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[Intervention Protocol]

Marine oil supplements for rheumatoid arthritis

Ken Cai[1], Samuel L Whittle[2], Bethan L Richards[1], Sofia Ramiro[3,4], Louise Falzon[5], Rachelle Buchbinder[6]

[1]Institute of Rheumatology and Orthopedics, Royal Prince Alfred Hospital, Camperdown, Australia. [2]Rheumatology Unit, Queen Elizabeth Hospital, Woodville South, Australia. [3]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands. [4]Zuyderland Medical Center, Heerlen, Netherlands. [5]Center for Behavioral Cardiovascular Health, Columbia University Medical Center, New York, NY, USA. [6]Monash Department of Clinical Epidemiology, Cabrini Institute and Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

Contact address: Samuel L Whittle, Rheumatology Unit, Queen Elizabeth Hospital, 28 Woodville Road, Woodville South, South Australia, 5011, Australia. sam@whit.tl, samuelwhittle@gmail.com.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the benefits and harms of marine oil supplements for people with rheumatoid arthritis (RA).

BACKGROUND

Description of the condition

Rheumatoid arthritis (RA) is a chronic, inflammatory joint disease that affects up to 1% of the population (Alarcon 1995). The condition involves predominantly synovial joints and without appropriate treatment can lead to pain, joint destruction and permanent disability (Smolen 2016). Ongoing disease activity can result in extra-articular manifestations, such as vasculitis, interstitial lung disease and end organ dysfunction (Hurd 1979). Patients with RA report pain management as their highest priority (Heiberg 2002). Modern treatment strategies, which emphasise early and aggressive use of disease-modifying anti-rheumatic drugs (DMARDs) including biologic DMARDs (bDMARDs), often in combination, have been effective in reducing the burden of inflammation and subsequent joint damage (Singh 2012; Smolen 2017). Despite improvements in RA management, the use of analgesic drugs and non-steroidal anti-inflammatory drugs (NSAIDs) remains highly prevalent among RA patients (Grijalva 2008; Khanna 2007). Complementary and alternative medicines (CAMs), including dietary manipulations, are also used commonly by RA patients. Dietary treatments are the most commonly used CAM, and of these, marine oil supplements remain the most prevalent (Buchbinder 2002). The lifetime prevalence of CAM usage among arthritis sufferers in England is 38% (Ernst 2011), and estimates of CAM usage by RA patients in the USA range from 28% to 90% (Efthimiou 2010). Similar findings have been found in other countries, with 74% of RA patients in an Australian community-based private practice reporting use of at least one CAM in the previous year (Buchbinder 2002).

Description of the intervention

Essential fatty acids are required for biological processes and must be ingested because they are not synthesised in the body. They comprise the omega-6 (n-6) and omega-3 (n-3) polyunsaturated fatty acids (PUFAs). Modern Western diets tend to be rich in n-6 and relatively lacking in n-3 PUFAs (Cleland 2006a). Dietary supplementation with marine oils provides an abundant source of the n-3 PUFAs eicosapentaenoic acid (EPA - C20:5n-3) and docosahexaenoic acid (DHA - C22:6n-3) (Calder 2012; Cleland 2006a). Marine oil supplementation can take the form of capsules or liquid. They are available in varying doses and types.

