



Access Economics Report: Fish Oils for rheumatoid arthritis

August 2010

Report by Access Economics Pty Limited for

The National Institute of Complementary
Medicine

5 Fish oils for rheumatoid arthritis (RA)

5.1 Background

Rheumatoid arthritis (RA) is a chronic, inflammatory disease characterised by pain and a loss of function in the joints (AIHW, 2009). Treatment and management of RA is designed reduce pain and stiffness, prevent joint damage, minimise disability, encourage disease remission and improve quality of life.

Treatments are based on medications as well as physical therapy (which include joint strengthening exercises) rest and on occasion surgery. A common class of medication prescribed for RA are the nonsteroidal anti-inflammatory drugs (NSAIDs). However, these traditional pharmaceuticals have also been shown to impart higher cardiovascular risks on an already higher risk population.

Alternatively, fish oils have been shown to be effective in managing symptoms associated with RA. RACGP (2008) advises (based on Goldberg and Katz, 2007 and Fortin et al, 1995) that GPs should recommend omega-3 supplementation as an adjunct for NSAID management of pain and stiffness in patients with RA.

5.2 Aim

This study aims to determine the cost effectiveness of using fish oil supplements as an adjunctive therapy (with lower NSAID use) rather than standard NSAID therapy alone.

5.3 Indication

Rheumatoid arthritis (RA) is a chronic, inflammatory disease caused by the body's autoimmune system attacking its own healthy tissues and joints. The condition is characterised by pain, joint stiffness (particularly in the morning), swelling, and a loss of function in the joints. The disease also results in problems associated with the heart, respiratory system, nerves and eyes (AIHW, 2009).

Maradit-Kremers et al (2005) showed that people with RA have a higher risk of cardiovascular death after controlling for the traditional cardiovascular risk factors and comorbidities. Risks of cardiovascular death were significantly higher among people with at least 3 ESR⁴⁹ values of ≥ 60 mm/hour (hazard ratio [HR] 2.03, 95% CI 1.45-2.83), RA vasculitis (HR 2.41, 95% CI 1.00-5.81) and RA lung disease (HR 2.32, 95% CI 1.11-4.84).

Treatment and management of RA is designed to target symptoms (AIHW, 2009):

- reduce pain and stiffness in affected joints;
- prevent joint damage;
- minimise disability caused by pain, joint damage or deformity;

⁴⁹ Erythrocyte sedimentation rate (ESR): rate at which red blood cells precipitate in a period of one hour. Common haematology test that is a non specific measure of inflammation.

- encourage disease remission; and
- improve quality of life.

Prevalence of RA in Australia was estimated as 513,261 or 2.5% of the population in 2007 (Access Economics, 2007) based on ABS National Health Survey data. Prevalence was higher in females (2.8%) than in males (2.1%) and was age-related (highest in the 65-74 year age group).

5.4 Intervention

5.4.1 Literature search

A literature search was undertaken on 14 July 2009 of NCBI and NIH Pubmed using search parameters of “Fish oil for rheumatoid arthritis”. Selection criteria were: (1) in English; (2) published in 2000 to present; and (3) studies in humans. This was followed by a bibliography search of sourced articles. A summary of literature reviewed for this study is in Table 5.1. Some studies were omitted from the meta-analysis (e.g. Geusens et al, 1994) because they did not report patient reductions in NSAID consumption or reliance.

Table 5.1: Results from the literature search for fish oil for rheumatoid arthritis

Study type	Study (within study type, from most recent to oldest)
Meta-analyses	MacLean et al (2004)
	Goldberg and Katz (2007)
Randomised controlled trials	Lau et al (1993)
	Geusens et al (1994)
	Galarraga et al (2008)

Detailed findings for these studies are in Table 5.14 in the Appendix (Section 5.13).

