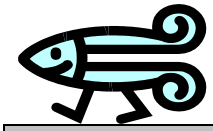
Shaded areas are specific to TQEH site ONLY	Enrolment	Randomisation	Treatment					Completion
	Visit 1 (-4weeks)	Visit 2 (0weeks)	Visit 3 (3month)	Visit 4 (6month)	Visit 5 (9month)	Visit 6 (12month)	Visit 7 (18month)	Visit 8 (24month)
Informed Consent for FOSTAR	X							
Informed Consent for PFT sub-study	X							
Informed Consent for DNA sub-study	X							
Medical History	X							
Surgical History	X	X	X	X	X	X	X	X
OA History		X						
Inclusion/Exclusion Criteria	X	X						
Concomitant medications	X	X	X	X	X	X	X	X
Physical Exam/Vital Signs	X	X	X	X	X	X	X	X
Serum Pregnancy Test		X						X
Blood sampling for FBC, CRP, LFT electrolytes and fasting lipids		X				X		X
Blood sampling for serum fatty acids		X	X	X	X	X	X	X
Blood sampling for DNA sub-study		X						
Lung Function sub-study test		X				X		X
Knee X-ray (if required)	X							X
MRI scan		X						X
DEXA scan		X						X
WOMAC Questionnaire	X	X	X	X	X	X	X	X
NRS pain Questionnaire	X	X	X	X	X	X	X	X
MAPT Questionnaire		X				X		X
AQoL Questionnaire		X	X	X	X	X	X	X
Diet Questionnaire		X						X
CES-D Questionnaire (Depression)		X				X		X
Fish Oil Dosing DVD	X	X						
Run-In Fish Oil	X							
Analgesic Medication		X	X	X	X	X	X	
Take-Home Diary	X	X	X	X	X	X	X	
Randomisation		X						
Study Fish Oil		X	X	X	X	X	X	
Diet information sheet		X						

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

Exercise information sheet		X						
Osteoarthritis Information sheet		X						
Pedometer Readings		X						X



FOSTAR STUDY

Visit 1 – ENROLMENT

Visit Date …… ☐☐/☐☐/☐☐☐☐
DD/MM/YYYY

INFORMED CONSENT

Date Written Informed Consent Obtained …… ☐☐/☐☐/☐☐☐☐
DD/MM/YYYY

	Yes	No
Has a copy been provided to the subject for their records	☐	☐
Has a copy been added to the subjects hospital records ☐	☐	
Has the original been filed in the subjects CRF	☐	☐

DEMOGRAPHICS

Date of Birth …….. ☐☐/☐☐/☐☐☐☐
DD/MM/YYYY

Gender ☐ Female ☐ Male

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

Ethnic Origin	☐ Caucasian ☐ Asian ☐ Hispanic ☐ Other (specify below) ☐

SURGICAL HISTORY	
Previous Surgical Procedures	Date of Procedure (DD/MM/YYYY)
If the subject is currently taking any medications for any of the above procedures, ensure that details are recorded in the Concomitant Medications record.	

CO-MORBIDITIES				
Have you ever been told by a Dr or a nurse that you have any of the following conditions?			If yes, Do you currently have these conditions?	
	YES	NO	YES	NO
Diabetes	☐	☐	☐	☐
Osteoporosis	☐	☐	☐	☐
High Blood Pressure	☐	☐	☐	☐
Asthma	☐	☐	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

Bronchitis	☐ ☐	☐ ☐
Emphysema/Chronic bronchitis	☐ ☐	☐ ☐
Stroke	☐ ☐	☐ ☐
Heart Attack	☐ ☐	☐ ☐
Angina	☐ ☐	☐ ☐
High Cholesterol	☐ ☐	☐ ☐
None of the above	☐ ☐	

MEDICAL HISTORY		
CURRENT MEDICAL CONDITIONS	Date of Onset (DD/MM/YYYY)	Date Resolved Or √ Ongoing (DD/MM/YYYY)
		☐
		☐
		☐
		☐
		☐
		☐
		☐
		☐
If the subject is currently taking any medications for any of the above procedures, ensure that details are recorded in the Concomitant Medications record.		

QUESTIONNAIRES		
	YES	NO
Has analgesic and anti-inflammatory medications been with-held today	☐	☐
Questionnaires supplied: YES NO	Questionnaires Completed	YES NO

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

WOMAC	☐	☐	☐	☐
NRS PAIN	☐	☐	☐	☐

INCLUSION CRITERIA	YES	NO
Is the subject aged 40 or over?	☐	☐
Does the subject experience symptomatic knee osteoarthritis (ACR criteria) a) Knee pain (at least 20mm on NRS pain scale) b) An osteophyte on x-ray c) At least one of the following: - knee age greater than 50 years - stiffness lasting less than 30 minutes - crepitus	☐	☐
Is the subject able to read, speak and understand English, capable of understanding the study requirements and willing to co-operate with the study instructions?	☐	☐
Is the subject able and willing to give informed consent?	☐	☐
Has the subject used an investigational drug within 30 days of the screening visit?	☐	☐
Is the subject willing and able to give blood samples	☐	☐
Is the subject willing and able to have MRIs performed	☐	☐
Is the subject willing and able to have DEXA scans performed?	☐	☐
A tick recorded in any of the shaded boxes above signifies that the subject is ineligible and should be excluded from entering the study		

EXCLUSION CRITERIA	YES	NO

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

	☐	☐
Does the subject suffer from dementia or be unable to give informed consent?		
Is the subject pregnant or breastfeeding, or is she unable or unwilling to use an adequate method of contraception?	☐	☐
Does the subject have Grade – 4 changes in their knee which is to be investigated	☐	☐
Has the subject ingested ≥10mL or ≥ 9 standard capsules of fish oil daily for the proceeding 3 months	☐	☐
Does the subject have any contra-indications for having MRIs or DEXA scans performed?	☐	☐
Does the subject have any clinically significant condition(s) such as (but not limited to) cancer, rheumatoid arthritis, psoratic arthritis, lupus or fibromyalgia? that in the opinion of the investigator may compromise their safety or compliance, interfere with evaluation or preclude completion of the study	☐	☐
A tick recorded in any of the shaded boxes above signifies that the subject is ineligible and should be excluded from entering the study		

ENROLMENT CODE
If ALL inclusion and NO exclusion criteria have been met, the study subject may be assigned an enrolment code: **E** ☐☐☐☐☐☐☐

