ACCESS ECONOMICS

Cost effectiveness of complementary medicines

August 2010

Report by Access Economics Pty Limited for

The National Institute of Complementary Medicine

The National Institute of Complementary Medicine (NICM) was established with seed funding provided by the Australian Government (Commonwealth Department of Health and Ageing) and the NSW State Government (NSW Office of Science and Medical Research) and is hosted by the University of Western Sydney.

Foreword

Australians spend over $3.5 billion each year on complementary medicines and therapies, most commonly to assist in the management of chronic disease and improve health and wellbeing.

Over the last twenty years, there has been a growing body of scientific knowledge on the efficacy of complementary medicine; understanding of mechanisms of action; and advances in processes to ensure quality and standardisation of materials and products. Research partnerships have increasingly focused on high burden of disease areas where mainstream medicine has yielded relatively poor results, particularly in the prevention and management of chronic disease, and towards enhanced results using a combination of complementary and mainstream interventions.

Once safety and efficacy have been established, a critical issue for consumers, practitioners and governments alike is understanding the cost effectiveness of medical interventions, whether mainstream or complementary.

In 2009, the National Institute of Complementary Medicine (NICM) commissioned Access Economics to undertake a series of cost effectiveness studies of selected complementary medicine interventions where a reasonable body of evidence for safety and efficacy was available. These were:

- Acupuncture for chronic low back pain;
- St John's wort for mild to moderate depression;
- Omega-3 fish oils for secondary prevention of heart disease;
- Omega-3 fish oils to reduce non-steroidal anti-inflammatory drug use in rheumatoid arthritis; and
- A proprietary herbal medicine for pain and inflammation of osteoarthritis.

Details of the analyses undertaken by Access Economics follow. It should be noted that only **direct** health costs are included in these analyses and indirect costs (such as loss of productivity at work) have been excluded. Cost savings would be expected to be higher if indirect costs were included in the analyses.

The findings detailed in this report provide evidence that selected complementary medicine interventions represent cost effective treatment options in an Australian practice context for specific medical conditions. Further, interventions were cost effective despite the addition of the GST to complementary medicine products.

In summary:

- acupuncture for chronic low back pain was found to be cost effective if used as a *complement* to standard care (medication, physiotherapy, exercises, education), although not generally cost effective when used as a *replacement* to standard care (unless co-morbidity of depression is included).
- Based on analyses of recent clinical trials St John's wort was determined to be cost effective compared to standard anti-depressants for patients with mild to moderate (not

severe) depression. The main driver for cost effectiveness is the lower unit cost of St John's wort.

- Fish oils rich in omega-3 fatty acids are highly cost effective when used as an adjunctive treatment in people with a history of coronary heart disease, achieving reduced death and morbidity. These findings are consistent with other international studies. Fish oils, however, were not cost effective in reducing non-steroidal anti-inflammatory drug use in rheumatoid arthritis.
- Phytodolor, a proprietary herbal medicine, was found to be cost saving in managing osteoarthritis compared with the principal non-steroidal anti-inflammatory drug Diclofenac.

This report is an important component of advancing our knowledge and understanding of complementary medicine, and supporting informed choices for individual care. Studies of this type will also contribute to funding choices in the broader context of national health reforms.

The findings strengthen the importance of ongoing research effort to determine and unlock the broader benefits of complementary medicines and therapies for the health of all Australians and to improve their use in an integrated healthcare practice environment.

I welcome this report and commend it to you.

Professor Alan Bensoussan

Executive Director

National Institute of Complementary Medicine

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Acknowledgements

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Glossary

ABS	Australian Bureau of Statistics
AIHW	Australian Institute of Health and Welfare
CGI	Clinical Global Impression (scale for depression)
CHD	coronary heart disease
CI	confidence interval
COT	conventional orthopaedic therapy
COX-2	cyclo-oxygenase 2
CPG	Chronic Pain Grade (questionnaire)
CVD	cardiovascular disease
DALY	disability adjusted life year
DART	Diet and Reinfarction Trial
DHA	decosahexaenoic acid
DMARDS	disease modifying anti-rheumatic drugs
DOHA	Department of Health and Ageing
EA	electroacupuncture
EPA	eicosapentaenoic acid
ESR	erythrocyte sedimentation rate
GDP	gross domestic product
GISSI-P	Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico Prevenzione
GP	general practitioner
GRIM	General Record of Incidence of Mortality (AIHW)
GST	Goods and Services Taxation
HAM-D	Hamilton depression (rating scale)
HIRF	Health Insurance Registration File
HR	hazard ratio
ICER	incremental cost effectiveness ratio
LBP	lower back pain
LYG	life year gained
MBS	Medicare Benefits Schedule
MI	myocardial infarction
NCBI	National Center for Biotechnology Information (United States)
NHMRC	National Health and Medical Research Council
NHS	National Health Service (UK)
NICE	National Institute for Health and Clinical Excellence (United Kingdom)
NICM	National Institute of Complementary Medicine
NIH	National Institutes of Health (United States)
NRS	Numeric Rating Scale
NSAIDS	non steroidal anti-inflammatory drugs

NSW	New South Wales
N-3 FA	Omega 3 fatty acid
OR	odds ratio
PBS	Pharmaceutical Benefits Scheme
PTCA	percutaneous transluminal coronary angioplasty
PUFAS	polyunsaturated fatty acids
QALY	quality adjusted life year
RA	rheumatoid arthritis
RACGP	Royal Australian College of General Practitioners
RCT	randomised controlled trial
RR	relative risk
SF36	Short Form 36 (health questionnaire survey)
SMD	standardised mean difference
SNRI	serotonin norepinephrine reuptake inhibitor (anti-depressant)
SSRI	selective serotonin reuptake inhibitor (anti-depressant)
TCA	tricyclic anti-depressant
TENS	transcutaneous electrical nerve stimulation
UK	United Kingdom
US	United States
VAS	Visual Analogue Scale
VSLY	value of a statistical life year
WHO	World Health Organization
YLD	years of life lost due to disability
YLL	years of life lost due to premature mortality

Executive summary

The National Institute of Complementary Medicine (NICM) commissioned Access Economics to undertake cost effectiveness analyses of a number of complementary medicine interventions. A Reference Group was established to assist in selecting interventions, indications and comparators for analysis, and nine criteria were identified to assist in selecting interventions including burden of disease and quality of evidence. After discussion and preliminary investigation of the literature, the interventions selected were:

- acupuncture for chronic low back pain (LBP);
- St John's wort for depression;
- fish oils for prevention of heart disease among those who have experienced myocardial infarction;
- fish oils for rheumatoid arthritis; and
- Phytodolor for osteoarthritis.

Methods

All analyses were conducted on an incremental basis (the additional cost compared with the additional benefit), and report cost ($) per disability adjusted life year (DALY) avoided. All costs are in 2009 Australian dollars. Only the direct health system costs were included in each analysis. Indirect costs such as productivity losses were excluded. Comprehensive literature reviews were undertaken to identify the effectiveness of complementary medicine therapies compared with usual or best practice standard care, or placebo, with a preference for double blind randomised controlled trials. A variety of benchmarks are used to determine cost effectiveness, and in this analysis the first has been selected.

- gross domestic product (GDP) per capita i.e. around $52,000 in 2008-09 – in line with the World Health Organization guidelines that interventions whose cost effectiveness is between one and three times GDP per capita per quality adjusted life year (QALY) gained (or DALY averted) are cost effective and those less than GDP per capita per QALY gained (or DALY averted) are very cost effective[1],
- $60,000 – in line with the Department of Health and Ageing (Applied Economics, 2003); or
- the Department of Finance and Deregulation's valuation of a statistical life year, of $151,000 in 2007.[2]

Acupuncture for chronic non-specific LBP

The National Institute of Complementary Medicine requested three analyses:

- a comparison of acupuncture as a complement to standard care versus placebo (sham acupuncture[3]) and standard care;

[1] http://www.who.int/choice/costs/CER_levels/en/index.html Average GDP per capita for the Western Pacific region including Australia is shown as US$30,708 with three times that shown as US$92,123 in the year 2005.
[2] http://www.finance.gov.au/obpr/docs/ValuingStatisticalLife.pdf

[3] Sham treatment consists of superficial needling at non acupuncture points.

- a comparison of acupuncture as a complement to standard care versus standard care alone; and
- a comparison of acupuncture alone versus standard care alone.

The meta-analyses conducted for this study found good evidence that acupuncture as a complement to standard care resulted in significantly better pain outcomes than standard care alone. However, acupuncture alone as an alternative to standard care alone provided a significant improvement in pain only for a short period. No statistically significant benefit of acupuncture over sham was found when all patients received standard care. Hence only the second two CEAs were conducted.

Chronic LBP was defined as persistent or recurrent LBP, which is non-specific in origin (i.e. excluding pain caused by cancer, infection, fracture, etc) and lasts for three months or more. It is commonly associated with psychological distress and depression. A literature review of epidemiological studies for this analysis led to an estimated prevalence rate in Australia of 11.4% in adults and found efficacy of the intervention relative to both comparators. The cost of acupuncture was obtained from a random sample of Victorian practices.

According to WHO benchmarks, acupuncture as a complement to standard care for relief of chronic non specific LBP is very cost effective (Table i), even more so if comorbid depression is alleviated at the same rate as pain. This finding is in line with international cost effectiveness studies (Thomas et al 2005 and Witt et al 2006) of acupuncture as a complement to standard care.

Table i: Cost ($) per DALY avoided, acupuncture as a complement to standard care versus standard care alone

	Without depression	With comorbid depression
Mean	48,562	18,960
Std Deviation	14,889	5,813

As a replacement for standard care for chronic non specific LBP, acupuncture was found not generally cost effective.

- Acupuncture was only cost effective in this setting if the findings from Haake et al (2007) were used as the basis for modelling (where acupuncture led to significantly improved pain outcomes compared with standard care lasting for six months) and only if comorbid depression was alleviated alongside back pain.
- Incorporating the cost of adverse events of NSAIDs did not make a marked difference to the results.

This second analysis was hampered by the lack of information about standard care for chronic non specific LPB in Australia and in particular, utilisation of health services for this condition. However, despite sensitivity analysis around the cost of standard care, acupuncture was not cost effective.

Around 1.9 million Australians aged 18 years or over experience chronic non-specific LBP (ABS 2009). Most experience pain that lasts for six months or more. Pain relief through cost

effective complementary acupuncture would therefore clearly benefit a substantial number of Australians.

The exclusion of productivity costs, means that these results may be conservative. Chronic pain is associated with absenteeism from work and reduced work effectiveness (presenteeism). Access Economics (2007) estimated that in 2007 while the health system costs of chronic pain accounted for 20% of the total costs, the burden of disease and productivity losses associated with chronic pain each accounted for 43% of the total cost. If the presenteeism and absenteeism costs of LBP are averted in a one to one ratio with the burden of disease as Access Economics (2007) would suggest, the benefits from acupuncture would double (or more than double if the other indirect financial costs such as informal carer costs were also included).

St John's wort for mild to moderate depression

The cost effectiveness of St John's wort was compared with standard anti-depressants – serotonin and noradrenaline reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs) and tricyclic anti-depressant (TCAs) etc – for mild to moderate (but not severe) depression. Australian and international studies suggest the prevalence of mild to moderate depression among males of 2.14% and among females of 3.52%, based on an approximate proportion of severe depression in total depression of 30.9%.

A systematic review and meta-analysis found that St John's wort is equally as effective for mild to moderate depression as standard anti-depressants, except that withdrawals from treatment are lower with St John's wort (Linde et al, 2008; Rahimi et al, 2009). Just taking into account the efficacy and safety findings (i.e. no difference in efficacy or safety, in statistically significant terms), showed **St John's wort to be cost saving relative to standard anti-depressants**.

The main driver of this result was that the unit cost of St John's wort was estimated as $0.17/day (from on-line pharmacy data) while that for standard anti-depressants was estimated as $0.57/day (from official data). Over the population of Australians with mild and moderated depression, of whom 56% were estimated to take medication, a saving of nearly $50 million per annum would be possible.

> If costs associated with switching treatments are taken into account in sensitivity analysis (including additional medical supervision and reduce quality of life for patients), **St John's wort dominates standard anti-depressants for mild to moderate depression** (i.e. St John's wort was both cost saving and also resulted in a reduced disease burden). Savings are $50 million plus 49 DALYs per annum.

St John's wort may need to be taken under medical supervision because, like standard anti-depressants, it can interact with other drugs leading to side effects. This analysis thus assumed that the other health system costs (GP and psychiatrist visits etc) were the same for St John's wort and standard anti-depressants. There may need to be some standardisation of St John's wort extracts due to the current heterogeneity on the market, and this may lead to an increase in the cost of St John's wort. However, even if the costs of St John's wort tripled, St John's wort would still dominate anti-depressants because it is associated with fewer treatment withdrawals.

Fish oils as adjunctive treatment for prevention of heart disease among those who have experienced myocardial infarction (MI)

The cost effectiveness of fish oils as a complement to current preventive therapies for reduced death and morbidity among people with coronary heart disease (CHD) was compared with no fish oils for people who have had a MI within three months and who are unable to eat sufficient amounts of oily fish to meet the recommended intake of eicosapentaenoic acid (EPA) and decosahexaenoic acid (DHA).

Evidence for the efficacy and safety of these interventions was broadly based on two large clinical trials (GISSI-P and DART1, notably Marchioli et al, 2002 and Cooper et al, 2007). Both of these trials showed that the primary benefit of fish oils is in the reduction of CHD death and morbidity as well as overall mortality within the populations. Health system costs were derived from AIHW data and fish oil costs ($112.15/person per annum on average) from on-line pharmacy data. Burden of disability weights were from Begg et al (2007). A second order Monte Carlo simulation was undertaken on the TreeAge decision model.

Fish oils were found to be highly cost effective — consistent with other international cost effectiveness studies. The incremental cost per person was $128 per annum and the incremental effectiveness 0.06 DALYs. The cost per DALY avoided was $2,041. Sensitivity analysis was conducted around treatment effect variables (MI, stroke, revascularisation, CHD mortality and other mortality). The results remained highly cost effective under all of the sensitivity scenarios, evaluated against all the cost effectiveness thresholds.

Applying the unit cost difference to overall CHD prevalence – estimated as 309,726 people (Begg et al, 2007) - provides an overall higher cost bound of the fish oil intervention of $39.6 million per year. The estimated maximum wellbeing gain was 19,424 DALYs averted per annum.

Where dietary changes cannot be made (or sustained) there is a clear role for the use of dietary supplements to provide the necessary dietary intake of EPA and DHA. The use of fish oil supplements was shown here to be a cost effective intervention to prevent future cardiovascular mortality in Australia.

Fish oils for rheumatoid arthritis (RA)

The intervention was fish oil supplements for RA for 12 months as adjunctive therapy to 3 months non-steroidal anti-inflammatory drugs (NSAIDS). The cost effectiveness of this intervention was compared with standard care (12 months of NSAIDs).

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 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 may have similar cardiovascular side-effects associated with their use, as well as gastro-intestinal bleeding adverse events.

This study expands on data used in a meta-analysis by Goldberg and Katz (2007), with the addition of a more recent study – Galarraga et al (2008). 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 his or her disease. These reductions in NSAID reliance would subsequently reduce the overall risk of cardiovascular side effects associated with NSAID treatment. This study examined the cost effectiveness of using fish oil supplements as an adjunctive therapy (with lower NSAID use) rather than standard NSAID therapy alone.

Health system costs were derived from AIHW data and fish oil costs from on-line pharmacy data. Burden of disease disability weights were from Begg et al (2007). A second order Monte Carlo simulation was undertaken on the TreeAge decision model. The incremental cost per person was $330 per annum and the incremental effectiveness 0.0006 DALYs.

The results of the cost effectiveness analysis indicate that the cost per DALY avoided is approximately $529,000. Sensitivity analysis was conducted around the meta-analysis results using the 95% confidence intervals as upper and lower bounds. Results were shown to be very sensitive to these changes with large variations observable. However, all the incremental cost effectiveness rations (ICERs) were above all the cost effectiveness thresholds.

> Fish oils as an adjunctive treatment with NSAIDs, to reduce a patient's reliance on NSAID treatment, were thus not considered cost effective under any of the scenarios considered.

Phytodolor for osteoarthritis

The final cost effectiveness analysis compared Phytodolor (a proprietary herbal medicine) with Diclofenac (a non-steroidal anti-inflammatory drug or NSAID) in the treatment of osteoarthritis. The literature review was relatively sparse, finding equivalence of efficacy and health outcomes, with cost thus being the major determinant of cost effectiveness.

> The per person difference in cost was $1.46-$1.18=$0.28 per day, or $102.20 per annum. Phytodolor was found to be cost-saving compared with Diclofenac.
>
> With osteoarthritis projected to affect 1.74 million Australians in 2009, if all these people currently use a NSAID such as Diclofenac, then there could be around 1.74*102.20=$178 million per annum in potential savings from switching to Phytodolor compared to using Diclofenac.
>
> In reality, the Diclofenac market is not this large, but similar savings might be achievable from other similar NSAIDs, although this research is yet to be done.

Due to the finding of comparable health benefits, the results of Phytodolor being cost saving compared to Diclofenac are naturally highly sensitive to price. The price margin is estimated as only a 24% premium of Diclofenac over Phytodolor™. As such a 10% reduction in the price of Diclofenac together with a 10% increase in the price of Phytodolor would make the two almost indifferent on cost.

The major uncertainty is in relation to additional health benefits from less adverse events from Phytodolor™, for which robust data were unavailable. Such data would strengthen the findings of this analysis and, given the conclusions from individual literature items, could potentially show Phytodolor to be dominant over Diclofenac (lower costs and greater efficacy when all health outcomes are included). However, a higher level of evidence is required to support such a postulate and hence we recommend further studies to this end. Future studies would benefit from more comparators, such as paracetomol (with its lower adverse event profile) as well as other interventions that have been found to be effective in the management of osteoarthritis.

Access Economics

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1 Background

The National Institute of Complementary Medicine (NICM) commissioned Access Economics to undertake cost effectiveness analyses of five complementary medicine interventions.

1.1 Selection of interventions

A Reference Group[4] was established to assist in selecting interventions, indications and comparators for analysis. Selection criteria were as follows.

1. Intervention — the disease application and population group for the intervention should be specific.
2. Size/burden of the problem — the condition should represent a high burden of disease in the community. The burden should include consideration not only of prevalence of incidence in the community but also the extent of disability the condition causes (loss of quality of life, illness duration, loss of productivity, increased co-morbidity, etc).
3. Importance — the intervention should be relatively important in managing the disease of concern.
4. Relevance — addressing disease burden from this condition should have political relevance, fitting into the current policy debate or addressing a data need and thus improving evidence to overcome any current political barriers to the intervention's use.
5. Evidence — there should be strong high quality evidence to demonstrate the effectiveness of the intervention in improving health outcomes related to the condition.
6. Risk/benefit — the risk in administering the intervention should be sufficiently small to justify the gain in health outcomes.
7. Specificity — the intervention (therapy or product) should be able to be specifically defined and therefore clearly identified in studies used to justify the strength of evidence.
8. Comparator — the main comparator that is likely to be used in cost effectiveness analysis should be able to be well defined.
9. Alternative opportunities — the intervention should offer an opportunity compared to current alternatives for the management of the condition.

A list of over 20 interventions was discussed by the Reference Group based on preliminary investigation of the literature. A matrix was drawn up ranking interventions against the criteria above and considering each in relation to a broader contextual filter to provide a mix of oral and non-oral interventions for different indications. The interventions selected for analysis were thus:

- acupuncture for chronic low back pain;
- St John's wort for depression;

[4] The Reference Group comprised Prof Alan Bensoussan (University of Western Sydney), Dr Lesley Braun (Alfred Hospital), Prof David Briggs (University of Western Sydney), Prof Marc Cohen (RMIT University), Assoc Prof David Colquhoun (University of Queensland), Dr Gary Deed (Australian College of Nutritional Medicine), Assoc Prof Chris Doran (University of New South Wales), Suzanne Pierce (Industry and Investment NSW), Chris Oliver (Blackmores), Prof Stephen Myers (Southern Cross University), Assoc Prof Caroline Smith (University of Western Sydney), Prof Con Stough (Swinburne University), and Prof Charlie Xue (RMIT University).

- fish oils for secondary prevention of heart disease among those who have experienced myocardial infarction; and
- fish oils for rheumatoid arthritis;
- Phytodolor™ for pain management in osteoarthritis.

1.2 Structure of the report

The cost effectiveness analyses for each intervention are described in the following chapters, one by one, based on the following structure for each chapter.

1. Background – a brief introduction to the context of the analysis.
2. Aim – the hypothesis (in all cases the viewpoint is that of society).
3. Indication – a description/definition of the indication.
4. Intervention – a description/definition of the Intervention.
5. Comparator(s) – a description of the selection of the alternative(s).
6. Effectiveness – a presentation of data from studies used to estimate effectiveness, with description and meta-analysis as appropriate.
7. Benefits – the nature, measurement and valuation of benefits, including reduction of any serious adverse reactions where relevant.
8. Model – a description of the model structure.
9. Costs – the identification, measurement and valuation (price and quantity) of costs, with results from the costing process.
10. Results and sensitivity analysis – a presentation of major findings including modelling to allow for uncertainty in relation to key results.
11. Conclusions – the implications of findings for policy or for further study.
12. References – a list of references at the end of each chapter.

Where applicable, any appendices follow the relevant references section within the chapters.

1.3 Conducting cost effectiveness analysis

Cost effectiveness analysis (CEA) is a form of economic analysis that compares the relative expenditure (costs) and outcomes (effects) of two or more courses of action. CEA is distinct from cost benefit analysis, which assigns a monetary value to the measure of effect (Bleichrodt and Quiggin, 1999). CEA is often used in the health sector, where it may be inappropriate to monetise health effect. Typically the CEA is expressed in terms of a ratio where the denominator is a gain in health from a measure (years of life, premature births averted, sight-years gained) and the numerator is the cost associated with the health gain. The most commonly used outcome measures are quality adjusted life years (QALYs) or Disability Adjusted Life Years (DALYs). When these metrics are used, this subset of CEA is called cost utility analysis.

Cost-effectiveness is typically expressed as an incremental cost-effectiveness ratio (ICER), the ratio of change in costs to the change in effects. Access Economics has historically utilised World Health Organization (WHO) guidelines for CEA which accord well with the ten-point checklist developed by Drummond (2005, 1992) and preferred by NICM for use here.

1. Study question: The economic importance of the research question should be outlined. The hypothesis being tested, or question being addressed, in the economic evaluation should be clearly stated. The viewpoint(s) – e.g. health care system, society-for the analysis should be clearly stated and justified.
2. Selection of alternatives: The rationale for choice of the alternative programmes or interventions for comparison should be given. The alternative interventions should be described in sufficient detail to enable the reader to assess the relevance to his or her setting – that is, who did what, to whom, where, and how often.
3. Form of evaluation: The form(s) of evaluation used – e.g. cost minimisation analysis, cost effectiveness analysis--should be stated. A clear justification should be given for the form(s) of evaluation chosen in relation to the question(s) being addressed.
4. Effectiveness data: If the economic evaluation is based on a single effectiveness study – e.g. a clinical trial – details of the design and results of that study should be given – e.g. selection of study population, method of allocation of subjects, whether analysed by intention to treat or evaluable cohort, effect size with confidence intervals. If the economic evaluation is based on an overview of a number of effectiveness studies details should be given of the method of synthesis or meta-analysis of evidence – e.g. search strategy, criteria for inclusion of studies in the overview. A clear summary of key effectiveness data is imperative.
5. Benefit measurement and valuation: The primary outcome measure(s) for the economic evaluation should be clearly stated – e.g. cases detected, life years, quality adjusted life years (QALYs), willingness to pay. If health benefits have been valued details should be given of the methods used – e.g. time trade off, standard gamble, contingent valuation – and the subjects from whom valuations were obtained--e.g. patients, members of the general public, health care professionals. If changes in productivity (indirect benefits) are included they should be reported separately and their relevance to the study question discussed.
6. Costing: Quantities of resources should be reported separately from the prices (unit costs) of those resources. Methods for the estimation of both quantities and prices (unit costs) should be given. The currency and price date should be recorded and details of any adjustment for inflation, or currency conversion, given. Results of the three-step costing process – identification, measurement and valuation, need to be outlined clearly in a table.
7. Modelling: Details should be given of any modelling used in the economic study – e.g. decision tree model, epidemiology model, regression model. Justification should be given of the choice of the model and the key parameters.
8. Adjustments for timing of costs and benefits: The time horizon over which costs and benefits are considered should be given. The discount rate(s) should be given and the choice of rate(s) justified. If costs or benefits are not discounted an explanation should be given.
9. Allowance for uncertainty: When stochastic data are reported details should be given of the statistical tests performed and the confidence intervals around the main variables. When a sensitivity analysis is performed details should be given of the approach used – e.g. multivariate, univariate, threshold analysis – and justification given for the choice of variables for sensitivity analysis and the ranges over which they are varied.
10. Presentation of results: An incremental analysis – e.g. incremental cost per life year gained-- should be reported, comparing the relevant alternatives. Major outcomes – e.g. impact on quality of life – should be presented in a disaggregated as well as aggregated form. Any comparisons with other health care interventions – e.g. in terms

of relative cost effectiveness – should be made only when close similarity in study methods and settings can be demonstrated. The answer to the original study question should be given; any conclusions should follow clearly from the data reported and should be accompanied by appropriate qualifications or reservations. The main emphasis in the reporting of study results should be on transparency. The main components of cost and benefit – e.g. direct costs, indirect costs, life years gained, improvements in quality of life – should be reported in a disaggregated form before being combined in a single index or ratio.

1.4 Cost effectiveness benchmarks

The World Health Organization defines cost effectiveness relative to gross domestic product (GDP) per capita[5] as:

- **cost effective**: one to three times GDP per capita to avert one lost DALY (for Australia in 2009, around A$52,000 to A$156,000 per DALY averted); and
- **very cost effective**: less than GDP per capita to avert one lost DALY (for Australia in 2009, less than A$52,000/DALY averted).

The WHO definition has been selected for use in this report.

Other cost effectiveness benchmarks include:

- $60,000 – in line with the Department of Health and Ageing (Applied Economics, 2003); or
- the Department of Finance and Deregulation's valuation of a statistical life year, of $151,000 in 2007.[6]

1.5 References

Applied Economist (2003) 'Returns on investment in public health: An epidemiological and economic analysis', *Report for the Department of Health and Ageing*.

Bleichrodt H, Quiggin J (1999) 'Life-cycle preferences over consumption and health: when is cost-effectiveness analysis equivalent to cost-benefit analysis?' *J Health Econ* 18(6):681–708.

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Drummond M (1992) 'Cost-effectiveness guidelines for reimbursement of pharmaceuticals: is economic evaluation ready for its enhanced status?' *Health Economics*, 1:85-91.

[5] See for example http://www.who.int/choice/costs/CER_levels/en/index.html Average GDP per capita for the Western Pacific region including Australia is shown as US$30,708 with three times that shown as US$92,123 in the year 2005.

[6] http://www.finance.gov.au/obpr/docs/ValuingStatisticalLife.pdf

2 Acupuncture for chronic non-specific low back pain

2.1 Background

Back pain is a leading (top 20) cause of disease burden in Australia (Begg et al, 2007) contributing around 1.2% of the total burden of disease and 2.2% of the non-fatal burden of disease. Chronic back pain is associated with:

- interference with normal daily activities (e.g. work, home duties, family and sporting activities) because of disability, both physical and psychosocial in origin;
- high and ongoing consumption of health treatments (e.g. GP visits, medication, physiotherapy);
- side-effects of treatment (typically due to medication, especially if on high doses and taking more than recommended or mixed with other substances, like alcohol – includes gastric problems, such as nausea and constipation; mental slowing or confusion which can affect functioning and operation of equipment or cars);
- mood disturbance (mostly depression or adjustment problems);
- sleep disturbance (trouble getting to sleep and/or frequent wakening during the night); and/or
- the effects of disuse (e.g. deconditioning of muscles or joints, loss of general fitness).

In the UK, the National Institute for Health and Clinical Excellence (NICE) recently released guidelines for treatment of chronic, non-specific low back pain (LBP) in a primary care setting suggesting that patients be offered a course of acupuncture as one of three non-pharmacologic options for treatment, depending on patient preferences (Savigny et al, 2009)[7]. The NICE guidelines are discussed in more detail in Box 2-1. In the US, Chou and Huffman (2007) reviewed evidence of non-pharmacologic therapies for chronic LBP for the American Pain Society/American College of Physicians Clinical Practice Guideline and similarly concluded that, for patients who do not improve with self care, the addition of non-pharmacologic therapy such as acupuncture should be considered.

2.2 Aim

The aim of this study is to assess — in an Australian setting — the cost effectiveness of acupuncture for the alleviation of chronic LBP. The National Institute of Complementary Medicine requested three analyses:

- a comparison of acupuncture as a complement to standard care versus placebo (sham acupuncture[8]) and standard care;
- a comparison of acupuncture as a complement to standard care versus standard care alone; and
- a comparison of acupuncture alone versus standard care alone.

[7] National Institute for Health and Clinical Excellence (2009) *Low back pain* Early management of persistent non-specific low back pain. NICE clinical guideline 88 Developed by the National Collaborating Centre for Primary Care, May.

[8] Sham treatment consists of superficial needling at non acupuncture points.

Consistent with the primary focus of the Pharmaceutical Benefits Advisory Committee (PBAC), the focus of this study is on health and health system costs[9]. This represents a conservative approach. As well as alleviating pain, acupuncture may also relieve associated restrictions on function (movement and mobility). Together, reductions in pain and improvements in function are likely to facilitate return to paid employment and/or improve productivity while at work of those who were previously disabled by their back pain. However, the impact of acupuncture on productivity outcomes was not included in the agreed scope of this project, and can be less influential in PBAC decision making.[10]

An outline of the three analyses for this project is provided in Table 2.1 (summarising cost differences but not efficacy differences).

Table 2.1: Analyses included in this study

Analysis	Intervention	Comparator	Difference in cost
1	Acupuncture and standard care	Standard care alone	The cost of acupuncture and any changes in other health system costs arising because of the intervention.
2	Acupuncture and standard care	Sham and standard care	The cost of acupuncture and sham acupuncture are the same, so only changes in other health system costs that arise because of the intervention are relevant to costs.
3	Acupuncture alone	Standard care alone	The difference between the health system costs of acupuncture and the health system costs of standard care.

[9] "*PBAC mainly considers the costs of providing health care resources. These extend beyond the costs of the drug to include possible cost offsets of reduced provision of health care resources as a result of listing a drug*" (Australian Government Department of Health and Ageing, Pharmaceutical Benefits Advisory Committee, 2008:4).

[10] "*PBAC may also consider costs and cost offsets of nonhealth care resources, but these might not be as influential in decision making as health care resources*" (Australian Government Department of Health and Ageing, Pharmaceutical Benefits Advisory Committee, 2008:4).