5.4.2 Definition of intervention

The relevant RACGP (2008) recommendations for fish oil based on Goldberg and Katz (2007) and Fortin et al (1995) state:

- GPs should recommend omega-3 supplementation as an adjunct for management of pain and stiffness in patients with RA (recommendation 13);
- GPs should consider using conventional NSAIDs or cox-2 inhibitors⁵⁰ for reducing pain and stiffness in the short-term treatment of rheumatoid arthritis where simple analgesia and omega-3 fatty acids are ineffective (recommendation 15); and
- GPs should consider short-term, low-dose, oral corticosteroid treatment when simple analgesics, omega-3 fatty acids, and NSAIDs or cox-2 inhibitors have failed to achieve symptomatic relief. This should be undertaken in consultation with a rheumatologist

⁵⁰ Cox-2 inhibitors are a type of NSAID.

and with a consideration of the patient's co-morbidities and individual risk factors (recommendation 19).

Galarraga et al (2008) found that people who use fish oil supplements are able to reduce their NSAID intake and wean off them after around three months.

Hence the intervention is defined as 12 months use of fish oil (omega-3) supplementation as an adjunct (with 3 months' use of NSAIDs) for management of RA symptoms.

5.5 Comparator

Two classes of medications are generally prescribed for RA:

- nonsteroidal anti-inflammatory drugs (NSAIDs) to control pain as well as inflammation; and
- disease modifying anti-rheumatic drugs (DMARDs) to alter the course of the disease as well as promote disease remission.

Both of these medications are potent and monitoring of patients is advised given the side effects that are associated with their use.

NSAIDs were selected as the comparator because RACGP (2008) recommends NSAIDs and cox-2 inhibitors first, with the (generally more expensive) DMARDs second-line (i.e. if people are refractive to fish oil, NSAIDs and other 1st line management).

Hence the comparator is defined as standard treatment with NSAIDs alone (no fish oil, and a full 12 months of NSAID therapy).

5.6 Effectiveness

5.6.1 Previous cost effectiveness studies

No other previous cost effectiveness studies examining fish oil supplementation in people with RA could be found in the literature review process.

5.6.2 Treatment effectiveness

Measures of treatment effectiveness are through the reduced reliance on NSAID therapy. A previous meta-analysis by Goldberg and Katz (2007) showed that fish oil supplements were effective in the short term in reducing NSAID reliance, although the statistical significance of this effect was lost in the long term (greater than 5 months).

Since this meta-analysis was published an additional study by Galarraga et al (2008) has been published which used the reduction of NSAID therapy as a primary outcome. The meta-analysis presented in this section uses the same methodology as that used in Goldberg and Katz (2007) with the additional treatment effects from Galarraga et al (2008) included. The

meta-analysis by Goldberg and Katz (2007) included the studies that are used in MacLean et al (2004), although only two studies reported relevant outcomes (reduction in NSAID by defined daily doses, for omega-3 polyunsaturated fatty acids versus placebo for joint pain). Studies included from the Goldberg and Katz (2007) meta-analysis are Skoldstam et al (1992) and Lau et al (2004) (Table 5.2). The Goldberg and Katz (2007) meta-analysis reported results for trials in the short term (3-4 months) as well as in the medium term (over 5 months). Trial results used in this meta-analysis are based on results that are greater than 5 months (presented in Table 5.2).

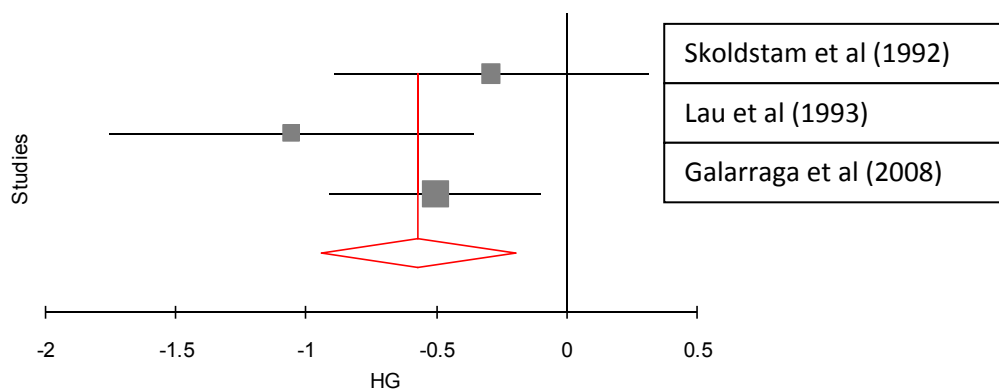
Table 5.2: Standardised mean difference in NSAID consumption, studies in our meta-analysis

	Treatment			Control		
	N	mean	SD	N	mean	SD
Skoldstam et al (1992)	22	1.0	0.47	21	1.2	0.60
Lau et al (1993)	21	40.6	37.53	16	84.1	43.67
Galarraga et al (2008)	49	74.0	42.00	48	91.0	20.78

Source: Access Economics. Means are standardised mean difference. SD is standard deviation.

