FULL TITLE OF THE STUDY

Omega–3 fatty acids for the prophylaxis of acute attacks of gout on initiating urate lowering treatment – feasibility study for a randomised controlled trial

SHORT STUDY TITLE / ACRONYM

Switch off gout attack study (SOGAS)

This protocol has regard for the HRA guidance and order of content

VERSION 5.2 – 1st April 2020

FULL / LONG TITLE OF THE STUDY Omega–3 fatty acids for the prophylaxis of acute attacks of gout on initiating urate lowering treatment – feasibility study for a randomized controlled trial

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PROTOCOL VERSION NUMBER AND DATE Version 5.2, 1st April 2020

RESEARCH REFERENCE NUMBERS

Trial Registry Number and date:	
IRAS Number:	240464
SPONSORS Number:	17RH007
FUNDERS Number:	Arthritis Research UK Project grant number 21506
EUDRA CT Number (date):	2018-000963-99 (3rd March 2018)
ISRCTN Number (date):	To be applied for

SPONSOR Nottingham University Hospitals NHS Trust

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature:

.....

Date:

...../...../.....

Name (please print):

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Position:

.....

Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

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Statistician

Signature: Date

…… ...../...../.....

Name (please print):

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Position:

……

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STUDY SUMMARY

Study Title	Omega–3 fatty acids for the prophylaxis of acute attacks of gout on initiating urate lowering treatment – feasibility study for a randomized controlled trial
Internal ref. no. (or short title)	Switch off gout attack study (SOG-AS)
Clinical Phase	Phase 2
Study Design	Randomised placebo controlled feasibility study
Study Participants	Age ≥ 18 years Known to have gout Willing to initiate or increase dose of urate lowering treatment ≥1 gout flare in previous 12 months
Planned Size of Sample	60
Randomisation	1:1
Treatment duration	28 weeks
Follow up duration	28 weeks for efficacy assessment, 32 weeks for safety assessment
Planned Study Period	18 months
Objectives	The objectives of this feasibility study are to assess: [1] dropout rate,

	[2] recruitment rate, [3] quality of data collection during acute gout, [4] choose primary outcome for the main randomized controlled trial, [5] calculate sample size for the phase-III randomized controlled trial, [6] explore if there is a preliminary signal that omega-3 fatty acids can prevent flares of gout, [7] to decide number of GP surgeries needed in the main trial, and [8] assess compliance with study drugs.
Investigational Medicinal Product	omega-3 fatty acid ethyl ester soft-gel capsules 1 gm, containing 840 mg of eicosapentaenoic acid and docosahexaenoic acid
Formulation, Dose, Route of Administration	Soft-gel capsules, 1 gm x 4/day, oral administration
Placebo	Olive oil 1 gm
Formulation, Dose, Route of Administration	Soft-gel capsules, 1 gm x 4/day, oral administration

FUNDING AND SUPPORT IN KIND

FUNDER(S)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Arthritis Research UK, Copeman House, St Mary's Court, St Mary's Gate, Chesterfield S41 7TD. Contact Mr Pete Morley, Email: p.morley@arthritisresearchuk.org	Study funder (Research Council UK member)
Nottingham City CCG, 1 Standard Court, Park Row, Nottingham NG1 6GN Contact: Ms Rachel Illingworth Email: rachel.illingworth1@nhs.net	Excess Treatment Cost for omega-3 fatty acids
Nottinghamshire County CCG, Duncan MacMillan House, Porchester Road, Nottingham NG3 6AA Contact: Mrs Shirley Mitchell Email: shirley.mitchell@nottshc.nhs.uk	Excess Treatment Cost for omega-3 fatty acids
Clinical Research Network East Midlands, Nottingham Health Science Partners, Queens Medical Centre Campus, Derby Road Nottingham NG7 2UH Contact: Mr Andrew Skeggs, Email: Andrew.skeggs@nihr.ac.uk	Screening of practice lists to identify people with gout, and metrologist time for consent

ROLE OF STUDY SPONSOR AND FUNDER

The study sponsor will monitor the study conduct against nationally agreed standards.

The study sponsor and study funder will have no role in the design, data analysis, interpretation, manuscript writing and dissemination of the results. The sponsor and funders do not control the final decision regarding any aspects of this study.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

Trial management group: will comprise of the Chief Investigator (AA), study statistician (WZ), trial manager (JD), data manager and the Research Metrologist. The role of this group will be to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to, and take appropriate action to safeguard participants and the quality of the trial itself.

Data monitoring committee (DMC): As this is a feasibility study using drugs that have been available and licenced for considerable number of years, we do not propose to convene a DMC with Sponsors' approval.

Trial steering committee (TSC): will comprise of members who are independent of the investigators, their employing organisations, study funders and sponsors. It will provide overall supervision of the trial. It will monitor trial progress and conduct and advice on scientific credibility. The TSC will ultimately carry the responsibility for deciding if a trial needs to be stopped on grounds of safety or efficacy. The members of TSC are:

Dr Nicholas Townsend, Associate Professor of Public Health, University of Bath (TSC chair and statistical expertise),

Prof George Nuki, Professor of Rheumatology, The University of Edinburgh (TSC member and clinical rheumatology expertise),

Professor Terence O'Neill, Professor of Rheumatology, University of Manchester (TSC member and clinical rheumatology expertise).

Protocol contributors

The protocol was developed by the principal investigator in collaboration with the co-investigators. The study funders and sponsors do not have any role in study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. The final decisions about these aspects of the study are not controlled by the sponsors or funders of the study. The sponsor will monitor the conduct of the study.

The study was discussed at an Arthritis Research UK Pain Centre patient and public involvement meeting in Nottingham. The PPI group fed back on the need for such a study, method of recruitment, and site and frequency of study visits.

KEY WORDS: Gout, flares, omega-3 fatty acid, urate lowering treatment

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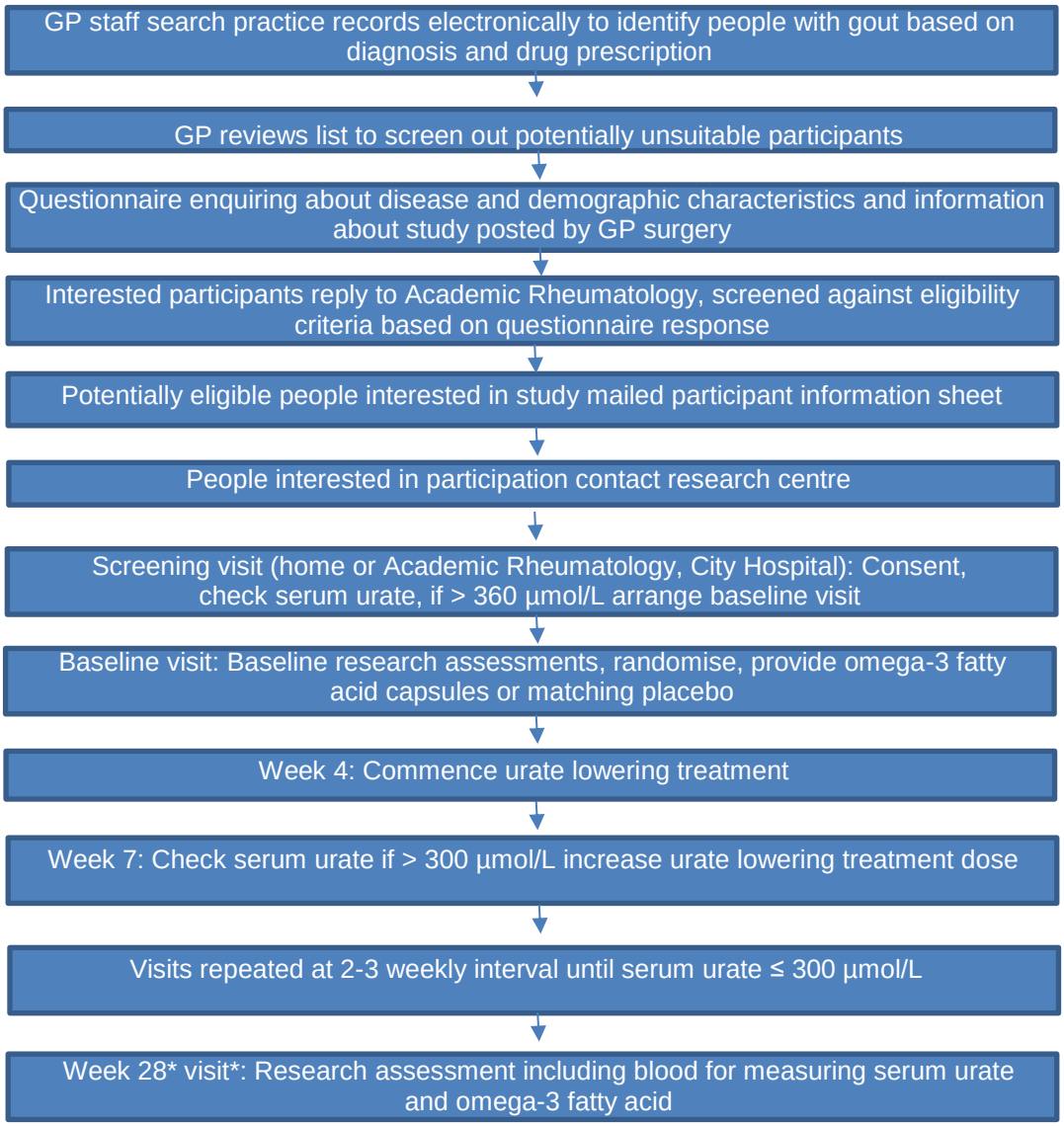
STUDY FLOW CHART