Box 2-1 UK guidelines for chronic, non specific LBP

NICE guidelines (Savigny et al, 2009) recommend:

- Provide people with advice and information to promote self-management of their LBP.

- Offer one of the following treatment options, taking into account patient preference: an exercise program (with a maximum of eight sessions over 12 weeks – either group or individual, aerobic activity, movement instruction, muscle strengthening, postural control, stretching); a course of manual therapy[11] (up to a maximum of nine sessions over a period of up to 12 weeks); or a course of acupuncture (needling comprising up to a maximum of ten sessions over a period of up to 12 weeks). Consider offering another of these options if the chosen treatment does not result in satisfactory improvement.

- Consider referral for a combined physical and psychological treatment program including cognitive behavioural therapy (around 100 hours over a maximum of eight weeks) for people who received at least one less intensive treatment and have high disability and/or psychological distress.

- The guidelines make various recommendations for pharmacological pain therapy.

- Do not offer X-ray of the lumbar spine for the management of non-specific LBP. Only offer an MRI scan[12] for non-specific LBP within the context of a referral for an opinion on spinal fusion.

- Do not offer injections of therapeutic substances into the back. Do not offer electrotherapy, transcutaneous electrical nerve stimulation (TENS), lumbar supports or traction.

- Consider referral for opinion on spinal fusion surgery if patient has completed a package of care and still has severe non specific LBP. Do not refer patients for intradiscal electrothermal therapy, percutaneous intradiscal radiofrequency thermocoagulation or radiofrequency facet joint denervation.

2.3 Indication

Chronic LBP is persistent or recurrent LBP, which is non-specific in origin (i.e. excluding pain caused by cancer, infection, fracture etc). The difference between chronic and acute LBP generally depends on the duration of pain. Chronic pain is most often defined as lasting for

[11] Spinal manipulation (a low-amplitude, high-velocity movement at the limit of joint range that takes the joint beyond the passive range of movement), spinal mobilisation (joint movement within the normal range of motion) and massage (manual manipulation or mobilisation of soft tissues).

[12] Consider MRI (magnetic resonance imaging) when a diagnosis of spinal malignancy, infection, fracture, cauda equina syndrome or ankylosing spondylitis or another inflammatory disorder is suspected, but not for chronic low back pain.

more than 12 weeks, and acute pain for less than 12 weeks, but exact durations differ across studies (Andersson 1999, Savigny et al 2009, Jensen 2004, and studies in Table 2.2).

2.3.1 Epidemiology

Prevalence

A literature search was conducted to find estimates of the prevalence of chronic non specific LBP. The search terms were "Prevalence chronic low back pain" and "Prevalence non-specific low back pain". The National Center for Biotechnology Information (NCBI) and National Institutes of Health (NIH) Pubmed databases were searched in August 2009 and selection criteria included articles: (1) in English; (2) published in the last five years; (3) in a journal of conventional medicine; and (4) concerning studies in humans.

Findings are summarised in Table 2.2. Studies of the prevalence of chronic LBP are rare and no studies matched the indication of LBP for this study (non-specific, and at least three months duration) (Table 2.2).

For this analysis, the estimates of the prevalence of LBP from Walker et al (2004) were used because they are based on the Australian population, and also because they focus on LBP rather than back pain *per se*. Walker et al (2004) found 13.4% of all Australians experienced LBP lasting or expected to last six months.

A review for development of the European guidelines for the management of chronic non-specific LBP (Airaksinen et al, 2005) concluded there is little scientific evidence on prevalence, with best estimates suggesting between 11% and 23% of the population are disabled by LBP. Specific (identifiable) causes of LBP are uncommon (less than 15% all back pain). Factoring down Walker et al (2004) by 15% to remove cases of specific pain (Airaksinen et al, 2005), suggests a prevalence rate estimate for non-specific chronic LBP of at least 11.4% (i.e. 85% of 13.4%).

Risk factors

The most important risk factor for a new episode of back pain is a previous history. The risk of experiencing LBP is twice as high for those with a previous episode of LBP (Hestbaek et al, 2003).

Mortality

Chronic pain, especially when it is widespread and with a long duration, may be associated with an increased risk of mortality. However, there are relatively few data available regarding the precise association between chronic pain and mortality. The AIHW reports that there is no increased risk of mortality due to chronic back pain (Begg et al, 2007).

Table 2.2: Epidemiology of chronic lower back pain

Source	Aim and method	Definitions	Outcome measures	Findings
ABS (2009) (Australia)	The National Health Survey was conducted throughout Australia from August 2007 to June 2008 Random sample of approximately 15,800 private dwellings. Interviews were conducted by trained interviewers	Long term medical conditions are classified based on the International Classification of Diseases 10th Revision.		In 2007-08, 14.4% of Australians had back pain lasting or expected to last six months or more.
Blyth et al (2001) (Australia)	In NSW, random sample of adults (aged >16 yrs) interviewed via telephone. 17,543 respondents (response rate of 70.8%).	Chronic pain was defined as pain experienced every day for three months in the six months prior to interview. No information was available about the site or cause of pain.	Respondents asked if they experienced chronic pain.	20% of females and 17.1% of males reported experiencing chronic pain.
Walker et al (2004) (Australia)	To determine prevalence of LBP and related disability in Australian adults (aged 18+). Population-based survey mailed to 3,000 adults on the Electoral Role. 69% response rate.	Subjects were provided with a diagram of a mannequin that defined the low back as a shaded area between the last ribs and the gluteal folds	Point, 6 month, 12 month and lifetime prevalence of LBP, and the level of associated disability as measured by the Chronic Pain Grade Questionnaire (CPG).	Prevalence of LBP lasting more than 6 months was 13.4%. 12 month prevalence was 67.6% and lifetime prevalence was 79.2%.
Cassidy et al (1998) (Canada)	The Saskatchewan Health and Back Pain Survey was mailed to 2184 Saskatchewan adults between 20 and 69 years of age. Response rate 55%. Sample was weighted, random and age-stratified.	A mannequin diagram was used to define the anatomic location of LBP. For the point prevalence, the question read, "Do you have LBP at the present time, that is, right now?" The cumulative lifetime prevalence question read, "In your lifetime, have you ever had LBP?"	Point, 6 month, 12 month and lifetime prevalence of LBP, and the level of associated disability as measured by the Chronic Pain Grade Questionnaire (CPG).	28.7% of the study sample had LBP at the time of the survey, and 84.0% reported having experienced LBP during their lifetime.

Source	Aim and method	Definitions	Outcome measures	Findings
Freburger et al (2009) (US)	To determine whether the prevalence of chronic LBP and the demographic, health-related, and health care–seeking characteristics of individuals with the condition have changed over the last 14 years. Cross-sectional, telephone survey of a representative random sample of North Carolina households with phone numbers was conducted in 1992 and repeated in 2006. 4,437 households were contacted in 1992 and 5,357 households in 2006 to identify adults 21 years or older with LBP or neck pain.	LBP was defined as pain at the level of the waist or below, with or without buttock and/or leg pain. An individual was considered to have chronic LBP if she or he reported (1) pain and activity limitations nearly every day for the past 3 months or (2) more than 24 episodes of pain that limited activity for 1 day or more in the past year.	Chronic LBP survey module included questions on symptoms (e.g. pain intensity, presence of leg pain), general health status (Medical Outcomes Study Short Form 12, presence of comorbidities), functional status (Roland-Morris Disability Questionnaire), and use of health care providers and treatments in the past year.	Prevalence rose from 3.9% (95% CI 3.4% to 4.4%) in 1992 to 10.2% (95% CI 9.3% to 11%) in 2006. The increase occurred among all sex, age and race/ethnic subgroups. Changes in the age composition of the state do not explain the increase since the rise in prevalence was similar across all age strata.

Recovery

Definitions of back pain vary and estimates of recovery also depend on the population studied (e.g. how patients were treated if at all). A systematic literature review of population studies by Hestbaek et al (2003) of the course of LBP without any known intervention found that the reported proportion of patients who still experienced pain after 12 months was 62% on average (range 42-75%). In 490 UK adults consulting a GP for LBP, Croft et al (1998) found that 21% had completely recovered at three months and 25% had completely recovered at 12 months (with the remaining 75% still retaining some degree of LBP).

2.3.2 Comorbidities — depression

Chronic pain is associated with psychological distress and depression (Blyth et al, 2001; NSW Health Department, 1999; Clarke et al, 2005; Magni et al, 1993; Von Korff et al, 1988).

> *… the association between chronic pain and depression is well-recognised in the literature … (Crombie et al, 1994).*

Two surveys conducted in the USA showed that up to 23% of primary care physicians prescribe anti-depressants for LBP, and 2%, 7% and 13% of visits for LBP to primary care physicians, neurologists and rheumatologists respectively involve the prescription of anti-depressant mediation (Urquhart et al, 2008).

2.4 Intervention

Acupuncture was defined to include traditional acupuncture with manual or electronic stimulation. Trigger point acupuncture, and acupuncture combined with heat therapy were excluded. Acupuncture methods varied across studies included in this analysis (see Table 2.3). For example, the frequency and duration of individual sessions differed (e.g. 10 sessions for 30 minutes each or 20 sessions for one hour each), the duration of treatment differed (e.g. ten weeks or three months), and, where these were specified, acupuncture needling points, needle dimensions and depth of insertion differed.

Where included as a complement to acupuncture, standard care generally included one — or a combination — of education about back care, back exercises, pain medication and/or physiotherapy (Table 2.3). In a number of the trials included here, standard care varied across study participants (e.g. nature of therapy, frequency and duration of therapy, dose and duration of pain medication and type of drug prescribed).

2.4.1 Literature search

A literature search was undertaken on 13 July 2009 of NCBI and NIH Pubmed using search terms: “acupuncture”, “chronic low back pain”, and “non-specific low back pain”. The focus of the initial search was on trials of acupuncture treatment and meta-analyses published since the Cochrane Review was released (Furlan et al, 2005). The bibliographies of the Cochrane Review and meta-analyses (Ernst and White 1998, Mannheimer et al 2005, Keller et al 2007, Yuan et al 2008, Machado et al 2009 and Madsen et al 2009) were then analysed and other studies drawn from these. Most of the studies were not relevant to this analysis because of the comparator, for example, acupuncture alone was compared with sham alone. Many studies of acupuncture are based on small sample sizes and, althouth this was not a reason for

exclusion, larger samples are preferable. A summary of the studies assessed and reasons for inclusion or exclusion is in Section 2.13 (Appendix). The studies used here, their sample sizes and a description of the intervention and relevant comparator(s) for each are in Table 2.3.

Table 2.3: Intervention and comparator treatments in the studies included here

Study	Standard care	Acupuncture	Sham
Thomas et al (2005)	N=81 Patients in the usual care group received NHS treatment according to their general practitioner's assessment of need. Mix of interventions received including drugs, exercise, physiotherapy, transcutaneous electrical nerve stimulation, massage, advice on diet and rest.	N=159 Up to 10 individualised treatment sessions over 3 months. Acupuncturists determined the content and the number of treatments according to patients' needs. All patients remained under the care of their general practitioner.	N/A
Yeung et al (2003)	N=26 Back exercise was group physiotherapy for one hour per week for 4 weeks. Patients were also advised on back care.	N=26 12 sessions electroacupuncture 3 times per week for 4 weeks by physiotherapists certified in acupuncture. UB23, UB25, UB40 and SP6 points. Manual manipulation until deqi, followed by electrical stimulation at 2Hz for 30 mins.	N/A
Meng et al (2003)	N=24 Non-steroidal anti-inflammatory drugs (NSAIDs), non-narcotic analgesics, and back exercises.	N=23 10 sessions, 2 times per week for 5 weeks with electrical stimulation.	N/A
Leibing et al (2002)	N=46 Physiotherapy with no other treatment.	N=40 20 sessions, 30 mins each of verum acupuncture by an experienced clinician. In the first 2 weeks, 5 sessions per week, and in the next 10 weeks, once a week. Combined body and ear acupuncture – 20 body acupoints (manual stimulation) and 6 ear acupoints. Needle depth of 10-30mm.	N=45 20 sessions of 30 mins each of minimal acupuncture by the same clinician who undertook the non-sham. Needles inserted superficially, away from verum-acupoints and not stimulated.

Molsberger et al (2002)	N=61 Physiotherapy, exercise, back school, mud packs, infrared heat therapy and NSAID	N=65 Verum acupuncture – 12 sessions 3 times per week, 30mins long, using standard points. Undertaken by experienced medical doctor who had studied acupuncture.	N=61 Sham – 12 sessions 3 times per week, 30mins long, needles applied superficially at non-acupuncture points.
Witt et al (2006)	N=1,390 Conventional treatments as needed – including analgesics.	N=1,451 Maximum 15 acupuncture sessions, with points and needles left to the discretion of physician. Needle acupuncture with disposable one-time needles and manual stimulation. Physicians educated to standard with 140 hours acupuncture education using different styles and techniques.	N/A
Tsui and Cheing (2004)	N=14 Back exercise including six mobilisation exercises and one abdominal stabilisation exercise. Subjects instructed to perform mobilisation exercises 20 times per set and stabilisation exercise 10 times per set– each set three times per day.	N=14 Electroacupuncture (EA) with six acupuncture points — four points lower back and two points buttock insertion and manipulation to achieve de qi. Total of 8 treatments twice per week and each session lasted 20 minutes.	N/A

Cherkin et al 2009	N=145 Care chosen by participant and his or her physician (mostly medications, physical therapy and primary care). All participants received a self care book with information on back care and exercise.	N=143 Traditional Chinese medical acupuncture for musculoskeletal pain. Sterile disposable 32 gauge needles at least 1.5 inches long. Needling depth varied depending on the point but generally between 1 and 3cm. Twice weekly treatment for three weeks and then weekly treatment for four weeks. **Individualised acupuncture** was prescribed by experienced acupuncturist using traditional Chinese medical diagnostic techniques. **Standardised acupuncture** included eight acupuncture points commonly used for CLBP. All points needled for 20 minutes with manual stimulation to achieve De Qi.	There was a sham arm, but the comparator is not relevant to the analysis being undertaken here.
Haake et al 2007	N=364 10 sessions with personal contact with a physician or physiotherapist who administered physiotherapy, exercise "and such" (Hakke et al 2007:1893). Physiotherapy supported by NSAIDs or pain medication up to the maximum daily dose during the therapy period.	N=373 Verum acupuncture in 10, 30-minute sessions, two sessions per week. Five additional sessions were provided if after the tenth session patients experienced 10% to 50% reduction in pain intensity. Sterile disposable needles. No electrical stimulation or moxibustion was allowed. 14 to 20 needles inserted with De Qi achieved through manual stimulation.	There was a sham arm, but the comparator is not relevant to the analysis being undertaken here.

N/A = not applicable.

2.4.2 Side effects

Side effects of acupuncture can include:

- needle pain;
- bleeding;
- feelings of faintness and syncope (loss of consciousness);
- pneumothorax (the accumulation of air or gas in the space between the lung and the chest wall — a serious complication); and
- infections (serious).

Furlan et al (2005) concluded that serious adverse events are rare, but more information is required for specific conditions. Cherkin et al (2003) reviewed the literature on effectiveness of complementary therapies for back pain published up to the year 2002, and concluded that side effects for acupuncture are extremely rare. The authors noted two prospective studies of practitioners in the UK found no serious events in 66,000 acupuncture consultations, and a systematic review of acupuncture safety including nine prospective studies and almost a quarter of a million treatments reported the most serious adverse effects were two cases of pneumothorax and two cases of a broken needle. Side effects reported in the trials included in this analysis are summarised in Table 2.4.

Table 2.4: Side effects

Source	Side effects
Molsberger et al (2002)	Not reported
Leibing et al (2002)	Minor, non-serious adverse events occurred in 3 acupuncture patients. 2 patients dropped out due to the painfulness of acupuncture and 1 stopped treatment because of problems with circulation during acupuncture.
Meng et al (2003)	1 acupuncture patient dropped out due to pain from needling. Acupuncture patients reported: minor aching (5), bruising (3) and light headedness (1).
Yeung et al (2003)	No adverse reaction to or complications arising from electroacupuncture were found.
Thomas et al (2005)	No serious adverse events were reported (a). 63% of patients reported a temporary worsening of low back symptoms at 3 months with 23% of these stating that this bothered them 'a lot' or 'a great deal'. 17 patients (12.8%) reported at least one response to treatment that they were not prepared to experience again — most frequently exacerbation of back pain, and next most frequently tiredness or drowsiness.
Cherkin et al (2009)	Of 477 participants, 11 receiving real or sham acupuncture reported a moderate adverse event experience possibly related to treatment (mostly short term pain) and one reported a severe experience (pain lasting one month). One participant reported dizziness and another back spasms. Rates of adverse experiences differed by treatment group: 6 of 157 participants for individualised acupuncture, 6 of 158 for standardised acupuncture, and 0 of 162 for simulated acupuncture (P=0.04).

Source	Side effects
Witt et al (2006)	In total, 6% of patients (n=646) reported side effects after acupuncture. 54% of patients had minor local bleeding or hematoma, 17% had pain from needling, 8% had vegetative symptoms and 21% had other side effects. No life threatening side effects were reported.
Haake et al 2007	Documented serious adverse events were deemed unrelated to the intervention. 476 clinically relevant adverse events were reported by 257 patients (22.6%) with no significant difference between therapy groups.
Tsui and Cheing (2004)	Not reported.

(a) Defined as an event resulting in hospitalisation and/or permanent disability or death.

2.4.3 Drop outs and adherence to treatment protocol[13]

The only study to formally report adherence to treatment protocols was Thomas et al (2005) who found acupuncture adherence was 90%. Sixteen out of 160 patients in the acupuncture arm stopped treatment (four were too busy, three cited lack of response to treatment, four cited adverse events, and five cited a mixture of these reasons). Adherence with control (standard care) was 100%. Thomas et al (2005) adherence results were adopted for the cost effectiveness analysis here.

2.5 Comparator

As noted above (Section 2.2), the comparators are

- sham acupuncture and standard care; and
- standard care alone.

Our search for Australian guidelines indicated a paucity for chronic non-specific LBP. Most guidelines for LBP focus on acute rather than chronic (e.g. National Health and Medical Research Council (NHMRC) 2004 for acute LBP).[14] This is consistent with Bogduk (2004), who claimed there were no evidence based guidelines for chronic LBP in Australia. An exception is NSW Therapeutic Assessment Group (2002), which recommended a multidisciplinary treatment program including education, physical activity, exercise, spinal mobilisation or manipulation, cognitive behavioural therapy and medications (paracetamol, NSAIDs or others).[15] It is not clear how many Australian clinicians refer to these guidelines.

[13] In the literature the term 'adherence' in the context of medical treatment refers to the following:

- compliance - taking medication correctly in terms of dosing and regime; and
- persistence - continuing to take medication for the recommended duration of time.

[14] We searched RACGP, NHMRC, WorkSafe Victoria, and a general internet search using search terms: chronic low back pain with and without the term 'guideline'.

[15] The NSW Therapeutic Assessment Group (2002) concluded there were no published studies to support the use of the acupuncture for treatment of chronic LBP. However, most RCTs used in this analysis were published in 2002 or more recently.

2.6 Effectiveness

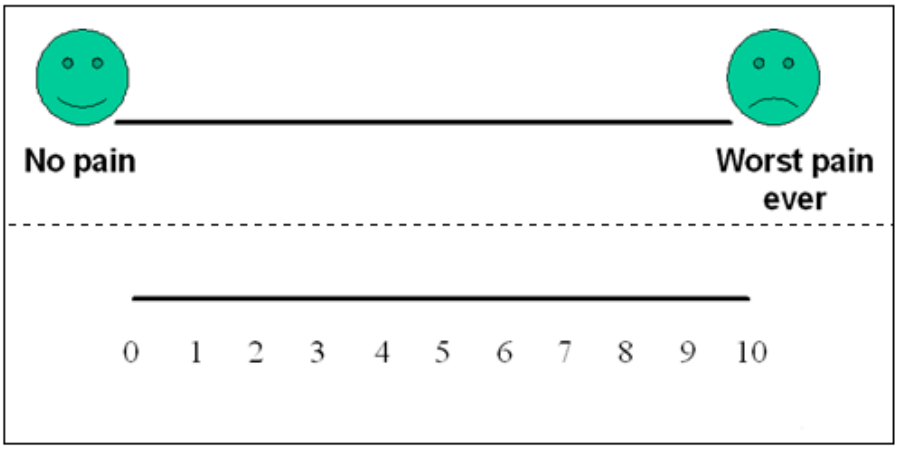
Meta-analyses were conducted to investigate the differential impact of the intervention versus the comparator on chronic non-specific LBP using Comprehensive Meta-analysis[16] software.

The results of studies reporting outcomes for a pain scale metric were used, with data drawn directly from the published article. Pain scales included the visual analogue scale (VAS) (used by Molsberger et al 2002, Leibing et al 2002, and Meng et al 2003), the numeric rating scale (NRS) (used by Yeung et al 2003 and Tui and Cheing 2004), the low back pain rating scale (used by Witt et al 2006), the SF-36 pain dimension (used by Thomas et al 2006), symptom bothersomeness index (used by Cherkin et al 2009) and the Von Korff Chronic Pain Grade Scale (used by Haake et al 2007). These are all validated indices which allow patients to indicate the intensity of their pain or changes in pain before and after treatment. Examples of the VAS and NRS are provided in Figure 2.1. The maximum end point may vary, for example, some indices use 0 (no pain) to 10 (extreme pain), while others use 0 to 100. The meta-analysis accounts for differences in indices by standardising the mean difference in pain scores by a measure of the standard deviation.

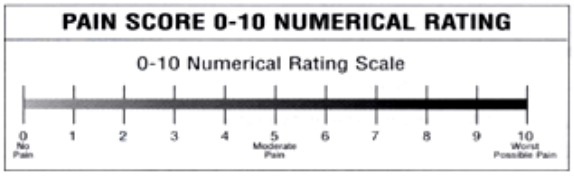
Standardised mean differences (SMD) for each trial were calculated using Hedge's g because of the small sample sizes in the majority of studies. Random effects models were applied because of expected heterogeneity. Studies were grouped according to length of follow-up. The findings of the meta-analyses are described below for each of the comparisons outlined in Table 2.1.

[16] Version 2.2.050, 2009, Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-analysis Version 2, Biostat, Englewood NJ (2005).

Figure 2.1: Visual Analogue Scale and Numeric Rating Scale of pain



Numerical rating scale (NRS)



Source: Victorian Quality Council, Department of Health, Victorian Government.[17]

2.6.2 Acupuncture and standard care vs. standard care alone

The outcome metric, follow-up and findings of the studies incorporated in the meta-analysis of acupuncture as a complement to standard care versus standard care alone are summarised in Table 2.5.

Table 2.5: Studies included — Acupuncture and standard care vs. standard care alone

	Outcome metric	Follow up	Finding
Yeung et al (2003)	Numerical rating scale (NRS) for pain	Week4 Week 8 Week 12	Significantly better NRS scores in the elecroacupuncture group than in the control group at week 4 and week 8.
Leibing et al (2002)	Visual Analogue Scale (VAS) pain	Week 12 Week 52	Acupuncture pain relief significantly better than control at week 12, but not significant (although better) at week 52.
Meng et al (2003)	VAS pain	Week 6 Week 9	Acupuncture improvement in pain significantly better than control at week 9, but not at week 6.

[17] http://www.health.vic.gov.au/qualitycouncil/activities/acute/index.htm#audit see Acute Pain Management Measurement Toolkit & Appendices Appendix 1 Pain rating scales.

Molsberger et al (20020	VAS pain	Week 4 Week 16	Significantly better pain reduction in acupuncture group than in control group at week 16, but not significant (although better) at week 4.
Witt et al (2006)	Low back pain rating scale	Week 12	Improvement in pain significantly more pronounced in acupuncture group than in control group.
Tsui and Cheing (2004)	NRS for pain	Week 4 Week 8	Significant reduction in pain in both EA and control, but significantly greater reduction for electroacupuncture group at both week 4 and week 8.
Thomas et al (2005), Thomas et al (2006), Ratciffe et al (2006) (all studies refer to the same trial)	SF-36 pain dimension	Week 52 Week 104	Weak evidence of an effect of acupuncture at 12 months (not significant) but stronger evidence of a small benefit at 24 months (significant)

Separate analyses were undertaken depending on length of follow-up:

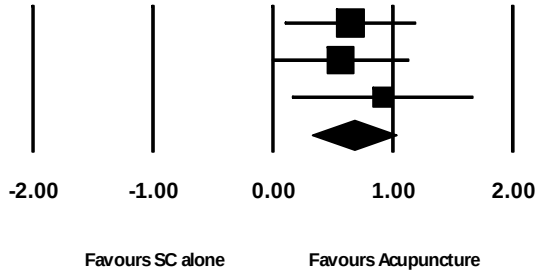
- weeks 8-9 based on Yeng et al (2003), Meng et al (2003) and Tsui and Cheing (2004);
- weeks 12-16 based on Yeng et al (2003), Leibing et al (2002), Molsberger et al (2002) and Witt et al (2006); and
- week 52 based on Leibing et al (2002) and Thomas et al (2006).

At each follow-up, the meta-analysis finding was a significant improvement in pain favouring the acupuncture arm (Figure 2.2). However, for weeks 12-16, a funnel plot suggested publication bias, suggesting an overestimate of the SMD. The results for weeks 12-16 were not therefore used in the cost effectiveness analysis.

Figure 2.2: Acupuncture as a complement to standard care — meta-analysis findings

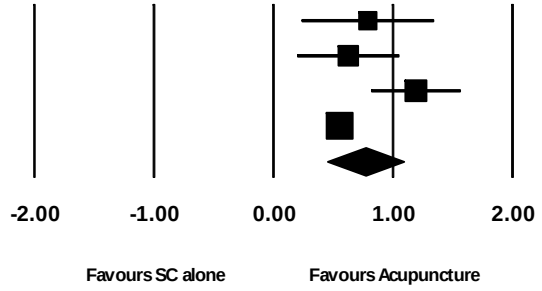
A + SC v SC alone, results weeks 8-9

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Yeung et al (2003)(8)	0.646	0.280	0.079	0.097	1.196	2.305	0.021
Meng et al (2003) (9)	0.565	0.293	0.086	-0.009	1.139	1.929	0.054
Tsui and Cheing (2004)(8)	0.916	0.387	0.150	0.158	1.674	2.368	0.018
	0.674	0.179	0.032	0.322	1.025	3.756	0.000



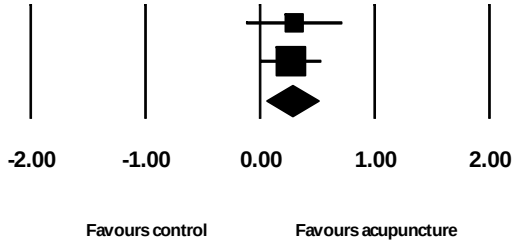
A + SC v SC alone, results weeks 12-16

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Yeung et al (2003)(12)	0.790	0.284	0.081	0.233	1.346	2.781	0.005
Leibing et al (2002)(12)	0.626	0.220	0.048	0.196	1.057	2.854	0.004
Molsberger et al (2002)(16)	1.193	0.192	0.037	0.815	1.570	6.197	0.000
Witt et al (2006)(12)	0.555	0.038	0.001	0.480	0.629	14.503	0.000
	0.767	0.163	0.026	0.448	1.086	4.711	0.000



A+SC v SC alone, results week 52

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Leibing et al (2002)(52)	0.298	0.215	0.046	-0.124	0.720	1.382	0.167
Thomas et al (2006)(52)	0.270	0.137	0.019	0.002	0.537	1.974	0.048
	0.278	0.115	0.013	0.052	0.504	2.407	0.016



2.6.3 Acupuncture as a complement to standard care vs. standard care and sham

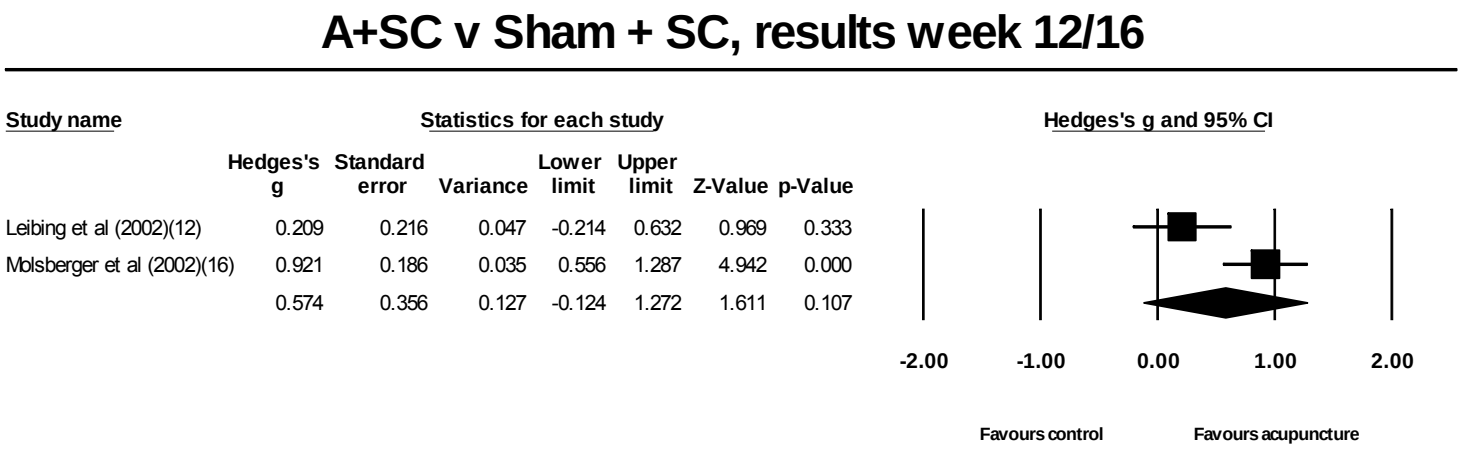
Only two studies were identified on which to base estimates of the effectiveness of acupuncture as a complement to standard care versus sham with standard care. The outcome metric, follow-up and findings of the studies incorporated in the meta-analysis of acupuncture as a complement to standard care versus standard care alone are summarised in Table 2.6.

Table 2.6: Studies included — Acupuncture and standard care vs. standard care and sham

	Outcome metric	Follow up	Finding
Leibing et al (2002)	Visual Analogue Scale (VAS) pain	Week 12 Week 52	No significant difference between acupuncture and sham at either time point.
Molsberger et al (20020	VAS pain	Week 4 Week 16	Significant improvement in pain favouring acupuncture over sham at week 4 and week 16.

A meta-analysis was conducted based on the results for weeks 12-16, as this was the only common time point for follow-up. A weak positive effect of acupuncture was found, but the difference was not significant (Figure 2.3). Testing of publication bias was not possible with only two studies.