How the intervention might work

An anti-inflammatory effect may be derived from an increase in the ratio of n-3 to n-6 PUFAs in cell membranes (Calder 2012). Normally, the n-6 PUFA, (AA - C20:4n-6) is metabolised by cyclooxygenase (COX) enzymes to inflammatory eicosanoids including prostaglandin E2 and leukotriene B4. In contrast, the n-3 PUFAs, EPA and DHA, are metabolised by COX to less inflammatory eicosanoids. Both omega-6 and omega-3 PUFAs are substrates for COX. Thus, an increase in the relative proportion of n-3 PUFAs in cell membranes has the potential to reduce the production of pro-inflammatory molecules. More COX activity is directed towards the n-3 pathway, theoretically producing less inflammatory eicosanoids. Furthermore, EPA and DHA may be metabolised to resolvins, a family of bioactive molecules with potent anti-inflammatory activity (Seki 2010). Amelioration of inflammation via these or other mechanisms in individuals with RA may reduce symptoms or allow a reduction in the use of NSAIDs, which carry a risk of adverse gastrointestinal, renal and cardiovascular effects (McGettigan 2011; Ng 2010). A daily dose of at least 2.7 grams of n-3 PUFAs is thought to be required to achieve an anti-inflammatory effect, and any symptomatic benefit may be delayed for up to three months (Cleland 2006a; Cleland 2006b). On mechanistic grounds, the effect of dietary supplementation with n-3 PUFAs on RA activity is likely to resemble that of NSAIDs - namely reduction in pain and stiffness. Nevertheless, one observational study demonstrated a significantly higher rate of disease remission in RA patients who took regular fish oil supplements in addition to DMARDs, compared with those using DMARDs alone, which suggests a potential disease-modifying effect of marine oils (Cleland 2006a).

A further putative benefit of marine oils is a reduction in cardiovascular risk. Patients with RA are known to be at increased risk for cardiovascular events (Peters 2009). Contributors to this increase in risk include both traditional risk factors and RA disease activity itself, in addition to RA medications, particularly NSAIDS (McGettigan 2011; Solomon 2010). Marine oils are thought to reduce cardiovascular risk via multiple mechanisms, including anti-thrombotic, anti-arrhythmic and anti-inflammatory effects and an improvement in lipid profile (Hooper 2004). Such benefits may be of particular relevance to individuals with RA. Should marine oil supplements allow a reduction in NSAID use, this may further attenuate the elevated cardiovascular risk faced by RA patients. While fish oil has been shown to improve lipid profiles in people with RA (Cleland 2006a), there is moderate to high-quality evidence that omega-3 supplementation has little or no effect on cardiovascular health in the general population (Abdelhamid 2018).

Why it is important to do this review

While some evidence exists for an analgesic and NSAID-sparing effect of marine oil supplementation in RA (James 2010), and a favourable effect on cardiovascular risk factors (Cleland 2006a), doubt remains about the efficacy and safety of marine oils as an adjunct to existing therapies in this population. Two previous studies suggested a beneficial effect of fish oil supplementation on pain, tenderness and morning stiffness in RA (Fortin 1995; Goldberg 2007). However, neither study comprehensively assessed both pain and disease activity outcomes, nor were potential harmful effects addressed. Both studies performed meta-analyses but restricted their literature search to English language papers, and Goldberg 2007 included patients with other painful conditions in addition to RA. A more recent systematic review suggested a small favourable effect of marine oil supplements in reducing pain in patients with arthritis and potential benefit in those with RA (Senftleber 2017). Despite the existing literature, current consensus guidelines for management of RA do not discuss the role of marine oils (Singh 2016; Smolen 2017), and neither do multinational evidence-based recommendations for pain management by pharmacotherapy in inflammatory arthritis (Whittle 2012). However, the use of marine oil supplements appears to be prevalent among RA patients in some parts of the world. In a community-based cohort in South Australia, fish oil use was reported by 6% of the general community and 18.8% of those with self-reported RA (Hill 2009). Potential harms of marine oil supplementation, particularly at high doses, include prolonged bleeding time, gastrointestinal intolerance, contamination with mercury and other environmental toxins, and interaction with prescription medications (Cleland 2006b; Melanson 2005; Salisbury 2012; Stanger 2012). The prevalence

and clinical importance of such effects at commonly used doses remains unclear. Clarification of the efficacy and safety of marine oil supplementation in this population is therefore required.

OBJECTIVES

To determine the benefits and harms of marine oil supplements for people with rheumatoid arthritis (RA).

METHODS

Criteria for considering studies for this review

Types of studies

We will include all published randomised controlled trials (RCTs). We will not impose any restrictions on length of follow-up or language of the paper. We will only include trials that are published as full articles or are available as a full trial report.