*** Week 32: final assessment for safety since last IMP/placebo dosing (phone call).**

LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form

ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial

REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File

STUDY PROTOCOL Omega–3 fatty acids for the prophylaxis of acute attacks of gout on initiating urate lowering treatment – feasibility study for a randomized controlled trial

1. BACKGROUND

Gout is the commonest inflammatory arthritis and affects 2.5% of the UK population (1), with higher prevalence reported from the USA (2) and in both European and Maori populations in New Zealand (3). However, despite an increase in its prevalence worldwide, the treatment of gout remains suboptimal (1-3). For instance, less than 40% patients with gout in the UK are on urate lowering treatment, and of these three in five are either non-adherent or only partially adherent to it (1, 4). The occurrence of frequent flares of gout (also termed acute gout attack) soon after starting on urate lowering treatment is one of the several factors reducing long-term adherence and persistence on it (5-8). Because initiation of urate lowering treatment can precipitate flares of gout (9, 10), the British Society for Rheumatology (BSR) (11), European League Against Rheumatism (EULAR) (12) and American College of Rheumatology (ACR) (13, 14) recommend that urate lowering treatment be initiated at a low dose, and with co-prescription of other drugs for a period of six months to potentially a few years depending on the clinical phenotype of gout in order to prevent recurrent flares of gout (11, 13, 14). This approach also provides immediate relief to the patients by preventing the flares.

Unfortunately, none of the drugs recommended in the prophylaxis of acute gout i.e. colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), or corticosteroids can be used safely for such long periods of time without running the risk of serious side effects. Colchicine, the first line drug for this indication has a narrow therapeutic index with multiple drug interactions and potentially serious side effects (15). It is cardiotoxic, contraindicated in renal impairment, and frequently causes diarrhoea (15-18). For instance, in a randomised placebo controlled trial designed to examine the efficacy of colchicine in preventing flares of gout, 38% patients on colchicine 0.6 mg twice a day for 6 months reported diarrhoea compared to 4.5% in the placebo group (16). In another 6 month randomized

controlled trial, over half of all patients on colchicine developed diarrhoea (17). In yet another four week RCT, 39.2% patients required colchicine dose reduction due to gastro-intestinal side effects (18). Similarly, in 2 randomised controlled trials of febuxostat for treatment of gout, patients on colchicine 0.6 mg once a day for 8 weeks were significantly more likely to have diarrhoea (8.4%) than those on naproxen (2.7%) (19, 20). The lower prevalence of diarrhoea in the Febuxostat trials compared to the previous trials is likely to be due to the fact that patients known to be intolerant to colchicine were excluded from this study. Other drugs that are recommended for prophylaxis of flares of gout e.g. non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids promote polypharmacy e.g. co-prescription of proton pump inhibitor, calcium and Vitamin D, bisphosphonates etc., and can be even more dangerous than colchicine when used regularly for several months. NSAIDs can cause gastro-intestinal, renal, and cardiovascular side effects, and their regular long-term use is discouraged (21, 22). Their use is contra-indicated in renal insufficiency (CKD 4 or greater) and in those with congestive cardiac failure. Cox-II inhibitors have a lower risk of gastro-intestinal upset but may be contraindicated in patients with gout due to co-existent ischaemic heart disease, or risk factors for cardiovascular diseases (21). Regular oral corticosteroid use is similarly fraught with complications, and may result in significant side effects e.g. weight gain, insulin resistance, hypertension, osteoporosis etc., if given for the recommended period of 6 months or longer. Recently, canakinumab and rilonacept were shown to be effective in preventing flares of gout (23). However, their use is limited by high cost and by the potential for serious side effects including infection. Thus, there is need for a safe and effective drug that can be used to prevent acute gout. .

2. RATIONALE

There is a need for a safe and effective drug that can be used to prevent acute gout. Such a drug will especially benefit patients with gout who continue to have flares for several years after starting on urate lowering treatment, possibly due to an unduly high urate load e.g. tophaceous gout.

Anti-inflammatory effects of omega-3 fatty acids

Results of several studies suggest that omega-3 fatty acids (eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3)) will provide effective prophylaxis against flares of gout. Omega-3 fatty acids inhibit several key processes by which monosodium urate (MSU) crystals cause inflammation. They block the activation of toll like receptors (TLRs), assembly of NALP-3 inflammasome, reduce prostaglandin synthesis (by replacing arachidonic acid as a substrate for cyclooxygenase and lipoxygenase enzymes) and inhibit neutrophil chemotaxis (25-27).

In an in vitro study using human bone marrow derived macrophages, pre-treatment with DHA or EPA inhibited caspase-1 cleavage and interleukin (IL)-1β secretion triggered by MSU crystals and other agonists, and this effect was absent when metabolites of DHA or EPA like protectin, resolvin, aspirin-triggered resolvin, and aspirin-acetylated COX-2 were used (26). Similarly, mice fed on 100mg/kg DHA twice a week for six weeks had significantly lower insulin resistance and lower levels of IL-1β, IL-18, and tumour necrosis factor (TNF)-α in response to a high fat diet than mice fed on a high fat diet alone, and this effect was absent in NLRP-/- mice suggesting that the effect of DHA occurred due to the inhibition of NALP-3 inflammasome (26). DHA and EPA also inhibit the NALP-3 inflammasome by their effects on G-protein coupled receptor (GPR) 40, and GPR 120 (26, 28).

The NALP-3 inflammasome plays a central role in inflammation due to MSU crystals, and knock out mice do not develop an acute inflammatory response after an intra-peritoneal injection of MSU crystals (29, 30). Omega-3 fatty acids do not inhibit NLRC4 or AIM2 inflammasome which are not activated by MSU crystals (26). Omega 3 fatty acid DHA also blocks the activation of TLR 2, by preventing its heterodimerization with TLR1 and reduces the expression of pro-IL-1β which is subsequently cleaved to IL-1β by caspase (27). Apart from this, omega-3 fatty acids inhibit neutrophil chemotaxis which plays a central role in the propagation of acute gouty arthritis, and this effect is apparent at a dose of 1.3 gm/day, with no further inhibition of neutrophil chemotaxis at higher doses (31). DHA and EPA

also activate GPR 120 and PPAR γ which in turn directly inhibits nucleating factor kB (NF-kB) (32). EPA is metabolized into both prostaglandin E3 (which is less inflammatory than prostaglandin E2) and leukotriene B5, which suppresses leukotriene B4 production by neutrophils and interleukin generation by macrophages (25). These effects are of particular relevance to the prophylaxis of acute gouty arthritis as MSU crystals cause acute inflammation by activating TLRs, which in turn activate the NALP-3 inflammasome (33) and NF-kB (34).