Figure 2.3: Acupuncture and standard care versus sham and standard care — meta-analysis findings



2.6.4 Acupuncture alone vs. standard care alone

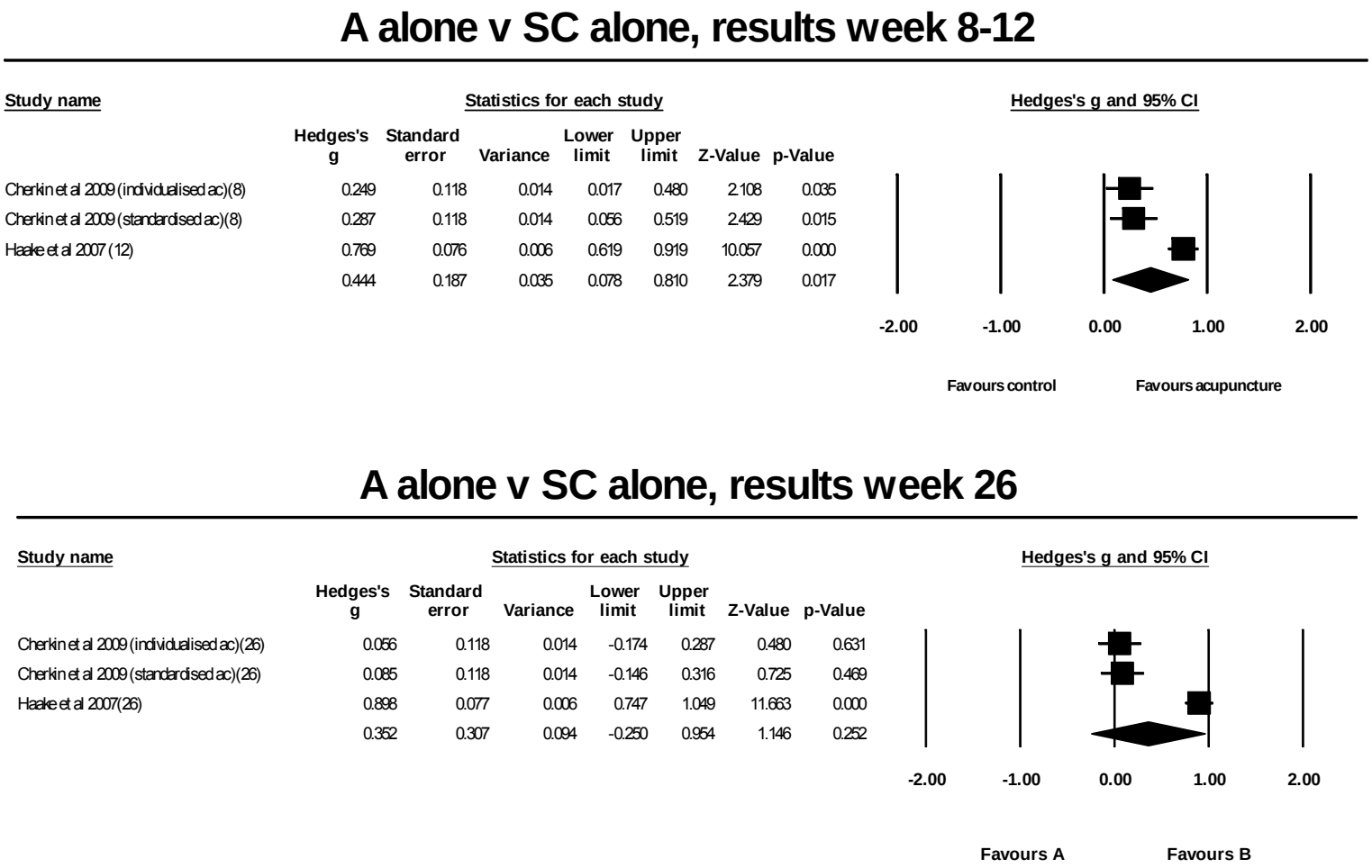
Two studies were included in the meta-analysis comparing acupuncture alone and standard care alone. However, two arms were relevant from the study by Cherkin et al, (2009) — the individualised and standardised acupuncture arms — and these were both included in the analysis (for a description see Table 2.3). The outcome metric, follow-up and findings of the studies incorporated in the meta-analysis of acupuncture as a complement to standard care versus standard care alone are summarised in Table 2.7.

Table 2.7: Studies included — Acupuncture alone vs. standard care alone

	Outcome metric	Follow up	Finding
Cherkin et al (2009) individualised acupuncture arm	Symptom bothersomeness pain scale	Week 8 Week 26 Week 52	Individualised acupuncture significantly better than control at week 8, and weakly but not significantly better at other time periods.
Cherkin et al (2009) standardised acupuncture arm	Symptom bothersomeness pain scale	Week 8 Week 26 Week 52	Standardised acupuncture significantly better than control at week 8 and week 26, and weakly but not significantly better at week 52.
Haake et al (2007)	Von Korff Chronic Pain Grade Scale	Week 12 Week 26	Acupuncture better than control at all follow-up points

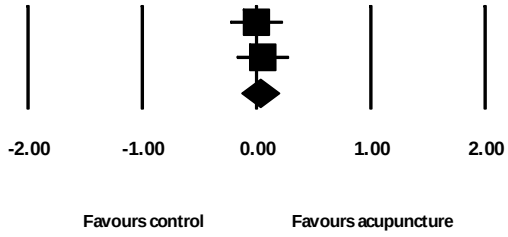
A meta-analysis was conducted based on the results at all follow-up time points. A significant positive effect of acupuncture was found at week 8, but not at week 26 or 52 (Figure 2.4). Funnel plots for weeks 8 and 26 found no publication bias. Testing of publication bias was not possible at week 52 because only two trial arms were available.

Figure 2.4: Acupuncture alone vs. standard care alone — meta-analysis findings



A alone v SC alone, results week 52

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Cherkin et al 2009 (individualised ac)(52)	0.000	0.119	0.014	-0.233	0.233	0.000	1.000
Cherkin et al 2009 (standardised ac)(52)	0.056	0.117	0.014	-0.174	0.287	0.481	0.631
	0.029	0.083	0.007	-0.135	0.192	0.342	0.733



2.7 Benefits

The primary outcome measure for the evaluation is the VAS converted into disability adjusted life years (DALYs). The meta-analysis outputs (SMDs) were converted to a percentage change in the visual analogue scale (VAS) pain score. The percentage change in VAS score was then applied to the relevant years of healthy life lost from the disability (YLD) weight.

The approach used to measure the benefits was based on the evidence (and outcome metrics) available (see Section 2.6.2). A similar method was proposed by another Australian study (Haby et al, 2004) for converting outcomes metrics to DWs where there were limitations to data.

The assumption underlying the approach used to convert the study metrics to DALYs is that the degree of change in the metric used for effect size in the RCTs can be directly related (in percentage terms) to the degree of change in disability weights. Further research is necessary to test this underlying assumption.

As explained below, the DALY weights (DW) are adjusted for severity of disease based on the relevant epidemiological literature, and the analysis is also adjusted for drop outs and for side effects (see the parameter summary in Table 2.11).

YLD weight

DALY weights are used to adjust a year according to the extent of disease burden experienced. Zero represents perfect health and one represents death.

The proportion of cases in each severity category was multiplied by the appropriate disability weight for the category to get a weighted average disability weight for the eligible group. The disability weight for moderate pain is 0.056 and for severe pain is 0.396.[18] The distribution of mild, moderate and severe pain from the ABS (2009) (combining mild and moderate consistent with the approach to estimating the DALYs) was used to estimate a DALY weight that reflects the balance between moderate and severe pain — 0.116.

Combined with moderate depression, the equivalent weights are 0.249 (moderate) and 0.519 (severe).[19] Again using the distribution of mild, moderate and severe pain from the ABS (2009), the weighted average DALY weight for chronic pain and depression becomes 0.296.

Years of life lost due to premature mortality (YLLs)

No premature mortality was attributed to chronic non-specific LBP (see Section 2.3.1).

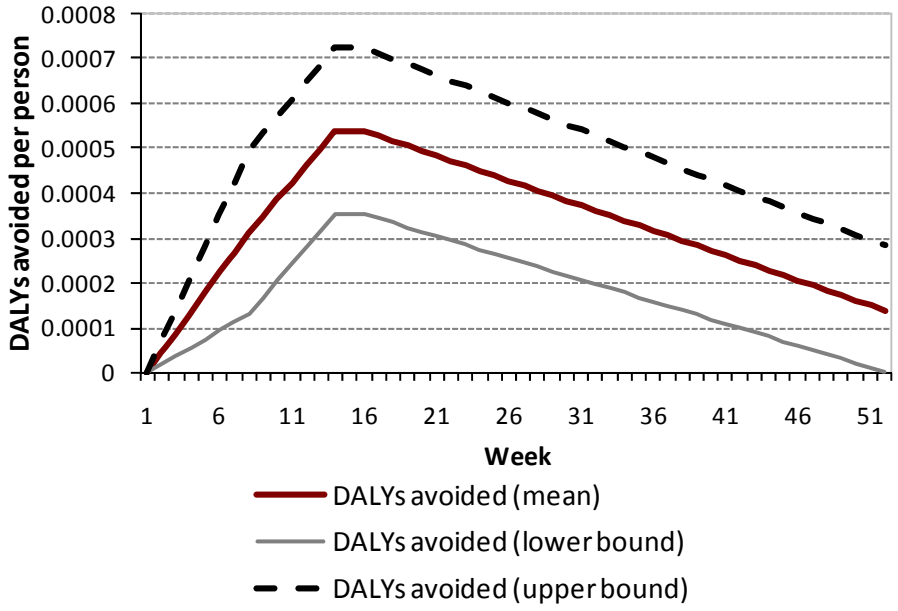
[18] Based on a regression analysis of EQ5D states and YLD weights used in the Australian Burden of Disease Reports, Begg et al (2007) and Mathers et al (1999).

[19] Based on a regression analysis of EQ5D states and YLD weights used in the Australian Burden of Disease Reports, Begg et al (2007) and Mathers et al (1999).

2.7.1 Benefit of acupuncture as a complement to standard care versus standard care alone

The pain scales for all studies were converted to a 0-100 scale, and three meta-analyses at week 8, weeks 12-16 and week 52 applied to determine the raw difference in means. A linear pathway was assumed between each time point (week zero to week 8, week 8 to week 14-16, and then to week 52). A depiction of the benefits based on this methodology (excluding depression) is in Chart 2.1. The upper and lower bounds reflect 95% confidence interval limits at each follow up time point.

Chart 2.1: Benefit of acupuncture and standard care versus standard care alone



2.7.2 Benefit of acupuncture alone versus standard care alone

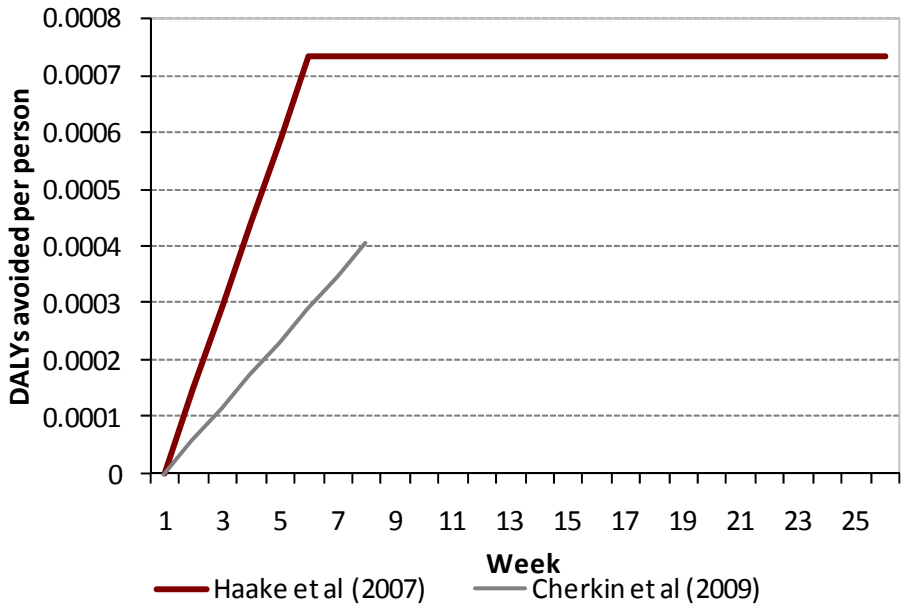
The pain scale used by Haake et al (2007) was not provided in the published article. The authors were contacted but did not respond within the timeframe for this study. Understanding of the absolute values on the scale metric is not required when using a standardised mean difference as per the meta analyses above (Section 2.6.3). However, conversion to an absolute measure is necessary for the cost effectiveness analysis. Hence, cost effectiveness analysis was undertaken using a different outcome metric — the proportion of patients with a clinically meaningful improvement (secondary outcome measures in Haake et al 2007 and Cherkin et al 2009).

- Cherkin et al (2009) found that — at 8 weeks follow up — 45% and 55% of participants in the individualised and standardised groups respectively showed clinically meaningful improvement in pain, whereas only 32% of those receiving standard care showed clinically meaningful improvement in pain (clinically meaningful was defined as two point improvement in their scale of 0-10 — around 18% reduction in pain). According to Cherkin et al (2009), the difference between acupuncture and standard care groups was significant at 8 weeks, but not at later follow up time points. Standard deviations were not provided.

- Haake et al (2007) presented the proportion of patients in each group who achieved 33% improvement or better in accordance with the pain scale they used (Haake et al 2007:table 5). The intergroup difference in the percent of patients who responded for verum acupuncture and standard care was 25.1%. No standard deviation measures were presented.

Using the same approach as above, a linear pathway was assumed for the reduction in pain lasting from before treatment (week zero) to the end of treatment, and then lasting to the point of follow up (8 weeks for Cherkin et al (2009) which coincided with the end of treatment, and 26 weeks for Haake et al (2007) where treatment ended at around week 6). A depiction of the benefits associated with each study based on this methodology (excluding depression) is in Chart 2.2. Note that the pain reduction for both arms of Cherkin et al (2009) was the same (as explained above — defined in the study as a clinical meaningful improvement in pain), but 13% of patients in the individualised acupuncture arm (over and above the standard care arm) achieved this improvement, whereas 23% of patients (over and above the standard care arm) in the standardised acupuncture arm achieved this improvement.

Chart 2.2: Benefit of acupuncture alone versus standard care alone



2.8 Model

The method for the cost effectiveness analysis was incremental, i.e. the additional costs of the intervention (ie acupuncture) over the comparator (ie standard care alone) were compared with the additional benefits. This was as per the agreed approach with NICM.

A model was built in Microsoft Excel, using @RISK software to conduct sensitivity analysis. The choice of key parameters for benefits is outlined in the section above and for costs is outlined in the section below, with a summary in Section 2.9.4.

Cost effectiveness analyses were conducted for the comparisons showing acupuncture had an effect on pain reduction which was significantly greater than the comparator, i.e. acupuncture

as a complement to standard care versus standard care alone, and acupuncture versus standard care alone.

2.9 Costs

2.9.1 Acupuncture

The average cost for a course of treatment consistent with the treatment protocols in the set of studies on which this analysis is based (Table 2.8) ranged from $656 to $1,281. The average cost per treatment session ranged from $64 to $66.

Table 2.8: Acupuncture charges, Melbourne 2009 ($)

Source	Charges per session	10 sessions	12 sessions	15 sessions	20 sessions
St Kilda					
Initial Consultation (Up to 1 hr)	85	85	85	85	85
Standard Consultation (Up to 45 min)	70	630	770	980	1,330
Total		715	855	1,065	1,415
Essendon					
Initial	75	75	75	75	75
Follow up	55	495	605	770	1,045
Total		570	680	845	1,120
Camberwell					
Initial	100	100	100	100	100
Follow up	70	630	770	980	1,330
Total		730	870	1080	1,430
Coburg					
Initial	115	115	115	115	115
follow up	55	495	605	770	1,045
Total		610	720	885	1,160
Average total cost		656.25	781.25	968.75	1,281.25
Average cost per session		65.60	65.10	64.60	64.10

Source: Charges advertised on the internet for randomly selected acupuncture clinics in Melbourne, search undertaken 10 September 2009.

2.9.2 The impact of acupuncture on health system costs

Based on the evidence outlined below (or lack of it in the case of antidepressants), the model assumed there were no changes to overall health system costs as a result of acupuncture treatment.

Overall health system costs

Other health system costs associated with LBP include visits to GPs, physiotherapists, chiropractors, and back care classes, pain clinics as well as hospitalisation. Two studies available suggested no significant savings in overall health system costs for LBP care associated with acupuncture.

- Thomas et al (2005) surveyed participants on their use of health services and found that while the health system costs in the acupuncture group were higher than for the standard care alone group, the difference was less than the additional costs of acupuncture, suggesting that use of other health services amongst those in the acupuncture group was lower than for those on standard therapy alone. Use of hospitals, GPs, outpatients and other UK National Health Service services was lower in the acupuncture than the control group, although the difference was not significant.
- Cherkin et al (2009) found mean total costs of back related health services for the year after randomisation were similar across treatment groups (P=0.65). This excluded the costs of the study's acupuncture treatments and the cost of one spine operation in the standard care group.

Pain medication

Medication for pain relief is part of standard care for LBP. Medication may include NSAIDs. Sustained use of NSAIDs has been associated with a heightened risk of myocardial infarction and gastrointestinal bleeding. In addition, tramadol and opioids may be associated with dependence.

A priori, it would be expected that by relieving pain, acupuncture would lead to a decline in medication use — reducing the associated monetary costs, as well as medication related adverse events. However, most studies investigating this issue found no significant change in use of medications as a result of acupuncture treatment.

- Of participants on medications for back pain in the trial by Meng et al (2003), most made no change to their medications, 16.3% decreased, and the same proportion increased their medication.
- The number of participants on analgesics increased in both arms during the trial by Yeung et al (2003).
- No significant changes were found in diclofenac (a NSAID) intake among participants in Molsberger et al (2002).
- Thomas et al (2005) found that while expenditure on medications for LBP in the acupuncture group was higher than in the control group, the difference was not significant.
- Witt et al (2006) found no significant difference between the acupuncture and control groups with regard to the number of patients prescribed analgesics during the three months following randomisation (acupuncture group 21.1% of patients and control group 22.7% of patients, p=0.29).

The exception is Cherkin et al (2009) who found that self reported medication use (mostly NSAIDs) in the acupuncture groups decreased significantly more than in the standard care group and remained lower throughout the one year follow-up.

Haake et al (2007) also reported that patients in both acupuncture groups had clinically meaningful better results for medication use than those in the standard care group, although unfortunately, there was no statistical comparison across groups of medication use rates or the changes due to acupuncture.

In an Australian study of acupuncture versus medication by Giles and Muller (2003), medications for back pain (the study prescribed either NSAIDS or paracetamol) caused adverse reactions in 6.1% of patients. The reactions were not described, and stopped once medication was stopped.

Antidepressants

Anti-depressants are not part of standard treatment for non-specific LBP, but depression is a common comorbidity and many of those with chronic LBP are likely to be taking anti-depressants (Section 2.3). Relief of pain is likely to reduce depression in many patients and thus decrease the use of anti-depressants. None of the studies referenced here reported on depression or consumption of anti-depressants.

2.9.3 Standard care

As mentioned above, there are no universally accepted Australian guidelines for the standard treatment of chronic non specific low back pain. The NSW Therapeutic Assessment Group (2002) recommends:

- education and physical activity review;
- muscle conditioning exercises;
- spinal mobilisation or manipulation;
- behavioural therapy and reassurance; and
- medications such as paracetamol, non steroidal anti inflammatory drugs NSAIDs, tramadol and long acting opioids.

The literature suggest that in practice, patients with chronic back pain commonly access both conventional and complementary medicine practitioners including chiropractors, osteopaths, and massage therapists. An expert reference group from the University of Sydney Pain Management Research Institute advised that a combination of medication, physiotherapy, chiropractic, and injection therapies were commonly used to treat chronic pain (Access Economics 2007). Molloy et al (1999) reported that in 1995-96, pain related claims comprised 12.6% of legal payments for back injury, 7.6% of payments for medical treatment, and 3% of payments for physiotherapy and chiropractic treatment. According to Sibbritt (2010), 78% of women with back pain who sought treatment consulted both a conventional and complementary practitioner compared with 20% who saw a conventional practitioner only. Walker (2004) found that 59% of low back pain care seekers visited more than one type of practitioner for their pain. This research suggests GPs, physiotherapists, chiropractors and massage therapists are commonly used by those with LBP. In addition, we contacted pain medicine specialist, Professor Nikolai Bogduk, (personal communication, 22 April 2010) who confirmed the lack of Australian health system utilisation data for LBP.

Neither Sibbritt (2010) nor Walker (2004) reported utilisation in a way that facilitated estimation of the cost of care for LBP. On the other hand, Thomas et al (2005) reported UK

healthcare utilisation rates across a broad range of providers for their standard care arm and unlike the aforementioned local studies, included emergency department visits and medication usage. The healthcare utilisation patterns for standard care from Thomas et al (2005) were adopted here because of the lack of Australian data, acknowledging that utilisation rates may vary between UK and Australia. Details of healthcare utilisation were collected by Thomas et al (2005) from two main sources, GP records and a resource-use questionnaire completed by trial patients (which may be affected by recall bias). Patients were recruited from 1999 to 2001 and unit costs for all resources used by trial patients were obtained for the financial year 2001–02. The standard care group could access hospital and private acupuncture too.

Australian unit costs were applied to the utilisation patterns from the standard care arm of Thomas et al (2005) (except acupuncture). Australian cost data were drawn from the following sources:

- The mean session cost for allied health practitioner was based on the advertised charges of a random sample of allied healthcare providers (physiotherapists, osteopaths, massage therapists and chiropractors) (internet search conducted in April 2010).
- Medication charges (dispensed price per maximum quantity) from the Pharmaceutical Benefits Schedule, April 2010.[20] The medications selected and their administration was based on the recommendations of the NSW Therapeutic Assessment Group (2002). These were the most difficult to estimate given uncertainty about dose, duration and frequency. Frequence of use was linked to utilisation of GPs from Thomas et al (2005) — ie 2.92 visits on average over 24 months. The method used is summarised in Table 2.9.
- Hospital charges (inpatient, outpatient, emergency) from the National Hospital Cost Data Collection (NHCDC) (Commonwealth Department of Health and Ageing in conjunction with state/territory health departments, public and private hospitals and private day hospital facilities, 2009). The Diagnosis Related Groups for inpatient costs were drawn from a list of possible procedures provided by pain medicine specialist, Professor Nikolai Bogduk (personal communication, 22 April 2010). A weighted average cost per separation was estimated based on public hospital costs data and separations for each relevant DRG. Hospital costs were inflated to 2009-10 using average growth in public hospital costs between 2003–04 to 2007–08 (AIHW 2009).
- Other charges were drawn from the Medicare Benefits Schedule (MBS) January 2010.

Table 2.9: Estimation method for CNSLBP medication costs

Medication	Dose etc	daily cost	days month	$ per month	Visit to GP	$ per 24 months
paracetamol (OTC) 500mg	$8.42 per 100 tablets, dose of 4g per day, $0.67 per day	$0.67	30	$20.10	No GP visit required	$482.40
NSAIDs (ibuprofen) 400mg	$9.19 per 30 tablets, dose of 1.2g per day, $0.92 per day	$0.92	10	$9.20	Linked to use of GP —	$26.86

[20] This approach is consistent with the method required by the Pharmaceutical Benefits Advisory Committee, Australian Government Department of Health and Ageing (DoHA) (2008).

tramadol 50mg	$9.16 per 20 tablets, dose of 400mg per day, $3.66 per day	$3.66	10	$36.60	average 2.92 visits over 24 months from Thomas et al (2005)	$106.87
morphine various doses	$33.56 (average cost of controlled release tablet preparations, various strengths) per 20 tablets, twice daily dosing, $3.36 per day	$3.36	5	$16.80		$49.06
oxycodone various doses	$32.08 (average cost of controlled release tablet preparations, various strengths) per 20 tablets, twice daily dosing, $3.21 per day	$3.21	5	$16.05		$46.87
Average cost of medication				**$19.75**		**$142.41**

The cost of standard care

The estimates, sources and methods for the cost of standard care for CNSLBP in Australia are summarised in Table 2.10. The average cost for standard care is $19 per week, and over a two year period, around $2,000 (Australian). This is substantially higher than international estimates of the cost of standard care for LBP reported by the trials used here.

- The cost estimate in Thomas et al (2005) for the standard care group over 24 months was (mean) £332.24 (standard deviation £426.50). This is equivalent to AUD$645 (in 2009).
- Cherkin et al (2009) reported the mean total cost of back-related health services for the year after randomisation were similar in all of the treatment groups in their study. The cost excluding the costs of acupuncture and excluding the cost of one spine operation in the standard care group was US$160-221 for the year. Converting to Australian dollars, and in order to be consistent with Thomas et al (2005), this is equivalent to AUD$410-567 for a two year period.

These differences in cost estimates are accommodated through sensitivity analysis.

Notably, the average weekly cost of standard care is applied for the treatment period, following Haake et al (2007). For that study, the protocol for standard care was "Physiotherapies supported by nonsteriodal anti-inflammatory drugs or pain medication up to the maximum daily dose during the therapy period" (Haake et al 2007:1894). The therapy period for Haake et al (2007) depended on whether patients had 10 or 15 sessions of acupuncture (see Table 2.3), but was around 6 weeks. The therapy period for Cherkin et al (2009) was 8 weeks.

The cost of adverse events associated with NSAIDs

Cherkin et al (2009) found that self reported medication use (mostly NSAIDs) in the acupuncture group decreased significantly more than in the standard care group (47% acupuncture groups versus 59% in the standard care group) and remained lower throughout the one year follow-up. This suggests that acupuncture — if associated with reduced medication — may reduce the adverse events associated with NSAIDS.

Adverse events associated with NSAIDs are very serious and include gastrointestinal bleeding and death from acute myocardial infarction. The cost of gastrointestinal adverse events are calculated based on:

- Average cost per separation for ARDRG code G61A and G61B (public hospital costs weighted by separations for each ARDRG code are used because of the greater scope of these costs compared with private sector costs) from Round 12, National Hospital Cost Data Collection, inflated to 2009 using the average health inflation rate between 1997-98 and 2007-08 from the AIHW health expenditure in Australia, 2007-08 ($2,797).
- The impact of NSAID intake on the chance of a gastrointestinal event (RR of 1.4 from Gonzalez-Perez and Rodrigues (2006)); and
- Separation rates for gastrointestinal events based on separations from both public and private hospitals from NHCDC Round 12 (12,854 separations).

The cost of acute myocardial infarction (AMI) deaths associated with NSAIDs are calculated based on:

- Average myocardial infarction death rates from the Australian Institute of Health and Welfare GRIM books www.aihw.gov.au;
- The cost per separation from the NHCDC Version 5.1, Round 11 for ARDRG code F60C inflated to 2009 using the same method for gastrointestinal events; and
- An odds ratio for the impact of NSAIDs on MI from Hippisley-Cox and Coupland (2005).

The difference between 47% and 59% from Cherkin et al (2009) was applied to the cost of side effects of NSAIDs assuming half of the 59% patients taking medications took NSAIDs. The total cost of gastrointestinal events and AMI deaths associated with NSAIDs taken by all Australians with chronic non specific low back pain in 2009 (around 1.9 million people) was estimated to be $4,603 per week.

Table 2.10: Estimation of the costs of standard care (Australian dollars 2009)

	Utilisation over 24 months(a)	Unit cost in 2009-10	Cost per 24 months	Sources and methods
Secondary				
Days in hospital	0.044	$1,349	$59	Weighted average cost per day (NHCDC cost per separation divided by average length of stay for relevant DRGs)
A+E visit	0.029	$406	$12	NHCDC(a)
Outpatient visits	0.545	$259	$141	NHCDC(a)
Pain clinic visits	0.916	$420	$385	NHCDC(a)
Hospital physio	1.934	$128	$248	NHCDC(a)
Primary				
GP visits for LBP	2.92	$34.30	$100	Level B surgery consultation, January 2010 MBS
GP visits not for LBP	6.53	$34.30	$224	Level B surgery consultation, January 2010 MBS
Practice nurse visits for LBP(b)	0.91	$11.35	$10	Item 10997 January 2010 MBS
Practice nurse visits not for LBP(b)	1.149	$11.35	$13	Item 10997 January 2010 MBS
Physio at GP	1.647	$58.85	$97	Item 10960 January 2010 MBS
Other NHS therapist visits	3.443	$58.85	$203	Item 10960 January 2010 MBS
Private				
Physiotherapist	1.104	$60.93	$67	The mean session cost for allied health practitioner was based on the advertised charges of a random sample of allied healthcare providers (physiotherapists, osteopaths, massage therapists and chiropractors) (internet search conducted in April 2010)
Chiropractor	1.379	$57.79	$80	
Osteopath	0.198	$80.82	$16	
Other private therapist visits (massage)	3.105	$83.75	$260	
Medications	0.59	$142.41	$84	According to Thomas et al (2005), 59% of participants used medications in the past week.
Total			**$2,000**	**Cost per week is $19**

(a) Thomas et al (2005). (b) Practice nurse visits for back pain are not available on the MBS in Australia.

2.9.4 Parameter summary

A summary of the parameters used in the analysis of:

- acupuncture as a complement to standard care versus standard care alone is in Table 2.11; and
- acupuncture alone versus standard care alone is in Table 2.12.

No statistically significantly benefit of acupuncture plus standard care versus sham plus standard care was found so no CEA was conducted. This may reflect that only two studies were available for this comparison.