A standardised mean difference (SMD or Hedges’ G) with a random effects model was used as the main effect measure, in line with method used in Goldberg and Katz (2007) study. The standardised mean difference is an effect size that divides the mean difference between the treatment and control groups by the standard deviation. Chart 5.1 shows the resulting forest plot with the corresponding results presented in Table 5.3.

Chart 5.1: Meta-analysis results, use of NSAIDs for those who use fish oil supplements



Source: Access Economics. HG = Hedges’ G.

Note: Negative values indicate a reduced reliance on NSAIDs for people using fish oil supplements

Table 5.3: Meta-analysis input data (SMD or Hedges' G)

	Hedges' G	95% CI	p value	Weight
Skoldstam et al (1992)	-0.29	-0.89 to 0.31	0.341	28.64%
Lau et al (1993)	-1.06	-1.76 to -0.36	0.003	22.70%
Galarraga et al (2008)	-0.51	-0.91 to -0.10	0.014	48.66%
Meta- analysis	-0.57	-0.94 to -0.20	0.002	

Source: Access Economics

Note: $T^2 = 0.0311$

These results indicate that there is a statistically significant SMD between NSAID reliance of those who use fish oil supplements and those who do not of -0.57 (95% CI, -0.94 to -0.20).⁵¹

The pooled result of -0.57 is the standardised mean difference between the treatment and control arms of the trials. To convert this back in to a measure for modelling purposes, the standardised mean difference is multiplied by the standard error from the meta-analysis (the standard error can be calculated from the resulting confidence interval shown in Table 5.3).

Trials used in this meta-analysis utilised similar treatment protocols. Trial participants commence a course of fish oil as an adjunct to NSAID therapy, and subsequently reduced their reliance on NSAID treatments. Reductions were observed in both the control and experimental groups; however, the reductions were greatest for those taking fish oil supplements.

The placebo arm of Galarraga et al (2008) was used as a base for the mean difference i.e. the observed reduction in NSAID reliance for people not taking fish oil was modelled based on the results of the placebo arm of this study. Galarraga et al (2008) was chosen for a number of reasons. First, it is the most recent study, with the greatest number of study participants. Second, it is the most highly weighted study in the meta-analysis and finally it was designed to primarily capture the effects of fish oils and the reduction in NSAID reliance.

5.6.3 Adverse events

The key benefits from reducing a patient's reliance on NSAID treatment is the subsequent reduction in potential adverse events. Sustained use of NSAID therapy for a chronic illness such as rheumatoid arthritis is associated with a number of adverse events, such as myocardial infarction related mortality as well as gastrointestinal bleeding.

As discussed previously, people with RA have an elevated risk of myocardial infarction related mortality (Maradit-Kremers et al; 2005). NSAID treatment therapy further increases this risk. Hippisley-Cox and Coupland (2005) is an observational study that reports the myocardial infarction outcomes of patients using different types of NSAID medication. Evidence for increased myocardial infarction morbidity from the consumption of NSAID medication for people with rheumatoid arthritis could not be found. In addition studies used in the meta-analysis (Chart 5.1) did not report an increase in myocardial infarction events, so these aspects

⁵¹ Tests confirmed there was no publication bias.

have been excluded from the modelling. Findings (adjusted for smoking status, comorbidities, deprivations and use of statins, aspirin and antidepressants are presented in Table 5.4. The increased risk associated with 'other non-selective NSAIDs' is used in the the modelling.