In keeping with these findings, mice fed on a diet rich in omega-3 fatty acids (menhaden fish oil EPA and DHA in a 3:2 ratio) for 30 days developed significantly less inflammation after subcutaneous injection of MSU crystals than those fed on a standard chow diet or on a diet rich in safflower oil (25, 35). There was a significant reduction in the pouch exudate volume, and protein and prostaglandin content in mice fed on menhaden fish oil (25, 35). The pouch exudate cell concentration, lysozyme activity, and MSU crystal phagocytosis were also reduced in mice fed on a diet rich in linolenic acid which can be converted to omega 3 fatty acids (25). However, only a small proportion of linolenic acid is converted to EPA and DHA, and supplementation with α-linolenic acid not effective in suppressing inflammatory cytokines in human beings (32,36, 37). For example, flaxseed oil (rich in α-linolenic acid) at a dose of 14 gm/day increased mononuclear EPA only by a modest amount (0.4%) and suppressed TNF-α and IL-1β by only 20% - 30% (36). Similarly, increased α-linolenic acid intake resulted in a significantly smaller reduction in pro-inflammatory arachidonic acid concentration than supplementation with either DHA or EPA alone (37).

Omega-3 fatty acids inhibit cytokine secretion in human beings. For example, omega-3 fatty acids (≥2.4 gm/day for 4 weeks or more) reduce IL-1β, IL-6, C reactive protein (CRP), and TNF-α concentration (36, 38).

In a healthy volunteer study, supplementation with EPA (1.6 gm/day) and DHA (1.1 gm/day) for four weeks reduced the basal TNF-α, and IL-1β concentration by 70%, and 80% respectively (36).

Additionally, the prostaglandin E and thromboxane B levels were halved (36). The mononuclear cell EPA concentration increased by 1.6% - 1.7% and the lipopolysaccharide stimulated TNF-α and IL-1β production was reduced by over 70% (34). Higher dose of EPA (>1.6 gm/day) did not have any additional anti-inflammatory effect (36, 39, 40). This may be as higher oral doses of omega-3 fatty acids do not result in a corresponding increase in their plasma concentration. In a dose finding study, 3 gm/day of DHA and EPA (in a ratio of 2:3) for 6 weeks increased plasma phospholipid optimally with only a small increase on doubling the dose to 6 gm/day (41).

The proportion of DHA and EPA in plasma phospholipid increased from 2.79% at baseline to 6.20%, 8.26% and 9.78% after supplementation with 1.5 gm, 3.0 gm and 6.0 gm omega 3 fatty acids per day (41). The anti-inflammatory effects of omega-3 fatty acids assessed by endotoxin stimulated IL-1, and TN-α secretion become apparent in 4 weeks and increase over time (39, 40). The amount of omega-3 fatty acids in usual diet is unlikely to have such a strong anti-inflammatory effect (42).

In summary, these findings suggest that anti-inflammatory doses of omega-3 fatty acids DHA and EPA has a biological effect in human beings, and as they inactivate TLRs, NALP-3 inflammasome activity, neutrophil chemotaxis, and reduce prostaglandin levels, it is likely that they will have a specific effect in preventing flares of gout. However, omega-3 fatty acids cannot be used to treat episodes of acute gout as their anti-inflammatory effects takes four weeks to be established, and for this reason their effects on prophylaxis of acute gout may also be only apparent after four weeks (39, 40).

Preliminary data regarding effects of omega 3 fatty acids on gout flare frequency

Omega-3 fatty acid levels were measured in the serum of 112 community dwelling men with primary gout who also self-reported their flare frequency in the preceding 12 months. People with plasma omega-3 fatty acid level >0.40 mmol/L were less likely to report >2 flares of gout in the preceding 12 months independent of age, disease duration, BMI, tophi, and current serum uric acid (aOR (95%CI) 0.27 (0.09-0.76), p=0.014) (24).

Apart from this, baseline data from an ongoing Arthritis Research UK funded clinical trial of nurse led package of care for gout (n=516) showed that the 27 patients on omega-3 fatty acid supplements at the time of the baseline visit reported fewer flares of gout in the preceding 12 months than those not taking these supplements (mean (standard deviation (S.D.) number of gout flares 3.07 (2.62) vs. 4.17 (5.44)), p=0.06 (equal variances not assumed) (Unpublished data Prof M. Doherty). We feel that the preliminary data is sufficient to justify a feasibility study.

Steady state plasma concentration

The steady state plasma concentration of DHA and EPA is achieved in between 1 and 4 weeks' time depending on the daily dose. For example, DHA 1gm/day results in steady state plasma concentration in 4 weeks, with EPA taking a shorter time (37); while EPA (3.48 gm/day) and DHA (2.2 gm/day) results in the steady state plasma concentration being achieved in 1-2 weeks, and 3 weeks respectively (43).

Beneficial effects of omega-3 fatty acids in other autoimmune inflammatory arthritis and cardiovascular diseases

Omega-3 fatty acids also improve symptoms in autoimmune inflammatory arthritis like rheumatoid arthritis (RA). Although individual trials report conflicting results, systematic review and meta-analysis of the published randomised controlled trials suggests that supplementation with omega-3 fatty acids reduces pain, stiffness and requirement of NSAIDs (Standardized Mean Difference: −0.40; 95% CI: −0.72 to − 0.08,) (44). Higher dose of omega-3 fatty acids (i.e., 2.7 g/day of EPA and DHA) results in a greater reduction in the number of painful joints, duration of morning stiffness, and NSAID consumption (SMD −0.52, 95% CI −0.92 to −0.12) in RA (44, 45). Of greater significance, in a recently reported trial, patients with recent-onset RA who were on omega-3 fatty acids were more likely to respond to initial disease modifying anti-rheumatic drugs and achieve remission than those on placebo (46).

Apart from this, patients on long term omega-3 fatty acids get as much anti-inflammatory effect from paracetamol as from full dose NSAIDs. For example, a single 1 gram dose of paracetamol was as effective in suppressing prostaglandin E2 and thromboxane B2 synthesis as the maximum recommended therapeutic dose of NSAIDs in early RA patients on long term omega-3 fatty acid supplementation (47). Omega-3 fatty acids also improve cardiovascular outcomes (48). In the GISSI - P trial, there was a 30% reduction in the risk of cardiovascular death in those on 1 gm omega-3 fatty acids/day (49). Thus, treatment with omega-3 fatty acids will also improve cardiovascular outcomes in gout patients (50).

Omega 3 fatty acids have effects comparable to weak NSAIDs in inflammatory arthritis. However, unlike gout, inflammation in inflammatory arthritis is not mediated by NALP-3 inflammasome. The NALP-3 inflammasome is specifically blocked by omega 3 fatty acids. Our preliminary data (24) and other evidence detailed in the application suggest that they will have an effect on preventing gout flares. Even if the effect of omega 3 fatty acids is similar to that of NSAIDs, it should still prevent gout flares, just like azapropanone (weak NSAID) and low dose naproxen (19, 51, 52).

Nutritional source of omega 3 fatty acids

Human beings lack the desaturase enzyme required to synthesize omega-3 fatty acids from omega-6 fatty acids (53). However, EPA and DHA can be synthesized endogenously from the 18-carbon omega-3 fatty acid α-linolenic acid (α-LNA; l8:3n-3) which is abundant in nuts and vegetable oils (53). The conversion of α-linolenic acid to EPA or DHA is variable. It is inversely related to the dietary intake of linoleic acid, and varies according to sex. Less than 10% and less than 30% α-LNA acid is converted to EPA or DHA in men and women respectively (34). As the average dietary intake of EPA, DHA and α-LNA is 0.11, 0.16 and 1.23 gm/day in community dwelling adults in the UK (42), the overall dietary intake of omega-3 fatty acids including that converted from α-LNA can be estimated to be 0.4

gm/day in men, and 0.6 gm/day in women (42). This is not high enough to have an anti-inflammatory effect.

It can be expensive and monotonous to increase the dietary omega-3 fatty acid intake to achieve an anti-inflammatory effect as this would involve consuming one serving of oily fish daily. A single lean fish meal (e.g. one serving of cod) provides about 0.2 to 0.3 g of omega-3 fatty acids, while a single oily fish meal (e.g.one serving of salmon or mackerel) provides 1.5 to 3.0 g of omega-3 fatty acids (30). However, regular intake of oily fish in patients with gout may result in worsening hyperuricaemia as salmon and mackerel have high total purine content (119.3 and 139.3 mg/100gm), and most of this is present as hypoxanthine which is directly metabolised to uric acid (54), and sea-food intake has been associated with risk of incident gout.

Other dietary supplements that prevent flares of gout

In a crossover study at least two servings (approximately one cup) of cherry in the preceding two day period reduced the risk of acute gout by 35% (55). In another study, supplementation with skimmed milk powder enriched with anti-inflammatory glycomacropeptide and G600 milk fat extract for three months reduced the frequency of gout flares (56).