Table 2.11: Parameters — acupuncture as a complement to standard care

Parameter	Estimate	Sensitivity Analysis
Benefit acupuncture plus standard care versus standard care alone	A significant positive effect of acupuncture at three time points up to 52 weeks	At each follow up time point (week 8-9, week 12-16 and week 52) a normal distribution was applied to the raw mean difference and standard error derived from the meta analyses.
Side effects acupuncture	No serious side effects from acupuncture.	N/A
Adherence acupuncture	10% drop out from acupuncture (Thomas et al 2005). For those who drop out, acupuncture costs were assumed to be half.	N/A
Adherence standard care	100% adherence with standard therapy alone (Thomas et al 2005).	N/A
Years of life lost due to disability (YLDs)	Average YLD weight, weighted by % with LBP in each severity category. DALY weight 0.116 for **pain alone**.	YLD weight 0.296 for **pain and depression**.
Mortality	No mortality attributable to chronic non specific LBP	N/A
Cost of acupuncture	$64.80 per session	Discrete distribution based on number of acupuncture sessions in trials. Sessions={5,10,12,15,20}, Probability of each number ={0.05,0.4,0.35,0.15,0.05}
Cost of standard care	No additional cost of SC — acupuncture is the only additional cost	N/A
Prevalence of chronic non-specific LBP	11.4%	N/A

Table 2.12: Parameters — acupuncture alone versus standard care alone

Parameter	Estimate	Sensitivity Analysis
Benefit acupuncture alone versus standard care alone	Proportion of patients with clinically meaningful improvement in pain	Different results from Haake et al (2007) and Cherkin et al (2009).
Side effects acupuncture	No serious side effects from acupuncture.	N/A
Side effects standard care	No side effects from NSAIDS for standard care	Side effects from NSAIDS for standard care applying a cost per week of side effects to the number of weeks according to the treatment protocols of Cherkin et al (2009) and Haake et al (2007) (cost of side effects of NSAIDs $4,603 per week among all Australians with chronic non specific low back pain) based on half of the 59% of patients (both Thomas et al 2005 and Cherkin et al 2009 reported 59% of patients on medications) taking NSAIDs.
Adherence acupuncture	10% drop out from acupuncture (Thomas et al 2005). For those who drop out, acupuncture costs were assumed to be half.	N/A
Adherence standard care	100% adherence with standard therapy alone (Thomas et al 2005).	N/A
Years of life lost due to disability (YLDs)	Average YLD weight, weighted by % with LBP in each severity category. DALY weight 0.116 for **pain alone**.	YLD weight 0.296 for **pain and depression**.
Mortality	No mortality attributable to chronic non specific LBP	N/A
Cost of acupuncture	$64-66 per session Number sessions calculated as 10*0.666 +15*0.334 consistent with treatment protocols in Haake et al (2007) and Cherkin et al (2009).	Acupuncture is associated with reduced used of NSAIDs and reduced costs of side effects associated with NSAIDs. 59% of patients taking NSAIDs in the standard care arm of Cherkin et al (2009) versus 47% in acupuncture arm.
Cost of standard care	$19 per week (applying Australian cost data to use rates from Thomas et al (2005)) for the therapy period (Haake et al 2007). Therapy period for Haake et al 2007 was 6 weeks and for Cherkin et al 2009 was 8 weeks.	$5 per week (based on findings from trial by Cherkin et al (2009)) for the therapy period (Haake et al 2007). Therapy period for Haake et al 2007 was 6 weeks and for Cherkin et al 2009 was 8 weeks.
Prevalence of chronic non-specific LBP	11.4%	N/A

2.10 Results

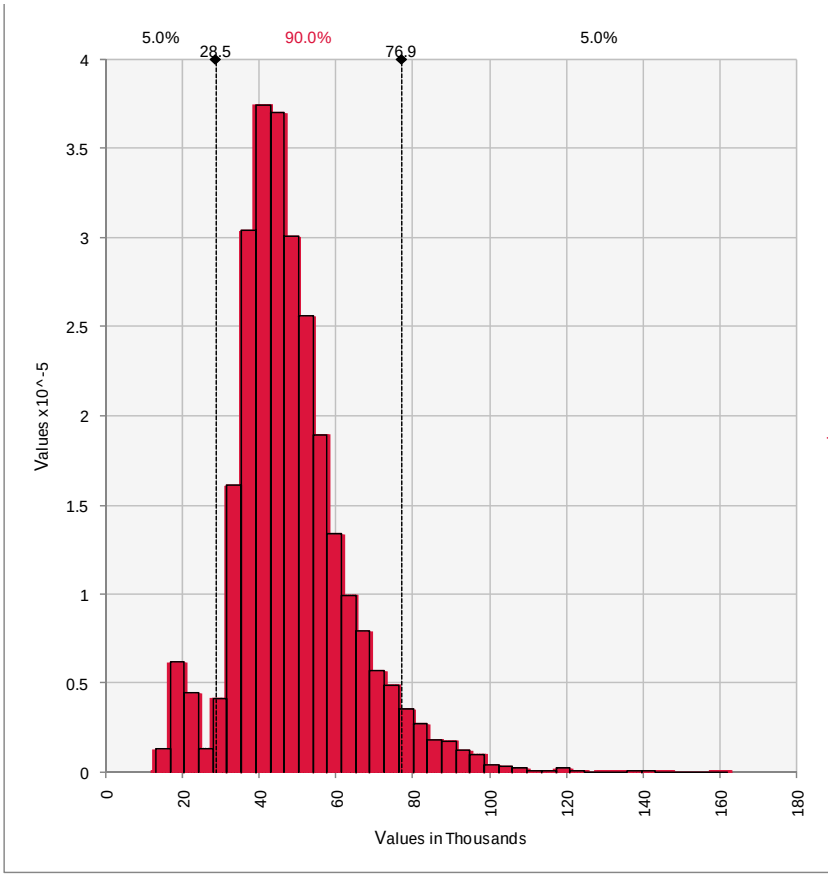
2.10.1 Acupuncture as a complement to standard care versus standard care alone

According to WHO benchmarks (Section 1.4), acupuncture as a complement to standard care for relief of chronic non specific low back pain is cost effective (Table 2.13). If acupuncture together with standard care alleviates comorbid depression at the same rate as pain, then acupuncture is very cost effective. The sensitivity analysis results for pain alone (excluding comorbid depression) are in Chart 2.3.

Table 2.13: Cost ($) per DALY avoided

	Without depression	With comorbid depression
Mean	48,562	18,960
Std Deviation	14,889	5,813
Minimum	13,054	5,097
90% CI lower limit	28,500	11,100
90% CI upper limit	76,900	30,000
Maximum	161,935	63,223

Chart 2.3: Cost per DALY avoided (excluding comorbid depression)(a)



(a) Cost per DALY avoided on the horizontal axis, probability on the vertical axis

2.10.2 Acupuncture alone versus standard care alone

Cost effectiveness analysis was conducted separately for the two arms in Cherkin et al (2009) (individualised and standardised acupuncture) and for Haake et al (2007). As noted in Section 2.7.2, the pain scale used by Haake et al (2007) was not provided in the published article so the cost effectiveness analysis was undertaken using a different outcome metric to that used for the comparison of acupuncture as a complement to standard care versus standard care alone. For the analysis here of acupuncture alone versus standard care alone, the secondary outcome metric was used — the proportion of patients with a clinically meaningful improvement in pain.

- The only follow up time period with results that were significant from Cherkin et al (2009) were for week 8. The later follow up time points did not find a significant difference between acupuncture alone and standard care alone. Hence — only the week 8 result from Cherkine et al (2009) were included in the cost effectiveness analysis here.
- Haake et al (2007) found a significant impact for acupuncture over standard care at both week 12 and week 26, so both of these time periods were included for the cost effectiveness analysis here.

The difference in the time period for pain relief between the Haake et al (2007) and Cherkin et al (2009) used for modelling is depicted in Chart 2.2.

Use of @RISK relies on knowledge of the likely distributions of the parameters used for sensitivity testing. Given the lack of distributional information from the published studies (Cherkin et al (2009) and Haake et al (2007)) of the proportions of patients experiencing clinically significant improvements in pain, and the gap in knowledge about the utilisation of health care resources in Australia for standard care for chronic non specific low back pain, sensitivity analysis was conducted on several key variables without using @RISK. The key variables tested were:

- The different reductions in pain found by Cherkin et al (2009) at 8 weeks, and by Haake et al (2007) at 12 and 26 weeks;
- The cost of standard care per week — $19 week (applying Thomas et al (2005) health care utilisation rates to Australian cost data) and $5 per week (based on international estimates);
- The reduction in the cost of adverse events associated with NSAIDs due to decreased use of medications by acupuncture patients (Cherkin et al 2009); and
- Inclusion and exclusion of depression as a comorbidity of back pain.

The cost effectiveness analysis results are in Table 2.14. As a replacement for standard care for chronic non specific back pain, acupuncture is generally not cost effective.

- Acupuncture is only cost effective if the results from Haake et al (2007) are used as the basis for modelling and only if comorbid depression is alleviated alongside back pain. This is likely to reflect the longer duration of pain relief experienced by found by patients involved in the study by Haake et al (2007) who experienced a clinically meaningful

improvement in pain (compared with patients involved in the study by Cherkin et al, 2009).

- Incorporating the cost of adverse events of NSAIDs (using the method applied here) does not make a marked difference to the results.

Table 2.14: Cost ($) per DALY avoided

Cost of SC	Pain reduction from:	AEs of NSAIDs included	$ per DALY avoided Without depression	$ per DALY avoided With comorbid depression
$19 per week	Cherkin et al 2009 individualised acupuncture		3,066,302	1,197,150
	Cherkin et al 2009 standardised acupuncture		1,733,127	676,650
	Haake et al 2007		161,226	62,946
$5 per week	Cherkin et al 2009 individualised acupuncture		3,617,684	1,412,421
	Cherkin et al 2009 standardised acupuncture		2,044,778	798,325
	Haake et al 2007		181,749	70,959
$19 per week	Cherkin et al 2009 individualised acupuncture	✓	3,066,199	1,197,109
	Cherkin et al 2009 standardised acupuncture	✓	1,733,069	676,627
	Haake et al 2007	✓	161,222	62,945

2.11 Conclusions

At least 11.4% of Australians aged 18 or over experience chronic non-specific LBP (around 1.9 million Australians aged 18 years or over in 2009 (ABS 2009)). Most experience pain that lasts for six months or more. Pain relief would therefore clearly benefit a substantial number of Australians.

Many of the earlier studies of acupuncture had very small sample sizes and very short followup periods. The quality of these earlier studies was often questioned (eg. Furlan et al 2005). The later studies by Thomas et al (2005), Witt et al (2006), Haake et al (2007) and Cherkin et al (2009) were larger, with generally longer follow-up — for example, Thomas et al (2005) and Cherkin et al (2009) followed up for a year, and Thomas et al (2005) followed up for 2 years.

The meta-analyses conducted for this study found good evidence that acupuncture as a complement to standard care resulted in significantly better pain outcomes than standard care alone. Moreover, consistent with international studies by Thomas et al (2005) and Witt et al (2006), acupuncture as a complement to standard care is cost effective.

However, acupuncture alone as an alternative to standard care alone provided a significant improvement in pain reduction only for a short period and was not found to be cost effective unless comorbid depression was also alleviated, and the benefits for both pain and depression

were significantly greater than standard care alone for six months. This analysis was based on two separate trials.

The focus of this study on health system costs means that our results are likely to be conservative. Chronic pain can be associated with absenteeism from work (eg. Blyth et al 2003), and reduced effectiveness while at work (presenteeism). Van Leeuwen et al (2006) estimated 9.9 million workdays were lost due to absence due to chronic pain annually in Australia, equating to a cost of A$1.4 billion per annum. The total number of lost workday equivalents due to reduced effectiveness was 36.5 million. Access Economics (2007) estimated that in 2007, the total cost of absenteeism and presenteeism due to chronic pain was $3.8 billion. Van Tulder et al (1995) estimated that the costs of back pain to society in The Netherlands in 1991 was 1.7% of gross national product and concluded that back pain was not only a major medical problem but also a major economic problem. The direct medical costs contributed only 7%, with all other costs indirect costs such as productivity losses. The mean costs per case of absenteeism and disablement due to back pain were US$4,622 (1991) and US$9,493 (1991), respectively. Thomas et al (2005) found that productivity costs were higher in the control group reflecting a higher reported absence from work in this group. At baseline, 4.6% of study participants (in a sample of 241) were permanently unable to work owing to LBP (Thomas et al, 2005).

Access Economics (2007) estimated that in 2007 while the health system costs of chronic pain accounted for 20% of the total costs, the burden of disease and productivity losses associated with chronic pain each accounted for 43% of the total cost. If the presenteeism and absenteeism costs of LBP are averted in a one to one ratio with the burden of disease as Access Economics (2007) would suggest, the benefits from acupuncture would double (or more than double if the other indirect financial costs such as informal carer costs were also included).

2.12 References

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2.13 Appendix: Detailed summary of literature studies relating to acupuncture for chronic non-specific LBP

Table 2.15: Literature on effectiveness of acupuncture for LBP - studies assessed for inclusion

Study	CNS LBP? (a)	R(b)	A+SC v Sham+SC	A+SC v SC alone	A alone v SC alone	Outcome measure	ITT (c)	Follow up	Included ?	Comment
Note: these all refer to the same trial Thomas et al (2005); Thomas et al (2006); Ratcliffe et al (2006)	Y	R	✖	✓	✖	SF-36 pain dimension (difference of 5-10 points clinically significant)	✓	3,12,24 months	✓	
Yeung et al (2003)	Y	R	✖	✓	✖	Numerical rating scale (NRS)	✓	End treatmt, 1 mo, 3 months	✓	
Meng et al (2003)	Y	R	✖	✓	✖	VAS pain	✓[21]	2,6,9 weeks	✓	
Leibing et al (2002)	Y	R	✓	✓	✖	VAS pain		End treatmt 9 months	✓	

[21] Not clear for VAS whether reporting was for ITT or treatment completers only.

Study	CNS LBP? (a)	R(b)	A+SC v Sham+SC	A+SC v SC alone	A alone v SC alone	Outcome measure	ITT (c)	Follow up	Included ?	Comment
Molsberger et al (2002)	Y	R	✓	✓	×	VAS pain	✓	End treatmt, 3 months	✓	Prospective analysis required 380 patients to achieve test power of 90% (α 0.05). Trial ended prematurely before 380 patients enrolled but authors claim statistically significant results not compromised.
Cherkin et al (2009)	Y	R	×	×	✓	Symptom bothersomeness (pain) (0-10 scale).	✓	8, 26, and 52 weeks	✓	
Haake et al (2007)	Y	R	×	×	✓	Von Korff Chronic Pain Grade Scale	✓	1.5, 3, and 6 months	✓	
Brinkhaus et al (2006)	Y		×	×	×				×	Comparator was no treatment or sham, (ie not standard care).
Witt et al (2006)	Y	R group and non-R group	×	✓	×	Low back pain rating scale	✓	3, 6 months for pain scale	✓	

Meta-analysis by **Madsen et al (2009)** included 13 trials of patients with a variety of pain conditions including migraine, osteoarthritis, postoperative pain, colonoscopy, fibromyalgia, scar pain etc. Studies from Madsen et al (2009) that did not examine low back pain excluded. Studies from Madsen et al (2009) that examined low back pain as below:

Study	CNS LBP? (a)	R(b)	A+SC v Sham+SC	A+SC v SC alone	A alone v SC alone	Outcome measure	ITT (c)	Follow up	Included ?	Comment
Brinkhaus et al (2006)	See above								See above	
Leibing et al (2002)	See above								See above	
Molsberger et al (2002)	See above								See above	
Meta-analysis by **Yuan et al (2008)** included 23 studies. The 6 high quality studies were as below.										
Witt et al 2006	See above								See above	
Brinkhaus et al 2006	See above								See above	
Thomas et a 2006	See above								See above	
Haake et al 2007	See above								See above	
Cherkin et al 2001	Y	R	×	×	? (see comment column)	Symptom bothersomeness (pain) (0-10 scale).	✓	4, 10, 52 weeks	×	Used traditional Chinese acupuncture but this was combined with indirect moxibustion, infrared heat, cupping and exercise.
Mendelsohn et al 1983	Y		×	×	×				×	Comparator not applicable to this study
Meta-analysis by **Yuan et al (2008)** included 23 studies. The other 17 are as below.										
Itoh 2006	Y		×	×	×				×	Comparator not applicable to this study

Study	CNS LBP? (a)	R(b)	A+SC v Sham+SC	A+SC v SC alone	A alone v SC alone	Outcome measure	ITT (c)	Follow up	Included ?	Comment
Kerr 2003	Y		×	×	×				×	Comparator not applicable to this study
Tsukayama 2002	Y		×	×	×				×	Comparator not applicable to this study
Carlsson 2001	Y		×	×	×				×	Comparator not applicable to this study
Grant 1999	Y		×	×	×				×	Comparator not applicable to this study
Thomas and Lundberg 1994	Y		×	×	×				×	Comparator not applicable to this study
Lehmann 1986	Y		×	×	×				×	Comparator not applicable to this study
MacDonald 1983	Y		×	×	×				×	Comparator not applicable to this study
Coan 180	Y		×	×	×				×	Comparator not applicable to this study
Gunn 1980	Y		×	✓	×	Did not use validated outcome measure	×	End treatmt 12, 27.3 weeks	×	All patients received 8 weeks of SC before entering trial and those for SC not successful entered trial. Control group continued to receive same SC despite it not being successful. Needed a sham arm.
Leibing 2002,	See above								See above	

Study	CNS LBP? (a)	R(b)	A+SC v Sham+SC	A+SC v SC alone	A alone v SC alone	Outcome measure	ITT (c)	Follow up	Included ?	Comment
Meng 2003,	See above								See above	
Molsberger 2002	See above								See above	
Yeung 2003	See above								See above	
Tsui 2004	Y	R	×	✓	×	NRS pain	✓	2,4 weeks (during treatment) 1 month	✓	
Giles and Muller 2003	?	R	×	×	✓[22]	VAS Pain	×	End treatmt 9 weeks	×	Some patients excluded from ITT and there were cross overs between treatment arms[23] No between group statistical comparison. Not clear that measuring low back pain – as refer to spinal pain (although Oswestry is for low back pain)

[22] Note – appears all patients had already received various medications before entry to study – so arguably AC+SC vs SC alone

[23] Authors state the cross overs were included but not in which arm.

Study	CNS LBP? (a)	R(b)	A+SC v Sham+SC	A+SC v SC alone	A alone v SC alone	Outcome measure	ITT (c)	Follow up	Included ?	Comment
Giles and Muller 1999	Y (spinal pain)	R	×	×	✓	VAS Pain (three were used including one for low back)	×	End treatmt (4 weeks)	×	High proportion of drop outs which differed significantly bw groups[24] –No between group statistical comparison.
Meta-analysis by **Mannheimer et al 2005** included 22 RCTs of low back pain										
Carlsson and Sjolund 2001	Y		×	×	×				×	Comparator not applicable to this study
Cherkin et al 2001	See above								See above	
Coan et al 1980	See above								See above	
Edelist 1976	Y		×	×	×				×	Comparator not applicable to this study
Giles and Muller 1999	See above								See above	
Giles and Muller 2003	See above								See above	
Grant 1999	See above								See above	
Ito 2000									×	Not able to obtain
Kerr 2003	See above								See above	

[24] 130 randomised but 49 did not complete baseline questionnaire or dropped out – so 77 included. Drop outs from treatment also high. Authors argue this did not confound results because drop out reasons were not related to the outcome of the intervention.

Study	CNS LBP? (a)	R(b)	A+SC v Sham+SC	A+SC v SC alone	A alone v SC alone	Outcome measure	ITT (c)	Follow up	Included ?	Comment
Lehmann et al 1986	See above								See above	
Leibing 2002	See above								See above	
Mazieres et al 1985	Y		×	×	×				×	Comparator not applicable to this study
Mendelsohn 1983	See above								See above	
Meng	See above								See above	
Molsberger	See above								See above	
Nobili et al 1985			×	×	×				×	Comparator not applicable to this study
Sakai et al 2001			×	×	×				×	Comparator not applicable to this study
Thomas and lundberg 1994	See above								See above	
Von Mencke 1988			×	×	×				×	Comparator not applicable to this study
Yeung	See above								See above	
Zhang et al 2002			×	×	×				×	Comparator not applicable to this study
Zhang 2002			×	×	×				×	Comparator not applicable to this study

Study	CNS LBP? (a)	R(b)	A+SC v Sham+SC	A+SC v SC alone	A alone v SC alone	Outcome measure	ITT (c)	Follow up	Included ?	Comment
The meta-analysis by **Machado et al (2009)** focused on various treatments for low back pain — 4 of the included trials were of acupuncture (3 for chronic LBP), 1 of electro acupuncture for chronic LBP and 4 of TENS (2 of which were for chronic LBP). It is not clear why certain studies in the Bibliography were rejected. Studies from the bibliography are										
Brinkhaus et al 2006	See above								See above	
Leibing et al 2002	See above								See above	
Mendelsohn et al 1983	See above								See above	
Molsberger et al 2002	See above								See above	
Sator-Katzenschlager et al 2004	Y	R	×	×	×				×	Comparator not applicable to this study
Weiner et al 2003	Y	R	×	×	×	McGill Pain Questionnaire Pain Severity scale of the Multidimensional Pain Inventory (MPI)	Y	End of treatment, 6 weeks, 3 months	×	Comparator not applicable to this study
Carlsson and Sjolund 2001	See above								See above	
Itoh et al 2006	See above								See above	
Kerr et al 2003	See above								See above	

Study	CNS LBP? (a)	R(b)	A+SC v Sham+SC	A+SC v SC alone	A alone v SC alone	Outcome measure	ITT (c)	Follow up	Included ?	Comment
Inoue et al 2006	Lumbar vertebral arthritis	R	✓ patients referred to acupuncture after standard care not successful	×	×	VAS		Immediate	×	ITT questionable. Not traditional acupuncture
Meta-analysis by **Keller et al (2007)** did not focus on only chronic LBP, but also on acute LBP. In addition, did not focus on acupuncture, but on other treatments as well including analgesics, NSAIDs, exercise, behavioural therapy, and spinal manipulation. For those trials included that were about the effect of acupuncture on chronic LBP Keller et al (2007) only examined the arms comparing acupuncture with no treatment or placebo.										
Coan et al 1980	See above								See above	
Mendelsohn 1983	See above								See above	
Thomas and Lundberg 1994	See above								See above	
Carlsson and Sjolund 2001	See above								See above	
Kerr et al 2001	Y	×	×	×	×	questionnaire	×		×	
Leibing et al 2002	See above								See above	
Molsberger et al 2002	See above								See above	
Meta-analysis by **Ernst and White 1998** covered 12 studies, one of which was of acute LBP (excluded here). Excluding the RCT for acute back pain, the 11 trials are …										
Edelist et al 1976	See above								See above	
Yue 1978	Chronic arthritic	×	×	×	✓(15 in total)	Not specified	×		×	

Study	CNS LBP? (a)	R(b)	A+SC v Sham+SC	A+SC v SC alone	A alone v SC alone	Outcome measure	ITT (c)	Follow up	Included ?	Comment
Lopacz and Gralewski 1979			×	×	×				×	Comparator not applicable to this study
Coan et al 1980	See above								See above	
Gunn et al 1980	See above								See above	
Gallacchi et al 1981			×	×	×				×	Comparator not applicable to this study
Macdonald et al 1983	See above								See above	
Mendelsohn et al 1983	See above								See above	
Lehmann et al 1983	Y	R	×	×	×	VAS pain	N	End of treatmmt	×	Comparator not relevant (acupuncture, TENS v TENS dead battery)
Garvey et al 1989	Y	R	×	?[25]	✓	NRS	×	2 weeks after injection	×	Some patients reported only "much better" instead of using NRS, only reported % improved but not necessarily clinically significant improvement, no ITT 20% attrition rate

[25] Patients had hot showers twice per day and restricted physical activity but cautioned against lumbosacral exercise program. There were 4 groups: Lidocaine injection; lidocaine+aristospan injection; acupuncture; spray of ethyl chloride+ acupressure.

Study	CNS LBP? (a)	R(b)	A+SC v Sham+SC	A+SC v SC alone	A alone v SC alone	Outcome measure	ITT (c)	Follow up	Included ?	Comment
Thomas and Lundeberg 1994	See above								See above	

(a) CNSLBP=Chronic non specific low back pain (b) R=Randomised. (c) ITT=Intent to treat analysis used

3 St John's wort for depression

3.1 Background

St John's wort refers to the plant species *Hypericum perforatum*. Some 370 species of the genus *Hypericum* exist worldwide and extracts of 'common' St John's wort (*H. perforatum*) can be quite heterogenous[26]. St John's wort has been used since ancient Greek times as a herbal treatment for depression (and as an anti-inflammatory and antiseptic). A Cochrane review by Linde et al (2008) found that:

> *'The available evidence suggests that the hypericum extracts tested in the included trials a) are superior to placebo in patients with major depression; b) are similarly effective as standard anti-depressants; and c) have fewer side effects than standard anti-depressants.'*
> *St John's wort*[27]

Rahimi et al (2009) in a systematic review of St John's wort and SSRIs similarly found St John's wort to be as effective as selective serotonin reuptake inhibitors (SSRIs). Both studies found that St John's wort was associated with fewer patient withdrawals from treatment due to adverse events. Although non-toxic to humans in these doses, in large quantities St John's wort is poisonous to grazing livestock.

St John's wort is available over the counter in most countries with extracts usually in tablets or capsules, but also as a tea or in other forms. The exact mechanism for the anti-depressant effects of St John's wort is unclear, and available research indicates that several components are relevant. Its anti-depressant mechanism is believed to involve inhibition of serotonin (5-HT) reuptake, similar to conventional SSRIs, with the major constituents thought to be hyperforin and hypericin (Leuner et al, 2007).

3.2 Aim

The aim of this study is to undertake a cost effectiveness analysis of St John's wort compared with standard anti-depressants – tricyclic anti-depressants (TCAs), SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) etc – for mild to moderate (not severe) depression.

3.3 Indication

The general lay term 'depression' is often used to describe the clinical condition of 'major depression'[28] as defined and classified in the Diagnostic and Statistical Manual of Mental Disorders (developed by the American Psychiatric Association). Depression is a mood disorder characterised by low mood and self-esteem, loss of interest or pleasure in normally enjoyable

[26] St John's wort refers to more than one commercial product and the results of this paper are based on products used in published clinical trials.

[27] Photo source: http://en.wikipedia.org/wiki/St_John%27s_wort

[28] Also known as 'major depressive disorder', 'clinical depression' or 'unipolar depression/disorder'.

activities, and adverse functional impacts on a person's family, work or school life, sleeping and eating habits, and general health. Diagnosis of depression is based on the patient's self-reported experiences, behaviour reported by relatives or friends, and a mental status exam.

3.3.1 Epidemiology

Prevalence

A literature search was conducted to find estimates of the prevalence of mild to moderate depression. The search terms were "Prevalence depression" and "prevalence AND epidemiolog* AND depress* AND Australia". The NCBI and NIH Pubmed databases were searched in August 2009 and selection criteria included articles: (1) in English; (2) published in the last five years; and (3) concerning studies in humans. Findings are summarised in Table 3.1.

The results of the Australian National Survey of Mental Health and Wellbeing conducted in 2007 (ABS, 2008) suggested that the one year prevalence of depression in adults was 3.1% among males and 5.1% among females. Mild, moderate, and severe categories were not reported separately. According to both Kessler et al (2005) and Bierut et al (1999), an approximate proportion of those with severe depression is 30.9%, suggesting prevalence of moderate to mild depression among males of 2.14% and among females of 3.52%.

Depression, like anxiety, often remains sub-optimally treated or untreated, with the Survey of Disability Ageing and Carers reporting that 56% of people with clinical depression received any form of professional care (ABS, 1998).

Mortality

In 2007 there were 0.26 deaths per 100,000 people with a depressive episode as the underlying cause (ABS, 2009a). The available data do not allow a distinction between deaths from mild to moderate versus severe depression.

Table 3.1: Epidemiology of depression

Source	Aim and method	Definitions	Findings
ABS (2008) (Australia)	The National Survey of Mental Health and Wellbeing conducted in 2007 surveyed Australians in private dwellings and reported prevalence of depression in those aged 16 to 85 years. Face to face interviews with 8,841 fully-responding households, representing a 60% response rate. The survey used the World Mental Health Survey Initiative version of the World Health Organization's Composite International Diagnostic Interview, version 3.0 (WMH-CIDI 3.0).	Based on Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and International Statistical Classification of Diseases and Related Health Problems (ICD-10).[29] Severe, moderate and mild depressive episodes	The lifetime prevalence of depression was 8.8% among males and 14.5% among females. The one year prevalence[30] was 3.1% among males and 5.1% among females. Mild/moderate/severe depression were not reported separately. Data for depressive episodes were not reported by age.

[29] As Linde et al (2008) note, there are two major classification systems to diagnose depressive disorders, the DSM and ICD. DSM-IV defined depressive diagnoses to include recurrent or persistent major depression and minor depression. ICD-10 diagnoses (codes F32 and F33 (WHO 2007)) include recurrent or persistent depression with mild, moderate or severe episodes. According to the DSM-IV diagnostic classification, either depressed mood or a loss of interest or pleasure in daily activities consistently for at least a two week period has to be present to diagnose a major depressive disorder. The ICD-10 system uses the term depressive episode instead of major depressive disorder, but lists similar criteria.

[30] The proportion of people who experienced relevant symptoms at any time during the preceding 12 months.

Source	Aim and method	Definitions	Findings
Kessler et al (2005) (USA)	To estimate the 12 month prevalence, severity and comorbidity of DSM-IV anxiety, mood, impulse control and substance disorders in the US National Comorbidity Survey Replication which surveyed English speakers in the coterminous US. Face to face interviews in households were conducted over 2001 to 2003. 9,282 English speaking respondents aged 18 yrs or older. Response rate 70.9%.	12 month DSM-IV disorder. Serious= 12 month suicide attempt with serious lethal intent; work disability or substantial limitation due to disorder; positive screening results for non-affective psychosis; bipolar I or II, substance dependence with serious role impairment, impulse control disorder with repeated serious violence or any disorder that resulted in 30 or more days out of role in a year.	12 month prevalence of major depressive disorder = 6.7% (standard error 0.3). In these people: 30.4%(1.7) were serious; 50.1%(2.1) were moderate; and 19.5% (2.1) were mild. Severity by gender not reported. Probably an underestimate of prevalence because those with mental illness less likely to respond, and exclusion of non-English speakers and homeless.
Bierut et al (1999) (Australia)	To examine the genetic and environmental contributions to major depressive disorder in a volunteer community based sample of male and female twins Subjects drawn from NHMRC volunteer sample of twins. Phone interviews conducted in 1992-93 of 2,685 pairs of twins Lay interviewees used Semi-Structured Assessment for the Genetics of Alcoholism instrument	DSM-III R major depressive disorder, DSM-IV major depressive disorder and DSM-IV severe major depressive disorder. DSM-IV major depressive disorder requires cluster of 5 symptoms during at least two weeks plus impairment of functioning or seeking treatment. Severe major depressive disorder requires 6 symptoms during at least 4 weeks.	Lifetime prevalence DSM-IV major depression in 15.7% of males (n=287) and 22.4% of females (n=784) Lifetime prevalence of severe DSM-IV major depression was 3.4% of males (n=63) and 9.2% of females (n=320).

3.4 Intervention

The intervention is St John's wort for the treatment of mild to moderate (not severe) depression depression, with more detail in Section 3.4.2.

3.4.1 Literature search

A literature search was undertaken on 14 July 2009 of NCBI and NIH Pubmed using search parameters of "St John's wort and depression". Selection criteria were: (1) in English; (2) published after July 2008 (the last search undertaken in Pubmed by Linde et al, 2008); and (3) studies in humans. New studies published after the Cochrane Review by Linde et al (2008) included: Brattström (2009), Rahimi et al (2009) and Kasper et al (2008). A summary of literature reviewed for this study is in Appendix A (Section 3.13). Linde et al (2008:2) reviewed:

> *'29 studies in 5,489 patients with depression that compared treatment with extracts of St. John's wort for 4 to 12 weeks with placebo treatment or standard antidepressants. The studies came from a variety of countries, tested several different St. John's wort extracts, and mostly included patients suffering from mild to moderately severe symptoms. Overall, the St. John's wort extracts tested in the trials were superior to placebo, similarly effective as standard antidepressants, and had fewer side effects than standard antidepressants. … Patients suffering from depressive symptoms who wish to use a St. John's wort product should consult a health professional. Using a St. John's wort extract might be justified, but important issues should be taken into account: St. John's wort products available on the market vary to a great extent. The results of this review apply only to the preparations tested in the studies included, and possibly to extracts with similar characteristics. Side effects of St. John's wort extracts are usually minor and uncommon. However, the effects of other drugs might be significantly compromised.'*

Rahimi et al (2009) conducted a meta-analysis of the efficacy and tolerability of Hypericum perforatum compared with selective serotonin reuptake inhibitors (SSRIs). Thirteen RCTs were included. The authors found no significant difference in efficacy between Hypericum and SSRIs although the risk of withdrawal from studies due to adverse events was significantly lower with Hypericum.