Types of participants

Adults (aged 18 years or older) with a diagnosis of rheumatoid arthritis (RA). We will exclude studies that include a mixed population of people with RA and other types of arthritis, unless we can separate out the results for the RA population in the analysis.

Types of interventions

We will include all studies that evaluate marine oil supplements. We will not impose any restrictions on the formulation of marine oil. We will include studies that evaluate marine oils as a supplement to other therapies, or, if available, studies that evaluate marine oil supplements as sole therapy for RA. We will include all possible variations (type, dosage, intensity, mode of delivery, frequency of delivery, duration of delivery, timing of delivery). We will also include trials with co-intervention in one group only (e.g. marine oil plus disease-modifying anti-rheumatic drugs (DMARDs) versus placebo).

Comparators could be:

1. placebo;
2. different types, doses or formulations of marine oil;
3. analgesic medications, such as paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs);
4. DMARDs (including conventional synthetic DMARDs (csDMARDs) and biologic DMARDs (bDMARDs));
5. non-pharmacological modalities (e.g. acupuncture, massage, transcutaneous electrical nerve stimulation (TENS)); and
6. any of the above in combination.

Types of outcome measures

Although marine oil supplementation in RA might have a disease-modifying effect, it is primarily used in clinical practice for its anti-inflammatory effect. Therefore, we consider that the most relevant patient outcomes are pain, function, quality of life, withdrawals due to adverse events, serious and total adverse events. Therefore these will be the six major outcomes in this review.

Major outcomes

1. Pain: measured as proportion of participants with a clinically important reduction in pain or mean pain, measured on a visual analogue scale, numerical rating scale or other scale.
2. Function: measured by the Health Assessment Questionnaire (HAQ; Fries 1980; Pincus 1983), Arthritis Impact Measurement Scale (AIMS; Meenan 1980), or other scales reported by authors.
3. Health-related quality of life: measured by the Medical Outcomes Study Short-Form Health Survey (SF-36) mental component and physical component, or any other scales reported by authors (Ware 1994).
4. Withdrawals due to adverse events.
5. Morning stiffness: measured as duration of morning stiffness.
6. Total adverse events: number of participants reporting an adverse event and type of adverse event.

Minor outcomes

1. Criteria for improvement: American College of Rheumatology (ACR) response criteria for 50% improvement (Felson 2011) ACR 50, which is defined as an improvement in response rates of 50% in tender and swollen joints, in addition to a 50% improvement observed in three out of five core measures, such as patient and physical global assessments, pain, functional status and an acute phase reactant.
2. Disease activity: measured by the Disease Activity Score in 28 joints (DAS28) or 44 joints (DAS44). In addition, we will consider remission rates as a useful measure of the disease activity measured in the range of either a DAS < 1.6 or < 2.6 (Prevoo 1995), or ACR/European League Against Rheumatitis (EULAR) 2011 remission definition, either Boolean (total joint count (TJC) 1, swollen joint count (SJC) 1, C-reactive protein (CRP) 1 mg/dL, patient global assessment 1) or index-based (Simplified Disease Activity Index ≤ 3.3) (Felson 2011).
3. ACR 20 and 70, which is defined as an improvement in response rates of 20% and 70% in tender and swollen joints, in addition to a 20% or 70% improvement observed in three out of five core measures, such as patient and physical global assessments, pain, functional status and an acute phase reactant.
4. Individual core measures: number of tender joints per patient; number of swollen joints per patient; pain (visual analogue scale (VAS)); physician global assessment (VAS); patient global assessment (VAS); acute phase reactants - including erythrocyte sedimentation rate (ESR; a measurement of how fast red blood cells (erthrocytes) fall to the bottom of a test tube filled with whole blood; those with RA have high levels of sedimentation).
5. Radiographic progression: measured by radiographic scores to detect a change in the score from baseline, which include: i) modified total Sharp score, with score range 0 to 448 (van der Heijde 1999); ii) erosion score; and iii) joint space narrowing score. Scores for erosions and joint space narrowing are summed to yield the total Sharp score.
6. Analgesic consumption (including NSAIDs, paracetamol and opioids).
7. Serious adverse events.
8. Cardiovascular events (deaths or acute coronary syndromes).