Thus, further studies are required to establish if treatment with omega-3 fatty acids is able to prevent episodes of acute gout. This is also supported by patient groups who identify research into the role played by diet and dietary supplements in gout to be the top two research priorities in this field (57).

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

We hypothesize that omega-3 fatty acids will prevent flares of gout in patients commenced on urate lowering treatment. The overall aim of this feasibility study is to establish the metrics for conducting a multicentre randomised controlled trial to definitively test whether omega-3 fatty acids can prevent flares of gout in patients starting on urate lowering treatment.

3.1 Objectives

The specific objectives are:

a) To assess the dropout rate (primary outcome)

b) To assess the recruitment rate,

c) To assess the quality of data collection during acute gout,

d) To choose primary outcome for the main randomized controlled trial (RCT),

e) To calculate sample size for the phase-III RCT,

f) To determine whether there is any signal for an effect of omega-3 fatty acids in preventing flares of gout,

g) To decide number of GP surgeries needed in the main trial, and

h) To assess compliance with study drugs.

3.2 Outcome

Primary outcome measure: Proportion of randomized patients completing the trial

Secondary outcome measures:

- proportion of patients approached by the GP with information about the study and requested to return the reply slip to the study team, who actually

i. reply to Academic Rheumatology, University of Nottingham
ii. meet the eligibility criteria
iii. agree for screening visit
iv. meet the eligibility criteria after checking serum uric acid and other blood tests
v. participate in the trial

- completeness of outcome data for each flare of gout
- number of gout flares between weeks 5 and 28*
- severity of flares of gout
- duration of flares of gout
- proportion of patients who withdraw from the study due to side effects related to omega-3 fatty acids
- number of gout patients not on ULT at each GP surgery – as this will allow us to decide the number of GP surgeries in the main trial
- compliance with study drugs

*Gout flares between weeks 1 and 4 will be disregarded as the anti-inflammatory effects of omega-3 fatty acids take up to 4 weeks to manifest. However, this data will be collected so that it can be analysed in the proposed study.

4. TRIAL DESIGN

Study design: single centre randomised double blind placebo controlled parallel arm feasibility study

Study population: patients with gout eligible to start on urate lowering treatment according to the British Society for Rheumatology Guidelines

Randomisation: 1:1

Randomisation time: Randomisation will occur once the results of screening blood tests performed at the screening visit are reviewed and eligibility and ongoing consent is confirmed.

Study groups:

Group A: placebo capsules (4 gm olive oil/day)*

Group B: omega-3 fatty acid capsules (4 gm/day; containing 3.36 gm of omega-3 fatty acids)

After four weeks participants in both arms will be commenced on uptitrated urate lowering treatment as recommended by the British Society for Rheumatology Guidelines

Olive oil is filled in the placebo as it not known to have an immunosuppressive effect on gouty inflammation.

Final efficacy visit: week 28

Final safety visit (telephone call): week 32

Primary endpoint: week 28 visit of last patient

Secondary endpoints: complete data analysis

Data will be collected in paper case report forms and stored on secured servers that are backed up on a daily basis. Data analysis will be performed using STATA version 15. Staff entering study data into the CRF and into the database will be trained in data entry. Trial manager will perform data verification

on a monthly basis on 10% of the data entered and any discrepant data will be checked against the source data. Data will be archived by the Nottingham University Hospitals NHS Trust as per SOP RES-028 for at least 25 years. Sponsor's data protection procedures will apply. Violations of eligibility criteria will be deemed to be a serious GCP breach and reported as such. Other deviations from protocol will be assessed and classified by the CI. Major protocol deviations (violations) from protocol will lead to exclusion of a participant from the per protocol set.

The database will be locked at the end of the study after cross validation of 5% of entered data against source data has occurred successfully, and all biologically implausible data are cross checked against source data.

5. STUDY SETTING

Number of sites: One

Recruitment activity:

[1] Primary care, with GP surgeries acting as participant identification sites.

[2] Posters and adverts publicly posted in hospital clinics, community pharmacies and in newspaper or on social media.

[3] Secondary care, with hospitals acting as participant identification sites

[4] People with gout who have participated in previous research at Academic Rheumatology, City Hospital Nottingham, and have indicated willingness for future research contact.

Study setting for recruitment: Primary care (GP surgeries to act as participant identification sites)

Setting for study visits: Secondary care.

Rarely, participants who cannot attend hospital visits will be seen at their own homes. Data collection, blood collection and prescription will occur in secondary care.

6. ELIGIBILITY CRITERIA

Inclusion criteria

(a) GP/physician diagnosed gout

(b) Meets the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) classification criteria for gout

(c) Willing to commence or increase dose of urate lowering treatment

(d) Serum uric acid ≥ 360 µmol/L at the screening visit

(e) Age ≥ 18 years at the screening visit

(f) Able to give informed consent

(g) No change in the average weekly dose of analgesics for at least 4 weeks prior to screening visit

(h) Be able to adhere to the study visit schedule and other protocol requirements

(i) Subjects able to communicate well with the investigator or designee, to understand and comply with the requirements of the study and to understand and sign the written informed consent

(j) At least one gout flare in the previous 12 months

Exclusion criteria

a) Other defined inflammatory arthritis e.g. reactive arthritis, rheumatoid arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme's disease, or plaque psoriasis

b) Other autoimmune inflammatory conditions like moderate/severe asthma or inflammatory bowel disease requiring corticosteroids or immune suppressing treatments

c) Active solid organ cancer

d) Dementia

e) Serious co-morbidities preventing prescription of treatment

f) On regular daily NSAIDs, or prednisolone, or colchicine and unable to discontinue them

g) On long-term anticoagulation: Because of the mild increase in bleeding time with 4 gm/day omega-3 fatty acids, there is a potential interaction with warfarin and an increased possibility of haemorrhage in patients at high risk because of severe trauma, surgery, etc. Patients receiving anticoagulant therapy will therefore be excluded.

h) Oral, intra-muscular, intra-arterial, or intra-venous corticosteroids during the last 1 month

i) Known allergy or hypersensitivity to omega-3 fatty acids, fish, gelatine, olive oil, and soya

j) Pregnant or planning to become pregnant during treatment period,

k) Breastfeeding or planning to breastfeed during treatment period,

l) Use of any investigational (unlicensed) drug within 3 month prior to screening or within 5 half-lives of the investigational agent, whichever is longer

m) Evidence of serious uncontrolled concomitant medical condition, including cardiovascular, nervous system, pulmonary, renal, hepatic, endocrine, gastro-intestinal disease or epilepsy, which in the opinion of the investigator makes them unsuitable for the study

n) Significant haematological or biochemical abnormality

Haemoglobin	<85 g/L
WCC	<3.5 x 10^9/L
Neutrophils	<1.5 x 10^9/L
Platelets	<100 x 10^9/L
ALT	>1.5 times upper limit of normal
Creatinine	>2 times upper limit of normal

Potential participants deemed ineligible at the screening will be allowed a second screening visit if the ineligibility status is temporary e.g. recent corticosteroid use.

o) Participants on nutritional omega-3 fatty acid supplements will be permitted to participate in the study provided they discontinue the omega-3 fatty acid supplements at randomisation.

p) Unable to take beef products for any reason

7. TRIAL PROCEDURE

7.1 Recruitment

7.1.1 Patient identification

Participants will be recruited from among all community dwelling people with gout registered with a GP surgery in the East Midlands.

Recruitment organised via a questionnaire sent from the GP practices to their patients with gout.

- Practice staff at GP surgeries in East Midlands (CRN East Midlands) will generate a list of gout patients by electronic medical record search using Read codes for gout diagnosis, previous prescription of colchicine, or previous prescription of urate lowering treatment
- This will be reviewed by a GP to identify patients unsuitable to be approached for a research study, e.g. dementia, terminal illness etc.
- Suitable patients will be mailed a letter informing them about the study along with a brief questionnaire.
- This will inquire about number of gout flares in the previous 12 months and about willingness to participate in the study.
- Patients who are interested in participating in this study will be requested to return their reply slip directly to Academic Rheumatology, University of Nottingham.
- People considered appropriate from their questionnaire response will be contacted by phone to discuss the study, and be sent a patient information leaflet and an invitation to participate in the RCT.

- People mailed a participant information sheet will be contacted by research team members after 2 weeks in case of non-response to clarify any queries they may have.
- Information on practice size, total number of patients with gout in each GP surgery, number of patients unsuitable for contact, number currently on urate lowering treatment, and the total number of participants sent an invitation letter will be collected from each GP surgery.
- A reminder letter will be sent to the non-responders from the GP surgeries, asking about their willingness to participate in the study. A copy of the questionnaire will also be included in this pack.