Kasper et al (2008) investigated the efficacy and safety of hypericum in preventing relapse during 6 months continuation treatment and 12 months long term maintenance treatment after recovery from an episode of recurrent depression compared with placebo. Brattstrom (2009) conducted an open multicentre safety study of Hypericum. [31]

3.4.2 Specification of St John's wort extract

St John's wort products available on the market are not standardised and hence unlikely to be equally effective (Linde et al, 2008; Williams and Holsinger, 2005; Hypericum Depression Trial Study Group, 2002). Trials have tested a variety of extracts and hence the findings of Linde et

[31] Two 2010 studies were published after most of this analysis was completed, and so were not included, but support the conclusions of this study (Kasper et al, 2010; Melzer et al, 2007).

al (2008) and Rahimi et al (2009) were not based on one homogeneous extract, but on a range of different extracts.

Linde et al (2008) argued that their findings most likely applied to products using ethanol 50% to 60% or methanol 80% for extraction from dried plant material, with daily extract dosages of 500 to 1200 mg with a ratio of raw material to extract of 3-7:1. This in a sense provides a base standard for St John's wort.

Our analysis is based on two St John's wort products available in Australia at a dose of 900mg per day. Both products are extracts of *H. perforatum* equivalent to dry flowering herb top, 1800mg, standardised to contain hypericin 990 mcg. These products were selected using an on-line pharmacy search on the basis that information regarding their formulation was easily accessible and accords with the base standard above, and tablets are easily divisible to provide this daily dose (some tablets identified in the search would need to be cut in thirds or into two-thirds). Also, where one product was available in two sizes, the larger size was selected as it was cheaper per dose – an important factor in consumer's selection of long term medications.

3.4.3 Interactions with other drugs

Both St John's wort and standard anti-depressants can result in adverse side effects when taken in combination with other anti-depressants, and other medications. For example, St John's wort can cause decreased levels of concentration in drugs that are dependent on dose to be effective, e.g. some statins (drugs for high cholesterol), HIV-AIDS, allergies, thrombosis and oral contraceptives (Williams and Holsinger 2005; Piscitelli et al, 2000).[32] Standard anti-depressants can also interact with these and other drugs (e.g. drugs for HIV-AIDS, migraine, NSAIDS, and thrombosis and cardiac medications) (Spina et al, 2008; Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression, 2004). Roughead et al (2007) noted the potential for interactions between anti-depressants and other drugs in the Australian Veteran Population.

Unlike standard anti-depressants, St John's wort is currently available without medical supervision (Hammerness, 2003; Whitten, 2006). Physicians are therefore recommended to regularly ask their patients about the use of products containing hypericum (Rahimi et al, 2009).

3.4.4 Side effects and adherence

> The literature suggests that St John's wort is associated with marginally fewer adverse events than standard anti-depressants, but this was not statistically significant.

However, patient withdrawals from clinical trials of St John's wort due to adverse events are significantly less than patient withdrawals from clinical trials of standard anti-depressants (Linde et al, 2008; Rahimi et al 2009 for SSRIs and Appendix B in Section 3.14).

For the purposes of cost effectiveness analysis, it is difficult to determine the impacts of the specific adverse events on health system costs and quality of life because:

[32] Interactions with these drugs does not occur for all St John's wort extracts (e.g. low hyperforin extracts have few if any substantial interactions). Drug interactions occur frequently between conventional drugs and this does not preclude their use, but means clinicians must be aware and either avoid or titrate doses accordingly.

- there is a potentially wide range of adverse events for both St John's wort and standard anti-depressants (e.g. Ferguson 2001 summarises the side effects of standard anti-depressants) and there is inconsistency across studies on the range of adverse events reported. For example, HDTSG (2002), Szegedi et al (2005) and van Gurp et al (2002) all published findings for a different selection of adverse events.
- serious adverse events e.g. deaths from serotonin syndrome or an injurious fall at work as a result of SSRI discontinuation syndrome are either too few to measure or without available data.
- there is little evidence on the long term/lifetime health impacts associated with adverse events from St John's wort or SSRI/anti-depressant use. There are no sources which make a direct comparison of long term impacts between St John's wort and pharmaceutical anti-depressants.

Odds ratios for discontinuation of treatment (or 'drop out' rates) because of adverse events and more broadly, drop out rates for any reason, were calculated by Linde et al (2008) based on five RCTs of older anti-depressants compared with hypericum and 11 RCTs of SSRIs compared with hypericum.

- Compared with standard anti-depressants, the odds ratio (OR) of dropping out from the hypericum group because of adverse events was 0.41 (95%CI 0.29 to 0.60).
- Compared with standard anti-depressants, the OR of dropping out of the hypericum group for any reason (including loss to follow up, insufficient/inadequate response, adverse events or protocol violation) was 0.77 (95% CI 0.62 to 0.95).

Reasons other than side effects for non-adherence can include the long duration of treatment and a lack of understanding of the importance of persisting with therapy in order to receive the benefits. Differences in adherence are important in cost effectiveness analysis as low adherence can incur costs but reduce efficacy.

> For this analysis, adherence with St John's wort is similar to that of anti-depressants reflecting the findings of Müller et al (2004), Szegedi et al (2005) and Van Gurp et al (2002). However the protective ORs for dropout rates are modelled in the sensitivity analysis.

3.5 Comparator

There are currently no National Health and Medical Research Council (NHMRC) guidelines for treatment of depression.[33] According to the Royal Australian and New Zealand College of Psychiatrists (2005) guide for consumers and carers, initial treatment for depression by a GP should include one or some combination of:

- referral to a psychiatrist or other health professional or hospital;
- anti-depressant medication and cognitive behavioural therapy/interpersonal psychotherapy;
- weekly checkups with a GP or another health professional.

[33] NHMRC Guidelines on treatment of depression in young people published in 1997 were rescinded in 2004 following the NHMRC's standard five-year publication review.

Following this, patients should visit their GP not less often than every six weeks to have a symptom review, a review of changes in problems and supports and a review of treatment side effects. Treatment may then be adjusted. Discussion of medications suggests that:

- SSRIs would generally be first line treatment because side effects are less common than with TCAs or venlafaxine;
- TCAs are more likely to be used if the depression is severe and or another treatment has not worked sufficiently. Side effects of TCAs are more common than with SSRIs; and
- Venlafaxine (SNRI) is useful when other treatments have been unsuccessful or for severe depression.

Hence the comparator is defined as treatment with standard anti-depressants available in Australia (as per Table 3.2).

The Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression (2004) recommend cognitive behavioural therapy/interpersonal psychotherapy or SSRIs as first line monotherapy for moderate depression. If there is either partial or no response to an SSRI as first line therapy, second line therapy involves a switch to TCA or Venlafaxine, with the addition of cognitive behavioural therapy. Partial or non-response to second line therapy would then involve augmentation and combination. Changes in dose at any stage may also be considered.

SSRIs were the most commonly used anti-depressant in Australia in 2006, although tricyclics and other anti-depressants were not uncommon (Table 3.2). In 2006, Sertraline (an SSRI) was the ninth most commonly dispensed drug of all in the Australian community (adjusted for differences in quantity per prescription and daily dose) (Australian Government Department of Health and Ageing, 2006).[34] Out of all the classes of anti-depressants, SSRIs had the highest average use (adjusted for differences in quantity per prescription and daily dose) (Table 3.2).

Table 3.2: Community scripts for anti-depressants, 2006

Type of anti-depressant	Number scripts dispensed	Defined daily dose/1,000 people/day (average)
Tricyclics	3,005,095	0.9
SSRIs	7,983,057	7.7
Monoamine oxidase inhibitors	220,491	0.6
Other	3,321,882	3.3

Source: Australian Government Department of Health and Ageing (2006).

Approach to treating patients who discontinue therapy because of side effects or inadequate response to treatment

The guidelines do not specify an approach to treating patients who discontinue therapy because of side effects or inadequate response to treatment. If a patient discontinues treatment, his or her GP or psychiatrist would be concerned about the potential for the condition to deteriorate leading to a possible adverse event (discontinuation syndrome,

[34] In terms of defined daily dose per 1,000 population per day.

hospitalisation or self harm). The health professional may encourage the patient to remain on the drug at a higher dose to see if the response improves, or the same dose to see if the side effects are a short term phenomenon and dissipate in the medium term. If this approach is not successful, the health professional may then consider switching the patient to another anti-depressant medication. Switching is associated with the danger of both serotonin syndrome, and discontinuation syndrome, and so it is likely that switching would be undertaken gradually over a number of weeks, with medical oversight.

3.6 Effectiveness

Based on double blind randomised controlled trials in adults with mild to moderate depression,[35] Linde et al (2008) found that St John's wort was as effective as standard treatment, with fewer side effects (but with statistically insignificant difference in risk). Rahimi et al (2009) made similar conclusions in their systematic review comparing St John's wort with SSRIs. These two studies together covered all the RCTs from the literature review except the predominantly German studies – Brattstrom et al (2009) and Kasper et al (2008). Linde et al (2008) found that trials from German-speaking countries reported findings more favourable to hypericum.[36] These two studies, however, were primarily safety focused and also supported the results from the higher quality meta-analysis and systemic review.

Rahini et al (2009) concluded that: "hypericum does not differ from SSRIs according to efficacy and adverse events in major depressive disorder" and Linde et al (2008) concluded that "trials of hypericum and standard antidepressants were statistically homogenous".

> Based on the findings of Linde et al (2008) and Rahimi et al (2009), the modelling applies the same efficacy for St John's wort and standard anti-depressants.

3.7 Benefits

Ideally the benefits of this study would be reported in DALYs, with benefits measured in terms of the efficacy of the intervention (St John's wort) and comparator (SSRIs) as well as DALYs lost from the adverse event profiles of the two arms.

However, since the conclusion was equal efficacy and safety, benefits of the two arms from efficacy and adverse events are treated as comparable in the model. In incremental terms this means there is no difference between the intervention and the comparator in relation to DALYs averted that are able to be measured on the basis of current evidence for these two health outcomes.

However, as discussed above, switching may occur under the comparator arm and the costs of this include DALY impacts, as estimated in Section 3.9. This is included in the sensitivity analysis.

[35] Evidence on SJW for severe depression insufficient so findings only apply to adults with mild to moderate depression (Linde et al 2008).

[36] Extracts of St. John's wort are licensed and widely used in Germany for the treatment of depressive, anxiety and sleep disorders (Linde et al 2008).

3.8 Model

A decision tree model was used and the method for the cost effectiveness analysis was incremental, i.e. the costs of St John's wort were compared with the costs of SSRIs.

The choice of key parameters for costs is outlined in the section below.

3.9 Costs

3.9.1 Direct cost of treatment

For this analysis, it was assumed that St John's wort would be taken under the same medical supervision as pharmaceutical anti-depressants, consistent with standard care for depression. Depression is a serious disease, and both standard antidepressants and St John's Wort can interact with other drugs. Thus, the only difference in unit health system costs in this analysis relates to the unit costs of St John's wort and standard anti-depressants. Other heath system costs such as GPs, psychologists or psychiatrists providing cognitive behaviour therapy or interpersonal therapy, are the same for patients whether taking St John's wort or standard anti-depressants.

The estimated cost to the Australian Government of anti-depressants dispensed to Australians in 2007-08 was $0.55 per day (AIHW, 2009)[37] — **in 2009, approximately $0.57 per day** (AIHW, 2008).[38] Notably, this does not include the patient copayments which were $5.00 (concession) and $31.30 per script in 2008. However, no data were found on the average patient copayment for anti-depressants, although in other (unpublished) analysis, Access Economics has found that for long term medications, gaps are relatively small in percentage terms due to safety nets.

The **average cost per day of St John's wort (at a dose of 900mg per day) in 2009 was $0.17** (an average of the daily cost of $0.13 and $0.17 in Table 3.3).

Table 3.3: Retail cost of St John's wort

Tablets per bottle	Dose per tablet*	Ingredient	Cost per bottle	Cost per day
60	1800mg	990 mcg hypericin	A$15.95	$0.13
90	1800mg	990 mcg hypericin	A$35.95	$0.20

Source: http://www.pharmacyonline.com.au/ accessed 10 September 2009. * Hence half a tablet per day.

3.9.2 Cost of changing treatment due to side effects or non response

Khandker et al (2008) found that patients with depression who are resistant to treatment and switch medications had higher all cause and depression related pharmaceutical and medical related costs than non switching patients after controlling for comorbidities. This study is not directly comparable to Australia because of differences in the US and Australian health

[37] Based on 1,494,587 Australians on anti-depressants in that year and Australian Government expenditure on anti-depressants of $301.1 million (AIHW 2009).

[38] Average annual health inflation between 1996–97 to 2006–07.

systems and also because it is not clear that indicated patients had mild to moderate depression — a proportion may have had severe depression.

A reasonable assumption for this analysis is that patients who drop out would incur at least one additional visit to a clinician (GP or psychiatrist) and would have experienced some diminution of their quality of life whilst switching to a different treatment. The Medicare cost is $63.75 for the GP visit[39] with an average patient contribution of $4.60[40] ($68.35 per visit in total).

A two week period of washout and changeover is assumed. In terms of the impact on the disease burden experienced by those who withdraw from treatment due to adverse events, it is assumed that they experience a return of, or exacerbation of depression whilst not taking medication, so the DALY weight for depression is applied for a length of two weeks.

The same costs are applied to those who drop out in both arms of the analysis (i.e. to St John's Wort as well as to standard antidepressants) — it is just the rate of drop out from treatment that differs (as explained earlier based on evidence from the systematic reviews by Linde et al, 2008 and Rahimi et al, 2008). The cost estimates discussed here are probably conservative (for example those who experienced side effects great enough to drop out of treatment would experience some diminution of quality of life while on that treatment as well as during the switching period).

3.9.3 Years of healthy life lost due to disability (YLD)

DALY weights are used to adjust a year according to the extent of disease burden experienced. Zero represents perfect health and one represents death.

The disability weight for mild depression is 0.14 and for moderate depression is 0.35 (Mathers et al, 1999). Using proportions of mild and moderate depression from Kessler et al (2005), the weighted average YLD weight is 0.291. Assuming depression is experienced for two weeks while treatment changes, the YLD is 0.011.

3.9.4 Parameter summary

A summary of the parameters used in the analysis of St John's wort versus standard anti-depressants for depression is in Table 3.4.

Table 3.4: Parameters used in the cost effectiveness analysis

Parameter	Sources and methods	Estimate
Efficacy	Linde et al (2008) and Rahimi et al (2009)	Standard anti-depressants and St John's wort have similar efficacy

[39] Medicare Benefits Schedule July 2009 item 36 – a level 'C' attendance covering a more detailed history and examination.

[40] Medicare statistics, Department of Health and Ageing, Table B6a, Medicare average patient contribution per service patient and bulk billed services out of hospital only, June 2009.

OR of dropping out due to adverse events	Linde et al (2008) — OR of discontinuing treatment/dropping out due to adverse/side effects Linde et al (2008) OR of drop out for any reason (including loss to follow up, insufficient/inadequate response, adverse events or protocol violation)	OR favouring hypericum was 0.41 (95%CI 0.29 to 0.60) OR favouring hypericum 0.77 (95% CI 0.62 to 0.95)
Cost of dropping out	Medicare Benefits Schedule July 2009 item 36 – a level 'C' attendance covering a more detailed history and examination and average patient contribution for non-referred attendances to GPs from Department of Health and Ageing, Medicare Statistics, Table B6a, June 2009. YLD from Mathers et al 1999 and distribution of depression from Kessler et al 2005.	$68.35 for a visit to a GP and YLD of 0.011.
Cost of anti-depressants	In 2007-08, anti-depressants were dispensed to 1,494,587 patients, at a cost to the Australian Government of $301.1 million (AIHW 2009)[41].	Cost to the Australian Government per patient per day in 2009 of $0.57.
Cost of St John's wort	Australian Pharmacy Online,[42] average price for bottles of 1800mg St John's wort hypericin 990mcg. Dose of 900mg per day.	In 2009, $0.17 per patient per day.
One year prevalence of mild to moderate depression	ABS (2009) one year prevalence of mild, moderate and severe depression — males 3.1% and females 5.1%. Kessler et al (2005) and Bierut et al (1999) proportion of those with severe depression — 30.9%.	Males 2.14% and females 3.52%
Mortality	ABS (2009) standardised death rates for depressive episodes ICD-10 F32 (zero deaths reported for F33).	In 2007 there were 0.26 deaths per 100,000 people with a depressive episode (mild, moderate or severe) as the underlying cause.

3.10 Results

The cost effectiveness analysis compares St John's wort with standard anti-depressants assuming equivalence of efficacy and health outcomes, with cost thus being the major determinant of cost effectiveness.

[41] Tables 11.6 and 14.11

[42] http://www.pharmacyonline.com.au/ accessed 10 September 2009.

The per person difference is thus \$0.57-\$0.17=\$0.40 per day, or \$146.00 per annum. **St John's wort is cost-saving compared with standard anti-depressants**.

From ABS (2009) above and demographic data, there are an estimated 878,003 Australians with depression of which 69.1% have mild and moderate depression and 56% (ABS, 1998) are treated, a total of 339,752 people.

With treated mild and moderate depression estimated to affect 339,752 Australians in 2009, there could be around 339,752*146=\$50 million per annum in potential savings from switching to St John's wort from standard anti-depressants.

Due to the finding of comparable health benefits, the results of St John's wort being cost saving compared to standard anti-depressants are naturally highly sensitive to price. The price margin for standard anti-depressants is estimated here as quite substantial – 3.35 times the price of St John's wort. However, it is possible that St John's wort might be more expensive if, for example, there was wastage from pill-halving (albeit pill-cutters are readily available in Australia and cost around \$12)[43], or if the product was subject to a regulatory regime that aimed to standardise active compounds, extraction processes etc. However, even tripling the price of St John's wort would leave the intervention cost saving.

The major uncertainty is in relation to additional health benefits from St John's wort relative to standard anti-depressants due to the potential cost of changing treatment due to side effects or non-response to stand anti-depressants. The sensitivity analysis including impacts of changing treatment shows that St John's wort would become dominant relative to standard anti-depressants, saving \$50 million in costs per annum and 49 DALYs per annum (Table 3.5). The additional GP costs are only \$0.3 million of the \$50 million total.

Table 3.5: Incremental sensitivity analysis, St John's wort versus standard antidepressants

1. Cost of ADs per day (average)	\$0.57
2. Cost of SJW per day (average)	\$0.17
3. Difference per day (2.-1.)	\$0.40
4. Difference per annum (3.*365)	\$146.00
5. Australians with depression 2008 (ABS, 2009)	878,003
6. % severe (Kessler et al 2005, Bierut et al 1999)	30.90%
7. % on medication (SDAC, ABS 1998)	56%
8. Target group for savings (5.*(1-6.)*7.)	339,752
9. \$m saved pa (4.*8./1,000,000)	\$49.6
10. Ratio of cost (1./2.)	3.35
11. OR drop out any reason (Linde et al 2008)	0.77
12. GP visit cost (MBS Item 36+copayment)	\$68.35
13. Extra disability weight, treatment change (Mathers et al, 1999)	0.011
14. % chance of drop out overall (Brattstrom, 2009)	5.7%
15. No. dropout with ADs (8.*14.)	19,366
16. No. dropout with SJW (11.*15.)	14,912

[43] https://secure.visionaustralia.org/visionaustralia/onlineshop/ProductDetail.aspx?ID=231

17. Difference (15.-16.)	4,454
18. Cost difference $m (17.*12./1,000,000)	0.3
19. Incremental DALY difference (17.*13.)	**49.0**
20. Incremental cost difference $m (18.+9.)	**$49.9**

Source: Access Economics calculations as detailed in this report. AD=antidepressants. SJW=St John's wort.

In the sensitivity analysis, St John's wort dominated standard anti-depressants for mild to moderate depression because it is cheaper than standard anti-depressants and fewer patients withdraw from St John's wort than from standard anti-depressants. Even if the unit cost of St John's wort was the same as that of standard anti-depressants, St John's wort would remain dominant due to the lower changeover rates compared to standard anti-depressants.

3.11 Conclusions

The cost effectiveness analysis in this report found St John's wort was cost-saving relative to standard anti-depressants in the treatment of mild to moderate (not severe) depression. If the lower rate of drop out from St John's wort relative to standard anti-depressants is taken into account, St John's wort dominated standard anti-depressants (i.e. St John's wort was both cost saving and also resulted in a reduced disease burden).

The exact mechanism for the anti-depressant effects of St John's wort is unclear, and available research indicates that several components are relevant. While the findings of equal efficacy in mild to moderate depression by the systematic reviews of Linde et al (2008) and Rahimi et al (2009) were not based on homogeneous extracts, it is unlikely that all St John's wort products are equally effective. The products available on the market are not identical, so it is difficult to extrapolate from clinical trials directly into community practice.

Standardisation of all St John's wort products might be required before St John's wort could be recommended as an alternative to pharmaceutical anti-depressants for mild to moderated depression. Further, St John's wort is currently sold in Australia with limited therapeutic claims which, importantly, exclude 'depression'. If St John's wort were to be sold in Australia with 'depression' as a therapeutic indication, a higher level of regulatory approval would be required. This may in turn increase the cost of commercial St John's wort products. However, even if the costs of St John's wort and standard anti-depressants were the same, St John's wort would be likely to remain cost effective because it is associated with fewer treatment withdrawals due to adverse events than standard anti-depressants.

Depression is a serious disease, and it may be advisable that St John's wort would need to be taken under medical supervision — the same as for standard antidepressants. In addition, both standard anti-depressants and St John's wort can interact with other medications with potentially serious adverse outcomes. This analysis thus assumed that the other health system costs (GP and psychiatrist visits etc) would be the same for St John's wort and standard anti-depressants. The principal potential for cost savings derived from the lower withdrawal rates from treatment associated with St John's wort, leading to reduced costs of switching medications.

The prevalence of mild to moderate depression among Australian males and females is approximately 2.1% and 3.5% respectively — around 226,100 males and 380,600 females in

2008. This is equivalent to 176,570 years of life lost due to disability in 2008 if these people were depressed for the entire year. Further, if all of these people took anti-depressants, the approximate cost to the Australian Government would be $122.2 million. This does not include patient copayments.

St John's wort has significant potential to be more cost effective than standard anti-depressants for some patients. Further research into St John's wort (including costs for ensuring product standardisation) would be worthwhile.

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3.13 Appendix A: Detailed summary of literature studies relating to St John's wort and depression

Table 3.6: Literature on effectiveness of St John's wort for depression

Source	Aim and method	Extract and comparator	Outcome measure	Findings
Rahimi et al (2009)	Meta-analysis Searched for studies comparing the efficacy and tolerability of Hypericum and SSRIs for major depressive disorder in the period 1966 to June 2008. 13 trials selected. All included trials in meta-analysis were randomised and double blinded and patients were diagnosed with major depressive disorder according to DSM-IV or ICD-10 criteria.	Extracts: LI-160, STW3-VI, Iperisan, WS 5570, STW3, Calmigen, Ze 117, LoHyp-57	'Clinical response', 'remission', 'mean reduction in HAMD score', 'total adverse events', and 'withdrawals due to adverse events' were the key outcomes of interest.	Efficacy of hypericum compared with SSRIs based on 11 trials had Relative Risk (RR) of 0.99 (95% CI 0.91-1.08) (p=0.83). Studies found to be homogeneous. The summary RR for adverse events of hypericum vs. SSRIs (8 trials) was 0.85 with a 95% CI of 0.7–1.04, (P=0.11) and the studies were significantly heterogeneous. A summary RR for withdrawal due to adverse events by hypericum vs. SSRIs (11 studies) was 0.53 (95% CI=0.35–0.82) (p=0.004) and studies were homogeneous. Hypericum does not differ from SSRIs according to efficacy and adverse events in major depressive disorder. Lower study withdrawal due to adverse events by hypericum is an advantage in management of major depressive disorder.

Source	Aim and method	Extract and comparator	Outcome measure	Findings
Kasper et al (2008) (Germany and Sweden)	The efficacy and safety of hypericum in preventing relapse during 6 months continuation treatment and 12 months long term maintenance treatment after recovery from an episode of recurrent depression were investigated. Double-blind, placebo controlled multicenter trial. 426 adults (18-65 yo) out-patients with a recurrent episode of moderate major depression[44], a 17-item HAM-D total score≥20, and≥3 previous episodes in 5 years participated. Excluded schizophrenia, acute anxiety disorder, adjustment disorder, chronic or psychotic depression, bipolar disorder, acute post-traumatic stress disorder, or substance abuse (except nicotine and caffeine). Patients with increased risk of suicide or previous attempted suicide were excluded and concomitant medical and non-medical anti-depressant treatment were prohibited.	Extracts: WS 5570 (3×300 mg/day) WS® 55701 is a stabilized dry extract from St John's wort, extraction solvent methanol 80%, with a defined contents of 3–6% hyperforin, 0.1–0.3% hypericin, not less than 6% flavonoids, and not less than 1.5% rutin. Coated tablets containing 300 mg of the extract were used. Trial phases included a 1 week washout, followed by 6 weeks acute treatment with WS5570. Responders were then randomised to 26 weeks continuation treatment with either WS5570 or placebo. Those on WS5570 were then rerandomised to either WS5570 or placebo for 52 weeks maintenance treatment. (Continuation placebo group continued with placebo during maintenance treatment phase.) Comparator: placebo	HAM-D, Beck Depression Inventory and CGI Relapse rate during continuation treatment (primary outcome measure) Average time to relapse during continuation treatment	WS 5570 prevented relapse after recovery from acute depression. WS 5570 was not associated with any unexpected drug-specific risks or problems of intolerance. Tolerability in continuation and long term maintenance was at the placebo level.

[44] ICD-10 F33.0 or F33.1, and DSM-IV 296.3

Source	Aim and method	Extract and comparator	Outcome measure	Findings
Linde et al (2008)	To investigate whether extracts of hypericum are more effective than placebo and as effective as standard anti-depressants in the treatment of major depression; and whether they have fewer adverse effects than standard anti-depressant drugs To be included trials had to be double-blind and randomised. 29 trials met the inclusion criteria. Patients had to suffer from major depression (meeting DSM-IV or ICD-10 criteria). Trials in children (< 16 years) were not eligible. Experimental and control treatments had to be given for at least four weeks. Last searches conducted CCDANTR July 2007 and in Pub-med July 2008.	Extract: The following comparisons were performed: 1. hypericum extracts vs. placebo 2. hypericum extracts vs. standard anti-depressants (synthetic anti-depressants (TCA and related anti-depressants, SSRIs, SNRIs). Trials using clearly inadequate synthetic anti-depressants (e.g. benzodiatepines) or a dosage clearly below the lower thresholds recommended in current guidelines (Härter 2003, ICSI 2007) were excluded.	The most frequently used instrument used for outcome measurement was the Hamilton Rating Scale for Depression (used in all trials). The main outcome measure for assessing effectiveness was the responder rate ratio (the relative risk of having a response to treatment). The main outcome measure for adverse effects was the number of patients dropping out due to adverse effects.	Trials of hypericum and standard anti-depressants were statistically homogeneous. Relative risks (RRs) for tri and related were 1.02 (95% CI, 0.90 to 1.15; 5 trials) and for SSRIs were 1.00 (95% CI, 0.90 to 1.11; 12 trials). St John's wort patients dropped out of trials due to adverse effects less frequently than those given older anti-depressants (odds ratio (OR) 0.24; 95% CI, 0.13 to 0.46) or SSRIs (OR 0.53, 95% CI, 0.34-0.83). Concluded St John's wort a) superior to placebo in patients with mild to moderate major depression; b) are similarly effective as standard anti-depressants; c) and have fewer side effects than standard anti-depressants. Note the evidence for severe major depression is still insufficient to draw conclusions.

Source	Aim and method	Extract and comparator	Outcome measure	Findings
Brattstrom (2009) (Germany)	To evaluate the long term safety and effects of St John's wort. Safety study with 440 out-patients in 35 psychiatric and internal medicine practices in Germany suffering from mild to moderate depression. Patients treated for up to one year. Patients 18 years or older with mild to moderate depression without immediate suicidal ideation met the ICD-10 criteria for depressive episodes (F32.0and F32.1) or recurrent depressive disorders (F33.0 and F33.1) having a minimum HAM-D score of 16 at both baseline visits.	Extract: Ze 117 500mg Ze 117 per day (2 tablets 250mg each per day)	Evaluation criteria were safety (adverse event frequency) and influence on depression — 17-item Hamilton depression rating scale (HAM-D), and the Clinical Global Impression (CGI) scale.	A total of 217 (49.3%) patients reported 504 events. 30 of these events were reported by 30 patients and were possibly or probably related to the treatment. 4 patients reported gastrointestinal disorders and 4 patients reported skin rash. 3 patients reported urticaria/pruritus and 3 reported insomnia. A total of 25 patients (5.7%) discontinued treatment due to adverse events, regardless of a relationship with the study medication. 6 patients were non-compliant with treatment. ZE 117 is a safe and effective way to treat mild to moderate depression over long periods of time

Source	Aim and method	Extract and comparator	Outcome measure	Findings
Hypericum Depression Trial Study Group (2002) (included in Linde et al 2008) (Included in Rahimi et al 2009)	To test the efficacy and safety of a well-characterized H perforatum extract (LI-160) in moderately severe major depressive disorder. Double-blind, randomised, placebo-controlled trial, Adult outpatients (n=340) with major depression and a baseline total score on the HAM-D of at least 20.	Extract: LI-160 Comparator 1: placebo Comparator 2: Sertraline (Zoloft) an SSRI HP vs placebo with daily dose of H perforatum 900 to 1500 mg Sertraline vs placebo with daily dose sertraline 50-100mg	Change in the HAM-D total score from baseline to 8 weeks; rates of full response, determined by the HAM-D and Clinical Global Impressions (CGI) scores.	Neither sertraline nor hypericum perforatum (LI-160) was significantly different from placebo. The efficacy of sertraline was demonstrated on the secondary CGI-I measure, resulting on average in much improvement, hypericum had no efficacy on any measure. Although not designed to compare sertraline with hypericum, the study showed superiority of sertraline on the CGI-I. Rates of diarrhea, nausea, and sweating (sertraline); anorgasmia (sertraline and hypericum); and frequent urination and swelling (hypericum) all were higher than those of placebo. No serious adverse events were found.

Source	Aim and method	Extract and comparator	Outcome measure	Findings
Moreno et al (2005) (included in Linde et al 2008) (Included in Rahimi et al 2009)	8-week double-blind trial of 72 patients with mild to moderate depression. Patients randomly assigned to receive hypericum perforatum 900 mg/day, fluoxetine 20 mg/day or placebo. Aim was to assess the efficacy and safety of hypericum perforatum in comparison with fluoxetine.	Extract: Iperisan®, Marjan Comparator 1: placebo Comparator 2: Fluoxetine (Prozac, SSRI)	Efficacy measures included the HAM-D scale, the Montgomery-Åsberg Rating Scale, and the Clinical Global Impression. Safety was assessed with the UKU Side Effect Rating Scale	Hypericum perforatum was less efficacious than both fluoxetine and placebo. Both drugs were safe and well-tolerated. There were no differences between the three groups regarding safety measures, including vital signs. Tension, nausea, postural dizziness, menorrhagia and diminished sexual desire were more frequent in the fluoxetine group at week 4. Those side effects tended to diminish with time and only menorrhagia persisted in a higher frequency in the fluoxetine group up the 8th week. At the 8th week, there was a higher incidence of insomnia, headache and diarrhea in the fluoxetine group.

Source	Aim and method	Extract and comparator	Outcome measure	Findings
Szegedi et al (2005) (included in Linde et al 2008) (Included in Rahimi et al 2009)	To investigate the efficacy of hypericum extract WS 5570 (St John's wort) compared with paroxetine in patients with moderate to severe depression. Randomised double blind, double dummy, reference controlled, multicentre non-inferiority trial. 251 adult outpatients with acute depression with total score ≥ 22 on the 17 item Hamilton depression scale.	Extract: WS 5570 Comparator: paroxetine (SSRI) 900 mg/day hypericum extract WS 5570 three times a day or 20 mg paroxetine once a day for six weeks. In initial non-responders doses were increased to 1800 mg/day hypericum or 40 mg/day paroxetine after two weeks.	Change in score on Hamilton depression scale from baseline to day 42 (primary outcome). Secondary measures were change in scores on Montgomery-Åsberg depression rating scale, clinical global impressions, and Beck depression inventory.	In the treatment of moderate to severe depression, hypericum extract WS 5570 is at least as effective as paroxetine and is better tolerated. 69/125 patients randomised to hypericum (55%) reported 172 adverse events and 96/126 treated with paroxetine (76%) reported 269 adverse events. Based on the rate ratio, the incidence of adverse events in the paroxetine group was 1.72 (95% confidence interval 1.42 to 2.10) of the rate observed for hypericum.

Note: Judgement has been exercised in reporting and not all RCTs are tabulated – just those considered of particular relevance.

3.14 Appendix B: Side effects of St John's wort and of SSRIs

3.14.1 St John's wort – side effects

Low doses of St John's wort are generally well tolerated according to Hammerness et al (2003) based on findings from Woelk et al (1994), which saw 2.4% of patients receiving 1.08 mg/day of hypericin reporting adverse events and Schulz (2001) which reported 95 incidents of adverse events out of approximately 8 million people using 1.08 mg/day of hypericin.

With higher doses the frequency of side effects increases. For example, Szegedi et al (2005) found 55% of patients on either 900mg/day or 1800mg/day experienced adverse reaction to hypericum with an incidence per day of exposure of 0.029 for 900 mg/day and 0.039 for 1800 mg/day.
The following are the more common side effects as reported in the literature:

- Allergy (dermatological) and alopecia;
- Photosensitisation;
- Neurological effects i.e. headache, neuropathy;
- Psychiatric effects i.e. anxiety;
- Gastrointestinal (GI) disturbances i.e. nausea, diarrhea; and
- Genitourinary effects i.e. sexual dysfunction.

Interactions with other drugs

When taken in combination with other treatments, St John's wort has multiple interactions which can cause more serious side effects than those which occur with sole St John's wort use. A number of studies such as Hammerness (2003) and Whitten (2006) highlight the potential problems of St John's wort being available 'over the counter' to people already using different medications, without medical consultation.

Serotonin syndrome is caused by an excess of serotonin in the central nervous system which can occur through combination use of SSRIs and St John's wort (Williams and Holsinger, 2005). A patient may experience confusion, agitation, nausea and a lack of co-ordination and there are reports of admissions to hospital as a direct consequence as noted by Hammerness et al (2003).

Hyperforin in St John's wort induces (to varying degrees depending on the extract) the cytochrome system, especially the 3A enzymes and the multidrug resistance transporter P-glycoprotein. More than 40% of prescription drugs are metabolised via the cytochrome 3A system and a significant proportion of the population are medicated by them. St John's wort can cause decreased levels of concentration in drugs used to lower cholesterol (simvastatin), HIV (indinavir), allergies, (fexofenadine), thrombosis (warfarin), and oral contraceptives among others (Williams and Holsinger, 2005). The potentially serious repercussions of this are highlighted by Piscitelli et al (2000) which found, during a clinic trial of healthy patients, a 57% decrease in concentrate of indinavir, an HIV protease inhibitor after St John's wort use. Indinavir is heavily dependent on dose to be effective as an HIV treatment and the reduction of concentration caused by St John's wort would have substantial health impacts for HIV patients using both drugs.

Long term impacts

In terms of long term effects as a result of adverse reactions Brattström (2009) concluded the following after a one year study using 500mg/day of St John's wort in mild-moderately depressed patients; that treatment with St John's wort is not associated with any long term safety concerns beyond those in short-term treatment and that long term use does not affect body weight, haematological and biochemical parameters, and there is no negative effect on the heart as seen by electrocardiography.

3.14.2 Side effects of SSRIs

Reported adverse events for SSRIs:

- Autonomic i.e. dry mouth, sweating;
- Central/peripheral nervous system i.e. headache, dizziness, sedation, aggression;
- Gastrointestinal disturbances i.e. nausea, diarrhea, constipation, abdominal pain;
- Musculoskeletal i.e. muscle pain/deficiency;
- Psychiatric i.e. insomnia, anorexia, anxiety, decreased libido;
- Upper respiratory i.e. infection, sinusitis, rhinitis;
- Urogenital i.e. ejaculation difficulty;
- Drug interaction problems;
- Dermatological reactions;
- Weight gain or weight loss; and
- Discontinuation syndrome.

Each SSRI treatment has a unique profile of associated side effects (Ferguson, 2001). Some side effects are more tolerable than others and some may only be present during the beginning stages of treatment decreasing or disappearing during the course of treatment.

Long term impacts

Serious or less tolerable side effects of SSRIs which can persist after discontinuation of treatment or throughout long term treatment are as follows.

- Sexual dysfunction – Montejo-González et al (1997) found that 58% of SSRI patients (male and female) experienced sexual dysfunction although Clayton et al (2006) reported higher figures; 98% of men and 96% of women experiencing impairment in at least one phase of sexual functioning. Bolton et al (2006) and Csoka et al (2007) used case studies of patients to assess the longevity of symptoms and found that in some cases sexual function did not return to baseline after discontinuation of SSRI treatment.
- Weight gain – Ferguson (2001) found that although some SSRIs are associated with weight loss during initial therapy, weight is often regained after 6 months and can be followed by additional weight gain with long term use. Uncontrolled studies have reported mean weight gains of 15 lb for sertraline, 21 lb (for fluoxetine, and 24 lb for paroxetine after 6 to 12 months of therapy. Although studies to date suggest that citalopram is less likely to cause weight gain, one clinical series of 18 patients reported 8 patients with mixed anxiety and mood disorders who had an average weight gain of 15.7 lb after receiving citalopram for 5 weeks.

3.14.3 Comparison of St John's wort and SSRI side effects

There are a number of studies which compare incidence of adverse events for St John's wort with SSRIs/anti-depressants (see Table 3.7 for a summary of the main studies). Generally the literature finds that St John's wort produces a lower number of adverse events with lesser severity. However there are limitations on the usefulness of this body of evidence in measuring the health benefits of St John's wort versus SSRIs/anti-depressants for the following reasons.

1. There is little consistency across St John's wort studies on the range of adverse events reported or at least published. For example HDTSG (2002), Szegedi et al (2005) and van Gurp et al (2002) all published findings for a different selection of adverse events.
2. Most adverse events that are reported would have little expected impact on quality of life and those that would such as deaths from serotonin syndrome as a result of St John's wort/SSRI/anti-depressant use are too few to measure or in the case of an injurious fall at work as a result of SSRI discontinuation syndrome, without available data.
3. There is little evidence on the long term/lifetime health impacts associated with adverse events from St John's wort or SSRI/anti-depressant use. There are no sources which make a direct comparison of long term impacts between St John's wort and SSRIs/anti-depressants.

Odds ratios for discontinuation of treatment (or 'drop out' rates) as a direct result of adverse events calculated by Linde et al (2008) were found to be the most appropriate alternate basis for a cost analysis of adverse events. This is because i) the study made direct comparisons between odds ratios (ORs) for St John's wort versus SSRIs and St John's wort versus older anti-depressants; and ii) a strong evidence base was used for both older anti-depressants and SSRIs analyses i.e. five and eleven randomised double blind clinical trials respectively.

Table 3.7: Comparison of studies for SSRI and St John's wort side effects

Source	Method	Intervention/comparator	Outcome measure	Findings
Linde et al (2008)	Meta-analysis of RCTs	Comparison of studies using hypericum and synthetic standard anti-depressants.	Patients dropping out due to adverse reactions.	Cases allocated to hypericum dropped out of clinical trials less frequently because of adverse reactions than patients allocated to older standard anti-depressants (OR = 0.24; 95%CI 0.13 to 0.46; I^2 = 0%) and SSRIs (OR 0.53, 95% CI, 0.34-0.83).
Szegedi et al (2005)	Randomised double blind, double dummy, reference controlled	900mg /day hypericum extract and 20mg/day paroxetine for 6 weeks. For non-respondents, 1800mg/day hypericum extract or 40mg/day paroxetine after two weeks. Moderate to severe depression.	Change in score on Hamilton depression scale from baseline to day 42 (primary outcome). Safety assumptions based spontaneous adverse event reports, semi-structured interview and physical exams.	55% hypericum patients reported 172 adverse events, 78% of paroxetine reported 269 events. 0.035 adverse events per day of exposure (0.029 at 900 mg/day and 0.039 at 1800 mg/day) for hypericum and 0.060 (0.062 at 20 mg/day and 0.059 at 40 mg/day) for paroxetine.
HDTSG (2002)	Double blind, randomised, placebo trial	Placebo, 900-1500mg/day hypericum or 50-100mg/day sertraline for 8 weeks	Adverse event recording based on patient interview and checklist completed by patient expanded from earlier scale	Hypericum users experienced a lower proportion of adverse events than the sertraline group in all but three adverse event categories ('forgetfulness', frequent urination' and 'swelling').
van Gurp et al (2002)	Double-blind randomised 12 week trial	Patients given either sertraline (50 - 100 mg/day) or St John's wort (900 - 1800 mg/day). Mild to moderate depression.	Changes from baseline in Ham-D and BDI scores and self-reported side effects	Significantly lower proportion of those using St John's wort than sertraline experienced adverse events at both 2 weeks and ever during the 12 week trial.

4 Fish oils for prevention of further morbidity and mortality in those with CHD

4.1 Background

Epidemiological studies have indicated links between the consumption of fatty fish (such as mackerel, herrings, sardines, salmon, tuna and other seafood) and lower incidence rates of Coronary Heart Disease (CHD), stroke and myocardial infarction (MI). However, studies that have used fish consumption as the main intervention have shown efficacy in the short term, although not in the long term. In addition, high levels of high levels of fish consumption may lead to poisoning with dioxin or methylmercury, although levels of these toxins in Australian fish stocks are very low.

Fish oil supplements offer a number of advantages through lower potential risk profiles as well as controllable concentrations of fish oil supplement per tablet. The World Health Organization (WHO), American Heart Association (Kris-Etherton et al, 2003), National Health and Medical Research Council (NHMRC), and the National Heart Foundation of Australia recommend fish oil as a complementary treatment in addition to standard treatments following a MI. These organisations mainly base their recommendations on the results of a large randomised clinical trial '*Gruppo Italiano per lo Studia della Sopravvivenza nell'Infarto Miocardico*' –Prevenzione (GISSI-P) and later the Japan eicosapentaenoic acid (EPA) Lipid Intervention Study (JELIS) trial (Yokoyama et al, 2007). Since these recommendations were published, another seminal trial (the GISSI-HF trial) has been published (GISSI-HF Investigators, 2008).

4.2 Aim

To undertake a cost effectiveness analysis of fish oils as a complement to current preventive therapies for reduced death and morbidity among people with CHD (through reducing serum triglycerides), versus no fish oils.

4.3 Indication

In line with the recommendations of the organisations above, the indication is for secondary prevention of morbidity and mortality from CHD, evidenced through previous MI.

The target population was defined in line with the trial data evidence as people who have had a MI within three months and who are unable to eat sufficient amounts of oily fish (2-4 portions per week) to meet the recommended intake of approximately 3.5g eicosapentaenoic acid (EPA) and 2.5g docosahexaenoic acid (DHA) per week. Fish oil supplements are thus indicated.

Australian specific incidence rates for MI and stroke events were sourced from Begg et al (2007). Rates of revascularisation procedures were sourced and calculated from the AIHW hospital morbidity database (Table 4.1). Mortality rates from CVD were sourced using the AIHW General Record of Incidence of Mortality (GRIM) books.

Table 4.1: Incidence and procedure rates in Australia, by age and gender

	MI		Stroke		Revascularisation	
	Males	Females	Males	Females	Males	Females
0-1	0.00%	0.00%	0.01%	0.01%	0.02%	0.02%
1-4	0.00%	0.00%	0.01%	0.01%	0.01%	0.01%
5-9	0.00%	0.00%	0.01%	0.01%	0.00%	0.00%
10-14	0.00%	0.00%	0.01%	0.01%	0.00%	0.00%
15-19	0.00%	0.00%	0.01%	0.00%	0.01%	0.00%
20-24	0.00%	0.00%	0.01%	0.01%	0.01%	0.00%
25-29	0.01%	0.00%	0.01%	0.04%	0.02%	0.01%
30-34	0.02%	0.01%	0.01%	0.05%	0.06%	0.02%
35-39	0.06%	0.01%	0.02%	0.03%	0.13%	0.04%
40-44	0.12%	0.03%	0.04%	0.03%	0.30%	0.12%
45-49	0.24%	0.05%	0.06%	0.06%	0.58%	0.22%
50-54	0.36%	0.07%	0.09%	0.09%	0.97%	0.39%
55-59	0.47%	0.13%	0.11%	0.09%	1.48%	0.62%
60-64	0.63%	0.22%	0.15%	0.09%	2.00%	0.92%
65-69	0.79%	0.33%	0.23%	0.15%	2.58%	1.30%
70-74	1.06%	0.54%	0.35%	0.25%	2.94%	1.61%
75-79	1.36%	0.81%	0.53%	0.39%	3.15%	1.93%
80-84	1.67%	1.14%	0.82%	0.69%	2.93%	1.67%
85-89	2.09%	1.64%	1.29%	1.26%	1.39%	0.61%
90-94	2.34%	1.75%	1.85%	1.99%	-	-
95-99	1.48%	1.52%	2.42%	2.72%	-	-
100+	0.50%	0.47%	2.88%	3.29%	-	-

Source: Begg et al (2007).

4.4 Intervention

The intervention is fish oils as a dietary supplement to current secondary prevention of CHD. The economic review by Cooper et al (2007) (discussed later) considers two branded forms of fish oil – Omacor and Maxepa, with dosageof 510-540mg EPA/day and 345-360mg DHA/day.[45]

4.4.1 Literature search

An initial literature review was undertaken in June 2009 based on of the bibliography of Colquhoun et al (2008). Further to this, on 15 July 2009 a literature search was undertaken of NCBI and NIH Pubmed applying the following criteria: (1) in English; (2) published in 2006 to present (Colquhoun et al 2008 covered those prior to this); (3) studies in humans; and (4) studies on primary prevention discarded. Search terms were “Fish oil and cardiovascular” and “Fish oil and coronary heart disease”. A final search used the search term “Fish oils and heart disease” and involved additional search parameters of: (1) studies of adults; (2) studies on

[45] Note these are above the recommended levels of EPA and DHA assuming no dietary intake.

prevention in people with heart disease preferred; (3) studies on ventricular tachycardia and implantable cardioverter defibrillators discarded; and (4) studies on stroke discarded.

A summary of findings is in Table 4.2

Table 4.2: Results from the literature search for fish oils and CHD

Study type	Study (within study type, from most recent to oldest)
Review	Colquhoun et al (2008)
Meta-analysis	Leon et al (2008)
	Gapinski et al (1993)
Randomised controlled trials	Yokoyama et al (2007) (JELIS)
	Marchioli et al (2002) (GISSI-P)
	Johansen et al (1999)(CART)
	von Shacky et al (1998) (DART)
	Singh et al (1997)(IEIS)
	Cairns et al (1996)(EMPAR)
	Eritsland et al (1996)(Norweigian Council of Cardiovascular Diseases)
	Sacks et al (1995)(HARP)
Economic studies	Cooper et al (2007) (DART1 and GISSI-P)

Note: CART: Coronary Angioplasty Restenosis Trial
DART: Diet and Reinfarction Trial
EMPAR: Enoxaparin MaxEPA Prevention of Angioplasty Restenosis
GISSI-P: Gruppo Italiano per lo Studio della Sopravvivenzo nell'Infarto miocardico – Prevenzione Trial
HARP: Harvard Atherosclerosis Reversibility Project
IEIS: Indian Experiment of Infarct Survival

Singh et al (1997), von Shacky et al (1998), Sacks et al (1995), Cairns et al (1996), and Johansen et al (1999) were subsequently removed on the advice of the Reference Group, since these trials studied the progression of coronary disease or restenosis and were thus irrelevant and distracting.

Detailed findings for the remaining studies are in Table 4.12 in the Appendix (Section 4.13).

4.5 Comparator

For the purpose of this study the comparator group is standard treatment without fish oil supplements.

4.6 Effectiveness

4.6.1 Previous cost effectiveness studies

Five cost effectiveness studies have been published previously on the use of fish oils for the prevention of further morbidity and mortality in patients with CHD. The majority of these studies are based on the clinical outcomes of treatment effectiveness from the GISSI-P trial. The standard length of duration for these studies is 3.5 years in line with the total study length of GISSI-P, although Quilici et al (2006) extrapolated the results to outcomes over a lifetime. Variations between study methodologies are mainly in the costing, including the perspective of the study as well as the country in which cost was determined (Table 4.3). Denominators in the incremental cost effectiveness ratios (ICERs) included life years gained (LYG) as well as deaths avoided, MIs avoided and QALYs gained.

Table 4.3: GISSI-Prevenzione based CEA studies

Perspective	Country	Endpoints	ICER
Franzosi et al (2001)			
Third party payer	Italy	MI Stroke Revascularisation rate Mortality	€24,603 / LYG 95% CI: 22,646 – 26,930
Quilici et al (2006)			
Health system (NHS)	United Kingdom	MI Stroke Revascularisation rate Mortality	£15,189 / QALY gained (4 years) £3,723 / QALY gained (lifetime) £12,011 / LYG (4 years) £2,812 / LYG (lifetime) £31,786 / death avoided (4 years)
Lamotte et al (2006)			
Healthcare payer	Australia Belgium Canada Germany Poland	MI Stroke Revascularisation rate Mortality	Varied between: €2,867 / LYG (Canada), and €5,154 / LYG (Belgium)
Schmier et al (2006)			
Health system *plus* productivity losses associated with CVD	United States	MI mortality CVD mortality	$16,340 per MI avoided (one year) $9,221 per MI avoided (3.5 years) Cost saving when productivity costs were included
Cooper et al (2007)			
Health system (NHS)	United Kingdom	MI Stroke Revascularisation rate CVD deaths Total mortality	£12,480 / QALY gained

Franzosi et al (2001) estimated that treatment with omega-3 acid ethyl esters resulted in a gain of 0.0332 life years compared to treatment without supplements. The ICER was

estimated to be €24,603 per life year gained, although this figure was sensitive to the cost of the supplements used.

Quilici et al (2006) was a cost effectiveness study conducted by Innovus Research on behalf of Solvay Pharmaceuticals and based on the perspective of the NHS. This study reported results for the short term (3.5 years) based on GISSI-P trial results as well as for the long term (life time) based on a survival curve extrapolated from the trial results. The intervention was cost effective as long as the NHS was willing to pay £15,189 per QALY in the short term or £3,717 per QALY over the lifetime. The NHS standard threshold to determine cost effectiveness is £20-30,000 per QALY. These results are comfortably below this threshold.

Lamotte et al (2006) conducted a cost effectiveness analysis based on five different countries (Australia, Belgium, Canada, Germany and Poland), using a decision model from the healthcare perspective. Costs of treatment were calculated for each specific country and converted back to a common currency (Euros). Country specific morbidity and mortality data were utilised as well in the estimation of treatment efficacy.

Differences in treatment outcomes ranged from gains of 0.261 (Poland) to 0.284 (Australia) in terms of life years gained. While, additional costs ranged between €787 (Canada) to €1,439 (Belgium). The resulting ICERs ranged between €2,788 (Canada) to €5,097 (Belgium) per LYG. Sensitivity analysis surrounding on effectiveness, costs of complications and discounting confirmed these results as robust. Results for each country were reported to be below specific societal willingness to pay thresholds[46].

Schmier et al (2006) used a numbers of different studies to determine the effectiveness of treatment[47], although the methodology used in this process was not outlined. Costs for this analysis were derived from hospitalization data as well as medication costs associated with prophylactic n-3 PUFA treatment. Lost earnings associated with CVD mortality were also included as a secondary analysis.

Both one year and 3.5 year results were reported, showing a cost per MI avoided of $16,340 in one year and $9,221 in 3.5 years (cost elements only included hospitalisations from MI and supplement costs). When lost earning was used in the calculations, supplementation became cost saving with a greater efficacy from a greater number of deaths avoided.

Cooper et al (2007) conducted cost effectiveness modelling as part of the NICE guidelines for post myocardial infarction secondary prevention review. Modelling was based on the meta-analysis of outcomes from GISSI-P and DART1 with sensitivity analysis including these results alone (Table 4.4). All of the studies in this area have analysed either the GISSI-P population or the DART1 population, hence the meta-analysis provided by Cooper et al (2007) is a comprehensive analysis of all available data.

[46] The willingness to pay threshold is the maximum amount a person or society would be willing to pay, sacrifice or exchange for a good, or for a particular benefit. If outcomes are far below thresholds, as in this case, the intervention is cost effective by this benchmark.

[47] Marchioli et al (2002), Nilsen et al (2001), Signh et al (1997) and von Schacky et al (1999).

Table 4.4: Treatment effect of fish oils for post myocardial infarction secondary prevention

	Meta-analysis			GISSI-P alone			DART1 alone		
Outcome	Mean	LCL	UCL	Mean	LCL	UCL	Mean	LCL	UCL
MI	1.14	0.75	1.74	0.96	0.80	1.14	1.49	0.97	2.30
Stroke	1.22	0.91	1.64	1.19	0.88	1.61	2.51	0.49	12.89
Revascularisation	1.05	0.97	1.13	1.05	0.97	1.13	1.05	0.97	1.13
CVD death	0.79	0.67	0.93	0.84	0.72	0.97	0.70	0.53	0.91
Total mortality	0.81	0.68	0.96	0.86	0.77	0.97	0.71	0.55	0.92

Source: Cooper et al (2007). LCL – lower confidence level. UCL – upper confidence level.

Gastrointestinal side effects were included in the modelling based on Hooper et al (2004), with costs estimated from the perspective of the NHS. Results produced an ICER of £12,480 per QALY, with further analysis showing that cost effectiveness improved for older patients. These results are in line with the results presented in the other health economic analyses.

Assuming a LYG is of similar value to a DALY, all the studies reviewed showed cost effectiveness as defined by the WHO and Department of Finance and Deregulation thresholds in Section 1.4. Almost all were also cost effective by the more stringent DOHA standard.

4.6.2 Treatment effectiveness

Treatment efficacy with fish oil was modelled using the meta-analysis outputs presented in Cooper et al (2007) and shown in Table 4.4. Few side effects were reported resulting from the use of fish oil dietary supplementation. One cost effectiveness study (Cooper et al, 2007) incorporated gastro-intestinal side-effects (citing Hooper et al, 2004). However, data relating to these side effects could not be found from the reference documents. Side effects of fish oil supplementation have not been included in this evaluation.

4.7 Benefits

4.7.1 Burden of disease

Disease states were measured using the DALY method. This methodology differs from the studies reported in Section 4.6.1, which utilised measures of QALYs. The DALY measure differs from the QALY measure, as it includes both loss of life due to morbidity and mortality (both the YLD and YLL). The QALY measures the reduction in a person's quality of life as a result of a disease or injury, but does not capture impacts of premature mortality. To compare the results presented in Section 4.10 to those from the literature in Section 4.6.1, additional analyses were completed using QALY (estimated as 1-YLD) values for disease states.

Disability weights for YLDs were sourced from AIHW reports on the burden of disease in Australia (Begg et al 2007 and Mathers et al 1999). These sources reported multiple disability weights depending on the disability present after the event, for example, disability weights for stroke were reported as follows.

- **No disability (0.00)**: First ever stroke, no long term disability after 6 months.

- **Mild disability (0.36)**: No mobility or self care problems, some problems with usual activities, pain, anxiety and depression.
- **Moderate/Severe disability (0.63)**: Some mobility and self care problems, some problems with usual activities, pain, anxiety and depression.
- **Profound disability (0.92)**: Some problems walking about, severe problems with self care, usual activities, pain, anxiety and depression.

Proportions of people with each disability (Table 4.5) reported by Mathers et al (1999) were used to estimate an overall disability weight for stroke events.

Table 4.5: Disability weights and severity of stroke events by age and gender

	No Disability	Mild	Moderate/ Severe	Profound	YLD weight
YLD	0.00	0.36	0.63	0.92	-
Males					
0-4	0.0%	84.6%	0.0%	15.4%	**0.45**
5-14	38.6%	51.9%	0.0%	9.5%	**0.27**
15-24	63.2%	31.1%	0.0%	5.7%	**0.16**
25-34	81.6%	15.6%	0.0%	2.8%	**0.08**
35-44	90.3%	8.2%	0.0%	1.5%	**0.04**
45-54	96.2%	3.2%	0.0%	0.6%	**0.02**
55-64	75.9%	1.7%	13.2%	9.2%	**0.17**
65-74	67.9%	11.5%	13.8%	6.8%	**0.19**
75+	58.0%	7.1%	6.7%	28.2%	**0.33**
Females					
0-4	0.0%	63.9%	29.4%	6.8%	**0.48**
5-14	0.0%	63.9%	29.4%	6.8%	**0.48**
15-24	17.1%	52.9%	24.4%	5.6%	**0.40**
25-34	68.9%	19.9%	9.1%	2.1%	**0.15**
35-44	86.2%	8.8%	4.1%	0.9%	**0.07**
45-54	93.3%	4.3%	2.0%	0.5%	**0.03**
55-64	87.3%	0.0%	0.0%	12.7%	**0.12**
65-74	48.3%	12.3%	8.8%	30.6%	**0.38**
75+	50.3%	2.7%	7.7%	39.3%	**0.42**

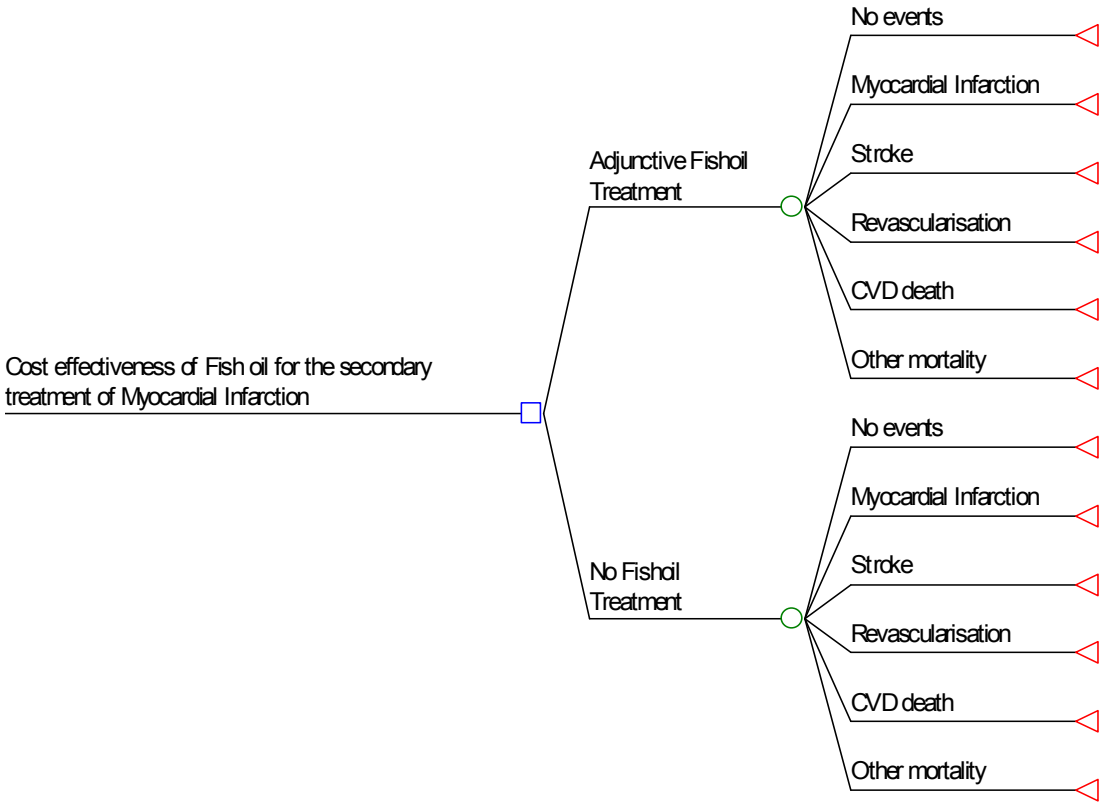
Source: Mathers et al (1999)

Disability weights for an acute MI were taken from Mathers et al (1999) at 0.395, while it was assumed that the disability weight for a revascularisation would be zero (with no associated long term disabilities).

4.8 Model

To estimate the cost effectiveness of fish oils in the treatment protocol for secondary prevention of MI, a two-arm decision model was constructed in TreeAge with a modelled time period of one year (Figure 4.1). Six health outcomes were modelled based on the evidence from clinical trials as well as the Australian age and gender specific incidence rate.

Figure 4.1: Model structure – fish oil for secondary prevention of MI



4.9 Costs

4.9.1 Health system costs

Health system costs for the five health states were included in the model. Costs associated with disease states were based on AIHW health expenditure by disease and injury estimates which were inflated to 2009 prices (Table 4.6). Cost estimates were converted into a cost per case using Australia incidence rate data.

Table 4.6: Cost in Australia per case of MI and stroke, 2009 ($)

	MI		Stroke	
Age group	Male	Female	Male	Female
0-4	83.3	27.3	0.0	891.6
5-14	32.0	0.7	0.0	448.4
15-24	132.2	115.1	0.0	1,111.1

25-34	1,647.8	523.5	3,587.8	1,513.0
35-44	3,054.5	3,515.1	2,271.5	1,146.4
45-54	4,487.8	2,652.1	2,088.4	3,459.0
55-64	3,704.3	2,442.5	2,236.8	3,225.3
65-74	3,179.4	2,915.8	5,264.7	4,246.2
75-84	3,993.9	2,912.4	7,940.0	6,875.2
85+	4,037.5	3,818.8	12,688.8	15,699.6

Source: AIHW (special data request), Access Economics.

Costs of revascularisation procedures and CVD death were estimated from published hospitalisation data. Private inpatient cost data for 2006-07 were obtained from the Department of Health and Ageing National Hospital Cost Data Collection and projected to 2009 values using an average health care cost inflation rate of 3.1% (AIHW, 2008).

However, as the National Hospital Cost Data Collection does not record expenditure on specialist fees within private hospitals, cost data was supplemented by schedule fee data derived from the Medicare Benefits Schedule (MBS). Adjustments to the schedule fees were made for additional out-of-pocket expenses.

In summary, cost components included in the model relate to:

- salaries, including ward medical, ward nursing, and non clinical;
- pathology and diagnostic imaging;
- allied health;
- in-hospital pharmacy;
- critical care;
- operating rooms;
- emergency department;
- supplies;
- special procedural suites;
- stents;
- specialist fees;
- on-costs;
- hospital bed (hotel); and
- depreciation.

These data showed that on average the cost of a revascularisation procedure was approximately $16,570, while the hospitalisation cost associated with a CVD related death was approximately $4,367.

4.9.2 Cost of fish oil supplements

Fish oil supplements are an over-the-counter medication with cost variations between brands.[48] Retail prices of fish oil supplements were sourced from Pharmacy Online. Supplements that included additional products such as Gingko were excluded. Supplements that had a EPA:DHA ratio of approximately 1.5:1 were included (in line with dosages used in the clinical trials). Table 4.7 shows the brands, volumes and retail prices sourced.

Table 4.7: Fish oil treatment costs

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	0.2993	109.23
Blackmores	400	1,000	180	120	37.50	0.0938	0.2813	102.66
Bio-Organics	220	1,000	180	120	29.95	0.1361	0.4084	149.07
Bioglan	200	1,000	180	120	19.95	0.0998	0.2993	109.23
Bioglan	400	1,000	180	120	33.75	0.0844	0.2531	92.39
clear Fish Oil	400	1,000	180	120	18.95	0.0474	0.1421	51.88
Natures Own	100	1,000	180	120	12.45	0.1245	0.3735	136.33
Natures Own	200	1,000	180	120	18.95	0.0948	0.2843	103.75
Natures Own	400	1,000	180	120	35.95	0.0899	0.2696	98.41
Natures Own - MaxEPA	100	1,000	171	114	18.95	0.1895	0.5685	207.50
Natures Way	100	1,000	180	120	9.96	0.0996	0.2988	109.06
Natures Way	200	1,000	180	120	17.95	0.0898	0.2693	98.28
Natures Way	400	1,000	180	120	32.95	0.0824	0.2471	90.20

Source: Pharmacy online, accessed on 10th September 2009

Note: Cost per diem is estimated on three capsules per day (as per the average trial dosages). Cost per annum uses 365 days per year.

A mean annual price of fish oil treatment ($112.15) was used in the cost effectiveness analysis.

4.9.3 Parameter summary

A summary of the parameters used in the analysis is in Table 4.8.

Table 4.8: Summary of model parameters

Parameter	Source and Methods	Estimate	Sensitivity
Efficacy of fish oil treatment	Cooper et al (2007)	Table 4.4	Upper and lower bound for the meta-analysis 95% confidence interval. Mean results for GISSI and DART1.

[48] For example, many patients use super strength or liquid formulations for convenience, e.g. Blackmore's Omega, Bioglan superstrength etc.

Incidence, mortality and procedure rates	Begg et al (2007) as well as AIHW hospital morbidity dataset	Table 4.1	N/A
Quality of life	Mathers et al (1999)	Disability weights for an MI event were taken as 0.395, while revascularisation rates were assumed to have a disability weight of 0. Disability weights associated with stroke used an age gender weighted average based on data describing post disability severities Table 4.5.	N/A
Costs – Fish oil	Pharmacy Online	$112.15	N/A
Costs – Revascularisation	National Hospital Cost Data Collection	$16,570	N/A
Costs – MI and Stroke	AIHW (special data request)	Table 4.6	N/A
Costs – CVD mortality	Department of Health and Ageing National Hospital Cost Data Collection	Approximately $4,367	N/A

4.10 Results

A second order Monte Carlo simulation was undertaken (with 1 million trials) on the decision model shown in Figure 4.1. Age and gender distributions were sampled in the model so that the overall results represented the same profile as those reported to have had a MI from Begg et al (2007).

Incremental effects are greater under the DALY approach compared to the QALY approach. The difference results from the inclusion of years of life lost due to premature mortality (YLLs) which is not included in the QALY approach. Meta-analysis of trial data in Table 4.4 shows that the main significant effect of fish oil treatment is the reduction of mortality from CVD or other causes. The DALY approach thus generates a lower ICER ($2,041 per DALY averted) compared to the QALY approach ($15,980 per QALY gained), as detailed in Table 4.9. Both the DALY and QALY approaches show that **fish oils are cost effective in the secondary prevention of CHD relative to all benchmarks in Section 1.4**.

The incremental cost per person is $128 per annum and the incremental effectiveness 0.06 DALYs. Incremental costs per person include the additional costs of fish oil supplementation as well as the expected costs per person of the health outcomes (myocardial infarction, stroke, revascularisation and CVD death).

Table 4.9: Cost effectiveness of fish oils for the secondary prevention of CHD ($ per annum)

Strategy	Cost	Incremental cost	Effectiveness	Incremental effectiveness	C/E	ICER
DALY approach						
No fish oil	450		0.33		1,360	
Adjunctive fish oil	579	128	0.27	0.06	2,159	2,041
QALY (1-YLD) approach						
No fish oil	450		0.95		475	
Adjunctive fish oil	580	130	0.96	0.008	607	15,980

Note: Incremental effectiveness refers to the average number of DALYs avoided or the average number of QALYs gained. C/E – cost effectiveness ratio. ICER – incremental cost effectiveness ratio. Cost difference is not exactly 128 due to rounding.

The ICER results in Table 4.9 are similar to those from previous cost effectiveness studies, reported in Section 4.6.1. 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.

Sensitivity analysis was undertaken to determine the influence of the trial results used in the modelling on the cost-effectiveness result. The treatment effect variables presented in Table 4.4. Results were most greatly affected by the upper bound of the 'other mortality' and 'myocardial infarction' variables (Table 4.10). Both the GISSI-P and DART1 variables increase the cost per DALY avoided and cost per QALY gained estimates.

Table 4.10: One way sensitivity analysis, fish oils for CHD

	$ per DALYs avoided	$ per QALYs gained
Results	**2,041**	**15,980**
Meta-analysis, upper bound		
MI	2,446	25,382
Stroke	2,390	20,211
Revascularisation	2,422	18,904
CVD mortality	2,811	21,888
Other mortality	4,782	35,528
Meta-analysis, lower bound		
MI	1,789	12,183
Stroke	1,782	13,762
Revascularisation	1,656	12,994
CVD mortality	1,606	11,700
Other mortality	1,435	10,165
GISSI-P	2,620	18,319
DART1	2,163	20,557

The results presented in Table 4.9 and Table 4.10 lie below all the cost effectiveness thresholds in Section 1.4. Fish oils for the secondary prevention of CHD are thus considered cost effective under all of the scenario analyses.

Applying the unit cost difference (using the DALY approach) of $128/person/annum to overall CHD prevalence – estimated as 309,726 people (Begg et al, 2007:282) - provides an overall higher cost of the fish oil intervention of $39.6 million per year. Naturally there is unlikely to be 100% treatment so this represents an upper cost bound. Given the ICER of $2,041/DALY, the estimated maximum wellbeing gain is thus 19,424 DALYs averted per annum.

Table 4.11: Population wide applications

1. Prevalence of CHD (Begg et al, 2007)	309,726
2. Unit cost difference (from model)	$128 pa
3. Total cost ($m) (1.*2.)	$39.6m pa
4. ICER ($/DALY) (from model)	$2,041/DALY
5. DALYs averted (3./4.*1,000,000)	19,424

4.11 Conclusions

Dietary interventions are commonly suggested by GPs following a MI. Evidence of the effectiveness of these interventions has been developed from the first epidemiological studies on different populations and their dietary intakes.

Where dietary changes cannot be made (or sustained) there is a clear role for the use of dietary supplements to provide the necessary dietary intake of EPA and DHA. Evidence for the benefit of these interventions is broadly based on two large clinical trials (GISSI-P and DART1). Both of these studies showed that the primary benefit of fish oils is in the reduction of CVD death as well as the overall mortality within the populations.

Cooper et al (2007) conducted a cost effectiveness analysis based on a meta-analysis of these two clinical trials. Our study has used the same treatment effects to model the cost effectiveness of fish oil intervention within the Australian setting. Results from our analysis are comparable to previous cost effectiveness studies and are within the bounds of broadly accepted cost effectiveness thresholds.

The use of fish oil supplements is a cost effective intervention to prevent future cardiovascular mortality and morbidity in Australia.

Despite evidence of effectiveness and cost-effectiveness of fish oils, these supplements are not currently subsided under the PBS, and indeed, are currently subject to the GST levy. As the evidence of improved health outcomes and cost effectiveness of complementary medicine interventions build it would be strategic for governments to review these arrangements.

4.12 References

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4.13 Appendix: Detailed summary of literature studies relating to fish oils and CHD

The findings of the literature review are summarised in Table 4.12.

Table 4.12: Literature on effectiveness of fish oils for CHD

Source	Aim of study	Method	Comparator	Outcome measure	Findings
REVIEWS					
Colquhoun et al (2008)	Determine whether a daily intake of low amounts of a number of nutrients would exert beneficial effects on risk factors and clinical variables in patients that suffered from MI and were following a cardiac rehabilitation program	RCT with 40 male MI patients. Supervised exercise training, lifestyle and dietary recommendation and instructed to consume products in addition to their regular diet. Blood extractions and clinical examinations were performed after 0, 3, 6, 9 and 12 months.	Active group 500 mL/day of a fortified dairy product containing EPA, DHA, oleic acid, folic acid and vitamins A, B-6, D and E. Control group 500 mL/day of semi-skimmed milk with added vitamins A and D.	Clinical outcome measures – through blood extractions and clinical examinations	Increased plasma concentrations of EPA, DHA oleic acid, folic acid, vitamin B-6 and vitamin E after supplementation ($P < 0.05$). Total plasma and LDL-cholesterol, apolipoprotein B and high-sensitivity C-reactive protein concentrations decrease in the supplemented group ($P < 0.05$). No changes in heart rate, blood pressure, or cardiac electrocardiographic parameters in either group.

Source	Aim of study	Method	Comparator	Outcome measure	Findings
META-ANALYSES					
León et al (2008)	Synthesise the literature on the effects of fish oil – DHA and EPA – on mortality and arrhythmias and to explore dose response and formulation effects	Meta-analysis of 12 RCTs of fish oil as dietary supplements in humans	Various control incl. 2g of high oleic acid & sunflower oil Conventional treatment Corn oil 4g olive oil No placebo 100mg aluminium hydroxide Mixtures of fatty acids without EPA and DHA	Primary Appropriate implantable cardiac defibrillator intervention Sudden cardiac death Secondary Deaths from cardiac causes All cause mortality	Associated with a significant reduction in deaths from cardiac causes (OR 0.80, 069-0.92) but had no effect on arrhythmias or all cause mortality. Evidence to recommend optimal formulation of EPA or DHA to reduce these outcomes is insufficient.
Gapinski et al (1993)	Examine the existing evidence for the use of n-3 FAs to reduce the rate of restenosis following percutaneous transluminal coronary angioplasty	Meta-analysis of seven existing RCT for complementary fish oil use in English were used.		Rates of restenosis after coronary angioplasty.	Restenosis after coronary angioplasty is reduced by supplementary fish oils, and the extent of the observed benefit may be dependent on the dose of n-3 FAs

Source	Aim of study	Method	Comparator	Outcome measure	Findings
CLINICAL TRIALS					
Marchioli et al (2002)	Assess the time course of the benefit of n-3 polyunsaturated fatty acids (PUFAs) on mortality documented by the GISSI-P trial in patients surviving a recent (<3 months) MI.	11,323 patients with a recent (≤3 months) MI were enrolled in a multicentre, open label, parallel, clinical trial with a follow-up of 3.5 years on the efficacy of n-3 PUFAs 1g/day, vitamin E 300 mg/day a combination of the two	Vitamin E alone Vitamin E plus PUFAs No treatment	Cumulative rate of: All-cause mortality Nonfatal myocardial infarction Nonfatal stroke Cumulative rate of: Cardiovascular death Nonfatal myocardial infarction Nonfatal stroke Sudden death	Early effect of low dose PUFAs on total mortality and sudden death support the hypothesis of an antiarrhythmic effect. Total mortality was significantly lower at 3 months (RR=0.59, 0.36-0.97). Reduction of sudden death was specifically relevant at 4 months (RR=0.47, 0.219-0.995)
Eritsland et al (1996)	To determine whether high dietary intake of long chain polyunsaturated omega-3 fatty acids (n-3 FAs) may reduce the risk of atherothrombotic disease	RCT of 610 patients undergoing coronary artery bypass grafting were assigned either to a fish oil group, received 4 g/day of fish oil concentrate, or a control group.	Anti thrombotic treatment (aspirin or warfarin) without a dietary supplement	Primary: 1-year graft patency assessed by angiography	Vein graft occlusion rates per distal anatomoses were fewer with fish oils OR=0.77 and fewer patients with > or = 1 occluded vein graft(s) compared to the control OR=0.72

Source	Aim of study	Method	Comparator	Outcome measure	Findings
ECONOMIC EVALUATION					
Cooper et al (2007)	Provide recommendations to clinicians and others about lifestyle modification, cardiac rehabilitation, drug therapy and advice about which patients to refer for further assessment for possible coronary revascularisation	Cost-effectiveness study of omega-3 fatty acid supplementation compared to no supplements for patients following MI	No fish oil consumption of supplementation	Myocadial infactions Strokes Revascularisation CVD mortality Total mortaility Health system costs Incremental cost-effectiveness	In patients after an MI, advice to increase consumption of oily fish reduced all-cause mortality. The only large trial of supplementation with 1g of omega 3 polyunsaturated fatty acids has shown a reduction in mortaility and cardiovascular morbidity, although there was a low uptake to statins and other secondary prevention drugs at baseline in this trial

Note: Judgement has been exercised in reporting and not all RCTs are tabulated – just those considered of particular relevance. Singh et al (1997), von Shacky et al (1998), Sacks et al (1995), Cairns et al (1996), and Johansen et al (1999) shown in Table 4.2 were subsequently removed on the advice of the Reference Group, since these trials studied the progression of coronary disease or restenosis and were thus irrelevant and distracting.

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 ESR[49] values of ≥60mm/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 inhibitors[50] 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).

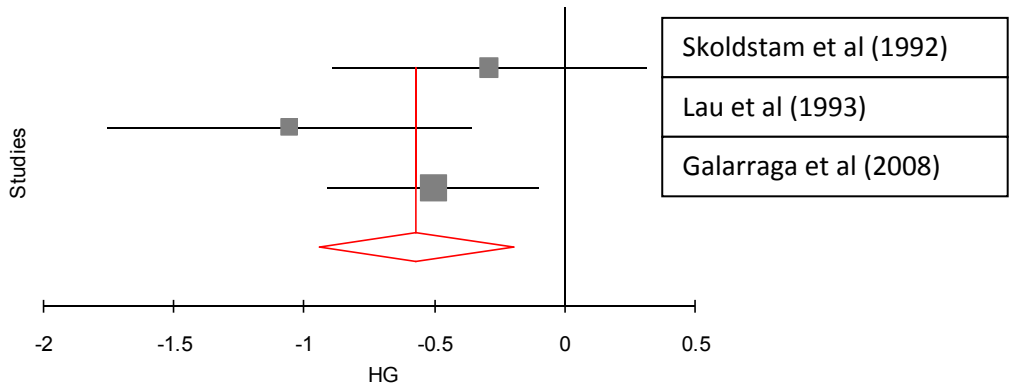
Table 5.2: Standardised mean difference in NSAID consumption, studies in our meta-analysis

	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 experiemental 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.

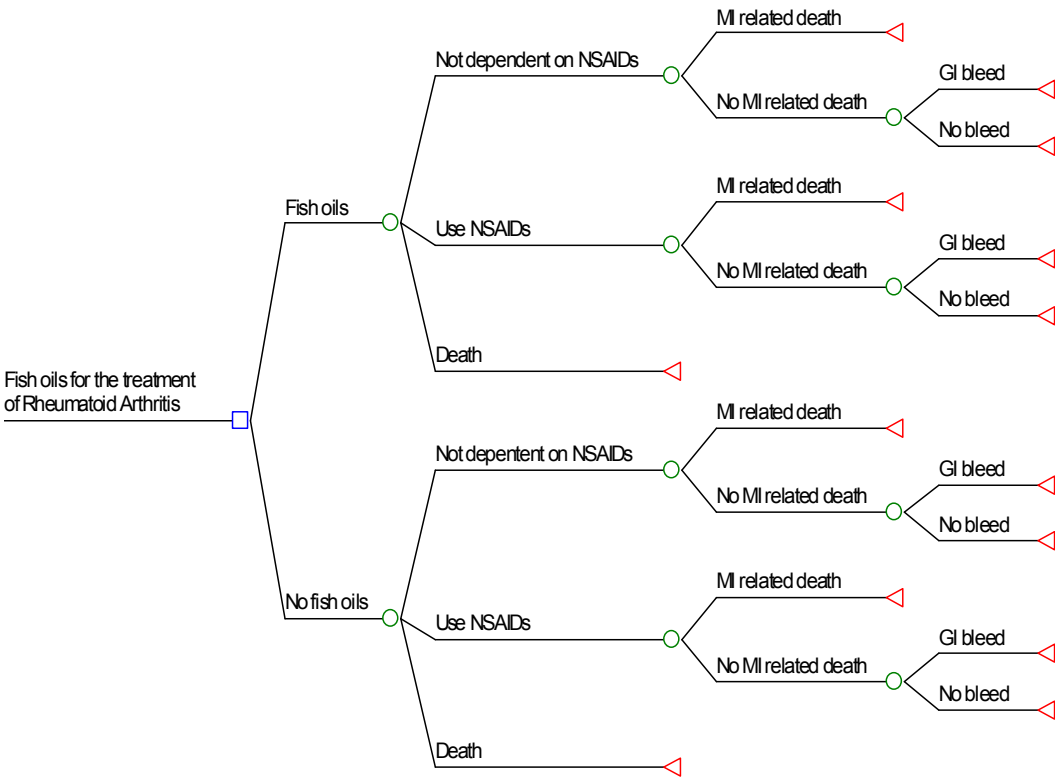
Disease states were measured using the DALY method, as well as a QALY equivalent (defined as 1-YLD) – for comparability with outcome measures in other studies of fish oils for RA.

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 gingko 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 vistis. 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	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-inflamatory/immunosuppresive drug requirement), renal disease, systemic lupus erythematosus, bone density/osteoporosis

Source	Aim of study	Method	Comparator	Findings	Outcome measure
Goldberg and Katz (2007)	Assess the effect of n-3 FAs on people with RA or joint pain secondary to inflammatory bowel disease and dysmenorrhea	Meta-analysis of 17 RCT assessing the pain relieving effects of n-3 PUFAs in patients with rheumatoid arthritis or joint pain secondary to inflammatory bowel disease and dysmenorrhea. Conducted with Cochrane Review Manager 4.2.8 for six separate outcomes using standardised mean difference.	Various placebos: Soy oil capsules. LA capsules Water Corn oil capsules Olive oil capsules Fish oil capsules Air-filled capsules Coconut oil capsules Typical dietary FA caps. Maize/olive/peppermint oil capsules Paraffin wax capsules	Reductions in patient reported joint pain intensity -0.26 (-0.49 to -0.03); minutes of morning stiffness -0.43 (-0.72 to -0.15); number of painful and/or tender joints -0.29 (-0.48 to -0.10) and NSAID consumption -0.40 (-0.72 to -0.08). No significant effects reported for the remaining measures.	(1) Patient assessed pain (2) Physician assessed pain (3) Duration of morning stiffness (4) number of painful and/or tender joints (5) Ritchie articular index (6) Nonselective NSAID consumption
CLINICAL TRIALS					
Skoldstam et al (1992)	Determine the therapeutic effects of fish oil (10g/day) in rheumatoid arthritis.	43 patients evaluated at 0, 3 and 6 months. Nutrient intake in the fish oil group and control group was essentially similar. Percentage of n-3 fatty acids in serum phosphatidylcholine increased by 9.6 (range 2.6-16.1).	Placebo	No change in biochemical markers for inflammation. Consuldes that fishoils have a small anti-inflammatory effect, which is at most NSAID saving.	Biochemcial markers NSAID reliance

Source	Aim of study	Method	Comparator	Findings	Outcome measure
Lau et al (1993)	To assess whether Maxepa (171mg EPA & 114mg DHA) has anti-inflammatory properties, that reduce the requirements for NSAIDs in patients with RA.	64 patients with stable RA requiring NSAID therapy only were studied. Patients received either 10 Maxepa or air-filled placebo capsules per day for 12 months. All then received placebo capsules for a further 3 months. Review occurred at 3 months intervals. Patients were instructed to slowly reduce their NSAID dosage providing there was no worsening of their symptoms.	Air-filled capsules	Significant reduction in NSAID usage in patients on Maxepa compared to placebo. Requirements were @3mths: 71.1 (55.9-86.2) and 89.7 (73.7-105.7) respectively @12mths: 40.6 (24.5-56.6) and 84.1 (62.7-10.05) respectively. Persisted to 15mths: 44.7 (27.6-61.8) and 85.8 (60.5-111.1), respectively. (P<0.001, ANOVA) Patients were able to reduce their NSAID requirement without experiencing any deterioration in the clinical and laboratory parameters of RA activity.	NSAID requirement

Source	Aim of study	Method	Comparator	Findings	Outcome measure
Geusens et al (1994)	To assess the long term effects of supplementation with n-3 FAs in patients with active RA.	90 patients we enrolled in a 12 month, double-blind, randomised study comparing daily supplementations with either 2.6g of n-3 or 1.3g of n-3 + 3g of olive oil or 6g of olive oil.	6g olive oil capsules	Significant improvement in the patient's global evaluation and in the physician's assessment of pain was observed only in those taking 2.6g/day of n-3. The proportions of patients who improved and of those who were able to reduce their concomitant antirheumatic medications were significantly greater with 2.6 g/day of n-3.	Physician global assessment of disease Patient's global assessment of disease Physician and patients assessment of pain Duration of morning stiffness Grip strength Ritchie articular index for pain Number of painful joints Number of swollen joints Concomitant medications (NSAIDs and/or DMARDs)
Galarraga et al (2008)	To determine whether cod liver oil supplementation helps reduce daily NSAID requirement of patients with RA	Dual centre, double-blind placebo controlled randomised study of 9 months duration. 97 patients with RA were randomised to take either 10g of cod liver oil or air-filled identical placebo capsules. Daily requirements of NSAIDs were documented. At 12 weeks patients were instructed to gradually reduce, and if possible, stop their NSAID intake.	Air filled placebo capsules.	39% of patients in the cod liver and 10% in the placebo arm were able to reduce their daily requirements of NSAIDs by >30%. No differences were noted in the clinical parameters of RA disease or in the side-effects observed.	Relative reduction of daily NSAID requirement by >30% after 9 months of treatment.

6 Phytodolor™ for the treatment of osteoarthritis

6.1 Background

Osteoarthritis is a highly prevalent musculoskeletal condition, responsible for 1.3% of the total burden of disease and injury in Australia in 2003 (Begg et al, 2007). It is among the top 20 leading causes of disease burden in Australia and can cause severe pain, stiffness, tenderness and 'crepitus' – a crunching or grating sound or feeling (AIHW, 2007).

Synthetic drugs (the non-steroidal anti-inflammatory drugs or NSAIDs) are typically used to manage pain and other symptoms of osteoarthritis. However, early studies dating back to 1988 have suggested that an alternative complementary medicine – Phytodolor™ – is also effective in treating people with osteoarthritis, and potentially as effective as the NSAIDs. Phytodolor™ is a proprietary mix of populus tremula (aspen), fraxinus excelsior (ash) and solidago virgaurea (goldenrod or woundwort) – Section 6.4 provides further detail of the intervention.

Common first-line treatments for relief of symptoms of degenerative joint diseases are NSAIDs, which include aspirin and other salicylic acid derivatives, acetaminophen, indomethacin, ibuprofen, and diclofenac (Hardman et al, 1996).

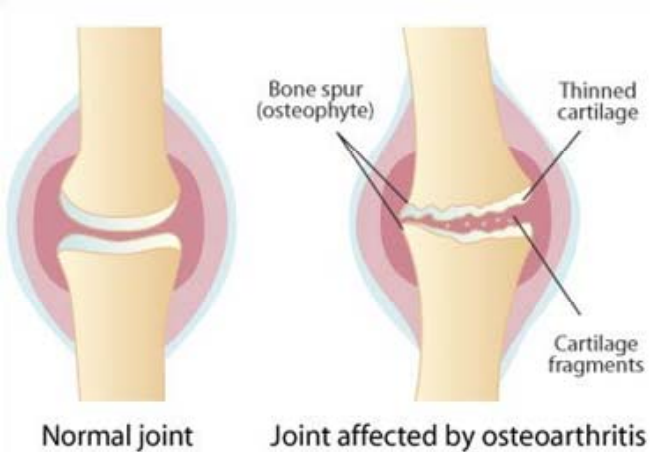
6.2 Aim

The aim of this study was to assess the cost effectiveness of Phytodolor™ in the management of pain, inflammation and other symptoms of osteoarthritis.

6.3 Indication

Osteoarthritis is a progressive rheumatic disease characterised by the degeneration of articular cartilage (Long et al, 2001). Unlike rheumatoid arthritis, where the bone joints become inflamed (the body's immune system attacks the membranes surrounding the joints), osteoarthritis is considered 'wear and tear' of bones resulting in thinned cartilage, cartilage fragments and bone spurs (osteophytes), as shown in Figure 6.1.

Figure 6.1: A normal joint and a joint affected by osteoarthritis



Source: ABC Health and Wellbeing (2007).

Osteoarthritis ranks 17th and 12th in the 20 leading causes of burden for males and females respectively, with the sex difference due to higher female life expectancy as well as higher incidence in women (Begg et al, 2007).

Osteoarthritis commonly affects the joints of the hips, knees, hands and spine but can involve any moveable joint. Other organs and tissues of the body are not directly affected by osteoarthritis, but many people will have other health problems (AIHW, 2007).

6.3.2 Risk factors

A range of risk factors are linked to the development of osteoarthritis.

- **Age and sex:** The epidemiological prevalence data below reflect that older age and female gender are risk factors for osteoarthritis (AIHW, 2007).
- **Genetics:** People who have a family history of the condition have a higher probability of developing osteoarthritis (Cimmino and Parodi, 2005). Genetics are an important risk factor (Wright el al, 1996) although some family studies could not rule out familial clustering from environmental causes (Lanyon et al, 2000).
- **Obesity:** Obesity is more strongly associated with osteoarthritis of the knee than the hip. It has been shown to be a predictor of osteoarthritis as early as 30 years before the onset of symptoms (Felson et al, 1995).
- **Joint trauma:** The dislocation or fracture of the bones can cause damage to the tissues within the joint, which can increase the stress on the cartilage (AIHW, 2007; Felson et al, 1995).
- **Overuse/occupation:** A number of epidemiological studies have shown strong relationships between hip osteoarthritis and heavy lifting including in farming (e.g. Axmacher et al, 1993; Croft et al, 1992); elite sports activity (Vingard et al, 1991) also can contribute to the onset of osteoarthritis.

6.3.3 Prevalence

In Australia, there are a few population-based epidemiological studies that provide information on prevalence of osteoarthritis. In their population sample, March et al (1998) found 10% definite osteoarthritis in males and 19.5% in females while Jones et al (1995) found 25% self-reported osteoarthritis among respondents from the Dubbo Osteoporosis Study. The varying results reflect different age composition of the samples, times and locations.

Begg et al (2007) estimated that in 2003, there were 300,655 people with osteoarthritis[52] in the hip and knee, with females accounting for approximately 60% of the total. The prevalence rate increases with age with more than 45% of those affected being over the age of 75 years. Applying these rates to 2009 population data (from the Access Economics Demographic Model, based on ABS demographic projections), hip and knee osteoarthritis affects approximately 334,000 people in 2009.

Table 6.1 shows prevalence of all osteoarthritis in 2007 from Access Economics (2007), based on data from the ABS National Health Survey 2004-05. Osteoarthritis is uncommon before the age of 25 years and is more prevalent in females than in males (Table 6.1).

[52] Begg et al (2007) base their estimates on findings of radiographic osteoarthritis (grade 2 and above).

Table 6.1: Prevalence of osteoarthritis by age and gender, Australia, 2007

	Rates (%)			People (numbers)		
	Men	Women	People	Men	Women	People
0-24	0.0	0.2	0.1	717	6,560	7,277
25-34	1.4	1.4	1.4	19,609	19,942	39,552
35-44	3.4	4.2	3.9	51,476	63,856	115,332
45-54	7.4	11.1	9.3	106,457	162,012	268,470
55-64	16.2	24.2	20.2	190,501	283,636	474,137
65-74	18.7	31.9	25.4	134,219	237,469	371,688
75+	23.0	28.2	26.0	125,979	220,700	346,496
Total	**6.1**	**9.5**	**7.8**	**628,776**	**994,175**	**1,622,951**

Source: Access Economics (2007).

The 2007-08 National Health Survey (NHS) found 1.613 million Australians self-reporting osteoarthritis in that year.

> Projecting to 2009 using the age prevalence from the 2007-08 NHS Survey and the gender splits from Access Economics (2007) above, provides an estimate of approximately 1.74 million Australians with osteoarthritis in 2009.

An estimated prevalence breakdown by age and gender for 2009 is in Table 6.2.

Table 6.2: Prevalence estimates of osteoarthritis by age and gender, 2009

	Rates (%)			Number ('000)		
	Men	Women	People	Men	Women	People
0-24	0.0	0.2	0.1	1,693	8,028	9,721
25-34	1.6	1.6	1.6	24,542	24,171	48,714
35-44	3.0	3.7	3.4	46,178	57,587	103,765
45-54	7.0	10.5	8.8	104,409	159,240	263,649
55-64	16.4	24.4	20.4	201,673	304,188	505,861
65-74	17.4	29.6	23.6	132,391	235,446	367,837
75+	28.3	34.7	32.0	161,226	276,181	437,407
Total	**6.1**	**9.5**	**7.8**	**672,114**	**1,064,841**	**1,736,954**

Source: Derived from ABS (2009) and Access Economics (2007).

A literature search was undertaken on 13 July 2009 of NCBI and NIH Pubmed using search parameters of "Prevalence AND osteoarthritis AND Australia" as well as "Prevalence AND osteoarthritis AND Australia AND Severe". Selection criteria were: (1) in English; (2) published in the last five years; and (3) studies in humans. A summary of literature reviewed for this study is in Table 6.3. There were only two Australian prevalence studies identified using the search protocol – the first being the ABS NHS and the second an epidemiological study from 1998 which validates the accuracy of self-reported data in people with arthritis aged 45-64 years at least.

Table 6.3: Epidemiology of osteoarthritis

Source	Aim and method	Definitions	Outcome measures	Findings
ABS (2009)	The National Health Survey was conducted throughout Australia from August 2007 to June 2008 Random sample of approximately 15,800 private dwellings. Interviews were conducted by trained interviewers	Long term medical conditions are classified based on the International Classification of Diseases 10th Revision.		In 2007-08, 15% of people reported they currently had arthritis; 13% of males and 17% of females. Of those with arthritis, 14% had rheumatoid arthritis and 51% had osteoarthritis. Overall, 2.4% of Australians or 1,794,179 Australians had long term osteoarthritis in 2007-08.
March et al (1998)	Questionnaires were posted to a random sample of residents of the Northern Sydney Health Area, aged 45–64 years old. Details of musculoskeletal complaints and diagnoses were requested from 2,250 residents.	A questionnaire diagnosis of 'definite' OA (in any joint) was made if OA was self-reported and respondents reported experiencing joint pain at any time in the previous 6 months and had been given a professional diagnosis. To validate questionnaire responses and to evaluate the accuracy of the definition, a subsample was derived using a list of randomly ordered questionnaire identification numbers of respondents who had indicated their willingness to participate further and who did not report having another musculoskeletal disorder.	After two mailouts, 59% responded (526 males and 796 females). Definite OA (excluding spine alone) was reported by 52 males (10%), 155 females (19.5%) and possible OA by 62 males (11.8%), 164 females (20.6%). Following examination, 81% of self-reported 'definite' OA was confirmed, while 57% of 'possibles' and one self-reported 'negative' were determined to have clinical OA.	In this study, it was shown that postal questionnaires have potential to detect OA in the community, with almost all self-reported diagnoses of OA being confirmed on clinical examination. If participants who had definite clinical changes and who had reported experiencing some joint pain in the previous 6 months but who did not have pain or stiffness on most days of the month before examination were included, all self-reported OA was confirmed.

6.4 Intervention

Phytodolor™ is a herbal anti-inflammatory medicine used in the pain relief of osteoarthritis and lower back pain. Phytodolor™ comprises the following ingredients.

- **Common aspen** (populus tremula) bark and leaves - which contains salicylates.
  - Salicylates are commonly known as ingredients of willow bark and acetylsalicylic acid (known as aspirin) and are commonly known for their ability to reduce inflammation, pain, and fever (Schulz et al, 2001).
- **Common ash** (fraxinus excelsior) bark, which contain coumarins that have anti-inflammatory and analgesic properties (Bruneton, 1999).
- **Goldenrod aerial parts** (solidago virgaurea). Its preparation contains flavonoids, saponins, and phenol glycosides. Extracts and individual constituents have demonstrated diuretic, anti-inflammatory, and analgesic activity (Blumenthal et al, 2000).

Phytodolor™ is made in Germany by Steigerwald Arzneimittelwerk GmbH and sold in Australia through Flordis. Phytodolor™ contains 45.6% alcohol (ethanol) by volume and combines the extracts of common aspen, bark and leaves, ash bark and goldenrod aerial parts in a ratio of 1:3:1. Studies (in Section 6.4) found that the full effectiveness of Phytodolor™ ranges from 10 to 14 days.

> Recommended dosage of Phytodolor™ is three to four times per day (1 ml to 1.5 ml each time[53]) (Gundermann and Muller, 2007), preferably 14 days before the onset of severe pain.

6.4.1 Literature search strategy

A literature search was undertaken on 13 July 2009 of NCBI and NIH Pubmed using search parameters of "Phytodolor AND osteoarthritis" as well as "Phytodolor AND rheumatic pain".

Selection criteria were: (1) in English; (2) published in the last five years; and (3) studies in humans. A summary of literature reviewed for this study is in Table 6.4, with a detailed presentation in the Appendix in Section 6.13 (Table 6.8).

[53] 20 to 30 drops each time. Converted using 1 drop = 0.05ml.

Table 6.4: Results from the literature search for Phytodolor™ and osteoarthritis/rheumatic pain

Study type	Study (within study type, from most recent to oldest)
Systematic reviews	Gundermann and Muller (2007)
	Long et al (2001)
	Ernst (2000)
	Cameron et al (2009)
Randomised controlled trials	
– osteoarthritis only	Schreckenberger (1988)
– rheumatic disease including osteoarthritis	Huber (1991)
	Herzog et al (1991)
	Hawel (1991)
	Bernhardt et al (1991)
	Bernhardt et al (1990)
	Baumann et al (1989)
	Hahn and Hübner-Steiner (1988)
	Ebert et al (1988)
	Schadler (1988)

Overall, there have been 42 published studies, including 13 double-blind, six single blind, four open comparative and 19 open, non-comparative studies. Table 6.4 lists only 10 randomised double-blind studies (see Appendix in Section 6.13). The remaining double blind studies were unable to be located and therefore have not been included.

6.5 Comparator

The most common treatment for relief of symptoms of degenerative joint diseases are NSAIDs, which include aspirin and other salicylic acid derivatives, acetaminophen, indomethacin, ibuprofen, and Diclofenac (Hardman et al, 1996). In cost effectiveness analysis, the comparator should be usual care and/or best practice care. Studies in the literature above mainly used Piroxicam and Diclofenac as the comparator for the treatment of osteoarthritis.

Piroxicam and Diclofenac both have analgesic properties (pain relieving properties). The mechanism of action of Piroxicam and Diclofenac are not completely understood but may be related to prostaglandin synthetase inhibition (blocking prostaglandins, which are responsible for inflammatory features such as swelling, pain, stiffness, redness and warmth).

Gerecz-Simon et al (1990) examined 80 patients with osteoarthritis in a 12-week double-blind study. Half the group were given Piroxicam (20 mg) daily and the other half Diclofenac (75–150 mg) daily. In the 70 patients who completed the study, both medications were effective with statistically significant improvements observed on all assessments of efficacy. There was slightly better tolerance in the Piroxicam treated patients although these results

were not significant (3 of the 40 Piroxicam treated patients versus 6 of the 40 patients on Diclofenac were discontinued from the trial due to intolerable adverse events).

6.6 Effectiveness

6.6.1 Findings

6.6.1.1 Meta-analysis and systematic reviews

Gundermann et al (2007) conducted a meta-analysis which was reported in the Flordis periodic safety update report (Gammelin, 2009). From a total of 42 clinical studies, 11 studies were included in the meta-analysis of efficacy and pain assessments. The results show that in the global assessment of outcomes, Phytodolor™ was significantly superior to placebo (Good and Very Good in 69.1% of the cases with Phytodolor™ versus 48.9% with placebo). In single blind studies, Phytodolor™ was not significantly different from NSAIDs (mainly diclofenac).

Gundermann et al (2007) found that no serious adverse events were reported although minor adverse events were reported by 8.1% of placebo patients verses 14.2% with Phytodolor™ and 18.9% with NSAIDs. This analysis suggested that Phytodolor™ was more effective than placebo in patients with 'rheumatic' pain, and equivalent to standard doses of NSAIDs.

Gundermann and Muller (2007) analysed 13 double-blind randomised trials which investigated the effectiveness of Phytodolor™ in treating patients with mixed rheumatic diseases including osteoarthritis, rheumatoid arthritis and other types of arthritis. **Results of all trials which had a placebo comparative group demonstrated that Phytodolor™ was significantly more effective in improving joint mobility and reducing pain, in addition to being as effective as Diclofenac and Piroxicam in reducing pain, swelling and stiffness in joints.**

Ernst (2000) included three trials of Phytodolor™ versus placebo and an active treatment control group (Diclofenac, Piroxicam and Indomethacin) and seven trials of Phytodolor™ versus other active medication (three of which also had a placebo control group). Results from the trials suggested that **Phytodolor™ is more effective than placebo and as effective as synthetic drugs (Diclofenac, Piroxicam and Indomethacin) in the symptomatic treatment of musculoskeletal pain, including osteoarthritis. There were also few adverse effects noted with its use.**

Long et al (2001) included the Ernst (2000) studies as well as a further six RCTs – also **concluding equal efficacy with NSAIDs (Dicolefenac) and fewer adverse events**.

Cameron et al (2009) provides a recent systematic review of 'herbal medicinal products' used in the treatment of osteoarthritis. The literature review searched electronic databases (Medline, Embase, Ciscom, Amed, Cinahl, Cochrane registers) and found 35 randomised controlled trials that compared herbal products with placebo or active controls.

> *'The review found that data were only adequate to support meta-analysis for three herbal products: topical capsaicin, avocado-soybean unsaponifi ables, and the Chinese herbal mixture SKI306X, which showed benefit in the alleviation of osteoarthritic pain. Notably, in relation to Phytodolor™, the review only located*

> *three of the above studies and concluded that* ***the data were of inadequate quality to undertake meta-analysis'****.* Cameron et al (2009:1497).

Three studies compared Phytodolor™ to placebo or active control (piroxicam) in 176 participants. They reported in favour of Phytodolor™ for less additional use of NSAIDs (diclofenac) and improvement in range of motion (Schadler, 1988; Bernhardt et al, 1991; Huber, 1991). No serious side effects were reported with any herbal intervention.

6.6.1.2 Randomised controlled trials

Three double-blind, placebo controlled trials were reviewed in 'The Handbook of clinically tested herbal remedies' by Barrett (2004), namely Huber (1991), Hahn and Hübner-Steiner (1988) and Schadler (1988) (detailed in the Appendix in Section 6.13, Table 6.8) – all of which were included in the systematic review by Ernst (2000). These trials were very small (n=38, n=30, n-41 respectively).

6.6.2 Side effects

NSAIDS are associated with gastrointestinal side effects such as dyspepsia (Wolfe and Singh, 1999) as well as both renal and cardiac toxicity, resulting in hospitalisations and occasionally, death (Day and Roughead, 1999).

The trials and reviews found that Phytodolor™ was relatively devoid of any adverse effects, although there were cases of gastrointestinal complaint or hypersensitivity reaction in some of the studies.

Although side effects were fewer and less severe than for NSAID comparators (see Appendix in Section 6.13), a meta-analysis of significant differences was unable to be established due to data quality issues.

This was disappointing as the *a priori* evidence suggests, if high quality studies were conducted, it may be possible to measure differences in sides effects, with potentially important findings for policy.

6.6.3 Summary of conclusions regarding effectiveness

The literature was relatively sparse and, where findings were significant, they showed that Phytodolor™ was as effective as synthetic drugs. Moreover, fewer adverse effects were noted with Phytodolor™ use. The most common comparator in the studies was Diclofenac and the side effects of both were relatively few and minor.

The short timeframes for the studies, differences in study design, comparators and outcome measures, limited number of studies restricted to osteoarthritis, differences in dosages and measures for intervention and comparator, and lack of composite statistics meant that the data were inadequate for input into our MIX meta-analysis software. This was true for effect sizes for the efficacy of Phytodolor™ versus Diclofenac as well as for the adverse event profile. Our conclusion of data inadequacy for meta-analysis has also been independently found by Cameron et al (2009), in a study released on 23 November.

6.7 Benefits

Ideally the benefits of this study would be reported in DALYs, with benefits measured in terms of the efficacy of the intervention (Phytodolor™) and comparator (Diclofenac) as well as DALYs lost from the adverse event profiles of the two arms.

However, since the conclusion was equal efficacy and insubstantial data from the adverse event findings, benefits of the two arms are treated as comparable in the model. In incremental terms this means there is no difference between the intervention and the comparator in relation to DALYs averted that are able to be measured on the basis of current evidence.

6.8 Model

A decision tree model was used and the method for the cost effectiveness analysis was incremental, i.e. the costs of Phytodolor™ were compared with the costs of Diclofenac.

The choice of key parameters for costs is outlined in the section below.

6.9 Costs

6.9.1 Costs of comparator - Diclofenac

The estimated average cost of Diclofenac (or more commonly known as Voltaren) was averaged across a range of products and applications listed below. The recommended dosages are dependent on how the medication is administered as well as the severity of the osteoarthritis. It is assumed that people with osteoarthritis follow the recommended dosage and 25%[54] of Voltaren tablet and suppository users also use Voltaren Emulgel. The various Diclofenac products are detailed below.

Voltaren Emulgel

Voltaren Emulgel is applied to the skin with absorption being proportional to the contact time and area of skin covered. According to the Novartis Consumer (1998) product information page, absorption amounts to about 6% of the dose (2.5 g/500 cm^2 skin) of diclofenac after topical application. It is recommended that Voltaren Emulgel is applied locally to the skin three to four times a day using a quantity of 2 to 4 grams each time.

Access Economics estimated the cost of Voltaren Emulgel by assuming that 3 grams of gel is applied three times a day. The cost per day is calculated by applying the recommended application amount per day by the cost per gram of gel. The average cost is therefore $2.22 per day.

[54] Initial consultation indicates 25%, confirmation with research articles in process

Table 6.5: Retail cost of Voltaren Emulgel

grams (g) per package	Grams per application	Ingredient	Cost per package	Cost per day
120 g	3 g	Diclofenac diethylammonium	$20.95	$1.57
50 g	3 g	Diclofenac diethylammonium	$11.95	$2.15
20 g	3 g	Diclofenac diethylammonium	$6.55	$2.95

Source: http://www.pbs.gov.au/html/consumer/home, accessed 10 September 2009.

Voltaren Suppositories

The suppositories should be inserted into the rectum after passing stools. According to the Novartis Consumer (2009) product information page, initial dosage is recommended as 75 to 150 mg daily with long term therapy reducing maximum dosage to 100 mg daily. Access Economics estimated the cost of Voltaren suppositories by assuming that 100 mg of Voltaren suppositories are taken daily. The average is cost is therefore $0.62 per day.

Table 6.6: Retail cost of Voltaren Suppositories

Tablets per package	Dose per tablet	Ingredient	Cost per package	Cost per day
40	100mg	Diclofenac sodium	$24.92	$0.62

Source: Novartis Consumer (2009)

Voltaren Tablets

According to the Novartis Consumer (2008) project information page, Voltaren tablets should be taken before meals, with a dosage of 75 to 150 mg per day. It is recommended that the lowest effective dose is taken orally with liquid, preferably before meals, spread out over 2 to 3 times per day. Access Economics estimated the cost of Voltaren tablets by assuming that 75 mg is taken daily (i.e. 25 mg x 3 times per day). The average is cost is therefore $0.42 per day.

Table 6.7: Retail cost of Voltaren Tablets

Tablets per package	Dose per tablet	Ingredient	Cost per package	Cost per day
100	25mg	Diclofenac sodium	$15.02	$0.45
50	50 mg	Diclofenac sodium	$13.01	$0.39

Source: Novartis Consumer (2008)

The overall average cost of Diclofenac was calculated by assuming that all Diclofenac users were split proportionately into the three equal groups with 25% of tablet and suppository users also using Voltaren Emulgel at the recommended dosage. The final cost of using Diclofenac was calculated to be $1.46 per day.

$$\left[\left(\frac{2.22+0.62+0.42}{3}\right)+\left(\frac{2}{3}\times 0.25\times 2.22\right)\right]=1.46$$

6.9.2 Costs of Phytodolor™

The cost of Phytodolor™ was sourced from Flordis Natural Medicines through direct contact with the company[55]. The recommended retail price for a 100 ml bottle of Phytodolor™, excluding GST, was given at $27. This is equivalent to $0.27 per ml.

Applying the average recommended dosage above (Section 6.4) of 25 drops[56], three and a half times a day (4.375ml), the average cost of Phytodolor™ was calculated to be $1.18 per day $[0.27 \times 4.375]$.

6.10 Results

The cost effectiveness analysis compares Phytodolor™ with Diclofenac assuming equivalence of efficacy and health outcomes, with cost thus being the major determinant of cost effectiveness.

> The per person difference is thus $1.46-$1.18=$0.28 per day, or $102.20 per annum. Phytodolor™ is cost-saving compared with Diclofenac.
>
> With osteoarthritis projected to affect 1.74 million Australians in 2009, if all these people currently use a NSAID such as Diclofenac, then there could be around 1.74*102.20=$178 million per annum in potential savings from switching to Phytodolor™ compared to using Diclofenac.
>
> In reality, the Diclofenac market is not this large, but similar savings might be achievable from other similar NSAIDs, although this research is yet to be done.

Due to the finding of comparable health benefits, the results of Phytodolor™ being cost saving compared to Diclofenac are naturally highly sensitive to price. The price margin is estimated as only a 24% premium of Diclofenac over Phytodolor™. As such a 10% reduction in the price of Diclofenac together with a 10% increase in the price of Phytodolor™ would make the two indifferent on cost.

The major uncertainty is in relation to additional health benefits from less adverse events from Phytodolor™, for which robust data were unavailable. Such data would strengthen the findings of this analysis and, given the conclusions from individual literature items, could potentially show Phytodolor™ to be dominant over Diclofenac (lower costs and greater efficacy when all health outcomes are included). However, a higher level of evidence is required to support such a postulate and hence we recommend further studies to this end.

[55] Elizabeth Greenwood from Flordis Natural Medicine Australia, September 2009.

[56] 1 drop =0.05ml

6.11 Conclusions

The analysis has shown substantial potential cost savings (perhaps in the order of $178 million per annum) from using Phytodolor™ rather than NSAIDs such as Diclofenac in the treatment of osteoarthritis.

A contemporaneous analysis by Cameron et al (2009) reviews studies that reported in favour of Phytodolor™ for less additional use of NSAIDs (diclofenac) and improvement in range of motion. Earlier, Ernst (2000) provided a comprehensive systematic review of Phytodolor™, evaluating ten studies and similarly concluding that Phytodolor™ is more effective than a placebo and as effective as synthetic drugs in the symptomatic treatment of musculoskeletal pain. Several subsequent systematic studies and reviews have also provided support for Ernst's findings.

A meta-analysis conducted by Gundermann (2007) showed Phytodolor™ was more effective than placebo in patients with 'rheumatic' pain, and equivalent to standard doses of NSAIDs. In the same study, minor adverse effects from NSAIDs were compariable to those of Phytodolor™.

Relying on these results, our analysis compared Phytodolor™ with Diclofenac assuming the efficacy and health outcomes of each were equivalent. Thus, the major determinant in the analysis became the cost of each product, which revealed that the treatment of osteoarthritis is cost saving for people using Phytodolor™ than Diclofenac, with around a 24% price premium estimated.

Like Cameron et al (2009), we conclude that the evidence is of poor quality, but what exists suggests an opportunity not just for cost savings but potentially also for health benefits if, as expected, future research finds there is a significant benefit from Phytodolor™ derived from its safer adverse event profile relative to NSAIDs.
However, a higher level of evidence is required than currently exists and we recommend further studies, which might *a priori* be postulated to show dominance (lower costs and greater efficacy) of Phytodolor™ over current first-line NSAID therapy. Future studies would benefit from more comparators, such as paracetamol (with its lower adverse event profile) as well as other interventions that have been found to be effective in the management of osteoarthritis.

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6.13 Appendix: Detailed summary of literature studies

Table 6.8: Literature on effectiveness of Phytodolor™ for osteoarthritis

Source	Aim and method	Intervention/ Comparator	Outcome measure	Findings
SYSTEMATIC REVIEWS				
Cameron et al (2009)	The aim was to provide an updated systematic review of herbal medicinal products used in the treatment of osteoarthritis. Any form of herbal intervention that compared herbal medicinal products with inert (placebo) or active controls in patients with osteoarthritis were included. Electronic databases searched included; MEDLINE, EMBASE, CISCOM, AMED, CINAHL, Cochrane registers (unrestricted by date or language).	All randomised controlled (placebo or active control) parallel and crossover trials examining the effects of herbal medicinal product interventions for treating osteoarthritis were included if patients were diagnosed with osteoarthritis. Thirty five randomised controlled trials evaluating the effectiveness of 22 herbal medicinal products were included. Three studies compared Phytodolor™ to placebo or Piroxicam in 176 participants.	Primary outcomes included: Pain, mobility and changes in finger-to-floor distance (lumbar spine flexion in standing).	The results demonstrated that the reduction of conventional drug therapy (diclofenac) could be achieved in the group receiving Phytodolor™. The adverse events quota for Phytodolor™ appeared to be better than for NSAIDs. Some adverse events were partly due to the alcohol content of Phytodolor™. No serious side effects were reported for Phytodolor™.

Source	Aim and method	Intervention/ Comparator	Outcome measure	Findings
Long et al (2001)	Literature searches were conducted to identify all randomised controlled trials of herbal medicines for osteoarthritis. The aim was to review systematically all randomised controlled trials on the effectiveness of herbal medicines in the treatment of osteoarthritis.	A systematic review of all double-blind randomised controlled trials for rheumatic conditions assessed using Phytodolor™ was included. Six randomised controlled trials were also examined, all assessing the efficacy of Phytodolor™ in the treatment of osteoarthritis. Trials were conducted against placebo and an active treatment control group (Diclofenac).	Pain (motor, constant), swelling, joint function, mobility and requirement of rescue medication	These data suggest that Phytodolor™ is as effective as NSAIDs in the reduction of pain with fewer adverse side effects.

Source	Aim and method	Intervention/ Comparator	Outcome measure	Findings
Ernst (2000)	Literature searches were conducted to identify all placebo-controlled, double blind, randomised, clinical trials of herbal remedies used for treating musculoskeletal pain, including osteoarthritis. The aim was to define one herbal remedy for which most trial data existed. This turned out to be Phytodolor™. The dose of Phytodolor™ ranged from 90 to 120 drops per day in liquid form and the equivalent of 200 drops in a tablet form. The treatment range lasted from two to four weeks, and the trials ranged in size from 30 to 432 people with rheumatic disease, with a total of 1,135 in all ten trials. All the trials included obtained a Jadad[57] score of three or four out of a possible maximum of five.	Ten randomised clinical trials were identified for Phytodolor™. All trials are listed above under 'Randomised clinical trials'. Three trials were conducted against a placebo and an active treatment control group (Diclofenac, Piroxicam and Indomethacin). Seven trials were conducted against other active medication (three of which also had a placebo control group).	The ten studies evaluated various clinical symptoms, such as pain, grip strength, physical impairment, morning stiffness, swelling, and joint function, as well as the use of rescue medication, as outcome measures.	These data suggest that Phytodolor™ is more effective than placebo and as effective as synthetic drugs in the symptomatic treatment of musculoskeletal pain. The reviews also suggest that Phytodolor™ is relatively devoid of any adverse effects.

[57] A scale used for measuring the quality of randomised controlled trials

Source	Aim and method	Intervention/ Comparator	Outcome measure	Findings
Gundermann and Muller (2007)	Literature searches were conducted to identify all placebo-controlled, double blind, randomised, clinical trials of Phytodolor™. The double-blind trials covered above all degenerative rheumatic diseases such as arthrosis deformans, activated arthroses and lateral epicondylitis as well as inflammatory diseases such as rheumatoid arthritis.	The clinical studies include 13 double-blind, five single blind, two open comparative and 19 open, non-comparative studies. 6 of these trials were specifically conducted on patients with osteoarthritis. Two of which evaluated the effectiveness of Phytodolor™ as compared to placebo, two compared the potential therapeutic effect of the herbal mixture with that of an active treatment control group and one compared its effectiveness with that of placebo or the active treatment control group. The active treatment control group, including Diclofenac, Pifoxicam, Indomethancin or Populus extract.	Pain (motor/constant/rest pain/ tenderness), extent of mobility, joint index and swelling. The reduction in the amount of NSAIDs, pain killers and analgesics required was also used to compare the therapeutic benefit of Phytodolor™.	Phytodolor™ is more effective than placebo in patients with rheumatic pain, and apparently equivalent to standard doses of NSAIDs. There are no adverse drug effects that contradict a long term administration, and the efficacy of the test product does not decrease or increase over time. There is a trend to reduce the intake of NSAIDs which should be confirmed by further investigations.

Source	Aim and method	Intervention/ Comparator	Outcome measure	Findings
RANDOMISED CONTROLLED TRIALS (RCTS) – OSTEOARTHRITIS ONLY – PLACEBO CONTROLLED TRIALS				
Schreckenberger (1988)	Schreckenberger (1988) conducted a trial on 45 persons with osteoarthritis. Fifteen people received 3x40 drops of Phytodolor™ per day, fifteen received a placebo per day and the other fifteen persons received 3x25 mg of Diclofenac per day. The treatment was continued for 2 weeks.	Double Blind – Placebo Single Blind- Diclofenac	Therapeutic success was evaluated on gripstrength.	Significant differences favouring Phytodolor™ treatments. The results show that after this period, grip strength improved significantly more in the Phytodolor™ compared to the control groups (P<0.001). No adverse effects were reported with Phytodolor™.
RANDOMISED CONTROLLED TRIALS (RCTS) - RHEUMATIC DISEASE (OSTEOARTHRITIS AND OTHER RHEUMATIC DISEASES) – PLACEBO CONTROLLED TRIALS				
Ebert et al (1988) (research report from Gundermann and Muller (2007))	Ebert et al (1988), treated two groups of patients with rheumatoid arthritis with Phytodolor™ for over one year. Diclofenac co-medication was restricted to maximum 6 × 25 mg daily	Double Blind - Placebo	The reduction in the amount of NSAIDs, pain killers and analgesics.	Treatment with Phytodolor™ enabled a mean, constantly lower intake of diclofenac from two months onwards.

Source	Aim and method	Intervention/ Comparator	Outcome measure	Findings
Hahn and Hübner-Steiner (1988) (research report from Gundermann and Muller (2007))	Hahn and Hübner-Steiner (1988) performed on patients with acute and chronic painful rheumatic conditions a double-blind study versus placebo and open against 3 x 1 to 3 x 2 teaspoonfuls Amuno per day (3 x 35 to 3 x 50 mg indomethacin per day).	Double Blind – Placebo Open Treatment- Indomethacin	Pain (motor, constant) and swelling.	Compared to placebo, "motor impairment" improved after one ($p < 0.01$), and motor pain after two weeks of treatment ($p < 0.05$). The results showed that the effects set in sooner with Amuno but were comparable to Phytodolor™ after four weeks
Schadler (1988)	Schadler (1988) conducted a trial on 30 persons with rheumatic pain. 15 people received 3x40 drops of Phytodolor™ per day and the other 15 received a placebo each day. Patients were offered Diclofenac as a rescue medication.	Double Blind - Placebo	Pain accompanying degenerative rheumatic diseases (custom-made pain score) and use of rescue medication. Patients were offered diclofenac as a rescue medication.	The results demonstrated that the experimental group required significantly less of that rescue medication than patients of the placebo group.

Source	Aim and method	Intervention/ Comparator	Outcome measure	Findings
Huber (1991)	Huber (1991) reported a trial on 38 in-patients suffering from mixed rheumatic diagnoses. Eighteen people received 3x40 drops of Phytodolor™ per day and the other twenty received a placebo each day. The primary aim of the trial was to test wether the dosage of the concomitant antirheumatic drugs could be reduced by the addition of the herbal mixture.	Double Blind - Placebo	Joint mobility, pain (constant, tenderness) and use of rescue medication. .	The results demonstrated that the reduction of conventional drug therapy could be achieved in the group receiving Phytodolor™. The effects became apparent after one week of treatment with no adverse reactions recorded.
Bernhardt et al (1990)	Bernhardt et al (1990) tested Phytodolor™ in a four armed two centre study on people with rheumatic pain (rheumatoid arthritis, osteoarthritis, or back pain). The subjects either received normal double or half strength Phytodolor™ (3x30 drops per day) or placebo drops per day.	Double Blind - Placebo	Pain (motor, constant) accompanying degenerative rheumatic diseases	Pain during movement was reduced in all 4 groups. Chronic paid was reduced only in the high strength treatment groups. 44% of the patients in the control group rated the overall clinical results as ‘very good’ or ‘good’.

Source	Aim and method	Intervention/ Comparator	Outcome measure	Findings
Bernhardt et al (1991)	Bernhardt et al (1991) tested Phytodolor™ in a three armed study on people with rheumatic pain. 36 people received 3x40 drops of Phytodolor™ per day. The second group of 36 received a placebo each day and the remaining thirty six people received 20 mg of Piroxicam per day.	Double Blind - Placebo Open Treatment- Piroxicam	Pain (motor/constant), mobility, changes in finger-to-floor distance and grasping strength.	The Phytodolor™ and Piroxicam reduced pain significantly compared to the placebo group at 2 and 4 weeks after commencement, with no significant differences between them. No adverse effects were reported with Phytodolor™. Seven people taking Piroxicam experienced side-effects.
Baumann et al (1989)	Baumann et al (1989) conducted a trial on 108 people with various musculoskeletal problems (mainly osteoarthritis). 52 people received the standard dose of Phytodolor™ and 56 people received 3x25 mg of Diclofenac per day.	Double Blind- Diclofenac	Pain, swelling and function were defined as the primary outcome variables.	Both treatments provide similar clinical results; however 10 cases of adverse effects were recorded in the Diclofenac group and 9 cases in the Phytodolor™ group.
Herzog et al (1991)	Herzog et al (1991) conducted a multicentre study where 423 patients with activated arthroses received either the standard dose of Phytodolor™ or Diclofenac (3x25mg) per day for 4 weeks. Patients were offered Diclofenac as a rescue medication.	Double Blind- Diclofenac	Therapeutic success was evaluated with a pain score.	No statistically significant differences were found in terms of clinical improvement between both groups Tolerance of Phytodolor™ was better than that of Diclofenac.

Source	Aim and method	Intervention/ Comparator	Outcome measure	Findings
Hawel (1991)	Hawel (1991) conducted a trial on 204 people with various types of arthroses, who received either the standard dose of Phytodolor™ or Diclofenac (3x25mg) per day for 3 weeks.	Double Blind- Diclofenac	The endpoints were defined as global symptom sore and joint mobility.	No statistically significant differences were found in terms of clinical improvement between both groups The results show equivalence for both treatments. There were significantly less adverse effects in the Phytodolor™ group compared to the Diclofenac group.