Table 5.4: Increased risk for myocardial infarction from NSAID therapy, by medication

	Adjusted odds ratio	95% CI	p value
Celecoxib	1.21	0.96 – 1.54	0.11
Rofecoxib	1.32	1.09 – 1.61	0.005
Other selective NSAIDs	1.27	1.00 – 1.61	0.046
Ibuprofen	1.24	1.11 – 1.39	<0.001
Diclofenac	1.55	1.39 – 1.72	<0.001
Naproxen	1.27	1.01 – 1.60	0.04
Other non-selective NSAIDs	1.21	1.02 – 1.44	0.03

Source: Hippisley-Cox and Coupland (2005)

Prolonged use of NSAIDs is associated with an increased risk of gastrointestinal events. Increased rates of gastrointestinal events were shown by Schaffer et al (2006) to persist with longer NSAID treatment lengths. A number of meta-analyses have examined the increased risks associated with the consumption of NSAIDs and gastrointestinal perforations, ulcers and bleeds (PUB) (Table 5.5).

Table 5.5: Effects of NSAID consumption on gastrointestinal events

	Effect size	95% CI
Gonzalez-Perez and Rodrigues (2006)	RR: 1.3 (fixed effects)	1.2 – 1.5
	RR: 1.4 (random effects)	1.1 – 1.6
Ofman et al (2002)	RCTs, OR: 5.36	1.79 – 16.1
	Cohort Studies, RR: 2.70	2.1 – 3.5
	Case control, OR: 3.00	2.5 – 3.7
Derry and Loke (2000)	OR: 1.68	1.51 – 1.88
	OR: 1.59 (doses below 163 mg/day)	1.40 – 1.81

Dose response has been shown in these studies through meta-regression between NSAID consumption and gastrointestinal bleeding events, although the results are mixed. Gonzalez-Perez and Rodriguez (2006) showed that higher rates of gastrointestinal bleeding were associated with higher dosages of NSAIDs. In contrast Derry and Loke (2000) showed no significant change in dose response associated with 100mg/day changes in NSAID consumption.

With this conflict in mind, the results from Table 5.5 have been used in the modelling process. The results from Derry and Loke (2000) are used in the base case, with the results from Gonzalez-Perez and Rodrigues (2006) (fixed effects) and Ofman et al (2002) (RCTs) used as the upper and lower bounds in sensitivity analysis, respectively.

5.7 Benefits

The main benefits of treatment with fish oils and with NSAIDs are gains in healthy life achieved through reducing the burden from RA, net of any adverse events or side effects of the treatment itself.

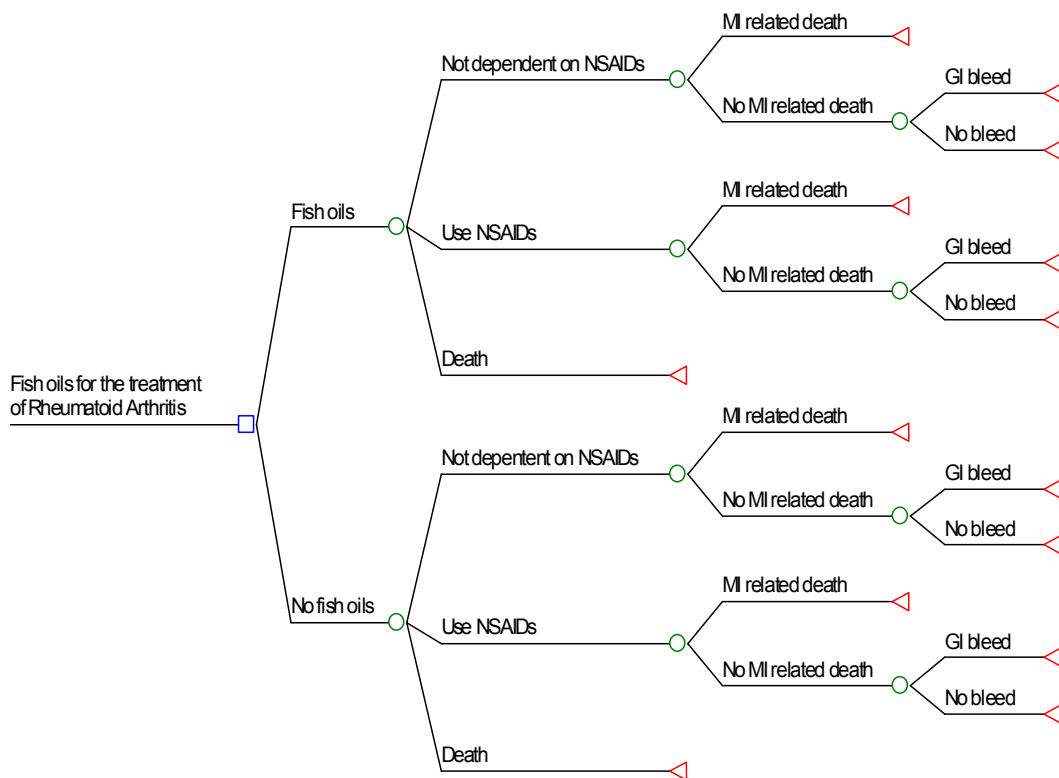
Disease states were measured using the DALY method, as well as a QALY equivalent (defined as 1-YLD) – for comparability with outcome measures in other studies of fish oils for RA.