Recruitment via a poster or advert

- People with Gout in Nottinghamshire will be able to approach the study team via a poster seen in hospital clinics, outpatient clinics, pharmacies or an advert seen in the newspaper or on social media.
- When the potential participants have contacted the team, they will be given the questionnaire and participant information sheet, and will be advised to return the questionnaire to the research team if interested in study participation.

Recruitment via hospitals:

People with gout seen in Nottingham University Hospitals will be informed about the study and if interested in participating will be given a PIS, initial questionnaire and freepost envelope to return the completed questionnaire to the research team. Any such contact will be made by the patients' usual clinical care team.

Recruitment via Academic Rheumatology: People that have previously participated in gout trials at Academic Rheumatology, University of Nottingham and have consented to being contact for future research will be invited to take part. An invitation letter, a PIS explaining why they have been invited and an initial questionnaire will be posted out to them.

7.1.2 Screening visit:

If the patient is willing to participate, a screening visit will be arranged at the participants' home or Academic Rheumatology, at which consent will be obtained and 10ml blood collected for measuring full blood count, liver function tests, renal function tests, and serum uric acid. Eligibility will only be confirmed once serum uric acid results are reviewed and noted to be ≥ 360 µmol/L. Costs for public transport, car travel mileage and hospital parking costs will be reimbursed. Women of childbearing potential (defined as having menstrual periods, peri-menopausal or within 12 months of cessation of menstrual periods) will undergo a blood pregnancy test within two weeks prior to first dosing of the IMP or placebo. As gout is extremely rare in premenopausal women, we anticipate that a serum pregnancy test (beta-HCG levels) will be requested only occasionally in this study.

Feasibility of recruitment: 33 of the 153 GP surgeries in Nottinghamshire and Nottingham City CCG are currently participating in gout intervention trials (ARUK Nottingham gout treatment trial phase 2, last recruited 2013 (25 GP surgeries) and in the febuxostat versus allopurinol streamlined trial (14 GP surgeries)). Eight GP surgeries contributed to both studies. There is a pool of >120 GP surgeries from where we can recruit participants. We recruited 9 patients from each GP surgery for a recently completed RCT. Assuming recruitment of 3-4 participants per surgery we need 15-20 of the local GP surgeries participating to recruit 60 participants.

A previous study in Nottingham recruited participants from general practice in a similar fashion without difficulty, and 116 gout participants were recruited in six months (66). The currently running ARUK funded gout trial in Nottingham recruited 93 participants within 4 months using this approach alone. We anticipate a lower response rate as this is a CTIMP. We expect recruitment will take place over a 6 month period (months 4-10).

7.2 Consent

All participants will provide written informed consent. The Consent Form will be signed and dated by the participant before they enter the trial. The Investigator will explain the details of the trial and

provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation. Written consent will be obtained on the day of screening visit, before screening blood tests are collected.

Informed consent will be collected from each participant before they undergo any interventions (including physical examination) related to the study. One copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient's hospital records.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

7.2.1 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies

It will be explained to the participants that they have the option of giving 10 ml blood at each of the baseline and final efficacy visits (20 ml in total), and that this will be used for future research including genetic research. It will be explained that this is entirely voluntary, and that they can opt out of this option. The collection of these additional blood samples will not require any extra venepunctures, and these are timed to coincide with other study related blood tests.

7.3 The randomisation scheme

Patients will be randomized into two arms using randomly permuted block sizes. Stratification will be used to evenly balance participants with contra-indications to allopurinol prescription at randomisation. This is as participants intolerant to allopurinol will be commenced on febuxostat which has a greater risk of precipitating flares than slow dose escalation of allopurinol.

7.3.1 Method of implementing the allocation sequence

Treatment allocation will be concealed from the investigator, patients and the blinded assessor for the full duration of the trial. Those who are un-blinded (e.g. Clinical Trials Pharmacy) will not have any contact with study participants. Study drugs will be dispensed by the Clinical Trials Pharmacy in the order of the randomisation schedule.

7.4 Blinding

Those administering the interventions, assessing the outcomes, and conducting the data analysis will be blinded to group assignment.

7.5 Unblinding

Unblinding of the study participant will only occur after the data analysis is completed. If a study participants' clinical care requires knowledge of whether they are on IMP or placebo, the responsible clinician in charge of patients' care and treatment can contact the Nottingham University Hospitals Clinical Trials pharmacy (Monday to Friday 9am to 5pm) requesting to know this information. Out of hours unblinding service will be available via the on call pharmacy service. Unblinded participants will be allowed to continue in the study and provide data.

7.6 Baseline data

Baseline visit: The study participant will see a Research Metrologist at the baseline visit. We anticipate this visit to last for 60-90 minutes.

At this visit, the Metrologist will confirm willingness to continue on the study and then enquire about the age at first gout flare, number of flares in previous 12 months, collect information about the current medications, confirm data on co-morbidity collected in the screening questionnaire, assess previous gout treatment, conduct a targeted musculoskeletal assessment, and measure height, weight, and blood pressure.

The participant will complete the gout activity questionnaire and the short-form 36 version 2 quality of life questionnaire. Approximately 5 ml blood will be collected for measuring omega-3 fatty acids, and, if

the participant agrees, approximately 10ml blood will be collected and stored for future research including genetic research.

The participants will be given a flare diary to collect information about the severity of flares of gout. The participants will be randomised prescribed and dispensed a 14 week supply of IMP or matching placebo. The participants will also be given a supply of urate lowering treatment (typically allopurinol 100 mg/day or febuxostat 80 mg/day if allopurinol is contra-indicated or has previously caused side-effects) not to be started until the 5th week and a rescue pack containing prednisolone tablets 30 mg/day and omeprazole capsule 20 mg/day for 1 week to be taken during a gout flare. In case corticosteroids are contraindicated, the rescue pack will contain tablet Naproxen 500 mg twice a day, and omeprazole 20 mg/day for 1 week with. The participants will be specifically asked not to start urate lowering treatment until day 29. They will be contacted by phone, or text 2-3 days prior to day 29 as a reminder.

7.7 Trial Assessment

Dose up-titration visit: After confirming continuing consent, information on the number of flares of gout since last visit, changes in medication, any side effects, will be collected. Bloods will be collected for measuring serum uric acid (upto 5 ml) every 2-3 weeks until Serum Uric Acid below ≤300 µmol/l. A bedside portable uric acid meter will be used to measure the serum uric acid, and a sample will be sent to the clinical pathology laboratories at Nottingham University Hospitals if the serum uric acid is ≤300 µmol/l to document reaching treatment target. Any completed gout flare diary will be collected. Once the results of serum uric acid are available, the dose of urate lowering treatment will be increased, and the next dose up-titration visit will be arranged. Rescue packs of prednisolone or Naproxen will be replaced. At the week 14 visit, participants will be given a fresh supply of IMP or matching placebo for 14 weeks, and any unused medicines will be collected. We anticipate the dose-up titration visit to last for up to 30 minutes. Telephone appointments will be substituted during the restrictions on research visits placed in the COVID-19 crisis as face-to-face researchappointments are

not allowed. We will accept serum urate <360 micromol/L as an acceptable treatment-target during this period. However, face-to-face appointments will be restarted once this advisory is lifted and provided the participant is still in the study. Any IMP/placebo or any study drugs will be posted to the participants as required.

End of study visit: The study participant will see a Research Metrologist. We anticipate this visit to last for 60 minutes. At this visit, the nurse will enquire about the number of flares since previous study visit, update information about the current medications, confirm data on co-morbidity conduct a targeted musculoskeletal assessment, and measure height, weight, and blood pressure. The participant will also complete the gout activity questionnaire and the short-form 36 version 2 quality of life questionnaire. All flare diaries will be collected, and, any unused IMP, placebo will be collected. Information about side-effects will also be collected. Blood will be collected for measuring serum uric acid and omega-3 fatty acids (upto 5 ml each), and, if the participant agrees, approximately 8ml blood will be collected and stored for future research including genetic research. Participants who discontinue IMP/Placebo and/or ULT will still be invited for end of study visit. During the restrictions on research visits due to the COVID-19 crisis, telephone appointments will be used to collect information on number of flares, medications, and to ask participants which intervention arm they believed they were in Participants will be given the option to complete the gout activity questionnaire and short-form 26 version 2 quality of life questionnaire as an online questionnaire (created in Microsoft Forms), or via a postal questionnaire. Participants who select the online option will be a sent a link to the questionnaire via email. Height, weight and blood pressure will not be recorded, and blood samples will not be taken. Face-to-face appointments will be restarted once the advisory on face-to-face research appointments is lifted and provided the participant is still in the study.