PHYSICAL EXAMINATION/VITAL SIGNS	
Height	cms
Weight	kgs
Blood Pressure	mmHG

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

RUN-IN FISH OIL		
	YES	NO
Has the run-in fish oil been supplied and explained?	☐	☐
Has the dosing DVD been shown to the subject?	☐	☐
Has the first dose of fish oil been taken under supervision in the clinic?	☐	☐

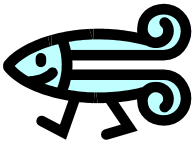
PREVIOUS FISH OIL USE		
	YES	NO
Have you ever used fish oil prior to your involvement in this study?	☐	☐
If yes, what was your average daily consumption of fish oil? Where 1 capsule OR 1 mL of liquid fish oil = 1g	……g/day	

PREPARATION FOR NEXT APPOINTMENT		
	YES	NO
	☐	☐
Has a baseline/randomisation appointment been made?	☐	☐
Has the subject been booked in for fasting blood tests prior to randomisation visit?	☐	☐
Has the take home diary been supplied and explained?	☐	☐
Has the subject been supplied with analgesic medication for pain relief? Make sure the details of this are recorded on the Paracetamol Accountability Sheet	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐



FOSTAR STUDY

Visit 2 (0 months) - RANDOMISATION

Visit Date…… ☐☐/☐☐/☐☐☐☐
DD / MM / YYYY

KNEE X-RAY

	YES	NO
If not available at Visit 1,has an x-ray (no older than 12 months) of the study selected knee been assessed by the PI	☐	☐
Does the subject meet knee inclusion criteria	☐	☐

1. Less than Grade – 4 changes in their study selected knee
2. An osteophyte on x-ray
   And at least one of the following:

- knee age greater than 50 years
- stiffness lasting less than 30 minutes
- crepitus

STUDY SELECTED KNEE

	LEFT	RIGHT
This subject's Study Selected knee is their	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

RUN-IN FISH OIL		
	YES	NO
Was the run-in oil well tolerated? If not, describe the symptoms below: …… ……	☐	☐
Any adverse events recorded here or in take-home diary to be transcribed to Adverse Events Record		
Has the run-in oil been returned Volume of the returned bottle ……mL % of returned oil ……% (% = amount returned/amount supplied x 100)	☐	☐
Was at least 75 % of expected run-in fish oil consumption confirmed?	☐	☐
Was tolerance and compliance adequate? If no, withdraw subject If yes, continue with visit……..	☐	☐

ANALGESIC USE		
	YES	NO
Has subject withheld taking anti-inflammatory and analgesic medications prior to appointment If YES, continue with questionnaires. If NO, ask subject to withhold analgesic and inflammatory	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

medications from today and complete questionnaires at home. The questionnaires are then to be returned in pre-paid envelopes.	

QUESTIONNAIRES				
	Supplied		Completed	
	YES	NO	YES	NO
NRS pain / PGA Does the subject still meet pain inclusion criteria (≥ score of 4 on NRS pain scale) If NO, withdraw the subject. If YES, continue……..	☐	☐	☐ ☐	☐ ☐
WOMAC	☐	☐	☐	☐
AQoL I	☐	☐	☐	☐
MAPT	☐	☐	☐	☐
Diet Diet Questionnaire Barcode …….	☐	☐	☐	☐
Physical Activity (PASE)	☐	☐	☐	☐

BLOOD TESTS		
	YES	NO
Has a fasting blood sample been taken for FBC, MBA, CRP, fasting lipids (HDL, TGC, LDL)	☐	☐
Has a serum pregnancy test been taken (if subject male, tick No box)	☐	☐
Has a fasting blood sample been taken to measure serum fatty acids?	☐	☐
Has a blood sample been taken for DNA sub-study?	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

INCLUSION CRITERIA		
	YES	NO
Did the subject consume at least 75% of the expected volume of run-in fish oil	☐	☐
Did the subject record a measurement of at least 20mm on the NRS pain scale for their study selected knee	☐	☐
Does the subject still consent to taking part in the FOSTAR study	☐	☐
Have knee x-rays, no older than 12 months old been reviewed	☐	☐
Does the subject meet inclusion criteria of: 1. Less than Grade – 4 changes in their study selected knee 2. .An osteophyte on x-ray 3. At least one of the following: - knee age greater than 50 years - stiffness lasting less than 30 minutes 4. crepitus	☐	☐
A tick recorded in any of the shaded boxes above signifies that the subject is ineligible and should be excluded from entering the study		

RANDOMISATION CODE
If ALL inclusion criteria have been met, the study subject may be assigned a randomisation code**:** **R** ☐☐☐☐☐☐☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

MEDICAL CHANGES		
Has the subject been diagnosed with any **NEW** medical conditions since their last visit?		
NEW MEDICAL CONDITION	Date of Onset (DD/MM/YYYY)	Date Resolved Or √ Ongoing (DD/MM/YYYY)
		☐
		☐
		☐
If the subject is currently taking any medications for any of the above conditions, ensure that details are recorded in the **Concomitant Medications record**.		

CONCOMITANT MEDICATIONS					
Has the subject started, stopped or changed the doses of any medications since their last visit? (Ask to see all medications used)					
Brand Name	Dose (4)	Units (mg)	Route (po)	Start/Stop Dates (DD/MM/YYYY)	Ongoing
				Start…../…../…… Stop…../…/……..	☐
				Start…../…../…… Stop…../…/……	☐
				Start…../…../…… Stop…../…/……	☐
				Start…../…../…… Stop…../…/……	☐
Please remember to transfer any details here to concomitant medications page					

HOSPITALISATIONS/DAY PROCEDURES			
Has the subject been to hospital for any medical procedures since their last visit? ☐YES ☐NO			
If Yes, please provide details below			
Date Admitted DD/MM/YYYY	Date Discharged DD/MM/YYYY	Doctor's Details	Purpose

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

Total Number of Hospitalisations since last visit: …….			