From the model structure shown in Figure 5.1, two initial health states are possible – ‘continue to have rheumatoid arthritis’ or ‘mortality’. Disability weights from Mathers et al (1999) have been used for the YLD measure – for RA this weight is 0.231. Subsequently, the model structure allows for individuals who have a gastrointestinal bleed and those who do not. Mathers et al (1999) do not provide a YLD for gastrointestinal bleeding, instead the disability weight for peptic ulcer disease is used, with a weight of 0.002.

5.8 Model

A decision model was constructed in TreeAge to undertake cost effectiveness analysis to evaluate the use of fish oil dietary supplements versus NSAIDs in the Australian setting, with a modelled time period of one year (Figure 5.1). The model compares two treatment arms the experimental arm evaluates standard NSAID therapy with fish oil supplements while the comparator arm evaluates standard NSAID therapy alone. Four health states were modelled based on the evidence from clinical trials as well as Australian specific age and gender mortality rates.

Figure 5.1: Model structure – fish oil for treatment of RA



Source: Access Economics.

5.9 Costs

5.9.1 Health system costs

Health system costs for RA were sourced from the AIHW. These estimates include costs associated with ‘admitted patient services’, ‘out-of-hospital services’ and ‘prescription pharmaceuticals’. The total cost of these expenditures is presented in Table 5.6.

Table 5.6: Health system costs per case of rheumatoid arthritis, 2009 (\$)

	Total health system costs (\$m) 2004/5		Prevalence ('000s) 2004/5		Cost per case	
	Male	Female	Male	Female	Male	Female
25-34	2.07	4.55	7.3	8.5	320	605
35-44	4.41	12.08	24.4	39.5	204	346
45-54	9.87	23.94	31.7	60.6	352	446
55-64	16.61	32.09	69.2	58.9	271	616
65-74	10.83	24.80	45.4	69.9	270	401
75-84	6.43	16.18	25.2	32.8	288	557
85+	0.69	1.69	4.8	3.9	162	490

Source: AIHW (2009), costs per case of rheumatoid arthritis were inflated to 2009 costs

Gastrointestinal bleeding events are considered emergency occurrences and require immediate hospitalisation. Costs associated with the hospitalisation of gastrointestinal bleeds have been sourced from round 12 of the National Hospital Cost Data Collection for 2009. Overall costs have been estimated from a weighted average (by separation) of public and private hospitals (Table 5.7), corresponding to the diagnosis related groups (DRG) of G61A and G61B, which record procedures associated with the diagnosis of a gastrointestinal bleed.

Table 5.7: Hospitalisation costs associated with gastrointestinal bleeds, 2009 (\$)

	Public	Private
Average cost per separation		
G61A	3,165	2,561
G61B	1,659	1,310
Number of separations		
G61A	7,217	1,216
G61B	3,637	314
Weighted average costs		
G61A		3,078
G61B		1,631
Overall		2,616

Source: Round 12, National Hospital Cost Data Collection (2009)

5.9.2 Cost of fish oil supplements

Fish oil supplements are an over-the counter medication with cost variations between brands. Retail prices of fish oil supplements were sourced from Pharmacy Online. Supplements that included additional products such as ginkgo were excluded. Only fish oil supplements that had a EPA:DHA ratio of approximately 1.5:1 were included. Table 5.8 shows the brands, volumes and retail prices sourced.

Table 5.8: Fish oil treatment costs, RA

Brand	Capsules per bottle	mg per capsule	mg (EPA) per capsule	mg (DHA) per capsule	Retail Price (\$)	Cost per capsule (\$)	Cost per diem (\$)	Cost per annum (\$)
Blackmores	200	1,000	180	120	19.95	0.0998	0.9975	364.09
Blackmores	400	1,000	180	120	37.50	0.0938	0.9375	342.19
Bio-Organics	220	1,000	180	120	29.95	0.1361	1.3614	496.90
Bioglan	200	1,000	180	120	19.95	0.0998	0.9975	364.09
Bioglan	400	1,000	180	120	33.75	0.0844	0.8438	307.97
clear Fish Oil	400	1,000	180	120	18.95	0.0474	0.4738	172.92
Natures Own	100	1,000	180	120	12.45	0.1245	1.2450	454.43
Natures Own	200	1,000	180	120	18.95	0.0948	0.9475	345.84
Natures Own	400	1,000	180	120	35.95	0.0899	0.8988	328.04
Natures Own - MaxEPA	100	1,000	171	114	18.95	0.1895	1.8950	691.68
Natures Way	100	1,000	180	120	9.96	0.0996	0.9960	363.54
Natures Way	200	1,000	180	120	17.95	0.0898	0.8975	327.59
Natures Way	400	1,000	180	120	32.95	0.0824	0.8238	300.67

Source: Pharmacy Online, accessed on 10th September 2009

Note: Cost per diem is estimated on 10 capsules per day (as per the average trial dosages from Galarraga et al (2008), Lau et al (1993) and Skoldstam et al (1992).

A mean annual price of fish oil treatment (\$373.84) has been used in the cost effectiveness analysis.

5.9.3 Cost of NSAID treatment

The AIHW Australian GP Statistics and Classification Centre (2006), reported that of people with arthritis who were taking NSAIDs as part of their treatment, 27.5% were taking celecoxib and 23.8% were taking meloxicam. A conservative cost estimate was adopted using the cheapest of these two NSAIDs (meloxicam) reported to have a mean prescribed daily dose of 15mg.

Table 5.9: Annual cost of NSAID treatment (meloxicam)

	Tablets per pack	Price for max quantity	mg per pack	Cost per mg	Daily dose*	Annual cost
Table 7.5mg	30	21.80	225	0.0969	1.45	530.47
		23.37	225	0.1039	1.56	568.67
Tablet 15mg	30	28.83	450	0.0641	0.96	350.77
		30.42	450	0.0676	1.01	370.11
Capsule 7.5mg	30	21.80	225	0.0969	1.45	530.47
Capsule 15mg	30	28.83	450	0.0641	0.96	350.77

Source: Schedule of Pharmaceutical Benefits (1 September 2009). * Prescribed.

The annual cost of NSAIDs used in the cost effectiveness analysis is \$350.77. For those who are able to reduce their NSAID intake, these costs are attributed to the first three months inline with Galarraga et al (2008). GP costs were not included since many NSAIDs are available OTC, in which case GP costs do not apply. Moreover, RA is a chronic condition so people will regularly attend their GP for care, and are likely to renew scripts for any PBS-listed NSAIDs in combination with their general GP care, so are thus unlikely to reduce GP visits. Moreover, the literature provided no evidence that they reduced GP visits. If people purchase over-the-counter they consider price and if they present a script at the pharmacy, the pharmacist will generally ask if they prefer the cheaper brand, hence the use of minimum pricing for NSAIDs. However, in the fish oil market there is little price differentiation and less information provided to consumers about relative prices per dose, so an average price was considered more appropriate.

5.9.4 Mortality rates and gastrointestinal events

Overall mortality rates have been taken from AE-Dem (a population forecast model developed by Access Economics). This model is analogous to the model used by the ABS series B population projections. In addition to overall population mortality rates, MI mortality rates (Table 5.10) were applied in the model (these rates are affected by the usage of NSAIDs). Gastrointestinal event rates have been sourced from the AIHW hospital morbidity datacube by diagnosis related group (DRG). The rates have been calculated DRG codes G61A and G61B.

Table 5.10: Myocardial infarction mortality rate (per 100,000 people)

	Mortality rate		Gastrointestinal events	
	Males	Females	Males	Females
25–29	1.4	0.9	21.9	14.8
30–34	4.4	1.1	25.2	16.8
35–39	10.6	2.8	27.4	17.8
40–44	22.5	5.0	31.7	21.3
45–49	41.7	9.9	38.7	24.1
50–54	65.8	11.6	48.8	29.5
55–59	99.1	21.4	65.9	37.1
60–64	158.0	44.4	83.4	44.5
65–69	257.3	87.2	132.0	77.7
70–74	414.5	173.0	210.3	138.2
75–79	789.8	403.4	319.9	238.4
80–84	1,516.5	930.0	456.6	343.0
85+	3,303.7	2,937.9	677.5	598.1

Source: AIHW GRIM books

5.9.5 Parameter summary

A summary of the parameters used in the analysis is in Table 5.11.

Table 5.11: Summary of model parameters

Parameter	Source and Methods	Estimate	Sensitivity
Efficacy of fish oil treatment	Random effects meta-analysis based on Skoldstam et al (1992) Lau et al (1993) and Galarraga et al (2008)	Standardised mean difference between fish oil treatment and placebo is -0.57 (95% CI -0.94 to -0.20)	Upper and lower bounds of the 95% CI.
Mortality rates	MI mortality rates: AIHW GRIM books Overall mortality: AE-Dem	Table 5.10	N/A
Myocardial event rates	Hippisley-Cox and Coupland (2005)	RR = 1.21	Upper bound RR = 1.44 Lower bound RR = 1.02
Gastrointestinal event rates	AIHW hospital morbidity data cube	RR = 1.68	Upper bound RR = 5.36 Lower bound RR = 1.30
Quality of life	Mathers et al (1999)	Disability weight for RA is 0.231 Disability weight for GI events is 0.002	N/A
Costs – Fish oil	Mean retail price from Pharmacy Online	\$373.84	N/A
Costs – NSAIDs	Lowest cost NSAID from Schedule of Pharmaceutical Benefits (1 Sept 2009)	\$350.77	N/A
Health system costs – RA	AIHW (special data request)	Table 5.6	N/A
Hospitalisation cost – GI events	National hospital cost data collection	Table 5.7	N/A
Costs – CVD mortality	National Hospital Cost Data Collection	\$4,367 (chapter 4)	N/A

5.10 Results

A second order Monte Carlo simulation was undertaken (with 1 million trials) on the decision model shown in Figure 5.1. Age and gender distributions were sampled in the model so that the overall results were representative of the RA disease profile reported in Begg et al (2007).

Incremental effects are greater under the DALY approach compared to the QALY approach. The differences results from the inclusion of years of life lost due to premature mortality (YLLs) which is not included in the QALY approach. The results from Table 5.12 indicate that the cost per DALY avoided is approximately \$529,000, while the cost per QALY gained is approximately \$5.5 million. Neither outcome is cost effective relative to the benchmarks in Section 1.4.

Table 5.12: Cost effectiveness of fish oil supplementation in RA

Strategy	Cost	Incremental cost	Incremental Effectiveness	Incremental effectiveness	C/E	ICER
DALY approach						
No fish oil	775.44		0.5165		1,501	
Adjunctive fish oil	1,105.68	330.24	0.5159	0.00062	2,143	529,224
QALY (1-YLD) approach						
No fish oil	775.70		0.7436		1,043	
Adjunctive fish oil	1,105.93	330.24	0.7437	0.00006	1,487	5,510,277

Note: Incremental effectiveness refers to the average number of DALYs avoided or the average number of QALYs gained. C/E – cost effectiveness ration. ICER – incremental cost effectiveness ratio.

The incremental cost per person is \$330 per annum and the incremental effectiveness 0.0006 DALYs.

Sensitivity analysis was undertaken to determine the influence of the trial results used in the modelling on the cost-effectiveness result. Sensitivity was conducted around the meta-analysis results presented in Table 5.3 using the 95% confidence intervals as upper and lower bounds as well as the trial results for MI events and GI events. Results were shown to be very sensitive to these changes with large variations observable, particularly with the upper bound values (Table 5.13).

Table 5.13: One way sensitivity analysis

	\$ per DALY avoided	\$ per QALY gained
Results	529,334	5,510,277
Meta-analysis, upper bound	352,0421	3,683,190
Meta-analysis, lower bound	939,920	20,349,993
MI events, upper bound	251,616	2,629,346
MI events, lower bound	5,602,302	56,663,008
RR of GI events, upper bound	523,538	5,415,460
RR of GI events, lower bound	529,459	5,521,851

The results presented in Table 5.12 and Table 5.13 lie above all the cost effectiveness thresholds in Section 1.4. Fish oils for the secondary prevention of RA are thus not considered cost effective under any of the scenario analyses.

A large difference in the ICER values can be observed between the QALY and DALY approaches, since the DALY approach places greater weight on mortality.

5.11 Conclusions

Rheumatoid arthritis is a painful and often very serious inflammatory condition, characterised by pain, joint stiffness, loss of joint function and swelling. The whole body is affected, with inflammation causing an increase in risk of cardiovascular events and mortality.

Pharmaceutical treatments have also been shown to impart higher cardiovascular risks on an already higher risk population. Most recently the use of cox-2 inhibitors has ceased as standard treatment, due to their influence on the cardiovascular system. Evidence is accumulating that NSAIDs have similar cardiovascular side-effects associated with their use. In addition, NSAIDs are associated with upper gastrointestinal bleeding and related consequences, such as hospitalisation.

Galarraga et al (2008) showed that by using fish oil supplements, a person's reliance on NSAID medication could be reduced without any statistically significant change in the condition of their disease. These reductions in NSAID reliance reduce the overall risk of cardiovascular side effects associated with NSAID treatment.

A previous meta-analysis by Goldberg and Katz (2007) showed that reductions in NSAID reliance were only maintained in the short term, with statistical significance lost in longer time periods. This study expands on the data used in the Goldberg and Katz (2007) meta-analysis with the addition of a more recent study, Galarraga et al (2008). The addition of this study provides a statistically significant result, indicating that reductions in NSAID reliance can be maintained into the long term.

However, avoiding NSAID consumption by using fish oils adjunctively was not shown in this analysis to offer health cost savings due to:

1. the higher cost of fish oil (\$373.84pa) relative to NSAIDs (\$350.77) where they were replaced (and double treatment cost for the period not replaced);
2. cost savings from fewer MI related deaths (\$4,367 per death as per Table 5.11), but relatively few deaths averted as the mortality risk is low; and
3. cost savings from fewer GI bleeds (\$2,616 per bleed on average as per Table 5.7), but again relatively few GI bleeds averted.

Taking these impacts together, the model showed that although there was a gain in quality of life through use of fish oils, it was achieved at a higher cost per DALY avoided than that normally paid for public reimbursement of medical interventions.

5.12 References

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5.13 Appendix: Detailed summary of literature studies relating to fish oils and RA

Table 5.14: Literature on effectiveness of fish oils for RA

Source	Aim of study	Method	Comparator	Findings	Outcome measure
META-ANALYSES					
MacLean et al (2004)	To assess the effect of omega-3 fatty acids (n-3 FAs) on pain, swollen and tender joint counts, acute phase reactants, patient global assessment, and requirement for anti-inflammatory or immunosuppressive therapy in rheumatoid arthritis.	Reviewed 83 RCTs and undertook meta-analysis.	Various comparators	n-3 FAs had no effect on patient report of pain, swollen joint count, ESR, and patient's global assessment. There was no effect on joint damage, contrary to a previous meta-analysis. There was a reduced requirement for anti-inflammatory drugs or corticosteroids. No studies assessed requirements for DMARDs.	Associations with diabetes (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, insulin sensitivity/glycemic control), inflammatory bowel disease (clinical effect, effect on requirement for steroids/other immunosuppressive drugs), rheumatoid arthritis (pain, swollen joints, disease activity, patients global assessment, joint damage, tender joint count, effect on anti-inflammatory/immunosuppressive drug requirement), renal disease, systemic lupus erythematosus, bone density/osteoporosis