7.8 Long-term follow-up assessment

We do not propose any long-term follow-up assessment in this study.

7.9 Withdrawal criteria

Participants who express a desire to withdraw from the study will be allowed to withdraw. Reasons for this will be documented in the CRF.

Other reasons for withdrawal from the study include:

(a) Physician decision due to side-effects

(b) Physician decision due to safety reasons e.g. participant develops a medical contraindication to continued prescription of IMP or placebo, and the aforementioned participant is in the IMP or placebo arm respectively.

(c) Self-report of overdose with an intention to self-harm.

Poor tolerability in itself e.g. unable to tolerate the full dose of the study medicine, and poor compliance with regular daily dosing will not form part of the withdrawal criteria as this is a feasibility study. Participants will be allowed to continue in the study on the lowest tolerated dose of IMP or placebo.

Participants who withdraw or are withdrawn from the study treatments, but are willing to continue with trial assessments e.g. week 14 and week 28 research visits will be allowed to do so.

7.10 Storage and analysis of samples

The blood samples collected as part of the study will be sent to analysis at the clinical pathology laboratories at the Nottingham University Hospitals NHS Trust. The additional blood samples collected in the study will be stored in Academic Rheumatology, City Hospital Nottingham.

7.11 End of Trial

Last safety assessment visit (via a telephone call) of the last participant will be defined as the end of the trial.

7.12 Assessment and management of risk

Participants in this study will be commenced on licenced urate lowering treatments and omega-3 fatty acids or matching olive oil filled placebo capsules. Participants will be made aware of common and serious side effects, and will be requested to contact the Research Metrologist if they experience any side effects. The Research Metrologist will liaise with the Chief Investigator and advise the patient accordingly. Both omega-3 fatty acid capsules and urate lowering treatments carry a very low risk of serious side effects. Common side-effects of Allopurinol include rashes, and feeling of sickness or gastro-intestinal disorders (BNF). Allopurinol induced side-effects will be managed as per BNF. Allopurinol can rarely cause Stevens Johnson syndrome or DRESS. This will be avoided by discontinuing allopurinol in those with moderate to severe rashes, and not challenging again.

8 TRIAL MEDICATION

8.1 Name and description of investigational medicinal product(s)

Generic name of IMP: Commercially available unmarked pharmaceutical grade gelatine coated soft-gel capsules with 840 mg omega-3 fatty acid ethyl esters in each 1 gm capsule (DHA : EPA 380 : 460), with Marketing Authorisation for use as a pharmaceutical agent in the UK or EU will be used in the study. The study medicine is an unmarked oblong translucent capsule containing pale yellow oil.

Strength: 1 gm capsules containing 840 mg ethyl esters of EPA and DHA.

Dosage form: soft-gel capsules

Product Licence holder: Generic omega-3 fatty acid ethyl esters supplier with marketing authorisation for pharmaceutical use in the EU.

Placebo: Matching soft-gel placebo capsules containing 1 gm olive oil will be manufactured by Catalent.

8.2 Legal status of the drug

The drug is licensed for use in the UK or other countries for hypercholesterolemia and prophylaxis of myocardial infarction.

8.3 Summary of Product Characteristics (SmPC)

The Summary of Product Characteristics (SmPC) for omega-3 fatty acid ethyl esters will be the reference safety data for the study.

This can be accessed from https://www.medicines.org.uk/emc/product/1706

8.4 Drug storage and supply

The IMP will be sourced by the Nottingham University Hospitals Clinical Trials Pharmacy via usual NHS supply chain. The IMP is not being manufactured specifically for use in this trial. IMP is supplied in white HDPE bottles. Catalent will supply the placebo in bulk. They will be stored and accounted for in Nottingham University Hospitals clinical Trials Pharmacy. The Nottingham University Hospitals Clinical Trials Pharmacy will supply the IMP and placebo upon receipt of a trial specific prescription signed by the PI or a prescriber delegated by the PI to prescribed study IMPs. The IMP and placebo can be stored at room temperature, and, must be consumed within 100 days of opening the bottle, which will be the date of dispensing. Unused IMP and placebo can be returned to the Nottingham University Hospitals Clinical Trials Pharmacy for destruction as per their SOP.

8.5 Preparation and labelling of Investigational Medicinal Product

The Nottingham University Hospitals Clinical Trials Pharmacy will repack the active IMP into a new HDPE bottle, and package the placebo in matching HDPE bottles. IMPs will be labelled with the approved study label. Preparation and labelling of the investigational medicinal products will be completed in accordance with the exemption from the need for an MIA (IMP) (Regulation 37 of SI2004/1031 of the Clinical Trials Directive 2001/20/EC).

8.6 Dosage schedules

Route: Oral

Frequency of administration: twice a day

Timing of each dose: with breakfast and with super

Maximum allowed each time a dose is taken: 2 capsules

Maximum duration of treatment of a subject: 28 weeks.

8.7 Dosage modifications

The dose of IMP or placebo can be reduced if the study participant develops an intolerance to the dose under investigation. They will be requested to reduce the dose to 2 capsules/ day in the first instance. After 3-5 days, they will be recommended to increase the dose to 3 capsules/day. If the study participant cannot tolerate 2 capsules/day, they will be allowed to reduce the dose to 1 capsule/day. The dose of study drugs will not be varied depending upon any laboratory results.

8.8 Known drug reactions and interaction with other therapies

Omega-3 fatty acids increase the prothrombin time and can increase the effect of anti-coagulants.

8.9 Concomitant medication

As omega-3 fatty acids can prolong prothrombin time, participants in the study should not be commenced on warfarin or any other anti-coagulant. If a study participant needs to commence on anticoagulation, then, they will be unblinded, and if on omega-3 fatty acids, this will be discontinued. Short course(s) of NSAIDs or colchicine (upto a maximum of 10 days at a time) can be prescribed to treat gout flares or other acutely painful conditions.

8.10 Trial restrictions

There are no contraindications whilst on the active phase of the trial including dietary requirements/restrictions. Women of childbearing potential (defined as having menstrual periods, peri-menopausal or within 12 months of cessation of menstrual periods) are required to use adequate contraception for the duration of the trial and for 28 days after the completion of the trial. This includes:

- Intrauterine Device (IUD)
- Hormonal based contraception (pill, contraceptive injection etc.)
- Double Barrier contraception (condom and occlusive cap e.g. diaphragm or cervical cap with spermicide)
- True abstinence

There is no need to adopt contraception for male participants.

8.11 Assessment of compliance

Returned capsule count of the IMP or placebo will be used to monitor compliance at week 14, and week 28. This will be recorded in the CRF. As this is a feasibility study, participants who are able to take fewer than 4 capsules/day will continue in the study, as, one of the study objectives is to assess compliance with study drugs. Compliance will be reported to the sponsor at study end. Participants will be advised to take the IMP or placebo capsules with food to increase compliance. Due to the theoretical possibility of the IMP and placebo being slightly different in appearance, returned pill count at week 14 will be done by the trial coordinator, an individual who does not conduct the other research assessment visits.

8.12 Name and description of each Non-Investigational Medicinal Product (NIMP)

All participants in the study will be commenced on urate lowering treatment as per the national British Society for Rheumatology recommendations. They will be commenced on Allopurinol as the first line urate lowering treatment. If this is contra-indicated, or causes side-effects, participants will be commenced on febuxostat as recommended in the NICE technology appraisal number 164. Participants who are able to tolerate allopurinol or febuxostat, but are unable to achieve serum uric acid < 300 micromol/L at the maximum licensed dose will be commenced on Benzbromarone. These medicines are recommended for treating gout in the UK and represent standard of care. For participants already on urate lowering treatment at the time of trial entry, but with serum urate > 360 µmol/L, the dose of urate lowering treatment will be increased or alternative urate lowering treatment will be prescribed as needed. People developing gout flares will be treated with courses of oral prednisolone, or NSAIDs as per patient and physician preference.