KNEE OSTEOARTHRITIS HISTORY	
With regard to the pain in your **study-selected knee**;	
How long have you experienced pain in that knee?	…….years
Have you had previous surgery to this knee	YES / NO
If yes, what type of surgery?	☐ YES ☐ NO ☐ Arthroscope ☐ Meniscal Surgery ☐ Cartilage Surgery ☐ Tendon Surgery ☐ Ligament Surgery ☐ Other .....
If yes, when did you have surgery?	Date:…../…../……

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

Have you had a previous injury to **this** knee, requiring use of walking stick, frame or wheelchair? If so, what year	☐ Yes ☐ No Year: ……

JOINT OSTEOARTHRITIS HISTORY	
Over the past month have you had pain on most days in any of the following joints?	☐ Other knee. **Not** the one being investigated in this study ☐ Lower Back ☐ Neck ☐ Shoulder ☐ Hands ☐ Other (details)……. ☐ No others

EDUCATION	
What is highest level of education?	☐ Didn't finish high school ☐ Finished high school

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

	☐ Trade/Apprenticeship ☐ Certificate/Diploma ☐ Bachelor degree or higher ☐ Didn't answer

EMPLOYMENT HISTORY	
What is your current work status?	☐ Full-time employed ☐ Part-time/casual employment ☐ Unemployed ☐ Home Duties ☐ Retired ☐ Student ☐ Other Please specify ……..……...

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

What kind of work have you done for most of your life? **(Study coordinator: please code into:-**	…… ☐ Manual ☐ Office/Professional ☐ Not Applicable

STUDY FISH OIL		
	YES	NO
Has the study fish oil been supplied and explained	☐	☐
Has the dosing DVD been shown to the subject (only if necessary)	☐	☐
Has the take home diary been supplied and explained	☐	☐

PHYSICAL EXAMINATION/VITAL SIGNS	
Height (without shoes)	cms
Weight (without shoes, with clothes)	kgs
Blood Pressure (sitting, after resting for 5 minutes)	mmHG

ANALGESIC MEDICATION	
Number of Paracetamol tablets supplied at previous visit	
Number of Paracetamol tablets returned	
Number of paracetamol tablets accounted for in diary	
Difference between number of tablets recorded taken and actual number of tablets removed from package.	

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

Remember to remind Subject the importance of returning the empty foil strips. Remember to record these details in the Analgesic Medication Record

PREPARATION FOR NEXT APPOINTMENT		
	YES ☐	NO ☐
Has an appointment been made for the subjects DEXA scan Details: ……/……/……. ..……am/pm DD/MM/YYYY	☐	☐
Has an appointment been made for the subjects MRI Details: ……/……/……. ..……am/pm DD/MM/YYYY	☐	☐
Has the subject been supplied an IMVS form for fasting bloods prior to next visit	☐	☐
Has the subject been supplied with a FOSTAR fridge magnet	☐	☐
Has the subject been supplied with a FOSTAR business card	☐	☐
Has the subject been issued with a pedometer, had it's use explained and been asked to use it over a 7 day consecutive period? Please record details in Pedometer Record	☐	☐
Has the subject been issued with analgesic medication for pain relief? Please ensure all details are recorded on the Analgesic medication Form	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

FOSTAR STUDY

Visit 3 (3 months) - TREATMENT

Visit Date……

☐☐/☐☐/☐☐☐☐

DD / MM / YYYY

	ANALGESIC USE	
	YES	NO
Has subject withheld taking anti-inflammatory and analgesic medications prior to appointment If YES, continue with questionnaires. If NO, ask subject to withhold analgesic and inflammatory medications from today and complete questionnaires at home. The questionnaires are then to be returned in pre-paid envelopes.	☐	☐

	QUESTIONNAIRES			
	Supplied		Completed	
	YES	NO	YES	NO
WOMAC	☐	☐	☐	☐
AQol I	☐	☐	☐	☐
NRS pain	☐	☐	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

MEDICAL CHANGES		
Has the subject been diagnosed with any NEW medical conditions since their last visit?		
NEW MEDICAL CONDITION	Date of Onset (DD/MM/YYYY)	Date Resolved Or √ Ongoing (DD/MM/YYYY)
		☐
		☐
		☐
If the subject is currently taking any medications for any of the above procedures, ensure that details are recorded in the Concomitant Medications record.		

CONCOMITANT MEDICATIONS					
Has the subject started, stopped or changed the doses of any medications since their last visit? (Ask to see all medications used)					
Brand Name	Dose	Units	Route	Start/Stop Dates (DD/MM/YYYY)	Ongoing
				Start…../…../…… Stop…../…/……..	☐
				Start…../…../…… Stop…../…/……	☐
Please remember to transfer any details here to concomitant medications page					

ANALGESIC MEDICATION	
Number of Paracetamol tablets supplied at previous visit	
Number of Paracetamol tablets returned	
Number of paracetamol tablets accounted for in diary	
Difference between number of tablets recorded taken and actual	

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

number of tablets removed from package.	
Remember to remind Subject the importance of returning the empty foil strips. Remember to record these details in the Analgesic Medication Record	

HOSPITALISATIONS/DAY PROCEDURES			
Has the subject been to hospital for any medical procedures since their last visit? ☐YES ☐NO If Yes, please provide details below			
Date Admitted DD/MM/YYYY	Date Discharged DD/MM/YYYY	Doctor's Details	Purpose
Total Number of Hospitalisations since last Appointment: …….			

BLOOD TESTS		
	YES	NO
Has a fasting blood sample been taken to measure serum fatty acids?	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

PHYSICAL EXAMINATION/VITAL SIGNS	
Height (without shoes)	cms
Weight (without shoes, with clothes)	kgs
Blood Pressure(sitting, after resting for 5 minutes)	mmHG

STUDY FISH OIL		
	YES	NO
Has the Visit 2 fish oil been returned (inc. any empty bottles) How many mLs are remaining? ……..mL What percentage of expected was taken? ……..% (=amount actually taken/amount expected to be taken x 100) We want at least 75% compliance so if necessary, encourage subject to keep taking the fish oil on a daily basis	☐	☐
Has Visit 3 fish oil been explained and supplied	☐	☐

VISIT 2 DIARY		
	YES	NO
Has the subject's Visit 2 diary been collected and reviewed	☐	☐
Have all diary concomitant medication records been transcribed into the CRFs Concomitant Medication Section	☐	☐
Have all diary adverse event records been transcribed into the CRFs Adverse Events Section	☐	☐

PREPARATION FOR NEXT APPOINTMENT		
	YES	NO
Has an appointment been made for the subjects next appointment in	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

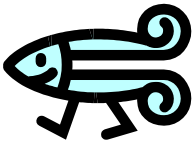
☐☐☐☐☐

3 months time Details: ……/……/……. ..……am/pm DD/MM/YYYY	
Has the subject been supplied an IMVS form for fasting bloods prior to next visit	☐ ☐
Has a Visit 3 take home diary been supplied and explained	☐ ☐
Has the pedometer issued at Visit 2 been collected and the information recorded in the Pedometer Record section	☐ ☐
Has the subject been issued with Analgesic medication to use for pain relief Please record this information on the Analgesic Medication Form	☐ ☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐



FOSTAR STUDY

Visit 4 (6 months) - TREATMENT

Visit Date…….…… ☐☐/☐☐/☐☐☐☐ DD / MM / YYYY

ANALGESIC USE		
	YES	NO
Has subject withheld taking anti-inflammatory and analgesic medications prior to appointment If YES, continue with questionnaires. If NO, ask subject to withhold analgesic and inflammatory medications from today and complete questionnaires at home. The questionnaires are then to be returned in pre-paid envelopes.	☐	☐

QUESTIONNAIRES				
	Supplied		Completed	
	YES	NO	YES	NO
WOMAC	☐	☐	☐	☐
AQol I	☐	☐	☐	☐
NRS pain	☐	☐	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

MEDICAL CHANGES		
Has the subject been diagnosed with any NEW medical conditions since their last visit?		
NEW MEDICAL CONDITION	Date of Onset (DD/MM/YYYY)	Date Resolved Or √ Ongoing (DD/MM/YYYY)
		☐
		☐
		☐
If the subject is currently taking any medications for any of the above procedures, ensure that details are recorded in the Concomitant Medications record.		

CONCOMITANT MEDICATIONS					
Has the subject started, stopped or changed the doses of any medications since their last visit? (Ask to see all medications used)					
Brand Name	Dose (4)	Units (mg)	Route (po)	Start/Stop Dates (DD/MM/YYYY)	Ongoing
				Start…../…../….. Stop…../…/……	☐
				Start…../…../…. Stop…../…/……	☐
Please remember to transfer any details here to concomitant medications page					

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

HOSPITALISATIONS/DAY PROCEDURES			
Has the subject been to hospital for any medical procedures since their last visit? ☐YES ☐NO If Yes, please provide details below			
Date Admitted DD/MM/YYYY	Date Discharged DD/MM/YYYY	Doctor's Details	Purpose
Total Number of Hospitalisations since last visit:……..			

BLOOD TESTS		
	YES	NO
Has a fasting blood sample been taken to measure serum fatty acids?	☐	☐

PHYSICAL EXAMINATION/VITAL SIGNS	
Height (without shoes)	cms

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

Weight (without shoes, with clothes)	kgs
Blood Pressure (sitting, after resting for 5 minutes)	mmHG

	STUDY FISH OIL	
	YES	NO
Has the Visit 3 fish oil been returned (inc. any empty bottles) How many mLs are remaining? ……..mL What percentage of expected was taken? ……..% (=amount actually taken/amount expected to be taken x 100) We want at least 75% compliance so if necessary, encourage subject to keep taking the fish oil on a daily basis	☐	☐
Has Visit 4 fish oil been explained and supplied	☐	☐

ANALGESIC MEDICATION	
Number of Paracetamol tablets supplied at previous visit	
Number of Paracetamol tablets returned	
Number of paracetamol tablets accounted for in diary	
Difference between number of tablets recorded taken and actual number of tablets removed from package.	
Remember to remind Subject the importance of returning the empty foil strips. Remember to record these details in the Analgesic Medication Record	

	VISIT 3 DIARY	
	YES	NO

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

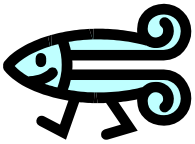
Has the subject's Visit 3 diary been collected and reviewed	☐ ☐
Have all diary concomitant medication records been transcribed into the CRFs Concomitant Medication Section	☐ ☐
Have all diary adverse event records been transcribed into the CRFs Adverse Events Section	☐ ☐

PREPARATION FOR NEXT APPOINTMENT		
	YES	NO
Has an appointment been made for the subjects next appointment in 3 months time? Details: ……/……/……. ..……am/pm DD/MM/YYYY	☐	☐
Has the subject been supplied an IMVS form for fasting bloods prior to next visit?	☐	☐
Has a Visit 4 take home diary been supplied and explained?	☐	☐
Has the subject been supplied with analgesic medication for pain relief? Please record all details on the Analgesic Medication Form	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐



FOSTAR STUDY

Visit 5 (9 months) - TREATMENT

Visit Date…… ☐☐/☐☐/☐☐☐☐ DD / MM / YYYY

ANALGESIC USE		
	YES	NO
Has subject withheld taking anti-inflammatory and analgesic medications prior to appointment If YES, continue with questionnaires. If NO, ask subject to withhold analgesic and inflammatory medications from today and complete questionnaires at home. The questionnaires are then to be returned in pre-paid envelopes.	☐	☐

QUESTIONNAIRES				
	Supplied		Completed	
	YES	NO	YES	NO
WOMAC	☐	☐	☐	☐
AQol I	☐	☐	☐	☐
NRS pain	☐	☐	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

MEDICAL CHANGES		
Has the subject been diagnosed with any NEW medical conditions since their last visit?		
NEW MEDICAL CONDITION	Date of Onset (DD/MM/YYYY)	Date Resolved Or √ Ongoing (DD/MM/YYYY)
		☐
		☐
		☐
If the subject is currently taking any medications for any of the above procedures, ensure that details are recorded in the Concomitant Medications record.		

CONCOMITANT MEDICATIONS					
Has the subject started, stopped or changed the doses of any medications since their last visit? (Ask to see all medications used)					
Brand Name	Dose (4)	Units (mg)	Route (po)	Start/Stop Dates (DD/MM/YYYY)	Ongoing
				Start…../…../…. Stop…../…./….	☐
				Start…../…../…. Stop…../…./….	☐
Please remember to transfer any details here to concomitant medications page					

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

HOSPITALISATIONS/DAY PROCEDURES			
Has the subject been to hospital for any medical procedures since their last visit? ☐YES ☐NO If Yes, please provide details below			
Date Admitted DD/MM/YYYY	Date Discharged DD/MM/YYYY	Doctor's Details	Purpose
Total Number of Hospitalisations since last Appointment: ……			

BLOOD TESTS		
	YES	NO
Has a fasting blood sample been taken to measure serum fatty acids?	☐	☐

PHYSICAL EXAMINATION/VITAL SIGNS	
Height (without shoes)	cms

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

Weight (without shoes, with clothes)	kgs
Blood Pressure (sitting, after resting for 5 minutes)	mmHG

STUDY FISH OIL		
	YES	NO
Has the Visit 4 fish oil been returned (inc. any empty bottles) How many mLs are remaining? ……..mL What percentage of expected was taken? ……..% (=amount actually taken/amount expected to be taken x 100) We want at least 75% compliance so if necessary, encourage subject to keep taking the fish oil on a daily basis	☐	☐
Has Visit 5 fish oil been explained and supplied	☐	☐

ANALGESIC MEDICATION	
Number of Paracetamol tablets supplied at previous visit	
Number of Paracetamol tablets returned	
Number of paracetamol tablets accounted for in diary	
Difference between number of tablets recorded taken and actual number of tablets removed from package.	
Remember to remind Subject the importance of returning the empty foil strips. Remember to record these details in the Analgesic Medication Record	

VISIT 4 DIARY		
	YES	NO
Has the subject's Visit 4 diary been collected and reviewed		

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:**

☐☐☐☐☐

	☐	☐
Have all diary concomitant medication records been transcribed into the CRFs Concomitant Medication Section	☐	☐
Have all diary adverse event records been transcribed into the CRFs Adverse Events Section	☐	☐

PREPARATION FOR NEXT APPOINTMENT		
	YES ☐	NO ☐
Has an appointment been made for the subjects next appointment in 3 months time Details: ……/……/……. ..……am/pm DD/MM/YYYY	☐	☐
Has the subject been supplied an IMVS form for fasting bloods prior to next visit	☐	☐
Has a Visit 5 take home diary been supplied and explained	☐	☐
Has the subject been issued with analgesic medication for pain relief Please record all details on the Analgesic Medication Form	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:** ☐☐☐☐☐

FOSTAR STUDY

Visit 6 (12 months) - TREATMENT

Visit Date……..…… ☐☐/☐☐/☐☐☐☐ DD / MM / YYYY

	ANALGESIC USE	
	YES	NO
Has subject withheld taking anti-inflammatory and analgesic medications prior to appointment If YES, continue with questionnaires. If NO, ask subject to withhold analgesic and inflammatory medications from today and complete questionnaires at home. The questionnaires are then to be returned in pre-paid envelopes.	☐	☐

	QUESTIONNAIRES			
	Supplied		Completed	
	YES	NO	YES	NO
WOMAC ☐	☐		☐	☐
AQol I ☐	☐		☐	☐
NRS pain	☐	☐	☐	☐
MAPT	☐	☐	☐	☐
Diet **Diet Barcode ……..**	☐	☐	☐	☐
Physical Activity (PASE)	☐	☐	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:** ☐☐☐☐☐

MEDICAL CHANGES		
Has the subject been diagnosed with any NEW medical conditions since their last visit?		
NEW MEDICAL CONDITION	Date of Onset (DD/MM/YYYY)	Date Resolved Or √ Ongoing (DD/MM/YYYY)
		☐
		☐
		☐
If the subject is currently taking any medications for any of the above procedures, ensure that details are recorded in the Concomitant Medications record.		

CONCOMITANT MEDICATIONS					
Has the subject started, stopped or changed the doses of any medications since their last visit? (Ask to see all medications used)					
Brand Name	Dose (4)	Units (mg)	Route (po)	Start/Stop Dates (DD/MM/YYYY)	Ongoing
				Start…../…../…… Stop…../…./……..	☐
				Start…../…../…… Stop…../…./……	☐
Please remember to transfer any details here to concomitant medications page					

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:** ☐☐☐☐☐

HOSPITALISATIONS/DAY PROCEDURES			
Has the subject been to hospital for any medical procedures since their last visit? ☐YES ☐NO If Yes, please provide details below			
Date Admitted DD/MM/YYYY	Date Discharged DD/MM/YYYY	Doctor's Details	Purpose
Total number of hospital admissions since last visit:……..			

CURRENT EMPLOYMENT	
What is your current work status?	☐Full-time employed ☐Part-time/casual employment ☐Unemployed ☐Home Duties ☐Retired ☐Student ☐Other Please specify …….....

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:** ☐☐☐☐☐

JOINT OSTEOARTHRITIS HISTORY	
Over the past month have you had pain on most days in any of the following joints?	☐ Other knee. **Not** the one being investigated in this study ☐ Lower Back ☐ Neck ☐ Shoulder ☐ Hands ☐ Other (details)……. ☐ No others

BLOOD TESTS		
	YES	NO
Has a fasting blood sample been taken to measure serum fatty acids?	☐	☐

PHYSICAL EXAMINATION/VITAL SIGNS	
Height (without shoes)	cms
Weight (without shoes, with clothes)	kgs
Blood Pressure (sitting, after resting for 5 minutes)	mmHG

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:** ☐☐☐☐☐

STUDY FISH OIL		
	YES	NO
Has the Visit 4 fish oil been returned (inc. any empty bottles) How many mLs are remaining? ……..mL What percentage of expected was taken? ……..% (=amount actually taken/amount expected to be taken x 100) We want at least 75% compliance so if necessary, encourage subject to keep taking the fish oil on a daily basis	☐	☐
Has Visit 5 fish oil been explained and supplied	☐	☐

ANALGESIC MEDICATION	
Number of Paracetamol tablets supplied at previous visit	
Number of Paracetamol tablets returned	
Number of paracetamol tablets accounted for in diary	
Difference between number of tablets recorded taken and actual number of tablets removed from package.	
Remember to remind Subject the importance of returning the empty foil strips. Remember to record these details in the Analgesic Medication Record	

VISIT 5 DIARY		
	YES	NO
Has the subject's Visit 5 diary been collected and reviewed	☐	☐
Have all diary concomitant medication records been transcribed into the CRFs Concomitant Medication Section	☐	☐
Have all diary adverse event records been transcribed into the CRFs Adverse Events Section	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:** ☐☐☐☐☐

PREPARATION FOR NEXT APPOINTMENT		
	YES ☐	NO ☐
Has an appointment been made for the subjects next appointment in 6 months time Details: ……/……/……. ..……am/pm DD/MM/YYYY	☐	☐
Has the subject been supplied an IMVS form for fasting bloods prior to next visit	☐	☐
Has a Visit 6 take home diary been supplied and explained	☐	☐
Has the subject been issued with a pedometer, had its use explained and been asked to use it for seven consecutive days. Please record details in Pedometer Record	☐	☐
Has the subject been supplied with analgesic medication for pain relief? Please ensure all details are recorded on the Analgesic Medication Form	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:** ☐☐☐☐☐

FOSTAR STUDY

Visit 7 (18 months) - TREATMENT

Visit Date…… ☐☐/☐☐/☐☐☐☐ DD / MM / YYYY

ANALGESIC USE		
	YES	NO
Has subject withheld taking anti-inflammatory and analgesic medications prior to appointment If YES, continue with questionnaires. If NO, ask subject to withhold analgesic and inflammatory medications from today and complete questionnaires at home. The questionnaires are then to be returned in pre-paid envelopes.	☐	☐

QUESTIONNAIRES				
	Supplied		Completed	
	YES	NO	YES	NO
WOMAC ☐	☐		☐	☐
AQol I ☐	☐		☐	☐
NRS pain	☐	☐	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:** ☐☐☐☐☐

MEDICAL CHANGES		
Has the subject been diagnosed with any NEW medical conditions since their last visit?		
NEW MEDICAL CONDITION	Date of Onset (DD/MM/YYYY)	Date Resolved Or √ Ongoing (DD/MM/YYYY)
		☐
		☐
		☐
If the subject is currently taking any medications for any of the above procedures, ensure that details are recorded in the Concomitant Medications record.		

CONCOMITANT MEDICATIONS					
Has the subject started, stopped or changed the doses of any medications since their last visit? (Ask to see all medications used)					
Brand Name	Dose (4)	Units (mg)	Route (po)	Start/Stop Dates (DD/MM/YYYY)	Ongoing (tick)
				Start…../…../…… Stop…../…./……..	☐
				Start…../…../…… Stop…../…./……	☐
Please remember to transfer any details here to concomitant medications page					

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:** ☐☐☐☐☐

HOSPITALISATIONS/DAY PROCEDURES			
Has the subject been to hospital for any medical procedures since their last visit? ☐YES ☐NO If Yes, please provide details below			
Date Admitted DD/MM/YYYY	Date Discharged DD/MM/YYYY	Doctor's Details	Purpose
Total number of hospitalisations since last visit:…….			

BLOOD TESTS		
	YES	NO
Has a fasting blood sample been taken to measure serum fatty acids?	☐	☐

PHYSICAL EXAMINATION/VITAL SIGNS	
Height (without shoes)	cms
Weight (without shoes, with clothes)	kgs
Blood Pressure (sitting, after resting for 5 minutes)	mmHG

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:** ☐☐☐☐☐

STUDY FISH OIL		
	YES	NO
Has the Visit 6 fish oil been returned (inc. any empty bottles) How many mLs are remaining? ……..mL What percentage of expected was taken? ……..% (=amount actually taken/amount expected to be taken x 100) We want at least 75% compliance so if necessary, encourage subject to keep taking the fish oil on a daily basis	☐	☐
Has Visit 7 fish oil been explained and supplied	☐	☐

ANALGESIC MEDICATION	
Number of Paracetamol tablets supplied at previous visit	
Number of Paracetamol tablets returned	
Number of paracetamol tablets accounted for in diary	
Difference between number of tablets recorded taken and actual number of tablets removed from package.	
Remember to remind Subject the importance of returning the empty foil strips. Remember to record these details in the Analgesic Medication Record	

VISIT 6 DIARY		
	YES	NO
Has the subject's Visit 6 diary been collected and reviewed	☐	☐
Have all diary concomitant medication records been transcribed into the CRFs Concomitant Medication Section	☐	☐
Have all diary adverse event records been transcribed into the CRFs Adverse Events Section	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:** ☐☐☐☐☐

PREPARATION FOR NEXT APPOINTMENT		
	YES ☐	NO ☐
Has an appointment been made for the subjects next appointment in 6 months time Details: ……/……/……. ..……am/pm DD/MM/YYYY	☐	☐
Has the subject been supplied an IMVS form for fasting bloods prior to next visit	☐	☐
Has a Visit 7 take home diary been supplied and explained	☐	☐
Has the pedometer that was issued to the subject at Visit 6 been returned and the details transcribed to the Pedometer record Section	☐	☐
Has the subject had a pedometer issued, had its use explained and been asked to use the pedometer over 7 consecutive days. Please record details in Pedometer Record Section of CRF	☐	☐
Has the subject been issued with analgesic medication for pain relief? Please ensure all details are recorded on the Analgesic Medication Form	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:** ☐☐☐☐☐

FOSTAR STUDY

Visit 8 (24 months) – Completion/Withdrawal

Visit Date…… ☐☐/☐☐/☐☐☐☐ DD / MM / YYYY

	ANALGESIC USE	
	YES	NO
Has subject withheld taking anti-inflammatory and analgesic medications prior to appointment If YES, continue with questionnaires. If NO, ask subject to withhold analgesic and inflammatory medications from today and complete questionnaires at home. The questionnaires are then to be returned in pre-paid envelopes.	☐	☐

	QUESTIONNAIRES			
	Supplied		Completed	
	YES	NO	YES	NO
WOMAC ☐	☐		☐	☐
AQol I	☐	☐	☐	☐
NRS pain	☐	☐	☐	☐
MAPT ☐	☐		☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:** ☐☐☐☐☐

Diet ☐ ☐ ☐ ☐ **Diet Barcode ……**	
Physical Activity (PASE) ☐ ☐	☐ ☐

MEDICAL CHANGES		
Has the subject been diagnosed with any NEW medical conditions since their last visit?		
NEW MEDICAL CONDITION	Date of Onset (DD/MM/YYYY)	Date Resolved Or √ Ongoing (DD/MM/YYYY)
		☐
		☐
		☐
If the subject is currently taking any medications for any of the above procedures, ensure that details are recorded in the Concomitant Medications record.		

CONCOMITANT MEDICATIONS					
Has the subject started, stopped or changed the doses of any medications since their last visit? (Ask to see all medications used)					
Brand Name	Dose (4)	Units (mg)	Route (po)	Start/Stop Dates (DD/MM/YYYY)	Ongoing
				Start…../…../…… Stop…../…./……..	☐
				Start…../…../…… Stop…../…./……	☐
Please remember to transfer any details here to concomitant medications page					

Site Number: ☐

Randomisation Number: ☐☐☐☐

Subject Initials: ☐☐☐

Study Selected Knee: ☐☐☐☐☐

HOSPITALISATIONS/DAY PROCEDURES			
Has the subject been to hospital for any medical procedures since their last visit? ☐YES ☐NO If Yes, please provide details below			
Date Admitted DD/MM/YYYY	Date Discharged DD/MM/YYYY	Doctor's Details	Purpose
Total Number of Hospitalisations since last visit: ……			

JOINT OSTEOARTHRITIS HISTORY	
Over the past month have you had pain on most days in any of the following joints?	☐ Other knee. **Not** the one being investigated in this study ☐ Lower Back ☐ Neck ☐ Shoulder ☐ Hands

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:** ☐☐☐☐☐

	☐ Other (details)…….. ☐ No others

CURRENT EMPLOYMENT	
What is your current work status?	☐ Full-time employed ☐ Part-time/casual employment ☐ Unemployed ☐ Home Duties ☐ Retired ☐ Student ☐ Other Please specify …….....

BLOOD TESTS		
	YES	NO
Has a fasting blood sample been taken to measure serum fatty acids?	☐	☐
Has a fasting blood sample been taken for FBC, MBA, CRP, fasting lipids (HDL, TGC, LDL)	☐	☐
Has a serum pregnancy test been taken (if subject male, tick No box)	☐	☐

PHYSICAL EXAMINATION/VITAL SIGNS	
Height (without shoes)	cms
Weight (without shoes, with clothes)	kgs
Blood Pressure (sitting, after resting for 5 minutes)	mmHG

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:** ☐☐☐☐☐

STUDY FISH OIL		
	YES	NO
Has the Visit 7 fish oil been returned (inc. all empty bottles) How many mLs are remaining? ……..mL What percentage of expected was taken? ……..% (=amount actually taken/amount expected to be taken x 100) We want at least 75% compliance so if necessary, encourage subject to keep taking the fish oil on a daily basis	☐	☐

ANALGESIC MEDICATION	
Number of Paracetamol tablets supplied at previous visit	
Number of Paracetamol tablets returned	
Number of paracetamol tablets accounted for in diary	
Difference between number of tablets recorded taken and actual number of tablets removed from package.	
Remember to remind Subject the importance of returning the empty foil strips. Remember to record these details in the Analgesic Medication Record	

VISIT 7 DIARY		
	YES	NO
Has the subject's Visit 7 diary been collected and reviewed	☐	☐
Have all diary concomitant medication records been transcribed into the CRFs Concomitant Medication Section	☐	☐
Have all diary adverse event records been transcribed into the CRFs Adverse Events Section	☐	☐

Site Number: ☐ **Randomisation Number:** ☐☐☐☐

Subject Initials: ☐☐☐ **Study Selected Knee:** ☐☐☐☐☐

FINALISING THE STUDY		
	YES	NO
Has an appointment been made for the subjects final DEXA scan on their study selected knee? Details: ……/……/……. ..……am/pm DD/MM/YYYY	☐	☐
Has an appointment been made for the subjects final MRI on their study selected knee? Details: ……/……/……. ..……am/pm DD/MM/YYYY	☐	☐
Has an appointment been made for the subjects x-ray on their study selected knee? Details: ……/……/……. ..……am/pm DD/MM/YYYY	☐	☐
Has the subject been sincerely thanked for their time, effort and cooperation during the study?	☐	☐
Has the pedometer that was issued to the subject at their last visit been returned? Please record all details in the Pedometer Record Section of the CRF	☐	☐
Has the subject's Hospital records been updated to show that they have completed/withdrawn from the study?	☐	☐
Has a letter been sent to the subject's GP to notify their Dr of their completion/withdrawal from the study?	☐	☐

Supplementary Tables and Figures

Table S1. Change in proportion of NSAID users and average daily NSAID dose in NSAID users at 12 and 24 months (compared with baseline) in participants treated with high dose or low dose fish oil.

NSAIDs	Intention to Treat			Per Protocol		
	Low Dose n=101	High Dose n=101	High Dose *vs* Low Dose	Low Dose n=80	High Dose n=65	High Dose *vs* Low Dose
NSAID Use (yes/no)	Odds Ratio relative to baseline (95% CI)		p	Odds Ratio relative to baseline (95% CI)		p
12 months	1.1 (0.7, 1.8)	1.5 (0.9, 2.4)	0.36	1.2 (0.8, 2.0)	1.5 (0.9, 2.4)	0.64
24 months	1.3 (0.8, 2.0)	1.9 (1.2, 2.9)*	0.20	1.3 (0.8, 2.1)	2.0 (1.3, 3.1)*	0.22
NSAID Dose[a]	Treatment/ baseline dose (95% CI)		p	Treatment/ baseline dose (95% CI)		p
12 months	1.2 (0.5, 2.3)	1.3 (0.4, 4.7)	0.87	1.1 (0.7, 1.9)	1.3 (0.6, 2.8)	0.74
24 months	0.8 (0.4, 2.3)	1.4 (0.4, 5.2)	0.48	1.2 (0.7, 2.0)	1.5 (0.7, 3.2)	0.50

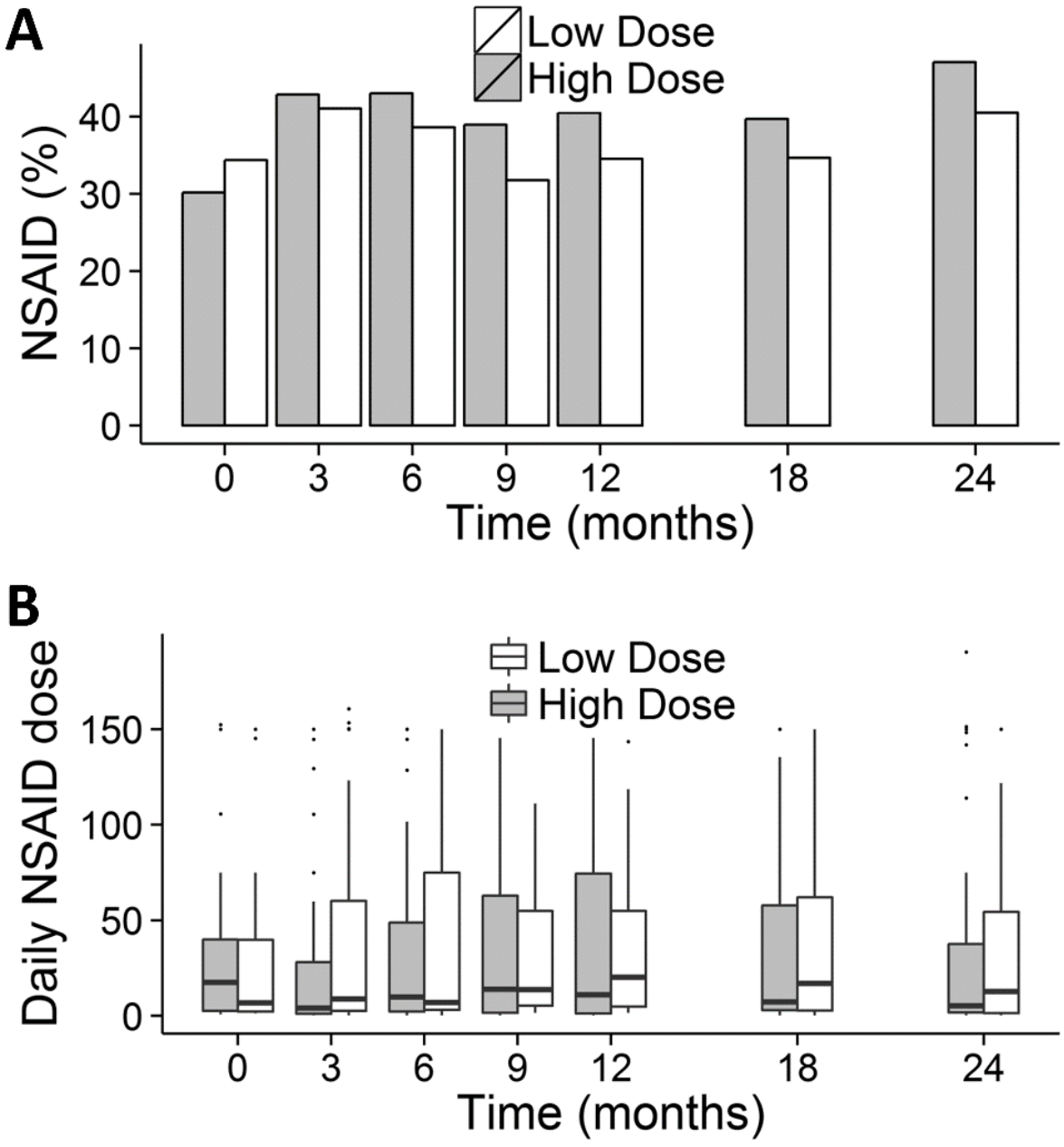
[a]Average daily NSAID diclofenac equivalence dose. p values are for the comparison between treatment groups (High Dose – Low Dose). Asterisks reflect the statistical significance of the change from baseline (* $p<0.05$) for a given treatment group.

Table S2. Changes weight at 12 and 24 months compared with baseline in groups treated with high dose or low dose fish oil.

Weight gain (Kg, from baseline)	Intention to Treat			Per Protocol		
	Low Dose n=101	High Dose n=101	High Dose *vs* Low Dose	Low Dose n=80	High Dose n=65	High Dose *vs* Low Dose
	Mean Change (se)		p	Mean Change (se)		p
12 months	0.7 (0.3)*	1.8 (0.4)*	0.026	0.8 (0.4)*	2.0 (0.4)*	0.026
24 months	0.3 (0.4)	1.8 (0.5)*	0.023	0.5 (0.5)	2.0 (0.5)*	0.042
Average[a]	0.6 (0.3)*	1.7 (0.3)*	0.004	0.7 (0.3)*	1.9 (0.3)*	0.007

[a]Weight gain averaged over all treatment visits. p values are for the comparison between treatment groups (High dose – Low Dose). Asterisks reflect the statistical significance of the change from baseline (* $p<0.05$) for a given treatment group.

Figure S1. NSAID use in participants treated with either high dose or low dose fish oil during the course of the study (A) Bar chart showing the proportion of NSAID users (yes/no) at each visit (B) Boxplot of the average daily NSAID dose (diclofenac equivalent) in NSAID users at each visit.



Annals of the Rheumatic Diseases
The EULAR Journal
BMJ
ard.bmj.com

High-dose fish oil is no better than low-dose for osteoarthritis of the knee

Standard fish oil capsules offer relief for people with painful osteoarthritis.

INTRODUCTION

Osteoarthritis is a condition that makes a person's joints stiff and painful. It is caused by thinning of the cartilage within the joints, which allows the bones to rub against each other. It is the most common of all the different types of arthritis, increasing as people get older. Fish oil may be useful in osteoarthritis to help reduce inflammation and stop the loss of cartilage. Many people buy and use low-dose fish oil capsules without prescription. These are often a daily dose of 1 mL of fish oil.

WHAT DID THE AUTHORS HOPE TO FIND?

The authors wanted to see whether a higher dose of fish oil would have a better effect than the low doses found in most commercially available capsules, and if this would reduce pain and stiffness in the affected knees.

WHO WAS STUDIED?

The study included 202 adults with painful osteoarthritis in one or both knees. All patients were over the age of 40 and had no long-term history of taking high-dose fish oil.

HOW WAS THE STUDY CONDUCTED?

This was a randomised, double-blind trial, which means that patients were assigned by chance to one of two treatment groups to receive either a high or low dose of fish oil every day for 2 years. Using chance in this way means that the groups will be similar and will allow the variable or treatment under investigation to be compared objectively. During the treatment neither patients nor their doctors knew which group they were in. Each group was given 15 mL of liquid oil each day. In the high-dose fish oil group, all of the 15 mL was fish oil. The low-dose fish oil group also got 15 mL of liquid oil each day, but only 2 mL was fish oil and the rest was plant oil. Patients in both groups were also allowed to use paracetamol for pain relief.

WHAT WERE THE MAIN FINDINGS OF THE STUDY?

The study found that there was no advantage to taking a very high dose of fish oil over taking low dose fish oil in terms of pain, joint stiffness or the amount of cartilage in the joint. In fact, after 1 year the people taking low-dose fish oil had less painful knees than the people taking high-dose oil.

ARE THESE FINDINGS NEW?

Yes, there has not been a trial before that has studied high- and low-dose fish oil in osteoarthritis, despite many patients using these oils.

HOW RELIABLE ARE THE FINDINGS?

There are some limitations which may affect how reliable the findings are. For example, the study did not use a placebo (dummy drug).

WHAT DO THE AUTHORS PLAN ON DOING WITH THIS INFORMATION?

It is possible that the plant oil that was mixed with the fish oil may have had an effect, and the authors are interested in looking at this in a future study.

WHAT DOES THIS MEAN FOR ME?

If you have osteoarthritis (but not rheumatoid arthritis or other types of inflammatory arthritis), you may find that taking fish oil capsules will help your pain and stiffness. There is no need to take very high doses of fish oil. A simple low dose of two normal capsules every day could give you relief and help to protect your joints. If you are taking any other medicines you should talk to your doctor before adding any dietary supplements.

Disclaimer: This is a summary of a scientific article written by a medical professional ("the Original Article"). The Summary is written to assist non medically trained readers to understand general points of the Original Article. It is supplied "as is" without any warranty. You should note that the Original Article (and Summary)

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