We will evaluate the outcomes for the following endpoints, if available in the included studies: (a) short term (< 12 weeks), and (b) long term (≥ 12 weeks).

Search methods for identification of studies

Electronic searches

We will use the highly sensitive Cochrane search strategy, which aims to identify all RCTs (Lefebvre 2011), and specific MeSH headings and additional keywords to identify all RCTs on marine oils in RA. We will search the following databases for RCTs or controlled clinical trials (CCTs) using search strategies developed in conjunction with an experienced librarian.

1. Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 1)
2. OVID MEDLINE 1946 to present (Appendix 2)
3. EMBASE 1980 to present (Appendix 2)
4. Clinicaltrials.gov (clinicaltrials.gov)
5. World Health Organization International Clinical Trials Registry (apps.who.int/trialsearch)

We will not apply any language restrictions.

Searching other resources

We will inspect the reference lists of included studies and other systematic reviews on marine oil supplementation in RA for additional trials.

We will also search abstracts from the two major international rheumatology scientific meetings in 2018 and 2019 (American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR)) to identify unpublished studies.

Data collection and analysis

Selection of studies

Pairs of reviewers will independently assess each title and abstract for suitability for inclusion in the review according to predetermined selection criteria (see Criteria for considering studies for this review). If there is any doubt, the full text article will be retrieved and read by the reviewers. Disagreements between the reviewers about the eligibility of the articles will be discussed in a consensus meeting. In case of non-consensus between the reviewers, a third reviewer will decide if the study is eligible.

Data extraction and management

Pairs of reviewers will independently extract the data regarding study design, study duration, characteristics of study population, interventions (including comparators), outcome measures and timing of outcome assessment, co-interventions, efficacy and adverse effect data, and loss to follow-up using a standardised data extraction form. Differences in data extraction will be resolved by referring back to the original articles and establishing consensus. A third reviewer will be consulted to help resolve differences, if necessary.

We will extract the results (i.e. raw data: means and standard deviations (SDs) for continuous outcomes and number of events for dichotomous outcomes) for outcomes of interest in order to assess efficacy and safety. For studies published in languages other than English, German, Portuguese, French, Spanish or Dutch, we will obtain the help of a native speaker or translator with content and methodological expertise.

Assessment of risk of bias in included studies

Pairs of reviewers will independently assess the risk of bias of each included study with regard to the following items: random sequence generation, allocation concealment, blinding of participants, care provider, and outcome assessor for each outcome measure (see Types of outcome measures), incomplete outcome data, selective outcome reporting, and other sources of bias, conforming to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). To determine the risk of bias of a study, for each criterion we will evaluate the presence of sufficient information and the likelihood of potential bias. We will rate each criterion as 'yes' (low risk of bias), 'no' (high risk of bias) or 'unclear' (either lack of information or uncertainty over the potential for bias). We will hold a consensus meeting to discuss and resolve disagreements. If consensus cannot be reached, a third reviewer (RB) will make the final decision.

Measures of treatment effect

We will analyse dichotomous data as risk ratios (RRs) and use 95% confidence intervals (CIs). We will enter data presented as a scale with a consistent direction of effect across studies.

For continuous data, we will analyse results as mean differences (MDs) between the intervention and comparator group, with corresponding 95% CIs. However, when different scales are used to measure the same conceptual outcome (e.g. functional status or pain), we will calculate standardised mean differences (SMDs) instead, with corresponding 95% CIs. Upon completion of the analysis, we will back-translate the SMD to a typical scale (e.g. 0 to 10 for pain) by multiplying the SMD by a typical among-person SD (e.g. the SD of the control group at baseline from the most representative trial) (Schünemann 2017b). We will calculate the absolute benefit as the improvement in the intervention group minus the improvement in the control group, in the original units, expressed as a percentage. We will calculate the relative difference in the change from baseline as the absolute benefit divided by the baseline mean of the control group, expressed as a percentage.

In the 'Effects of interventions' results section and the 'Comments' column of the 'Summary of findings' table, we will provide the absolute percentage difference, the relative percentage change from baseline, and the number needed to treat for an additional beneficial outcome (NNTB), or the number needed to treat for an additional harmful outcome (NNTH) (we will only provide the NNTB or NNTH when the outcome shows a clinically important difference between groups). For pain, we will assume a minimal clinically important difference (MCID) of 1.5 on a 0 to 10-point scale (Farrar 2001), and for the Health Assessment Questionnaire (HAQ) we will assume a MCID of 0.22 (Kosinski 2000; Wells 1993).

For dichotomous outcomes, we will calculate the NNTB or NNTH from the control group event rate and the relative risk using the Visual Rx NNT calculator (Cates 2008). We will calculate the NNTB or NNTH for continuous measures using the Wells calculator (available at the Cochrane Musculoskeletal editorial office). We will calculate the absolute risk difference (RD) using GRADEpro software (GRADEpro GDT 2015), and express the result as a percentage. We will calculate the relative percentage change for dichotomous data as the RR - 1 and express this as a percentage.

Unit of analysis issues

We do not expect major unit of analysis problems in this review. In the event that we identify cross-over trials, in which the reporting of continuous outcome data precludes paired analysis, we will not include these data in a meta-analysis, in order to avoid unit of analysis error. Where carry-over effects are thought to exist, and where sufficient data exist, we will only include data from the first period in the analysis (Higgins 2011a).

For studies containing more than two intervention groups, making multiple pair-wise comparisons between all possible pairs of intervention groups possible, we will include the same group of participants only once in the meta-analysis. If more than one intervention group can be included in our subgroup analyses, we will extract the data from both arms with that goal.

In the case of a trial with multiple time points in which the outcomes are assessed, we will choose the time point closest to our cut-off (12 weeks).

Dealing with missing data

Where important data are missing or incomplete, we plan to seek further information from the study authors.

In cases where individuals are missing from the reported results, we will assume the missing values to have a poor outcome. For dichotomous outcomes (e.g. number of withdrawals due to adverse events), we will calculate the withdrawal rate using the number of patients randomised in the group as the denominator (worst-case analysis).

For continuous outcomes (e.g. mean change in pain score), we will calculate the MD or SMD based on the number of patients analysed at that time point. If the number of patients analysed is not presented for each time point, we will use the number of randomised patients in each group at baseline.

Where possible, we will compute missing SDs from other statistics, such as standard errors, CIs or P values, according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). If we cannot calculate SDs, we will impute them (e.g. from other studies in the meta-analysis) (Higgins 2011a).

Assessment of heterogeneity

In this review, we will explore both clinical and statistical heterogeneity between the studies.

Firstly, we will assess studies for clinical homogeneity with respect to the study population, intervention groups (marine oil formulations, dosages), control groups, timing of outcome assessment and outcome measures.

For any studies judged as clinically homogeneous, we will assess statistical heterogeneity with the I^2 statistic (Deeks 2017), using the following as a rough guide for interpretation: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% considerable heterogeneity. In cases of considerable heterogeneity (defined as $I^2 \geq 75\%$), we will explore the data further, including subgroup analyses, in an attempt to explain the heterogeneity (Deeks 2017).

Assessment of reporting biases

In order to determine whether reporting bias is present, we will determine whether the protocol of the RCT was published before recruitment of patients of the study was started. For studies published after 1 July 2005, we will screen the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organization (apps.who.int/trialsearch; DeAngelis 2004). We will evaluate whether selective reporting of outcomes is present (outcome reporting bias).

We will compare the fixed-effect estimate against the random-effects model to assess the possible presence of small sample bias in the published literature (i.e. in which the intervention effect is more beneficial in smaller studies). In the presence of small sample bias, the random-effects estimate of the intervention is more beneficial than the fixed-effect estimate (Sterne 2017).

We will further explore the potential for reporting bias using funnel plots if at least 10 studies or more are available.

Data synthesis

We will pool the results of clinically and statistically homogeneous studies using the random-effects model, per default, and using a fixed-effect model in sensitivity analyses. When assessing clinical homogeneity, we will take into account the types of interventions, comparators and the study population. If it is possible for us to meta-analyse, then we will conduct pooling in such a way that we will take into account the different comparators and analyse them separately. We will perform analyses using Review Manager 5 (Review Manager 2014), and produce forest plots for all analyses. We will present the results for all the studies first and then split them into subgroups, where data are available, to explore potential sources of heterogeneity.

'Summary of findings' table

We will present the main results of the review in a 'Summary of findings' table, which will include an overall grading of the evidence using the GRADE approach (GRADEpro) and a summary of the available data on the main outcomes as described in chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017a). We will present marine oil supplements versus placebo in the 'Summary of findings' table. We will include an additional table to summarise the minor outcomes.

We plan to include the following six outcomes in the 'Summary of findings' table.

1. Pain
2. Function (HAQ)
3. Health-related quality of life
4. Withdrawals due to adverse events
5. Morning stiffness
6. Total adverse events

Grading of the evidence involves consideration of within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias. However, other factors can affect the quality of evidence, for example, it can be increased by a large magnitude of effect, plausible confounding, and dose-response gradients. Using this system, we will grade the quality of

the body of evidence as high, moderate, low or very low (GRADE Working Group 2004).

Subgroup analysis and investigation of heterogeneity

Where sufficient data are available, we plan to perform the following subgroup analyses.

1. High-dose (≥ 2.7 g/day) versus low-dose n-3 polyunsaturated fatty acid (PUFA) supplementation - it has been suggested that a daily dose of n-3 PUFA or at least 2.7 grams is required to achieve an anti-inflammatory effect, although the putative cardiovascular benefits may occur at lower doses (Cleland 2006a; Cleland 2006b).
2. Marine oil supplementation for < three months versus ≥ three months - it is thought that it may take up to three months for the full symptomatic benefit of n-3 PUFA supplementation to be achieved (Cleland 2006a; Cleland 2006b).
3. Liquid marine oil versus marine oil capsules - marine oil supplements are typically consumed in one of these two preparations; liquid marine oil is thought to provide a more convenient and cheaper method of consuming a high dose of n-3 PUFAs, but it is not clear whether the two preparations are otherwise equivalent (Cleland 2006b).
4. Disease duration < 12 months versus ≥ 12 months - although there is no clear definition of early arthritis and what it means in terms of disease duration, most trials in early RA include patients with < 12 months duration (Bakker 2012; van Vollenhoven 2012).

For analyses 1 to 3, we expect that we will compare outcomes from different trials, e.g. high-dose marine oil versus placebo in one trial and low-dose marine oil versus placebo in another trial. For analysis 4, we expect to extract within-trial data, i.e. trials that report these subgroups separately.

Where available, we will extract data on subgroups and present with subgroup totals. We will compare the magnitude of the effects between the subgroups by means of assessing the overlap of the CIs of the summary estimated. Non-overlap of the CIs indicates statistical significance.

Sensitivity analysis

Where sufficient studies exist, we plan to conduct sensitivity analyses to assess the impact of any bias attributable to inadequate or unclear treatment allocation (including studies with quasi-randomised designs), blinding of patient/assessor and loss to follow-up compared to studies without these study limitations ('yes' versus 'no' or 'unclear').

ACKNOWLEDGEMENTS

Elements of the methods section are based on the standard Cochrane Musculoskeletal Group Protocol Template.

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APPENDICES

Appendix 1. CENTRAL search strategy

BOX 1

fatty acids OR essential fatty acids OR EFA OR polyunsaturated OR PUFA OR omega3 OR omega-3 OR EPA OR DHA OR eicosapentaen OR docosahexaeno OR icosapentaenoic OR ((fish OR krill OR Euphausiacea OR marine OR haddock OR cod OR Gadiformes OR salmon OR Salmon OR mackerel OR herring OR anchov OR sardine OR tuna OR Tuna OR skipjack OR halibut OR Flounder OR coalfish OR shark OR Sharks OR whale OR Whales OR Seals, Earless OR Fur Seals OR seal OR calamari OR squid OR Decapodiformes OR (algae or algal) OR spirulina OR Spirulina OR seaweed or Seaweed OR euphausia superba OR haematococcus pluvialis OR lithothamnion calcareum OR (lithothamnion adj (calcareum or corallioides)) OR dulse OR ascophyllum nodosum OR Chlorella OR chlorella OR gigartina OR mussel OR exp Bivalvia OR perna canaliculus) AND (oil OR fatty acid OR triglyceride OR lipid))

BOX 2
arthritis rheumatoid OR (rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat or reumat or revmarthrit) adj3 (arthrit or artrit or diseas or condition or nodule) OR (felty adj2 syndrome) OR (caplan adj2 syndrome) OR (sjogren adj2 syndrome) OR (sicca adj2 syndrome) OR still disease AND (disease OR condition OR syndrome OR nodule)

Appendix 2. OVID MEDLINE and EMBASE search strategy

1. exp arthritis rheumatoid/
2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.
3. (felty$ adj2 syndrome).tw.
4. (caplan$ adj2 syndrome).tw.
5. (sjogren$ adj2 syndrome).tw.
6. (sicca adj2 syndrome).tw.
7. still$ disease.tw.
8. or/1-7
9. fish oils/
10. exp fatty acids/
11. EFA.tw.
12. MaxEPA.tw.
13. omega3$.tw.
14. omega-3$.tw.
15. (EPA or DHA).tw.
16. (eicosapentaen$ or icosapentaenoic or docosahexaeno$).tw.
17. fish.tw.
18. krill.tw. or Euphausiacea/
19. marine.tw.
20. haddock.tw.
21. cod.tw. or Gadiformes/
22. salmon.tw. or Salmon/
23. mackerel.tw.
24. herring.tw.
25. anchov$.tw.
26. sardine$.tw.
27. tuna.tw. or Tuna/
28. skipjack.tw.
29. halibut.tw. or Flounder/
30. coalfish.tw.
31. shark$.tw. or Sharks/
32. whale$.tw. or Whales/
33. Seals, Earless/ or Fur Seals/ or seal.tw.
34. calamari.tw.
35. squid.tw. or Decapodiformes/
36. (algae or algal).tw.
37. spirulina.tw. or Spirulina/
38. seaweed.tw. or Seaweed/
39. euphausia superba.tw.
40. haematococcus pluvialis.tw.
41. lithothamnion calcareum.tw.
42. (lithothamnion adj (calcareum or corallioides)).tw.
43. dulse.tw.
44. ascophyllum nodosum.tw.
45. Chlorella/ or chlorella.tw.
46. gigartina.tw.

47. mussel$.tw. or exp Bivalvia/
48. perna canaliculus.tw.
49. or/9-48
50. randomized controlled trial.pt.
51. controlled clinical trial.pt.
52. randomized.ab.
53. placebo.ab.
54. drug therapy.fs.
55. randomly.ab.
56. trial.ab.
57. groups.ab.
58. or/50-57
59. exp animals/ not humans.sh.
60. 58 not 59
61. and/8,49,60

WHAT'S NEW

Date	Event	Description
2 December 2019	New citation required and major changes	Updated review methodology to align with the revised MECIR standards proposed by Cochrane Musculoskeletal and new authorship

HISTORY

Protocol first published: Issue 11, 2012

Date	Event	Description
16 July 2019	Amended	Protocol reviewed and feedback incorporated. Reviewed by team members. Changes and suggestions added
5 February 2018	Amended	CMSG ID A069-P
19 January 2018	Amended	Update of protocol - review protocol expanded to include all available marine oils, search strategies expanded and included as appendices

CONTRIBUTIONS OF AUTHORS

SW, SR and KC wrote the protocol. BR, LF and KC developed the search strategies. All authors provided comments and suggestions on draft versions of the protocol.

All authors will participate in study selection, extraction of data and analyses.

All authors have approved the current version of the protocol.

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