9. SAFETY REPORTING

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

	The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product
Expected Serious Adverse Events/Reactions	Nil

9.2 Operational definitions for s(AE)s or s(AR)

Known side effects of omega-3 fatty acids as listed in the section 4.8 of the Summary of Product Characteristics (https://www.medicines.org.uk/emc/product/1706) will be documented in the CRFs but will not be classed as s(AE) or s(AR) and will not be reported to the sponsor. All other side-effects will be reported.

Reference safety information: information on the safety of omega-3 fatty acids is obtained from the Summary of the Product characteristic (https://www.medicines.org.uk/emc/product/1706). All other s(AE)and s(AR) will be reported to the sponsor according to their SOPs.

Similarly, treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition, e.g. pre-planned hip replacement operation which does not lead to further complications, any admission to hospital or other institution for general care where there was no deterioration in condition, and treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious as given above and not resulting in hospital admission will not be classed as s(AE) or s(AR).

Routinely breaking the blind in double blind trials could compromise the integrity of the trial. Breaking the blind will only take place where information about the participant's trial treatment is clearly necessary for the appropriate medical management of the participant. In all cases the Investigator would evaluate the causality and expectedness of SAEs as though the participant was receiving the active medication.

9.3 Recording and reporting of SAEs AND SUSARs

The period of time over which AEs, ARs, SAEs, SARs and SUSARs must be recorded and reported is:

- For SAEs – consent
- For ARs / SARs and SUSARs – from 1st IMP dose.

As omega-3 fatty acid capsules take 28 days to have an anti-inflammatory effect, any SAEs will be monitored for 28 days after last treatment dose. If the CI becomes aware of any SARs or SUSARs after the active monitoring period end, he will still inform the sponsor.

In all cases SAEs and SARs will be reported to the Sponsor, unless they are known side effects of omega-3 fatty acids.

All **SAEs** occurring from the time of **written informed consent** until 28 days post cessation of trial treatment must be recorded on the appropriate Form and faxed to the Sponsor **within 24 hours** of the research staff becoming aware of the event. Once all resulting queries have been resolved, the Sponsor will request the original form should also be posted to the Sponsor and a copy to be retained on site.

For each **SAEs** the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken

- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All SAEs assigned by the CI or delegate as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The Sponsor will inform the MHRA, the REC and the Sponsor of SUSARs within the required expedited reporting timescales.

All **SUSARs** occurring from the time of **start of trial treatment** until 28 days post cessation of trial treatment must be recorded on the relevant form and faxed to the Sponsor **within 24 hours** of the research staff becoming aware of the event. Once all resulting queries have been resolved, the Sponsor will request the original form. The original form should be posted to the Sponsor and a copy to be retained on site.

For each **SUSARs** the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome

- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

Sponsor Contact Details for SAEs:

I. Email (RDSAE@nuh.nhs.uk)

II. Hand delivered not mailed (R&I, NHSP, C Floor, South Block, QMC)

III. Telephone (0115 9709049) if written report not immediately possible

9.4 Responsibilities

Principal Investigator (PI):

Checking for AEs and ARs when participants attend for treatment/follow-up.

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality and expectedness [in Phase III and late Phase II CTIMPs] using the Reference Safety Information approved for the trial.
3. Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness [in Phase I and early Phase II CTIMPs] using the Reference Safety Information approved for the trial.

4. Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the Sponsor (with the exceptions as outlined earlier), within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
5. Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.
6. Immediate review of all SUSARs.
7. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
8. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
9. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor:

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the Trial Steering Committee (TSC) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.

6. The unblinding of a SAE for the purpose of expedited SUSAR reporting [For double blind trials only].
7. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the sponsor regarding safety issues.

Data Monitoring Committee (DMC):

Given the feasibility nature of this study, and low-risk profile of omega-3 fatty acids we will not convene a DMC. Additionally, the safety profile of omega-3 fatty acids is well known and this medicine has been licenced for several years for indications other than gout.

9.5 Notification of deaths

Only deaths that are assessed to be caused by the IMP will be reported to the sponsor. This report will be immediate.

9.6 Pregnancy reporting

People who are pregnant, breastfeeding, or women planning a family will be ineligible for inclusion in the study. All pregnancies within the trial (either the trial participant or the participant's partner) will be reported to the Chief Investigator and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. Any woman who becomes pregnant during the study will be referred to the

Nottingham University Hospital feto-maternal unit and study drugs will be discontinued. They will have access to the usual NHS care. If the outcome meets the serious criteria, this would be considered an SAE.

If a woman becomes pregnant during the study, then, study drugs will be discontinued and she will be referred to the feto-maternal clinic.

9.7 Overdose

Information about any overdose will be placed in the deviation log, and will be reported to the study sponsor. It will be recorded in the CRFs. Overdoses can be observed from patient comment. Participants who self-report overdose with an intention to self-harm will be withdrawn from the study. Given the feasibility nature of the study, we will not exclude participants with overdose from the analysis. If an SAE is associated with the overdose, the overdose will be fully described in the SAE report form

9.8 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

9.9 The type and duration of the follow-up of subjects after adverse events.

Usual NHS care and treatment proportionate to the severity of AE and AR will be available to the study participants. The GPs of study participants will be informed of the study end. The AEs and ARs for the next 28 days after study end (last dose of IMP for that participant) will be recorded and reported. Any SUSAR related to the IMP will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

9.10 Development safety update reports

The CI will provide (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and Sponsor. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

The main outcome of this study is dropout rates. A sample size of 60 will be able to estimate a dropout rate of 20% or higher to within a 95% confidence interval of +/- 10%.

The other purpose of this study is to calculate the sample size of the main trial, and to get a signal of efficacy of omega-3 fatty acids. Such a study does not require a formal sample size calculation, but the sample size for a pilot trial can be justified based on published rules of thumb and expected effect size. Several rules of thumb exist and suggest that a two arm pilot trial should have between 24 and 70 participants to allow calculation of the sample size of a definitive trial (58-61). Others recommend that a pilot randomized controlled trial should have 10, 14 and 24 participants in each arm if the treatment is expected to have an effect size of 0.8, 0.5, and 0.2 respectively, using the 80% CI approach in order to accurately estimate the sample size of the main trial (61). However, the ES of omega 3 fatty acids for preventing flares of gout is not known. Thus, we propose to include 60 participants (allowing for a c. 20% drop out rate) in this study to allow us to estimate the SDp with a reasonable degree of certainty, even if the effect size is 0.2 (61).

10.2 Planned recruitment rate

We aim to recruit 10 participants into the study each month.

10.3 Statistical analysis plan

10.3.1 Summary of baseline data and flow of patients

Mean (SD) age, body mass index, baseline serum uric acid, gout disease duration, serum creatinine, and n (%) female, with tophi will be used to assess the suitability of randomisation.

10.3.2 Primary outcome analysis

N (%) will be used to assess drop-out rate.

10.3.3 Secondary outcome analysis

Mean (SD) and n (%) will be used to assess secondary outcomes. Mean difference in number of flares between the two arms, and pooled SD will be used to estimate the effect size of the intervention.

10.4 Subgroup analyses

As this is a feasibility study, we do not intend to perform subgroup analysis.

10.5 Adjusted analysis

As this is a feasibility study, we do not intend to perform adjusted analyses.

10.6 Interim analysis and criteria for the premature termination of the trial

As the main purpose of this study is to determine the metrics of an adequately powered definitive trial we will not perform any interim analysis. This is also given the fact that omega-3 fatty acids are safe, low-risk, and do not carry risk of serious adverse events.

10.7 Subject population

As this is a feasibility study, with feasibility outcomes, data for all randomised population will be analysed. When estimating a signal for efficacy of the drug, an intention to treat analysis will be performed.

10.8 Procedure(s) to account for missing data

As this is a feasibility study, with quality of data as an outcome measure, we will not impute for missing data.

10.9 Other statistical considerations.

All deviations from previously agreed statistical analysis plan will be reported as post-hoc analysis.

10.10 Economic evaluation

Economic evaluation will not be undertaken in this feasibility study.

10.11 Criteria for terminating the trial

Given the feasibility nature of the study, we do not propose to terminate the trial prematurely unless the study sponsor or TSC decides so for patient concern.

10.12 Procedures for reporting protocol deviation

Protocol deviations will be reported to the CI who will inform the sponsor of any major protocol deviations.

11 DATA HANDLING

11.1 Data collection tools and source document identification

Data will be entered directly into a paper case report form (CRF), and the CRF would be considered a source document. Data in the CRF include standardised questionnaires e.g. gout activity questionnaire, short form 36 version 2, and self-reported questions about disease and demographic characteristics. We will maximise completeness of data by telephoning subjects who provide incomplete data. As this is a single site study, the CI will keep records of all participating patients (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages.

11.2 Data handling and record keeping

The data will be entered into a database that is validated for use in CTIMPs. Data validity will be checked by cross-validation against the source data, and performed by the trial coordinator. 10% of all entered data will be checked for validity. The anonymised data will be entered on the Redpill database, a validated database that is approved for use in CTIMPs. This is provided by Sealed Envelope, and, is web based, with daily backup of data. Source data will be kept securely in a locked cabinet in a locked room. Data anonymization will be done by the Research Metrologist, and a paper copy of the anonymization schedule will be stored securely in a locked cabinet in a locked room. Paper CRFs will be available if the web-based server breaks down. The Research Metrologist will be responsible for data entry and the trial coordinator will be responsible for checking data quality. Data analysis will be performed by the study statistician. Anonymised data and biological samples collected in this study may be transferred to other sites either inside or outside of the EEA for research purposes. Consent will be explicitly sought from the study participants regarding this. Any transfer of data or biological samples to other sites either inside or outside of the EEA will require a material transfer agreement between the Study sponsor and the receiving institution.

If anonymised data are to be transmitted outside of the EEA, they will be transferred in password protected files. The password will be sent separately from password protected files containing the anonymised data.

11.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

11.4 Archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. All source data (CRF) and consent forms will be archived by the sponsor. All essential documents will be archived for 25 years and the trial database will be archived for 25 years. Destruction of essential documents will require authorisation from the Sponsor.

12 MONITORING, AUDIT & INSPECTION

A Trial Monitoring Plan will be developed and agreed by the Sponsor, Trial Management Group (TMG) and TSC. The sponsor will adopt a risk-based approach to monitoring the conduct of the study..

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review& reports

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), Health Research Authority and the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department. Should a protocol amendment be required, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the Sponsor, REC HRA and MHRA. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the Sponsor, MHRA, HRA and REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed as soon as possible.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the UK policy framework for health and social care research (7 Nov 2017)

An annual progress report (APR) will be submitted by the Chief investigator to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

The Chief Investigator will notify the REC of the end of the study

If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC. All correspondence with the REC will be retained.

13.2 Peer review

This study has previously been reviewed by the Arthritis Research UK OA and Crystals Clinical Study Group, six independent expert international peer reviewers and the Arthritis Research UK Clinical Studies research subcommittee as part of a competitive research grants process.

13.3 Public and Patient Involvement

This research proposal was reviewed and supported by the Arthritis Research UK Pain Centre PPI group in Nottingham. The methods of recruitment, randomisation, burden of study visits etc. were discussed and felt to be appropriate by the PPI group.

13.4 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA, and the protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

13.5 Protocol compliance

Protocol deviations, non-compliances, or breaches will be documented on the relevant forms and reported to the CI and Sponsor immediately. If deviations from the protocol which are found to frequently recur are not acceptable, these will require immediate action and potentially be classified as a serious breach.

13.6 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

a. the safety or physical or mental integrity of the subjects of the trial; or
b. the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase, and the sponsor will notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or
(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

13.7 Data protection and patient confidentiality

All trial staff and investigators will endeavour to protect the rights of the trial’s participants to privacy and informed consent, and will adhere to the General Data Protection Regulation 2018.

All investigators and study site staff will comply with the requirements of the General Data Protection Regulation 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Regulation’s core principles.

The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above).

All de-identified study data will be stored on a secure dedicated web server. Computer held data including the trial database will be held securely and password protected. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method). Minimum number of individuals will have access to the database for quality control, audit and analysis. Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

Each participant in the study will be given a unique participant ID comprising of unrelated sequence of characters. Data and the code linking it to individual participants will be stored in separate locations using encrypted digital files within password protected folders and storage media.

Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Only de-identified data will be transmitted to sponsors and co-investigators. In compliance with the ICH/GCP guidelines, the CI will maintain all records and documents regarding the conduct of the study. These will be retained for at least 25 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The CI will be the data custodian. The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the Nottingham University Hospital NHS Trust. This archive shall include all trial databases and associated meta-data encryption codes.

13.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

None of the study investigators have any conflicts of interest with regard to this study.

13.9 Indemnity

As Nottingham University Hospitals NHS Trust is the sponsor for this study, NHS indemnity applies. NHS bodies are legally liable for the negligent acts and omissions of their employees. Non-negligent harm is not covered by the NHS indemnity scheme. The sponsor agrees to indemnify for harm to participants arising from the management, design, and conduct of the research. The Nottingham University Hospitals NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

13.10 Amendments

The CI will approach the sponsor to discuss any amendments to the protocol. It will be the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC. If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor will submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice, informing the HRA of the amendment. Site R&D departments will also need to be provided with the information on the amendment in order to assess their -0 their level of review will be dictated by the category as assessed by the REC or HRA (A, B or C). All amendments to the protocol will be made by the CI with sponsor approval. The substantive changes to the protocol will be notified to the R&D department in writing at the earliest possible time. Amendment history will be tracked with version and date control to identify the most recent protocol.

Non-substantial amendments will also be notified to the HRA as well as the relevant R&D departments of participating sites to assess whether the amendment affects the continued capacity for that site. Any

substantive changes will be communicated to relevant stakeholders (e.g., REC, trial registries, R&D, regulatory agencies) via usual methods e.g. IRAS submission, email, updates on website.

13.11 Post trial care

All patients in the study will be commenced on urate lowering treatment. This is standard treatment for gout and will be prescribed by the participants' GP after the end of the study.

In this study we will evaluate whether Omega-3 fatty acids can provide prophylaxis against flares of gout. The British gout treatment guidelines recommend such prophylaxis only for 6 months. Thus, the participants' GP will not be requested to continue prescribing this drug after study end.

13.12 Access to the final trial dataset

The final locked dataset will be accessible to the trial coordinator and the study statistician (WZ). The study statistician will perform the data analysis. After initial data analysis, the dataset will be available to the chief investigator. A copy of the dataset will be archived by the sponsor.

14 DISSEMINIATION POLICY

14.1 Dissemination policy

The Consort Guidelines and checklist will be reviewed prior to generating any publications for the trial to ensure they meet the standards required for submission to high quality peer reviewed journals are met. The data arising from the trial will be owned by the sponsor. On completion of the trial, the data will be analysed and tabulated and a Final Study Report prepared. It can be accessed by contacting the chief-investigator or the study sponsor. No participating investigator will have rights to publish the trial data without consent of the CI. There are no time limits or review requirements on the publications. Arthritis Research UK will be acknowledged as the study funders in all publications, however, they do not have review and publication rights of the data from the trial. Given the feasibility nature of the study, we will not notify any trial participants of the results. However, a lay summary of the results will be

available from the CI on request, once the results are published. The trial protocol, full study report, anonymised participant level dataset, and statistical code for generating the results will be made publicly available in clinicaltrials.gov after study start for full protocol, and within one year of study end for full study report and anonymised participant level datasets.

14.2 Authorship eligibility guidelines and any intended use of professional writers

The International Committee of Medical Journal Editors authorship criteria will be used to decide on authorship on the final study report. We do not intend to use professional writers.

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APPENDICIES

Appendix 1- Required documentation

Postal questionnaire for recruitment

Telephone checklist

Screening visit

Participant information sheet

Consent form

Case Report Form: baseline, follow-up, and study end visits

Gout flare diary

Ad hoc telephone call

GP letter with patients consent: start of study, treatment change, end of study

Appendix 2 – Schedule of Procedures

	1	2	3	4	5	6	7	8	9	10	11	12	13
	Screening	Baseline	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Final efficacy visit	Final safety visit[2]
Week	**1**	**1**	**5**	**7**	**10**	**12**	**14**	**17**	**20**	**22**	**25**	**28**	
Informed Consent	X												
Inclusion / Exclusion	X												
Research questionnaire including SF36, GAQ, tophus count		X										X	
Blood collection	X	X		X[1]	X[1]	X[1]	X	X[1]	X[1]	X[1]	X[1]	X	
Randomise		X											
Start IMP or placebo		X					X						
Unused IMP or placebo return							X					X	
ULT start/dose change			X	X	X	X	X	X	X	X	X		
Assess side-effects			X	X	X	X	X	X	X	X	X	X	X[2]

[1] Only if serum urate > 300 µmol/L, [2]telephone call.

Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee.