Intra-articular viscosupplementation for treatment of osteoarthritis of the knee

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MSAC application 1045

Assessment report

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The Medical Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

This report was prepared by the Medical Services Advisory Committee with the assistance of Mr. Brent Hodgkinson, Ms Tracy Merlin, Professor Janet Hiller and Mr. John Moss, from the Health Technology Assessment Unit, Department of Public Health, University of Adelaide; and Professor Les Cleland from the Rheumatology Unit, Royal Adelaide Hospital. The report was endorsed by the Commonwealth Minister for Health and Ageing on March 9, 2003.

Publication approval number: *3155*

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the Health Technology Assessment Unit, Department of Public Health at the University of Adelaide was engaged to conduct a systematic review of literature on intra-articular viscosupplementation for treatment of osteoarthritis of the knee. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of intra-articular viscosupplementation for treatment of osteoarthritis of the knee

Clinical need

Osteoarthritis (OA) is a progressive degenerative disorder of the cartilage and is one of the 10 leading causes of disease burden in Australia. In an Australian survey of older adults (over 65 years of age) living in the community, over 55 per cent of females and 40 per cent of males experienced some form of long-term arthritis or rheumatism. It has been estimated that in European and North American populations one -third of all adults aged 25-74 years have features of OA as determined by radiographic methods. Osteoarthritis sufferers can experience a significant loss in the quality of life. In a study comparing quality of life of OA sufferers over 65 years of age with control patients suffering no chronic illnesses, OA patients scored significantly lower than controls on all quality of life domains of the Short Form 36 questionnaire. In an Australian community survey of older adults (65 years or older), presence of self-reported OA was a significant predictor of higher disability scores when assessed by a Health Assessment

Questionnaire. Recent figures (1999-2000) from the National Hospital Morbidity Database of the Australian Institute of Health and Welfare suggest that OA of the knee was the primary diagnosis in 11 per cent of all musculoskeletal disorders resulting in hospitalisation. The final step in the clinical pathway for the treatment of knee OA is total knee replacement. The National Joint Replacement Registry reports that OA was the most common diagnosis for all forms of primary knee replacement. Of the 5,974 reported knee replacements performed in Australia between September 1999 and December 2000, 84 per cent had a primary diagnosis of osteoarthritis.

Safety

In studies examining the effectiveness of viscosupplementation with HA compared to treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, little attention has been paid to the identification of possible adverse events. Only one study included in this review provided more than a cursory discussion of the safety of viscosupplementation with HA. Results suggest that the risk of local adverse events (eg pain, swelling) associated with HA use was similar to that from IA corticosteroids but significantly higher than experienced with NSAIDs. Conversely, however, NSAIDs appear to cause significantly more gastrointestinal adverse events compared to treatment with HA. No studies comparing COX-2 inhibitors to HA were found.

There is little consistent evidence for the safety of hylan G-F 20 when compared to NSAIDs, appropriate care or a lower molecular weight hyaluronic acid, and no evidence for any comparison(s) with COX-2 inhibitors. In a single study, with the most comprehensive adverse event collection protocol and longest follow-up of any included study, an incidence of up to 61 per cent for local adverse events was reported in the group receiving hylan G-F 20. However, unblinded assessment determined that only 18 per cent of these events were due to treatment with hylan G-F 20. The remaining studies reported a wide-ranging incidence of adverse events (3-14%); however, the rigour of adverse event data collection in these studies is questionable. Therefore, results are only suggestive that viscosupplementation with hylan G-F 20 produces a similar incidence of local adverse events as injection with lower molecular weight hyaluronic acid viscosupplement and with NSAIDs. Hylan G-F 20 combined with appropriate care showed a higher incidence of local adverse events when compared with appropriate care only. Conversely, hylan G-F 20 was found to have a lower incidence of systemic adverse events than NSAIDs. There was no difference in systemic adverse events when hylan G-F 20 combined with appropriate care was compared with appropriate care only. However, hylan G-F 20 plus appropriate care was found be associated with a lower risk of side effects and gastrointestinal adverse events when compared with appropriate care only. As research design allowed for the possibility of significant bias in this final study, care should be taken when interpreting these results.

Effectiveness

From the limited evidence available, HA was found to as effective as, but no more effective than, NSAIDs at improving patient perceived pain scores, physical function, patient global assessment or stiffness scores. HA was found to be as effective as, but no more effective than, IA corticosteroids for alleviating night, rest and touch pain but showed a trend for reduced risk of pain under load. HA improved physical functioning and patient global assessment scores in comparison to IA corticosteroids. Results of

stiffness scores and analgesic use when comparing HA to IA corticosteroids were inconclusive and contradictory.

Overall, hylan G-F 20 was associated with some level of improvement in measures such as mean pain scores at 26 weeks when blinding was instituted and only in combination with NSAID therapy. However, this result is found in a single study of relatively small size. Therefore, treatment with hylan G-F 20 alone is, with one exception, no more effective in improving outcome measures of pain, global assessment, physical function or stiffness than treatment with NSAIDs. Comparison with a lower molecular weight HA is inconclusive due to poor data reporting. The combination of hylan G-F 20 with appropriate care has produced significant improvements in pain, global assessment, physical function and stiffness compared to appropriate care alone. However, these results are questionable due to potential bias inherent in the study design.

Cost-effectiveness

Only one identified study performed cost-effectiveness and cost-utility analysis. The authors reported the incremental cost per patient improved in the first year of treatment to be $3,322, and the incremental cost per Quality Adjusted Life Year (QALY) gained in that time to be $13,260. Sensitivity analysis suggested an upper bound on the incremental cost of $5,672 per patient improved and of $55,381 per QALY gained. However, critical appraisal uncovered numerous flaws in the research design, which impacted on the economic analysis. Therefore, based on this one study against the comparator of appropriate care alone, the evidence for the comparative cost-effectiveness of hylan G-F 20 specifically must be regarded with caution.

Little valid information on the cost-effectiveness of viscosupplementation products could be obtained from the existing literature. Wide variations in the incremental effectiveness of these interventions led to different incremental cost-effectiveness ratios, even between studies making identical comparisons of treatment. Issues of study quality made the resulting data even less reliable. The majority of studies were underpowered, some were unblinded, and only one had a time horizon that extended past six months. No studies compared viscosupplementation with COX-2 inhibitors and there is no data comparing hylan G-F 20 with IA corticosteroids.

An estimate was calculated of the cost that could be expected over a 1-year time period if any of the four identified comparators (NSAIDs, COX-2, viscosupplements or IA corticosteroids) was provided to the identified population of knee OA sufferers. One course of NSAID treatment was least expensive at $316 per patient per year, with one course of any viscosupplement the most expensive, in the range $700–1140 per patient per year, depending on the product and the number of injections per course.

Per year for the entire population of knee OA sufferers in Australia, one or more courses of viscosupplementation was the most expensive treatment option, costing $390 million for hylan G-F 20 and up to $470 million per year for Supartz™. Overall, NSAIDs were the least expensive treatment option at $114 million per year. While a single injection per course per year of the IA corticosteroid triamcinolone acetonide was less expensive than NSAID treatment ($80 million), a four-injection course per year increased the price to almost 60 per cent more than that of NSAIDs ($190 million). COX-2 inhibitors were up to two times more expensive to provide than NSAIDs.

Recommendation

MSAC recommended that on the strength of evidence pertaining to intra-articular viscosupplementation for treatment of osteoarthritis of the knee public funding should not be supported for this procedure.

- The Minister for Health and Ageing accepted this recommendation on March 9, 2003.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of hylans and hyaluronic acid products in viscosupplementation for the treatment of osteoarthritis of the knee. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health issues and health administration.

This report summarises the assessment of current evidence for the effectiveness, safety and cost-effectiveness of hylans and hyaluronic acids as viscosupplementation treatment for osteoarthritis of the knee.

Background

Bayer Australia Limited has sought approval from the Medical Services Advisory Committee (MSAC) for the funding of Synvisc™ (hylan G-F 20) as a viscosupplementation treatment of osteoarthritis (OA) of the knee. The MSAC Supporting Committee, on advice from the Medicare Benefits Branch, decided that all of the viscosupplementation products should be reviewed. Viscosupplementation is considered a new medical service that would require a new Medicare item number.

Currently there are two distinct groups of viscosupplementation products available: hyaluronic acid derivatives (HA) and hylans. Pure and immunogenically inert HA is generally prepared from rooster combs. However, this 'isolated' HA has a much lower molecular weight (MW) than biological HA ($2x10^6$ Da vs $4\text{-}5x10^6$ Da), generally due to the problem of degradation during preparation (Weiss & Band 1999). Therefore, the viscoelastic properties of these solutions are lower than those of osteoarthritic HA. In an effort to improve the viscoelastic properties of the HA, crosslinked polymers of HA (hylans) have been developed that have similar viscoelastic properties to normal HA. The most recent compounds are Synvisc™ and Orthovisc™. Both have a reported MW of around $4x10^6$ Da.

The procedure

The concept of viscosupplementation to ameliorate OA symptoms was suggested as early as 1960, resulting in investigations into the rheological (flow) properties of synovial fluid and the realisation that these properties decline with age (Balazs & Denlinger 1993). The procedure involves the intra-articular (IA) injection of the viscosupplement into the synovial cavity of the knee. Generally, the product is provided in either 2 mL vials or prefilled syringes. However, injection schedules differ from product to product. For example, Hyalgan® (an HA) is recommended to be given in 2 mL doses, once per week for 5 weeks. Synvisc™ (a hylan) is normally injected in 2 mL doses once per week for 3 weeks. If effusion (ie build-up of fluid) is present, it is recommended that aspiration of the joint be performed prior to injection of the viscosupplement (Wen 2000).

Intended purpose

In OA the size of individual chains of biological HA becomes reduced and/or the concentration within the synovial fluid decreases, limiting molecule to molecule interactions (Balazs & Denlinger 1993). Therefore, there is a reduction in the viscoelastic properties of synovial fluid, limiting the protection provided to the joint. The cartilage and therefore the associated chondrocytes are subjected to increased stresses and can become damaged. With the presence of collagen and proteoglycan fragments in the synovial fluid, inflammation can result in an increase in the production of cytokines such as interleukin 1 (IL-1). This stimulates the synthesis of proteases such as collagenase. In a vicious circle, proteases break down collagen and proteoglycans, further stimulating an inflammatory response (Pelletier & Martel-Pelletier 1993). Clinical manifestations of this disorder are joint pain, stiffness and a reduction in movement. Viscosupplementation involves the IA injection of HA with the purpose of replenishing it in the affected joint. Both *in-vitro* and *in-vivo* evidence suggests that HA treatment may be chondroprotective (Marshall 1997). The exact mechanism of action of this treatment is unknown but it is

believed that it increases the viscoelastic properties of the synovial fluid (Wen 2000), and temporarily restores the environment of the joint, stimulating renewed production of native HA. Placebo controlled trials have suggested that HA could produce significant improvements in pain symptoms for several weeks or months, and up to 26 weeks with hylan G-F 20 (Synvisc™) (Peyron 1999).

Clinical need / burden of disease

Osteoarthritis is a progressive degenerative disorder of the cartilage that is one of the 10 leading causes of disease burden in Australia (Mathers et al 1999). In an Australian survey of older adults (over 65 years of age) living in the community, over 55 per cent of females and 40 per cent of males experienced some form of long-term arthritis or rheumatism (March et al 1998). It has been estimated that in European and North American populations one-third of all adults aged 25-74 years have features of OA as determined by radiographic methods (Creamer & Hochberg 1997). The principal risk factors for radiographically determined knee OA are age, female gender, obesity and/or joint trauma (Creamer & Hochberg 1997). Osteoarthritis sufferers can experience a significant loss in the quality of life. In a study comparing quality of life of OA sufferers over 65 years of age with control patients suffering no chronic illnesses, OA patients scored significantly lower than controls on all quality of life domains of a Short Form 36 (SF-36) questionnaire (Briggs et al 1999). In an Australian survey of community older adults (65 years or older), presence of self-reported OA was a significant predictor of higher disability scores when assessed by a Health Assessment Questionnaire (HAQ) (March et al 1998). Recent figures (1999-2000) from the National Hospital Morbidity Database of the Australian Institute of Health and Welfare suggest that OA of the knee was the primary diagnosis in 11 per cent (35305/330448) of all musculoskeletal disorders resulting in hospitalisation (AIHW 2001). Therefore, this value is probably a conservative estimate of the number of people suffering from this condition. The final step in the clinical pathway for the treatment of knee OA is total knee replacement. The National Joint Replacement Registry reports that OA was the most common diagnosis for all forms of primary knee replacement (Graves et al 2001). Of the 5,974 reported knee replacements performed in Australia between September 1999 and December 2000, 4,997 (84%) had a primary diagnosis of osteoarthritis.

Existing procedures

In Australia initial treatment of OA has traditionally been non-pharmacological interventions such as exercise programs, weight loss, prostheses and patient education (March 1997). In many cases, simple analgesics are also indicated. If these measures do not control the symptoms, non-steroidal anti-inflammatory drugs (NSAIDs) may be prescribed. However, the recognised side effects of this treatment, specifically gastrointestinal disruption (Henry et al 1996), either preclude some patients from this treatment or limit its effectiveness. Other steps may include corticosteroid injections, aspiration of fluids from the joint, or surgery. More recently, viscosupplementation has been used as a treatment alternative before surgery but after other non-pharmacological or pharmacologic methods have failed (Altman et al 2000; March 1997).

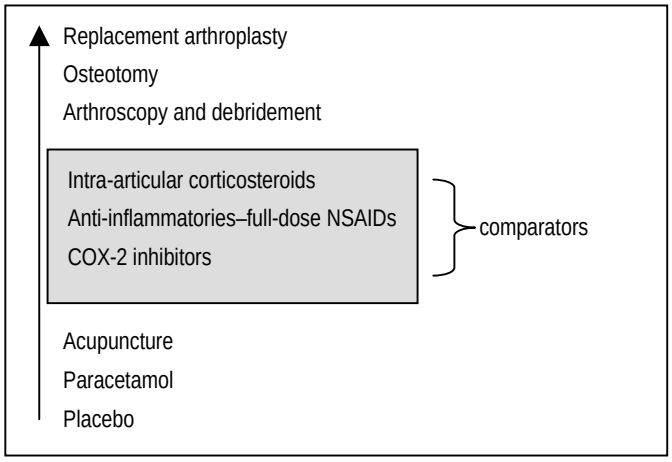
Viscosupplementation products have been available in some countries for more than 10 years. Supartz™ (previously known as Artz) has been marketed worldwide since 1987

(Peyron 1999). In Canada hylan G-F 20 has been available for treatment of OA of the knee since 1992 (Lussier et al 1996).

Comparator

Despite established guidelines for the management of OA prepared by the American College of Rheumatology (OMERACT III consensus conference, (Altman et al 2000)) and the EULAR task force (Pendleton et al 2000), current practice is understood to be quite variable. The applicant has suggested that 'current practice' is the appropriate comparator for this review. In OA of the knee, it is conceivable that current practice could be defined as any treatment modality along the clinical pathway or any combination of these modalities. In this complex situation, we have assumed that a comparator is the treatment(s) which would be most likely to be replaced by the treatment under investigation if it were shown to be at least as effective and more cost-effective, or as the existing treatment(s) to which the treatment under investigation would be added if it were shown to be of acceptable cost-effectiveness. There may be more than one comparator. Accordingly, the supporting committee has endorsed a narrower definition of the acceptable comparators in this review and limited it to the three interventions in the shaded area (Figure 1).

Figure 1 Hierarchy of interventions for the identification of appropriate comparators for viscosupplementation[a]



Numerous studies have used a placebo as the comparator against which viscosupplements have been assessed for effectiveness. Administration of a placebo usually involves the injection of an equal volume of saline. However, this procedure is not part of the clinical pathway for the treatment of knee osteoarthritis. Therefore, the use of placebo was not considered a legitimate comparator for viscosupplementation and can only be used to measure the efficacy of viscosupplementation, not its effectiveness.

[a] Due to the variability in clinical practice, the comparators may also be used in conjunction with, rather than instead of, viscosupplementation of the knee.

Marketing status of the device / technology

Hylan G-F 20 (Synvisc™) has been included on the Australian Register of Therapeutic Goods (ARTG, Aust R 67234: Product No. 130290). Apart from Synvisc™, only Supartz™ (Smith and Nephew), a hyaluronic acid, has been registered with ARTG (Aust R 81545). However, neither viscosupplementation product has been included in the Medical Benefits Schedule (MBS) to date.

Current reimbursement arrangement

Currently, no viscosupplementation product is listed on the Medicare Benefits Schedule. However, the procedure of injection of a substance into the synovial cavity or aspiration of fluid (MBS item number 50124) is listed. Common analgesics used in conjunction with viscosupplementation, along with the comparator medications and treatments such as NSAIDs and corticosteroids, are listed in the Pharmaceutical Benefits Schedule (PBS) (Figure 2).

Figure 2 Items listed on the PBS that are used in treatment of OA (as related to this review).

NSAIDs	**Analgesics**
Ibuprofen	Paracetamol
Diclofenac	Codeine 30 mg plus paracetamol
Aspirin	Dextropropoxyphene with paracetamol
Sulindac	Codeine < 20 mg with paracetamol
Naproxen	
Indomethacin	**COX-2 inhibitors**
Ketoprofen	Celecoxib
Piroxicam	Rofecoxib
Meloxicam	
Tenoxicam	
Difusinal	
Corticosteroids	
Methylprednisolone acetate (MPA)	
Betamethasone (BTM)	
Triamcinolone	

Approach to assessment

Review of literature

The medical literature was searched to identify relevant studies and reviews for the period between 1966 and August 2002. Searches were performed on the databases and Health Technology Assessment (HTA) websites listed in Table 1 using the search terms in Table 2.

Sources of prevalence data

- Australian Institute of Health and Welfare (AIHW)–Hospital Morbidity Database
- National Joint Replacement Registry (Australian Orthopaedic Association)
- Australian Patient Safety Foundation (for adverse events associated with viscosupplementation)
- Prevalence information was also retrieved, where possible, from literature that was included in the review.

Literature sources

Table 1 Electronic databases used for literature search

Electronic database	Time period
Medline (SilverPlatter)	1966 – 8/2002
Embase (Embase.com)	1966 – 8/2002
Current Contents (Ovid)	1993 – 8/2002
Cochrane Library: including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness (DARE), the Cochrane Controlled Trials Register, the Health Technology Assessment Database, the NHS Economic Evaluation Database	Issue 4, 2001
Web of Science. Science Citation Index Expanded	1995 – 8/2002
ProceedingsFirst	1993 – 8/2002
EconLit	1969 – 12/2001

Table 2 Search terms used for electronic databases

Area of enquiry	Search terms
All headings	**MeSH** Randomized-controlled-trial, Controlled-clinical trial, randomized-controlled-trials, random-allocation, double-blind-method, single-blind-method, clinical-trial, clinical trials, research-design, comparative study, evaluation studies, follow-up studies, prospective studies, cohort studies, hyaluronic acid **Text words** Clin*, trial*, singl*, doubl*, trebl*, tripl*, blind*, mask*, random*, control*, prospectiv*, volunteer*, hylan, viscosuppl*

An example of a search strategy is shown in Appendix C.

Internet

The following electronic internet databases were searched up until 8/2002:

- Scirus – for Scientific Information Only (http://www.scirus.com): 1973-08/2002
- Trip database http://www.tripdatabase.com

The following general databases of health technology assessment reports were searched up until 2/2002:

- International Society of Technology Assessment in Health Care http://www.istahc.org/en/welcome.html
- International Network for Agencies for Health Technology Assessment http://www.inahta.org/
- National Library of Medicine Health Services / Technology Assessment Text http://text.nlm.nih.gov/
- National Library of Medicine Locator Plus database http://locatorplus.gov

Country specific HTA websites searched are found in Appendix D.

Hand searching

For completeness, the most recent issues of several rheumatology and arthritis journals were searched. These included:

- Arthritis and Rheumatism – Volume 46 (2) 2002
- Arthritis Care and Research – Volume 47 (1) 2002
- Rheumatology – Volume 41 (1) 2002
- Annals of Rheumatic Diseases – Volume 61 (3) 2002

Pearling

The reference lists of all retrieved articles were searched for additional relevant source material.

Inclusion criteria

Identified citations were then selected for second round inclusion based on strict inclusion and exclusion criteria that described the study patient composition, intervention

evaluated, study design, outcomes measured, the comparator and the language of publication (Figure 3).

Patients

Patients had documented symptomatic OA of the knee generally diagnosed by radiological changes such as asymmetrical joint space narrowing, subchondral bone sclerosis, subchondral cyst formation and, in severe cases, deformity of bone ends (Creamer & Hochberg 1997), in which:

- non-pharmacological, non-invasive and first-line pharmacological methods have failed to provide adequate pain relief, or are not an option
- previous knee realignment surgery has failed or the patient is not a candidate for total knee replacement.

Intervention

The proposed intervention was viscosupplementation for treatment of OA of the knee. The recommended dosage varies from 1 to 6 mL for 1 to 5 weeks with HA, and generally 2 mL injected weekly for 3 weeks for hylan G-F 20.

Outcomes

Outcome measures were identified as per the recommendations of the Outcome Measures in Arthritis Clinical Trials (OMERACT) III consensus conference (Bellamy et al 1997). The core set of outcomes that are essential to an evaluation of the effectiveness of viscosupplementation are: pain, physical function and patient global assessment. Joint imaging, to evaluate the extent of joint space narrowing, is also a core outcome if trials are long-term (≥ 1 year). Quality of life, utility measures and a global assessment performed by a medical practitioner are strongly recommended as outcome measures. Finally, optional assessment outcome variables can include extent of inflammation, stiffness, biologic markers and others (eg analgesic use). Where possible, length of time until total knee replacement surgery was also evaluated.

Comparators

Due to the variability in practice, the supporting committee developed a hierarchy of interventions in order to identify comparative treatments of OA of the knee (see Figure 1). From this list the comparators identified were IA corticosteroids, NSAIDs, and COX-2 inhibitors. It should be noted, however, that these comparators could also be used in conjunction with viscosupplementation in some patients. In addition to the list of comparators identified, other viscosupplementation products and 'appropriate care' were also included as comparators.

Eligible study designs

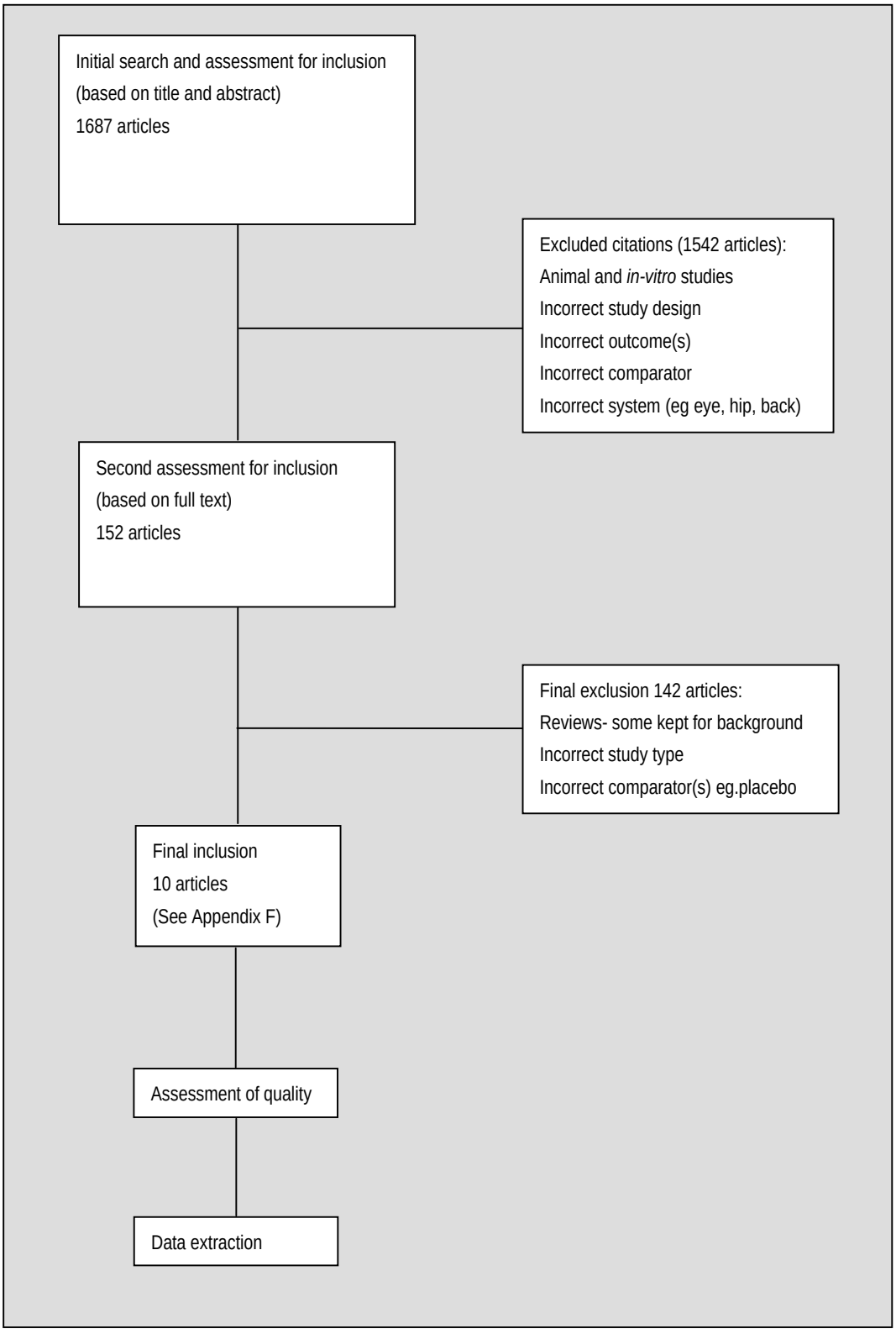
To determine the effectiveness of an intervention such as viscosupplementation, randomised controlled trials (RCT) are considered the gold standard. However, in the absence of RCTs, controlled trials were also considered. For the determination of safety of viscosupplementation, RCT and cohort designs were considered.

Languages

Searches included English and foreign language publications. Assessment for inclusion of foreign language publications was based on the English language abstract, where available.

Search phases

Figure 3 Schema of the stages of searching and inclusion/exclusion of references for the review



Data extraction and analysis

Data were extracted from the included articles by a single researcher using tables developed *a priori* and outcome definitions provided in the original protocol.

Descriptive statistics were extracted or calculated for all safety and effectiveness outcomes in the individual studies, including numerator and denominator information, means and standard deviations. The power of individual studies to detect a clinically important effect was calculated, assuming that $\alpha = 0.05$.

Relative risk / risk ratio (RR), number needed to treat (NNT) or harm (NNH) and associated 95% confidence intervals (95% CI) were calculated from individual comparative studies containing count data. Mean differences and 95% confidence intervals were calculated for normally distributed continuous outcomes in individual studies using the independent t-test.

Meta-analyses were not performed as the evidence-base was heterogeneous — studies were conducted against different comparators, measured different outcomes or presented data in formats that could not be combined (eg graphical).

All statistical calculations and testing were undertaken using the biostatistical computing software package, Stata version 7.0 (Stata Corporation 2001).

Assessment of quality

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (National Health and Medical Research Council 2000).

These dimensions (Table 3) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The other two require expert clinical input.

Table 3 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design*
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

*See Table 4

The three subdomains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 4.

Table 4 Designations of levels of evidence*

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

*Modified from (NHMRC 1999)

The appraisal of intervention studies for the research questions pertaining to IA viscosupplementation for the treatment of OA of the knee was undertaken using a checklist developed by Downs and Black (Appendix E) (Downs & Black 1998). This checklist is suitable for trials and cohort studies and has been psychometrically assessed to have overall high internal consistency, good test–re-test and inter-rater reliability, and high criterion validity (Downs & Black 1998). As in a paper by Coster and colleagues, it was decided to modify the checklist by dropping the five items relating to the power subscale and evaluate power independently (Coster et al 2000). Therefore, the checklist produced an overall Quality Index Score (total = 27), along with subscale scores (Reporting, External validity, Bias and Confounding). Information on specific methodological components shown empirically to impact on treatment effect sizes were also included in this checklist — specifically, concealment of allocation, blinding, and completeness of data (Juni et al 1999; Moher et al 1998; Schulz et al 1995).

Expert advice

A supporting committee with expertise in rheumatology, orthopaedics, general practice, consumer health issues and health economics was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations, and consumer bodies for nominees. Membership of the supporting committee is provided in Appendix B.

Results of assessment

Viscosupplementation is a treatment that has evolved into two distinct forms. The first involves the use of the hyaluronic acids (HA), which are derived from sources such as rooster combs and umbilical cords. The second form is the use of cross-linked HA to form highly viscous solutions called hylans.

Is it safe?

To determine the incidence of adverse events, randomised controlled trials (RCTs) and cohort studies were analysed. Only studies identified as having comparators of interest to this review (NSAIDs, IA corticosteroids, COX-2 inhibitors) were examined in order to determine whether the incidence of adverse events is significantly different from present treatments that viscosupplementation is intended to substitute.

For a study to be considered as having an adequate safety assessment component, it should have addressed at least the following two criteria:

- A protocol for the collection of adverse events must be described.
- A definition of an adverse event should be included.

While most studies included in this review provided at least a rudimentary description of an adverse event collection protocol, only one study provided a definition of what would constitute an adverse event (Raynauld et al 2000). Further description of adverse event collection protocols of included studies can be found in Appendix F.

Hyaluronic acid

Six RCTs that met the inclusion criteria for this review addressed the safety of HA against either NSAIDs (Petrella et al 2002; Altman & Moskowitz 1998) or IA corticosteroids (Leardini et al 1991; Leardini et al 1987; Pietrogrande et al 1991; Tekeoglu et al 1998). Profiles of these studies are provided in Appendix F. Despite their widespread use as a treatment for OA, no studies were found that compared HA with COX-2 inhibitors. Studies of Supartz™, the only HA available for viscosupplementation use in Australia, did not satisfy the inclusion criteria for this review.

HA vs NSAIDs

In the highest quality study evaluated, Altman (Altman & Moskowitz 1998) compared the effectiveness and safety of the hyaluronic acid product Hyalgan® in 164 patients against the NSAID Naproxen in 163 patients for a period of six months. Adverse events were collected over a 26-week period. Routine laboratory and haematological assessments were also performed at baseline and weeks 9 and 26. No specific description of these tests was given. Synovial fluids when obtained were analysed for volumes, crystals, bacteria and leukocytes. The authors found the occurrence of numerous adverse events over the 26-week study period (Table 5). However, as only adverse events with an incidence of 5 per cent or greater were reported the total number of adverse events for

each treatment arm could not be ascertained. Therefore, the incidence of the most common adverse events was compared. Patients receiving Hyalgan® had a 30 per cent reduced risk of gastrointestinal complaints compared to those taking Naproxen. Conversely, Hyalgan® was associated with 2.7 times the risk of injection site pain, and trends indicated nearly twice the risk of headache, and local joint pain and swelling. The risk of local skin rash and pruritis was no different between the treatments. There were reports of severe knee swelling, one in the Naproxen group and two in the Hyalgan® group. Six reports (3.6%) of pain at the injection site in the Hyalgan® group and one (0.6%) in the Naproxen group resulted in premature terminations of treatment. Gastrointestinal problems resulted in premature termination in 14 (8%) of Naproxen treated patients, and 4 (2%) in the Hyalgan® group. Excess synovial fluid was aspirated from 29.3 per cent (48/164) of HA treated patients but was not reported as performed in the Naproxen group. No changes in synovial fluid were noted in the Hyalgan® group. No clinically significant changes in laboratory test values were reported in either of the treatment groups. No discussion of the resolution of symptoms in patients suffering adverse events was described. General or systemic reactions were uncommon and were not described.

Table 5 Reported adverse events (HA vs NSAIDs)

Study	Quality[a]	Outcomes	Treatment group				Relative risk		Number needed to harm	
			HA		NSAID					
			r/n[b]	%	r/n	%	RR	95% CI	NNH	95% CI
Altman (1998)	QS: 26/27 CI: 4 P: under-powered	Gastrointestinal complaints	48/164	29	68/163	41	0.7	0.5-0.9	NNTB 8[c]	NNTB 4-50
		Injection site pain	38/164	23	14/163	9	2.7	1.5-4.8	7	4-14
		Headache	30/164	18	17/163	10	1.7	1.0-3.0	12	7-333
		Local skin ecchymosis and rash	23/164	14	29/163	18	0.8	0.5-1.3	NNTB 25	NNTB 8-NNTH 25
		Local joint pain and swelling	21/164	13	10/163	6	2.1	1.0-4.3	14	8-250
		Pruritus (local)	12/164	7	7/163	4	1.7	0.7-4.2	33	12-50

[a] Quality score (QS) determined from checklist created by Downs and Black (Downs & Black 1998); clinical importance (CI) scored from 1 to 4 with 1 = clinically important benefit for the full range of plausible estimates, 2 = point effect clinically important but confidence interval includes clinically unimportant effects, 3 = confidence interval does not include any clinically important effects, 4 = range of estimates include clinically important effects but range of estimates compatible with no effect or harmful effect (National Health and Medical Research Council 2000); power (P). [b] r/n = number of subjects with condition / number of subjects in intervention group. [c] NNTB designates the number of patients required to be treated with HA to have a protective effect on one additional patient compared to NSAID treatment alone.

In a study of somewhat lower quality score (22/27), the effectiveness of HA (Suplasyn) in 25 patients was compared to oral diclofenac (an NSAID) taken with misoprosotol twice daily for 12 weeks in 26 patients (Petrella et al 2002). No description of the collection procedure for adverse events was given. No serious adverse events were reported in either group at 12 weeks follow-up. However, examination of the 95% CIs suggests that the incidence of serious adverse events could be as high as 3/25 (12%) or 3/26 (11%) in the HA and NSAID groups respectively. No definition of a serious adverse event was provided. The authors claim that minor adverse events occurred primarily in the NSAIDs only group, but these data were not presented. Only participants who completed the course of treatment were followed up to 12 weeks. The

reasons for dropout were reported but were not defined for each treatment arm. Small treatment groups and the lack of reported data after the 4-week time period are also weaknesses of this study. Therefore, this article does little to describe the safety of either treatment, and any stated conclusions by the authors should be treated with caution.

HA vs IA corticosteroids

Four studies included in this review examined the safety of hyaluronic acid compounds compared to IA injection of corticosteroids.

In an unblinded RCT (quality score 19/27) of patients exhibiting radiographic evidence of OA, weekly intra-articular injections of HA (Orthovisc™) in 20 female patients were evaluated against weekly injections of Betamethasone in another 20 female patients (Tekeoglu et al 1998). The assessor at each clinical examination monitored the incidence of any adverse events. The authors reported that no patient from either group presented with any local or systemic adverse events. However, determination of the 95% CIs indicated that the incidence of an adverse event in either group could be as high as 3/20 (15%) patients. Again, there was a failure to define what was considered as an adverse event. Other weaknesses of this study are the all-female population and therefore its external validity, the small sample size and the lack of blinding.

Three studies compared Hyalgan®, a 500-730 kDa HA, with methyl prednisolone acetate (MPA), a corticosteroid (Pietrogrande et al 1991) Assessment of treatment safety in one unblinded RCT (quality score 18/27) consisted of noting the type, duration and severity of any reported adverse event and determining its possible relationship to the drug administered (Pietrogrande et al 1991). The authors claim that there were no systemic adverse events reported in either treatment group (Table 6). Again however, examination of the 95% CIs suggests that incidence of systemic adverse events could be as high as 4/45 in both groups. Locally, inflammation was reported in one case treated with Hyalgan® after the fourth injection. Here the 95% CI suggests that incidence of a local adverse event could be as high as 5/45 in HA treated patients and 4/45 in the group treated with IA corticosteroid. This inflammation subsided spontaneously after 24 hours.

A small study of 2 months (Leardini et al 1991) recruited 20 patients into each arm of a trial comparing MPA and HA (Table 6). The authors stated that the dose of MPA used in this study was half of that used in some previously published studies in order to allow for MPA injections at the same time points as for HA. Tolerance of the treatments was determined by assessment for any adverse local and systemic reactions at each observation time. No systemic or local adverse events were reported at 2-month follow-up in either group. Again, examination of the 95% CIs suggests that incidence of an adverse event as high as 3/20 might be expected in either group. However, this study was limited by several study design flaws. The small size of the sample population reduces the power of this study, and the duration of the study (only 2 months) may not have been long enough to detect any longer term negative effects of either treatment. The lack of blinding, and inadequate description of patient recruitment, reduces both the internal and external validity of the results.

Finally, a 12-month study (quality score 15/27) compared 20 knees in 20 patients injected with Hyalgan® and 20 knees in 16 patients injected with MPA (Leardini et al 1987). There was no mention of further courses of HA or MPA during the study time period. This study found no difference in the risk of adverse events for knees treated with HA, as compared to MPA (Table 6). The authors state that any local side effects were modest

and transient. However, there was no description as to how adverse events were monitored and collected, or why patients were lost to follow-up. Therefore, the number of reported adverse events should be considered an underestimation. A second weakness of this study is its size. Twenty knees per group gives this study little power and small, but possibly clinically relevant differences in treatment effectiveness could be missed. There are also some serious reporting deficiencies associated with this study. It is not possible to determine if the sample group studied is representative of the target population as no information on selection is provided and only the gender ratio and mean age (±SD) are reported for each study group.

Table 6 Reported adverse events (HA vs corticosteroids)

Study	Quality[a]	Outcomes	Treatment group				Relative risk		Number needed to harm	
			HA		Corticosteroid					
			r/n[b]	%	r/n	%	RR	95% CI	NNH	95% CI
Pietrogrande (1991)	QS: 18/27 CI: NE for primary outcome, 2 for no pain under load P: NE from primary outcome, under-powered for pain under load	Adverse events	0/20	0	0/20	0	NE[c]			
Leardini (1991)	QS: 18/27 CI: NE for primary outcome P: NE for primary outcome, 70% for secondary outcomes	Adverse events	0/20	0	0/20	0	NE[c]			
Leardini (1987)	QS: 15/27 CI: 4 P: under-powered	Adverse events	4/20[d]	20	3/16[e]	19	1.1	0.3-4.1	100	NNTB 4 to ∞ to NNTH 4[f]

[a] Quality score (QS) determined from checklist created by Downs and Black (Downs & Black 1998); clinical importance (CI) scored from 1 to 4 with 1 = clinically important benefit for the full range of plausible estimates, 2 = point effect clinically important but confidence interval includes clinically unimportant effects, 3 = confidence interval does not include any clinically important effects, 4 = range of estimates include clinically important effects but range of estimates compatible with no effect or harmful effect (National Health and Medical Research Council 2000); power (P). [b] r/n = number of subjects with condition / number of subjects in intervention group. [c] NE- not estimable. [d] 1 joint pain, 3 slight joint swelling. [de]All joint pain. [f] The 95% confidence intervals (95% CI) for number needed to treat to harm (NNTH) and number needed to treat to benefit (NNTB) were calculated by the method described by Altman and Moskowitz (1998).

Summary: The safety of viscosupplementation with hyaluronic acid compounds

In studies examining the effectiveness of viscosupplementation with HA compared to treatment with NSAIDs and corticosteroids, little attention has been paid to the identification of possible adverse events. Only one study included in this review provided more than a cursory discussion of the safety of viscosupplementation with HA;

therefore, the safety of HA versus the comparator NSAIDs is based primarily on this study (Altman & Moskowitz 1998). This study found that HA causes a significantly higher incidence of local adverse events (eg pain, swelling) than NSAIDs. Conversely, NSAIDs appear to cause significantly more gastrointestinal adverse events compared to treatment with HA. Further, from the limited information available, treatment with HA produces a similar incidence of local and systemic adverse events compared with IA corticosteroid injections. However, these studies are of poor quality and any conclusions should be regarded with caution.

Hylans

Two studies to date have assessed the safety of hylans when compared to NSAIDs (Adams et al 1995; Dickson et al 2001). One study also compared hylans with appropriate care (Raynauld et al 2000) whilst another compared hylans with a lower MW HA (Wobig et al 1999). These studies all evaluated the compound hylan G-F 20 (Synvisc^{TM}) and are profiled in Appendix F. Again, despite widespread use of COX-2 inhibitors, no studies were found that compared their effectiveness to hylans.

Hylan G-F 20 vs NSAID

One double blind RCT compared the safety of hylan G-F 20 in conjunction with oral placebo capsules in 53 patients with the NSAID diclofenac combined with arthrocentesis in 55 patients (Dickson et al 2001). At each visit the patient was asked open-ended questions relating to the experience of any local or systemic adverse events since the previous visit. No significant difference in the incidence of local adverse events was found between the hylan and the diclofenac treatment arms (Table 7). The authors stated that all local adverse events resolved without sequelae. Patients treated with hylan G-F 20 experienced an overall 60 per cent reduced risk of systemic adverse events compared to patients in the NSAID treatment arm (Table 7). This is primarily due to the 70 per cent reduced risk of gastrointestinal complaints in the hylan G-F 20 treated group.

Table 7 Local and systemic adverse events for hylan G-F 20 versus NSAID (diclofenac)[a]

Study	Quality[b]	Outcomes	Treatment group				Relative risk		Number needed to harm	
			Hylan G-F 20		NSAID					
			r/n[c]	%	r/n	%	RR	95% CI	NNH	95% CI
Dickson (2001)	QS: 24/27 CI: 4 P: under-powered	Local adverse events at 12 weeks[d]	7/50[e]	14	4/52[f]	8	1.8	0.6-5.8	17	NNTH 5 to ∞ to NNTB 17
		Headache	2/50	4	0/52	0	NE		25	NNTH 11 to ∞ to NNTB 100
		Swollen ankle	1/50	2	1/52	2	1.04	0.07-16.2	1250	NNTH 20 to ∞ to NNTB 20
		General infection	0/50	0	0/52	0	NE			
		Gastrointestinal	6/50	12	20/52	38	0.3	0.1-0.7	NNTB 4	NNTB 2-10
		Fluid retention, oedema	0/50	0	1/52	2	NE		NNTB 20	NNTH 7 to ∞ to NNTB 25
		Other	2/50	4	2/52	4	1.04	0.1-7.1	1000	NNTH 14 to ∞ to NNTB 12
		Total number of adverse events	11/50	22	25/52	48	0.4	0.2-0.8	NNTB 3	NNTB 2-12

[a] Values described are for number of patients experiencing at least one adverse event. [b] Quality score (QS) determined from checklist created by Downs and Black (Downs & Black 1998); clinical importance (CI) scored from 1 to 4 with 1 = clinically important benefit for the full range of plausible estimates, 2 = point effect clinically important but confidence interval includes clinically unimportant effects, 3 = confidence interval does not include any clinically important effects, 4 = range of estimates include clinically important effects but range of estimates compatible with no effect or harmful effect (National Health and Medical Research Council 2000); power (P). [c] r/n = number of subjects with condition / number of subjects in intervention group. [d] Type of adverse event not described for most cases. [e] Four cases were mild, 1 moderate and 2 severe (1 with pain, 1 with swelling). [f] Three cases were determined to be moderate and one severe (pain).

A multicentre double blind RCT (quality score 22/27) compared the safety of viscosupplementation with hylan G-F 20 in 31 patients, an unidentified NSAID treatment in 34 patients, and a combined treatment of hylan G-F 20 and NSAIDs in 37 patients over a period of 26 weeks (Adams et al 1995). Patients were interviewed at each study visit to determine if there had been any adverse events experienced since the last clinical visit. Investigators were instructed on criteria to determine whether an adverse event was considered treatment related. These criteria were not provided in the article. Few adverse events, systemic or local, were reported. Three of 68 total patients (4%) injected with G-F 20 (G-F 20 alone and combined with NSAIDs) developed a local

adverse event presenting as pain within 24 hours of injection. In two cases pain was reported within 24 hours and was accompanied by warmth and effusion. Arthrocentesis was performed but found to be unremarkable other than a high macrophage count in one case. Both patients recovered within several days without sequelae. The third adverse event in the hylan group was not reported for several months after the injections. One NSAID-only treated patient (3%) experienced an adverse event (not described). The risk of local or systemic adverse events for viscosupplementation with hylan G-F 20 as compared to treatment with NSAIDs could not be determined as the study was underpowered with wide confidence intervals (RR 1.6, 95%CI 0.2-15.1; NNB 50, 95% CI NNTH 20 to ∞ to NNTB 11).

Hylan G-F 20 plus appropriate care vs appropriate care only

In a recent unblinded RCT in Canada (Raynauld et al 2000), the effectiveness of hylan G-F 20 in addition to appropriate care in 127 patients was compared to appropriate care only in 128 patients in a 1-year study. Appropriate care was defined as: 'the preferred management strategy of a treating physician who was encouraged to follow the Recommendations for the Medical Management of Osteoarthritis of the Hip and Knee proposed by the American College of Rheumatology' (Altman et al., 2000).

An adverse event was described to the patient as 'an unusual problem (that) may occur only once or repeatedly. If your medical condition gets worse or you develop a new medical condition then this is an unusual problem'. All adverse events, whether considered related to the treatment or not, were recorded. The severity of the event, the outcome, the action taken and the possible relationship to hylan G-F 20 was determined. The authors established guidelines to determine the relationship between time of adverse event and the treatment component. Any adverse event occurring within the first hour was rated as related to the injection procedure. An adverse event appearing after one hour but before 48 hours was probably due to hylan G-F 20, while any adverse event after 48 hours was associated with the disease status.

Initially, events in the viscosupplementation group were reported as occurring either within 48 hours of injection or greater than 48 hours after injection. Adverse events for the appropriate care only group were recorded as occurring over the entire study period. Therefore, for comparison purposes adverse events at any time after injection were summed for the hylan G-F 20 plus appropriate care group (Table 8). The number of local adverse events experienced by the hylan G-F 20 group was almost three times that experienced by the appropriate care only group. Patients treated with hylan G-F 20 experienced twice the risk of knee pain, three times the risk of swelling and nine times the risk of stiffness. However, the investigators determined that at least 70 per cent of all the local adverse events experienced by the hylan G-F 20 group were attributable to the injection procedure. The local adverse events probably directly related to hylan G-F 20 were determined to occur in 11 per cent of cases, and remotely related in 7 per cent of cases.

Patient global assessment revealed that patients in the hylan G-F 20 plus appropriate care group had a 40 per cent lower risk of side effects than the appropriate care only group (Table 8). Patients in the combined therapy group had a 50 per cent reduced risk of at least one gastrointestinal adverse event compared to the appropriate care only group (Table 8).

While comprehensive in its attention to data collection, there are several weaknesses of this study which suggest that the results should be treated with some caution. This study was initiated and financially supported by the company that distributes hylan G-F 20 in Canada. Further, the study is completely unblinded and any assessment of adverse events and their association with treatment by unblinded investigators has the considerable risk of bias. This is especially true when investigators are determining whether there is any association of hylan G-F 20 with the occurrence of an adverse event.

Table 8 Local adverse events, hylan G-F 20 plus appropriate care vs appropriate care only

Study	Quality[a]	Outcomes	Treatment group				Relative risk		Number needed to harm	
			Hylan G-F 20 plus appropriate care		Appropriate care					
			r/n[b]	%	r/n	%	RR	95% CI	NNH	95% CI
Raynauld (2000)	QS: 23/27 CI: 1 P: 100%	Pain	55/127	43	25/128	19	2.2	1.5-3.3	4	3-8
		Swelling	19/127	15	6/128	5	3.2	1.3-7.7	10	6-33
		Effusion	1/127	0.8						
		Pain and swelling	12/127	9						
		Stiffness	9/127	7	1/128	0.8	9.1	1.2-70.5	17	9-100
		Other	3/127	2						
		Total local adverse events	78/127	61	29/128	23	2.7	1.9-3.8	3	2-4
		Total side effects	48/127	38	76/128	59	0.6	0.5-0.8	NNTB 5	NNTB 3-10
		Gastrointestinal adverse events	15/127	12	32/128	25	0.5	0.3-0.8	NNTB 8	NNTB 4-25

[a] Quality score (QS) determined from checklist created by Downs and Black (Downs & Black 1998); clinical importance (CI) scored from 1 to 4 with 1 = clinically important benefit for the full range of plausible estimates, 2 = point effect clinically important but confidence interval includes clinically unimportant effects, 3 = confidence interval does not include any clinically important effects, 4 = range of estimates include clinically important effects but range of estimates compatible with no effect or harmful effect (National Health and Medical Research Council 2000); power (P). [b] r/n = number of subjects with condition / number of subjects in intervention group.

Hylan G-F 20 vs low MW HA

Finally, a multicentre double-blind RCT (quality score 19/27) compared the effectiveness of hylan G-F 20 with a low MW HA (~750 kDa) in 38 and 35 patients respectively over a 12-week period (Wobig et al 1999). The occurrence of adverse events was investigated by interviewing the patient at each visit. The investigator then determined the likelihood that the reported or observed event was related to the treatment. Each event was also described according to whether the event was local or systemic, how long the event had lasted, and any treatment measures that resulted. Any adverse events localised to the knee were categorised as pain, swelling or effusion. At the end of the study (12 weeks), three local adverse events were noted, two (5%) in the hylan G-F 20 group (swelling after first injection) and one (3%) in the HA group (characterised as joint pain). Therefore, in this study there was low incidence of local adverse events in both groups and the difference between the two treatment arms was not significant (RR 1.8, 95% CI 0.2-19.4; NNH 50, 95% CI NNTB 17 to ∞ to NNTH 9). No systemic adverse events were noted over this time period. As this study is underpowered with very wide confidence intervals, no definitive conclusions can be made.

Summary: The safety of hylan G-F 20

Based on the four studies included in this review there is little consistent evidence for the safety of hylan G-F 20 when compared to NSAIDs, appropriate care or a lower MW hyaluronic acid. In a single study with the most comprehensive adverse event collection protocol and longest follow-up of any included study, an incidence of up to 61 per cent for local adverse events was reported in the group receiving hylan G-F 20 and appropriate care as compared to appropriate care only (Raynauld et al 2000). However, unblinded assessment determined that only 18 per cent of these events were due to treatment with hylan G-F 20.

The remaining studies reported a wide-ranging incidence of adverse events (3-14%); however, the rigour of adverse event data collection in these studies is questionable. Therefore, results only suggest that viscosupplementation with hylan G-F 20 produces a similar incidence of local adverse events as injection with lower MW hyaluronic acid viscosupplement or with NSAIDs. Hylan G-F 20 combined with appropriate care showed a higher incidence of local adverse events when compared with appropriate care only. Conversely, hylan G-F 20 was found to have a lower incidence of systemic adverse events than NSAIDs. There was no difference in overall systemic adverse events when hylan G-F 20 combined with appropriate care was compared with appropriate care only. Unfortunately, due to faulty study design, the results of this article must be regarded with caution.

The safety of viscosupplementation could not be compared with COX-2 as no studies comparing these two treatments were found.

Is it effective?

The primary effectiveness outcome measures that are addressed in this review have been identified in the OMERACT III consensus conference paper (Bellamy et al 1997) (Figure 4). As already described, the core or primary set of outcome measures essential to an evaluation of the effectiveness of viscosupplementation are:

Figure 4 Core outcome measures for OA as defined by the OMERACT III consensus statement

Pain (this measure is considered the primary outcome measure in determining the effectiveness of an intervention for the treatment of knee OA)

The most common measurement tool for pain used in studies included in this review was the Visual Analogue Scale (VAS). In general this was a 10 cm (or 100 mm) horizontal line in which the patient or the assessor recorded the level of perceived pain by making a vertical line somewhere between the two ends of the line. The zero cm (or mm) point would represent no pain and the 10 cm (100 mm) end would represent the most extreme pain imaginable. The distance from 0 cm (mm) to the mark was measured.

Another common measure of patient pain and function used in the included studies was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). As its name suggests it is specifically designed for OA sufferers. The tool consists of three subscales:

A. Pain: Five questions that can each be scored on a 100 mm VAS or as Likert scales on a scale of 0 (no pain) to 4 (extreme pain). Scores can be summed and a mean VAS score calculated, or scored from 0 to 20 (Likert model), or each question's value can be kept separate.

B. Stiffness: Two questions to rate severity of stiffness scored on 100 mm VAS or as Likert scales on a scale of 0 (none) to 4 (extreme). Scores can be summed and a mean VAS score calculated, or scored from 0 to 20 (Likert model), or each question's value can be kept separate.

C. Physical function: Seventeen questions rating degree of difficulty with defined physical activities. Can either be scored on 100 mm VAS or as Likert scales on a scale of 0 (none) to 4 (extreme). Scores can be summed and a mean VAS score calculated, or scored from 0 to 20 (Likert model), or each question's value can be kept separate.

Physical function

In many instances this outcome was measured with the WOMAC C physical function subscale (see above for description).

Patient global assessment

Joint imaging radiography, to evaluate the extent of joint space narrowing if trials are long-term (≥1 year).

Outcome measures categorised as secondary (ie desirable but not essential) to an assessment of the effectiveness of viscosupplementation of the knee are:

- quality of life / utility measures
- global assessment performed by a medical practitioner

Other outcome measures such as inflammation, stiffness, biologic markers and analgesic use are considered useful but optional.

In addition to these outcomes the supporting committee decided that the length of time until total knee replacement surgery would also be an important outcome to consider if it was reported.

Hyaluronic acid

The format of this section is to look first at studies that examined the effectiveness of hyaluronic acid (HA) in comparison to the identified comparators (IA corticosteroids, NSAIDs, COX-2 inhibitors) and then to examine the effectiveness of hylans against these same comparators. Within each comparison, primary and then secondary outcome measures were addressed as identified in the OMERACT III consensus conference (see Figure 4). Data from studies that also had a placebo arm of the trial are not included in the discussion of viscosupplement effectiveness. Tables 9 and 10 summarise the conclusions of each treatment comparison as determined by the highest quality studies available.

Table 9 Summary of HA effectiveness vs comparators[a]

Intervention(s)	Outcome measures	Study	Quality	Result
HA vs NSAID	Pain	Altman (1998)	QS: 26/27, CI: 4, P: under-powered	No difference at 26 weeks
	Physical function	Petrella (2002)	QS: 22/27, CI: 4, P: under-powered	No difference at 4 weeks
	Stiffness	Petrella (2002)	QS: 22/27, CI: 4, P: under-powered	No difference at 4 weeks
HA vs IA corticosteroids	Pain	Pietrogrande 1991	QS: 18/27, CI: 4, P: 60%	Trend for reduced risk under load at 60 days; no difference for night, touch or pain at rest at 60 days
	Physical function	Tekeoglu (1998)	QS: 19/27, CI: 1, P: 93%	Significant improvement at 15 weeks
	Patient global assessment	Tekeoglu (1998)	QS: 19/27, CI: 1, P: 93%	Higher % of good to very good ratings at 15 weeks
		Pietrogrande (1991)	QS: 18/27, CI: 4, P: 60%	Higher % of good to very good ratings at 60 days
	Stiffness or joint motion	Tekeoglu (1998)	QS: 19/27, CI: 1, P: 93%	No difference at 3 weeks or 15 weeks
	Analgesic or NSAID consumption (as rescue therapy)	Tekeoglu (1998)	QS: 19/27, CI: 1, P: 93%	No difference at 3 weeks

[a] This table summarises the results of only the highest quality studies available for each comparison and outcome measure, and results are described in favour of HA.

Table 10 Summary of hylan G-F 20 effectiveness vs comparators[a]

Intervention(s)	Outcome measures	Study	Quality	Result
Hylan G-F 20 vs NSAID	Pain	Dickson (2001)	QS: 24/27, CI: 4, P: under-powered	Greater improvement in scores for pain at night, walking on a flat surface, pain sitting or lying at 12 weeks
	Pain on motion	Adams (1995)	QS: 22/27, CI: 4, P: under-powered	Greater number of patients symptom free of pain with motion at 26 weeks
	Physical function	Dickson (2001)	QS: 24/27, CI: 4, P: under-powered	No difference in change in function scores at 12 weeks
	Stiffness	Dickson (2001)	QS: 24/27, CI: 4, P: under-powered	No difference in mean change in stiffness scores at 12 weeks
	Overall opinion of treatment	Dickson (2001)	QS: 24/27, CI: 4, P: under-powered	No trend for improvement distribution of opinion scores at 12 weeks
	Paracetamol use	Dickson (2001)	QS: 24/27, CI: 4, P: under-powered	No difference in use at any time point up to 12 weeks
Hylan G-F 20 and NSAID vs NSAID only	Pain	Adams (1995)	QS: 22/27, CI: 4, P: under-powered	Reduced mean pain scores at 26 weeks Greater number of patients symptom free of pain with motion, at rest and at night at 26 weeks
Hylan G-F 20 vs low MW HA	Pain	Wobig (1999)	QS: 19/27, CI: NE, P: NE	Data unavailable for conclusion
Hylan G-F 20 and appropriate care vs appropriate care only	Pain	Raynauld (2000)	QS: 23/27, CI: 1, P: 100%	Lower mean pain score at 1 year
	Physical function	Raynauld (2000)	QS: 23/27, CI: 1, P: 100%	Lower mean physical function score at 1 year
	Patient global assessment	Raynauld (2000)	QS: 23/27, CI: 1, P: 100%	Significant positive trend for improvement in assessment rating for overall health and treatment knee
	Stiffness	Raynauld (2000)	QS: 23/27, CI: 1, P: 100%	Lower mean stiffness score at 1 year

[a] This table summarises the results of only the highest quality studies available for each comparison and outcome measure, and results are described in favour of hylan G-F 20.

Hyaluronic acid vs NSAIDs

One study of over 160 patients per group (Altman & Moskowitz 1998) and another of only 25 per group (Petrella et al 2002) compared the effectiveness of HA with NSAIDs in patients suffering from OA of the knee. However, due to differences in study design, analysis and presentation of results, these two studies could not be combined in a meta-analysis.

Pain

In the highest quality study the primary outcome measure was patient-recorded pain on a 100 mm VAS after completing a 50-foot walk (Altman & Moskowitz 1998). This study had a high dropout rate (35%, 58/163) in the HA group and a lower (31%,51/161) dropout rate in the NSAID group by the end of the 26-week study period. For the

purposes of an intention-to-treat (ITT) analysis, the authors included the last recorded score from the VAS obtained from these dropouts in an analysis of mean VAS score at 26 weeks. There was no significant difference in between-group VAS scores at either baseline or 26 weeks follow-up (Table 11). (Petrella et al 2002)

Table 11 VAS and WOMAC outcome scores for pain with treatment (HA vs NSAIDs)

Study	Quality[a]	Outcomes	Treatment group				Mean difference		P value
			HA		NSAID				
			mean	SD	mean	SD	mean difference	95% CI	
Altman (1998)	QS: 26/27 CI: 4 P: under-powered	Patient pain after 50-ft walk (VAS, mm) baseline	54 (n=163)	29	54 (n=162)	28	0	-6.2-6.2	1.0
		Patient pain after 50-ft walk (VAS, mm) 26 weeks	27[b] (n=160)	27	25 (n=160)	28	2	-4.0-8.0	0.5
Petrella (2002)	QS: 22/27 CI: 4 P: under-powered	Self-report pain VAS–WOMAC	n=25		n=26				
		Baseline (cm)	3.32	2.42	4.22	3.25	-0.9	-2.5-0.7	0.3
		4 weeks (cm)	2.42	2.34	2.86	2.75	-0.4	-1.9-1.0	0.5
		Self-report pain VAS							
		Baseline (cm)	3.29	1.75	3.34	1.39	-0.05	-0.9-0.8	0.9
		4 weeks (cm)	2.6	1.64	1.58	1.34	1.0	0.2-1.9	0.02
		Self-paced walking (SPW) pain VAS							
		Baseline (cm)	3.94	2.79	3.78	3.42	0.2	-1.6-1.9	0.8
		4 weeks (cm)	2.89	1.72	1.81	1.72	1.1	0.1-2.0	0.03
		Self-paced stepping (SPS) pain VAS							
		Baseline (cm)	3.49	3.06	5.17	3.18	-1.7	-3.4-0.1	0.06
		4 weeks (cm)	1.67	1.52	2.46	1.41	-0.8	-1.6-0.0	0.06

[a] Quality score (QS) determined from checklist created by Downs and Black (Downs & Black 1998); clinical importance (CI) scored from 1 to 4 with 1 = clinically important benefit for the full range of plausible estimates, 2 = point effect clinically important but confidence interval includes clinically unimportant effects, 3 = confidence interval does not include any clinically important effects, 4 = range of estimates include clinically important effects but range of estimates compatible with no effect or harmful effect (National Health and Medical Research Council 2000); power (P). [b] Values at end of study for both Hyalgan® and Naproxen group obtained from last observed value of each patient (ITT analysis).

In a categorical assessment of pain on patients who completed treatment (ie not ITT) a strong trend indicated almost twice as many patients in the HA group reported no pain at 26 weeks compared to patients treated with NSAIDs (Table 12). However, due to the number of dropouts not included in this analysis this result should be treated with caution. Patients were considered as improved if their VAS score had reduced by 20 or more millimetres from baseline to 26 weeks. In an ITT analysis, no difference was found

between either treatment group in the number of patients who improved from baseline to 26 weeks (Table 12).

In a study where results were only reported for patients who completed treatment, numerous measures of patient evaluated pain were recorded (Petrella et al 2002). Mean patient-reported pain measured by VAS (100 mm scale) at 4 weeks after the start of treatment was significantly lower in the NSAID treatment group compared to the HA group (Table 11). Similarly, VAS scored self-paced walking (SPW) pain was found to be significantly lower in the NSAID group at 4 weeks compared to the HA group. No significant difference between groups was found for self-report pain using the WOMAC pain subscale or the self-pain stepping (SPS) VAS scores in comparisons between groups at 4 weeks. The authors claim that week 12 VAS measures were relatively unchanged from week 4 values, resulting in similar significant differences between groups. However, week 12 values were not presented in the article and therefore this conclusion could not be independently verified. This study also looked at the effectiveness of combining HA with NSAID treatment. No significant differences in pain scores were found when combined treatment was compared to NSAID treatment only at 4 weeks (Table 13). No week 12 data were presented but the authors claim that the WOMAC VAS score improved further compared to week 4. No other pain measure was claimed to have improved at week 12 for the combined therapy group. Due to weaknesses of small sample size, a failure to perform an intention-to-treat analysis and a very short follow-up period with no report of week 12 data, results from any of the comparisons should be regarded with caution.

Table 12 Number of patients with outcome of no pain or classed as improvers (HA vs NSAIDs)

Study	Quality	Outcomes	Treatment group				Relative risk		Number needed to treat	
			HA		Corticosteroid					
			r/n[a]	%	r/n	%	RR	95% CI	NNT	95% CI
Altman (1998)	26/27	No pain								
		Baseline	1/105	0.9	0/113	0	NE		105	NNTH 111 to ∞ to NNTB 36
		26 weeks	23/105	21.9	13/113	11.5	1.90	1.0-3.6	10	5-200
		Number of patient improvers (≥20 mm reduction in VAS score) baseline to 26 weeks	59/164	36.0	51/163	31.3	1.15	0.8-1.6	21	NNTH 18 to ∞ to NNTB 7

[a] r/n = number of subjects with condition / number of subjects in intervention group.

Table 13 VAS and WOMAC outcome scores for pain with treatment (HA and NSAIDs vs NSAID only)

Study	Quality	Outcomes	Treatment group				Mean difference		P value
			HA and NSAID		NSAID				
			mean n=29	SD	mean n=26	SD	Mean difference	95% CI	
Petrella (2002)	22/27	Self-report pain VAS–WOMAC							
		Baseline (cm)	3.65	2.73	4.22	3.25	-0.57	-2.2-1.0	0.5
		4 weeks (cm)	2.59	2.59	2.86	2.75	-0.27	-1.7-1.2	0.7
		Self-report pain VAS							
		Baseline (cm)	3.60	1.85	3.34	1.39	0.26	-0.6-1.1	0.6
		4 weeks (cm)	1.56	1.34	1.58	1.34	-0.02	-0.7-0.7	0.9
		Self-paced walking (SPW) pain VAS							
		Baseline (cm)	3.84	2.92	3.78	3.42	0.06	-1.6-1.8	0.9
		4 weeks (cm)	2.05	1.32	1.81	1.72	0.24	-0.6-1.1	0.6
		Self-paced stepping (SPS) pain VAS							
		Baseline (cm)	4.50	3.29	5.17	3.18	-0.67	-2.4-1.1	0.4
		4 weeks (cm)	3.12	1.76	2.46	1.41	0.66	-0.2-1.5	0.1

Physical function

One study comparing HA to NSAIDs measured patient function (Petrella et al 2002). Using the WOMAC disability subscale the authors determined that treatment with HA did not significantly improve physical function compared to treatment with NSAIDs (Table 14). Although the study continued on to week 12, no data for any time point past 4 weeks was provided. Again, combined therapy was also compared to NSAIDs alone (Table 15). No significant difference in disability scores was found between combined therapy and NSAID only treatment. Due to the small sample size and very short follow-up, the results of this analysis should be regarded with caution.

Table 14 Disability and stiffness scores (HA vs NSAIDs)

Study	Quality	Outcomes	Treatment group				Mean difference		P value
			HA		NSAID				
			Mean (n=25)	SD	Mean (n=26)	SD	Mean difference	95% CI	
Petrella (2002)	22/27	WOMAC disability subscale							
		Baseline (cm)	4.10	2.71	4.32	3.22	-0.22	-1.9-1.5	0.8
		4 weeks (cm)	2.45	2.23	2.76	2.61	-0.31	-1.7-1.1	0.6
		WOMAC stiffness subscale							
		Baseline (cm)	4.60	2.45	5.14	3.21	-0.54	-2.1-1.1	0.5
		4 weeks (cm)	2.95	2.41	2.80	2.72	0.15	-1.3-1.6	0.8

Table 15 Disability and stiffness scores (HA and NSAID vs NSAID only)

Study	Quality	Outcomes	Treatment group				Mean difference		P value
			HA and NSAID		NSAID				
			Mean (n=29)	SD	Mean (n=26)	SD	mean difference	95% CI	
Petrella (2002)	22/27	WOMAC disability subscale							
		Baseline (cm)	3.90	2.72	4.32	3.22	-0.42	-2.0-1.2	0.6
		4 weeks (cm)	2.73	2.64	2.76	2.61	-0.03	-1.4-1.4	1.0
		WOMAC stiffness subscale							
		Baseline (cm)	4.82	2.88	5.14	3.21	-0.32	-2.0-1.3	0.7
		4 weeks (cm)	2.71	2.70	2.80	2.72	-0.09	-1.6-1.4	0.9

Stiffness

Stiffness was also evaluated in the Petrella study (Petrella et al 2002) using the WOMAC stiffness subscale. No significant improvement in stiffness scores was found for HA treatment when compared to NSAID therapy over the 4-week period (Table 14). Week 12 data were not provided, but the authors state that no further improvement in scores was noted for either group at this time point. Comparison of combined treatment with NSAIDs alone (Table 15) showed no significant differences in WOMAC stiffness subscale scores in either comparison.

Other measures

Altman also examined several other secondary outcome measures (Altman & Moskowitz 1998). No data were provided for any of these measures.

Summary: The effectiveness of HA compared with NSAIDs

The effectiveness of HA at reducing pain compared to NSAIDs is based primarily on one study of high quality that was unfortunately underpowered (Altman & Moskowitz 1998). This study found no difference in pain scores at 26 weeks follow-up. Improvement in physical function and stiffness using HA compared to NSAIDs was measured in one study of somewhat lower quality (Petrella et al 2002) which was also underpowered. No differences in either of these outcomes were seen at 4 weeks after initial treatment. It should be noted that because these studies were underpowered, any significant difference between treatment groups may have gone undetected.

Hyaluronic acid vs intra-articular corticosteroids

Four studies of between 20 and 45 patients per group (Leardini et al 1987; Leardini et al 1991; Tekeoglu et al 1998; Pietrogrande et al 1991) compared the effectiveness of a hyaluronic acid with an IA corticosteroid. Three studies compared the HA Hyalgan® with methylprednisolone acetate (MPA) (Leardini et al 1987; Leardini et al 1991; Pietrogrande et al 1991) while the fourth compared Orthovisc™ with Betamethasone (Tekeoglu et al 1998). All four of these studies are of lower quality than those examining HA with NSAIDs, primarily due to presentation of primary outcomes in graphical form only in two of the studies and generally poor description of recruitment and lack of blinding in all of the studies. These weaknesses raise questions of study validity. Again, due to differences in study design and presentation of results, no meta-analysis could be performed for any outcomes within this treatment comparison.

Pain

Spontaneous pain (not defined by the authors) was the primary outcome variable in three studies and was measured using a 100 mm VAS (Pietrogrande et al 1991; Leardini et al 1991; Leardini et al 1987). However, tabulated data were provided in only one poor quality study (Leardini et al 1987). In this study all patients were included in the analysis up to 60 days follow-up. There was no significant difference in VAS pain scores at 60 days or at 1 year follow-up between the two treatments (Table 16). However, at the 1 year follow-up some patients had dropped out and were not included in the analysis. The internal validity was limited as it was unclear as to whether it was the patient or the assessor who measured patient pain in each instance and the study size was small.

Table 16 Spontaneous pain scores, number of joints (HA vs corticosteroid)

Study	Quality[a]	Outcomes	Treatment group				Mean difference		P value
			HA		Corticosteroid				
			mean (n)	SD	mean (n)	SD	mean difference	95% CI	
Leardini (1987)	QS: 15/27 CI: 4 P: under-powered	Spontaneous pain number of joints (mm)							
		Baseline	41.3 (20)	21.0	33.4 (20)	21.9	7.9	-5.8-21.6	0.2
		60 days	11.2 (20)	20.6	9.1 (20)	21.0	2.1	-11.2-15.4	0.7
		1 year	20.3 (15)	25.6	17.8 (17)	24.7	2.5	-15.7-20.7	0.8

[a] Quality score (QS) determined from checklist created by Downs and Black (Downs & Black 1998); clinical importance (CI) scored from 1 to 4 with 1 = clinically important benefit for the full range of plausible estimates, 2 = point effect clinically important but confidence interval includes clinically unimportant effects, 3 = confidence interval does not include any clinically important effects, 4 = range of estimates include clinically important effects but range of estimates compatible with no effect or harmful effect (National Health and Medical Research Council 2000); power (P).

The remaining two studies provided the spontaneous pain scores in graphical form only and therefore the raw data could not be extracted (Pietrogrande et al 1991; Leardini et al 1991). In both studies spontaneous pain was claimed to be significantly lower in the group treated with HA compared to the MPA treatment group at 60 days follow-up.

Pain under load and pain with walking was evaluated in three studies. When recorded as number of joints presenting with pain (Leardini et al 1987) there were no significant differences between the two treatment groups at any time point (Table 17).

Table 17 Number of painful joints (HA vs corticosteroid)

Study	Quality	Outcomes	Treatment group				Relative risk		Number needed to treat	
			HA[a]		Corticosteroid[b]					
			r/n[c]	%	r/n	%	RR	95% CI	NNT	95% CI
Leardini (1987)	15/27	Pain under load (number of joints)								
		Baseline	18/20	90	19/20	95	0.95	0.8-1.1	20	NNTH 5 to ∞ to NNTB 10
		60 days	6/20	30	7/20	35	0.9	0.3-2.1	20	NNTH 3 to ∞ to NNTB 5
		1 year	8/15	53	11/17	65	0.8	0.5-1.5	10	NNTH 2 to ∞ to NNTB 5
		Walking pain (number of joints)								
		Baseline	20/20	100	20/20	100	1	1-1	NE	
		60 days	8/20	40	10/20	50	0.8	0.4-1.6	10	NNTH 2 to ∞ to NNTB 4
		1 year	11/15	73	12/17	70	1.0	0.7-1.6	33	NNTH 3 to ∞ to NNTB 3

[a] 20 joints evaluated in 20 patients. [b] 20 joints evaluated in 16 patients. [c] r/n = number of subjects with condition / number of subjects in intervention group.

Two other studies analysed patients that presented with pain under load (Leardini et al 1991; Pietrogrande et al 1991). Despite very similar protocols, meta-analysis revealed significant heterogeneity that could not be explained; Therefore, these studies were not combined. The study with the larger sample size (45 per group) (Pietrogrande et al 1991) found a trend for little or no pain under load at 60 days with HA compared to MPA treated patients (Table 18). No significant differences were found in pain scores for night, rest or touch pain between the two treatment arms.

Table 18 Number of patients with specific pain score of 0-1 (little or no pain) for HA and corticosteroid treatment arms

Study	Quality[a]	Outcomes	Treatment group				Relative risk		Number needed to treat	
			HA		Corticosteroid					
			r/n[b]	%	r/n	%	RR	95% CI	NNT	95% CI
Leardini (1991)	QS: 18/27[c] CI: 4 P: 70%[d]	No night pain baseline	8/20	40	3/20	8	2.7	0.8-8.6	4	2-10
		No night pain day 60	20/20	100	16/20	80	1.2	1.0-1.5	5	2-50
		No rest pain baseline	0/20	0	0/20	0	NE		NE	
		No rest pain day 60	14/20	70	5/20	25	2.8	1.2-6.3	2	1-6
		No pain under load baseline	0/20	0	0/20	0	NE		NE	
		No pain under load day 60	7/20	35	0/20	0	NE		3	2-7
		No touch pain baseline	3/20	8	3/20	8	1	0.2-4.4	∞	NE
		No touch pain day 60	18/20	90	9/20	45	2	1.2-3.3	2	1-5
Pietrogrande (1991)	QS: 18/27[c] CI: 4 P: 60% [c]	No night pain baseline	14/45	31.1	18/45	40.0	0.78	0.4-1.4	NNH 11	NNTH 3 to ∞ to NNTB 9
		No night pain day 60	44/44	100	43/45	95.5	1.05	1.0-1.1	23	9-62
		No rest pain baseline	11/45	24.4	14/45	31.1	0.78	0.4-1.5	NNH 14	NNTH 4 to ∞ to NNTB 8
		No rest pain day 60	43/44	97.7	42/45	93.3	1.05	1.0-1.1	23	NNTH 24 to ∞ to NNTB 8
		No pain under load baseline	2/45	4.0	2/45	4	1.0	0.1-6.8	NE	
		No pain under load day 60	31/44	70.4	22/45	48.9	1.44	1.0-2.0	5	2-50
		No touch pain baseline	17/45	37.8	23/45	51.1	0.74	0.5-1.2	NNH 8	NNTH 3 to ∞ to NNTB 14
		No touch pain day 60	40/44	90.9	38/45	84.4	1.08	0.9-1.3	17	5-14

[a] Quality score (QS) determined from checklist created by Downs and Black (Downs & Black 1998); clinical importance (CI) scored from 1 to 4 with 1 = clinically important benefit for the full range of plausible estimates, 2 = point effect clinically important but confidence interval includes clinically unimportant effects, 3 = confidence interval does not include any clinically important effects, 4 = range of estimates include clinically important effects but range of estimates compatible with no effect or harmful effect (National Health and Medical Research Council 2000); power (P). [b] r/n = number of subjects with condition / number of subjects in intervention group. [c] Power (P) and clinical importance (CI) calculated for pain under load at 60 days. [d] Underpowered.

A smaller study (Leardini et al 1991) also found a trend favouring HA treated patients for no pain under load at 60 days follow-up compared to MPA-treated patients (Table 18). The results showed that for every three patients treated one more would benefit from no

pain under load at 60 days than if all patients were treated with the IA corticosteroid MPA.

Physical function

One study measured patient physical function after treatment with either HA or betamethasone (Tekeoglu et al 1998). Using the WOMAC physical functional subscale, patients in the HA group had significantly lower functional scores (indicating better function) at 15 weeks follow-up (Table 19). Despite a determination of adequate power, a lack of blinding indicates these results should be interpreted with caution.

Table 19 WOMAC functional subscale scores (HA vs corticosteroid)

Study	Quality[a]	Outcomes	Treatment group				Mean difference		P value
			HA		Corticosteroid				
			mean (n=20)	SD	mean (n=20)	SD	mean difference	95% CI	
Tekeoglu (1998)	QS: 19/27 CI: 1 P: 93%	WOMAC physical function subscale (mm)							
		Baseline	45.5	8.2	45.6	10.3	-0.01	-6.0-5.8	0.97
		3 weeks	34.3	8.8	31.3	8.6	3.0	-2.6-8.6	0.28
		15 weeks	30.9	8.7	39.9	7.9	-9.0	-14.3- -3.7	0.0015

[a] Quality score (QS) determined from checklist created by Downs and Black (Downs & Black 1998); clinical importance (CI) scored from 1 to 4 with 1 = clinically important benefit for the full range of plausible estimates, 2 = point effect clinically important but confidence interval includes clinically unimportant effects, 3 = confidence interval does not include any clinically important effects, 4 = range of estimates include clinically important effects but range of estimates compatible with no effect or harmful effect (National Health and Medical Research Council 2000); power (P).

Patient global assessment

This outcome measure was assessed in three studies, two comparing HA to MPA (Pietrogrande et al 1991; Leardini et al 1991) and one with betamethasone (Tekeoglu et al 1998). The two better quality studies found that patients were twice as likely to rate HA treatment effectiveness as good to very good compared with patients treated with betamethasone at 15 weeks or MPA at 60 days follow-up (Table 20) (Pietrogrande et al 1991; Tekeoglu et al 1998). In the lower quality study (Leardini et al 1991) results are suggestive of a benefit of HA treatment but are inconclusive. However, due to lack of patient blinding in all of these studies, the results should be treated with considerable care.

Table 20 Patient rating of treatment effectiveness as good to very good (HA vs corticosteroid)

Study	Quality	Outcomes	Treatment group				Relative risk		Number needed to treat	
			HA		Corticosteroid					
			r/n[a]	%	r/n	%	RR	95% CI	NNT	95% CI
Tekeoglu (1998)	19/27	3 weeks	10/20	50.0	12/20	60.0	0.83	0.47-1.47	NNH 10	NNTH 2 to ∞ to NNTB 5
		15 weeks	15/20	75	8/20	40	1.87	1.03-3.39	3	1-17
Pietrogrande (1991)	18/27	21 days	16/45	35.5	19/45	42.2	0.84	0.50-1.42	NNH 14	NNTH 4 to ∞ to NNTB 8
		60 days	31/45	69.0	15/45	33.3	2.07	1.31-3.26	3	2-6
Leardini (1991)	18/27	21 days	9/20	45.0	10/20	50.0	0.90	0.47-1.73	NNH 20	NNTH 3 to ∞ to NNTB 4
		60 days	10/20	50.0	7/20	35.0	1.43	0.68-2.99	NNH 7	NNTH 7 to ∞ to NNTB 2

[a] r/n = number of subjects with condition / number of subjects in intervention group.

Stiffness

This outcome measure was evaluated in two studies (Pietrogrande et al 1991; Leardini et al 1991). Both studies presented the data in graphical format and therefore the raw data could not be extracted. Stiffness was evaluated in both studies in terms of duration (in minutes) upon waking in the morning. Pietrogrande (Pietrogrande et al 1991) claimed that there were significant decreases in joint stiffness from baseline to 60 days follow-up and that HA treated patients had a significantly reduced time of joint stiffness at 60 days follow-up compared to patients treated with MPA.

Joint motion was assessed in all four studies and expressed as number of degrees of flexion and extension. Only two studies provided data that could be extracted (Leardini et al 1987; Tekeoglu et al 1998), and results were contradictory. At no measured time point did HA or betamethasone treatment produce significantly improved joint movement over the other treatment (Table 21) (Tekeoglu et al 1998). Comparison of MPA and HA in the other study showed significantly greater joint movement in the HA group at both baseline and 60 days, but not at 21 days or 1 year (Table 21) (Leardini et al 1987). Two other studies comparing HA and MPA stated either that there was no significant differences between the groups at any time point (Leardini et al 1991) or that there was a significant improvement in joint movement in the HA group compared to the MPA group at 21 and 60 days follow-up (Pietrogrande et al 1991). However, these results were presented in graphical form only. Lack of blinding and small study population sizes suggest that the results of all these studies should be viewed with caution.

Table 21 Joint motion in degrees (HA vs corticosteroids)

Study	Quality	Outcomes	Treatment group				Mean difference		P value
			HA		Corticosteroid				
			mean	SD	mean	SD	mean difference	95% CI	
Tekeoglu (1998)	19/27	Joint movement (degrees)	n=20		n=20				
		Baseline	110.5	22.7	116.0	14.4	-5.5	-17.7-6.7	0.4
		3 weeks	117.3	19.2	122.2	11.4	-4.9	-15.0-5.2	0.3
		15 weeks	121.2	16.3	128.2	10.2	-7.0	-15.7-1.7	0.1
Leardini (1987)	15/27	Active movement (degrees)	n=20		n=20				
		Baseline	108.4	2.6	104.2	2.2	4.2	2.6-5.7	<0.001
		21 days	113.4	2.9	112.4	3.4	1.0	-1.0-3.0	0.3
		60 days	116.7	2.8	114.3	2.5	2.4	0.7-4.1	0.007
		1 year[a]	109.6	5.9	108.1	4.4	1.5	-2.0-5.0	0.4

[a] At 1 year only 15 patients in the HA and 17 in the MPA group were analysed.

Other measures

Analgesic or NSAID consumption was evaluated in three studies (Leardini et al 1991; Pietrogrande et al 1991; Tekeoglu et al 1998). In the larger study (Pietrogrande et al 1991), patients in the HA treatment group were found to consume significantly more analgesia or NSAIDs at 21 days, with a trend towards more at 60 days follow-up (Table 22). In the two smaller studies no significant differences in analgesic or NSAID consumption were noted between the HA and corticosteroid treatment arms at any time point up to 60 days (Leardini et al 1991) or 15 weeks follow-up (Tekeoglu et al 1998) (Table 22).

Table 22 No analgesic or NSAID consumption (HA vs corticosteroids)

Study	Quality	Outcomes	Treatment group				Relative risk		Number needed to treat	
			HA		Corticosteroid					
			r/n[a]	%	r/n	%	RR	95% CI	NNT	95% CI
Tekeoglu (1998)	19/27	baseline	4/20	20.0	2/20	10.0	2	0.4-9.7	10	NNTH 8 to ∞ to NNTB 3
		3 weeks	11/20	55.0	10/20	50.0	1.1	0.6-2.0	20	NNTH 4 to ∞ to NNTB 3
		15 weeks	6/20	30.0	1/20	5.0	6	0.8-45.4	4	2-50
Pietrogrande (1991)	18/27	baseline	23/45	51.1	27/45	60.0	0.8	0.6-1.2	NNH 11	NNH 3 to ∞ to NNTB 9
		21 days	35/45	77.8	44/45	97.8	0.8	0.7-0.9	NNH 5	NNTH 3-NNTH 14
		60 days	36/44	81.8	42/45	93.3	0.9	0.7-1.0	NNH 9	NNTH 4 to ∞ to NNTB 50
Leardini (1991)	18/27	baseline	0/20	0.0	0/20	0	NE			
		21 days	1/20	5.0	3/20	15.0	0.3	0.04-2.9	NNH 10	NNTH 3 to ∞ to NNTB 12
		60 days	7/20	35.0	5/20	25.0	1.4	0.5-3.7	10	NNTH 5 to ∞ to NNTB 3

[a] r/n = number of subjects with condition / number of subjects in intervention group.

Summary: The effectiveness of HA compared with IA corticosteroids

Due to the poor quality of the majority of included studies, conclusions were based on only two of the studies (Leardini et al 1991; Pietrogrande et al 1991; Tekeoglu et al 1998). From Pietrogrande et al (1991) a trend for reduced risk of pain under load at 60 days is evident. Tekeoglu et al (1998) found improved physical function at 15 weeks in the HA treated group. However, no other measures of pain, stiffness, global assessment or analgesic consumption were found to be improved in the HA treated groups in either study, compared to those given IA corticosteroids.

Summary: The overall effectiveness of HA

In conclusion, from the limited evidence available, HA is found to be no more effective than NSAIDs at improving patient perceived pain scores, physical function, patient global assessment or stiffness scores. In unblinded patient reports HA was found to be no more effective than IA corticosteroids for alleviating night, rest and touch pain but did show a trend for reduced risk of pain under load. HA improved physical functioning and patient global assessment scores in comparison to IA corticosteroids. Results of stiffness scores and analgesic use when comparing HA to IA corticosteroids were inconclusive and contradictory. No studies were identified that assessed the effectiveness of HA compared with COX-2 inhibitors.

Hylans

Hylan G-F 20 vs NSAIDs

Two high quality studies were included that examined the effectiveness of a specific hylan (hylan G-F 20 or Synvisc™) compared to diclofenac specifically (Dickson et al 2001) or the standard NSAID therapy of the patient (Adams et al 1995). Due to the differences in outcome measures and study design, no meta-analysis was possible with the resultant data.

Pain

In a comparison of hylan G-F 20 with the NSAID diclofenac, the primary outcome was knee pain as determined using the WOMAC A pain scale (Dickson et al 2001). This measure was used both as an overall score and in its five separate components: 1) pain when walking on a flat surface, 2) pain going up or down stairs, 3) pain at night, 4) pain when sitting or lying and 5) pain when standing upright. Each component was measured using a 100 mm VAS.

In the second study the efficacy of hylan G-F 20 with the normally prescribed NSAID was compared (Adams et al 1995). The primary outcome variable here was pain with motion assessed by the patient using a 100 mm VAS. An intention to treat analysis was not performed. Only results of the evaluable population were reported. However, dropouts were not considerable, with losses of 3 per cent and 6 per cent for the NSAID and hylan G-F 20 groups respectively.

The results are contradictory. In the Dickson study (Dickson et al 2001) the authors found that mean improvement in the WOMAC A overall pain score (100 mm VAS) in patients receiving hylan G-F 20 treatment was significantly greater than in diclofenac treated patients at 12 weeks follow-up (Table 23). Three of the five subscales of the WOMAC A pain score (pain walking on a flat surface, pain at night and pain on sitting or lying) also showed significantly larger improvements in pain scores from baseline to 12 weeks compared to diclofenac treated patients. Adams (Adams et al 1995), however, found no significant difference in improvement of mean pain scores at 12 weeks follow-up (Table 23) or at 26 weeks follow-up for the mean pain scores between hylan G-F 20 treated patients and patients treated with NSAIDs (Table 25). Combined hylan G-F 20 and NSAID therapy showed no significant difference in mean improvement of pain scores compared to NSAID alone (Table 24) at 12 weeks follow-up. However, mean pain scores at 26 weeks were significantly lower for combined therapy on all pain measures compared to NSAIDs only (Table 26).

Patient overall assessment of pain and the number of patients determined to be symptom free were also examined in the Adams study (Adams et al 1995). Mean improvement in scores for overall assessment of pain at 12 weeks follow-up was found to be similar for hylan G-F 20 and NSAID only (Table 23). This was also found for combined therapy of hylan G-F 20 and NSAIDs, and for NSAID only treated patients (Table 24). The mean VAS score for overall assessment of pain at 26 weeks was found to be significantly lower in the combined treatment group when compared to NSAID treatment only (Table 26).

Table 23 Mean improvement in pain scores for hylan G-F 20 and NSAIDs from baseline to follow-up

Study	Quality[a]	Outcomes	Treatment group				Mean difference		P value[c]
			Hylan G-F 20		NSAID				
			mean (n)	SD	mean (n)	SD	mean difference	95% CI[b]	
Dickson (2001)	QS: 24/27 CI: 4 P: under-powered	WOMAC pain questionnaire overall score (100 mm VAS) 12 weeks	33 (53)	29.1	23 (55)	29.7	10.0	-1.2-21.2	0.03
		Pain walking on a flat surface (in mm) 12 weeks	39 (53)	36.4	25 (55)	29.7	14.0	1.3-26.6	0.008
		Pain going up or down stairs (in mm) 12 weeks	32 (53)	36.4	27 (55)	29.7	5.0	-7.6-17.6	0.35
		Pain at night (in mm) 12 weeks	29 (53)	36.4	16 (55)	29.7	13.0	0.3-25.6	0.01
		Pain sitting or lying (in mm) 12 weeks	29 (53)	29.1	15 (55)	29.7	14.0	2.8-25.2	0.004
		Pain on standing (in mm) 12 weeks	34 (53)	29.1	26 (55)	29.7	8.0	-3.2-19.2	0.14
Adams (1995)	QS: 22/27 CI: 4 P: under-powered	Pain on motion (100 mm VAS) 12 weeks	23 (25)	20	19 (32)	22.6	4.0	-7.5-15.5	0.5
		Pain at rest (100 mm VAS) 12 weeks	19 (25)	20	9 (32)	22.6	10.0	-1.5-21.5	0.09
		Pain at night (100 mm VAS) 12 weeks	21 (25)	20	13 (32)	28.3	8.0	-5.4-21.4	0.2
		Overall assessment of pain (100 mm VAS) 12 weeks	24 (25)	25	19 (32)	28.3	5.0	-9.4-19.4	0.5

[a] Quality score (QS) determined from checklist created by Downs and Black (Downs & Black 1998); clinical importance (CI) scored from 1 to 4 with 1 = clinically important benefit for the full range of plausible estimates, 2 = point effect clinically important but confidence interval includes clinically unimportant effects, 3 = confidence interval does not include any clinically important effects, 4 = range of estimates include clinically important effects but range of estimates compatible with no effect or harmful effect (National Health and Medical Research Council 2000) power (P). [b] Unadjusted values based on a t-test comparing mean±SD. [c] In the Dickson et al (2001) study adjusted p values reported from the study. Values derived using a repeated measures analysis of variance adjusted for statistically significant covariates.

Table 24 Mean improvement in pain scores for combined hylan G-F 20 and NSAIDs treatment compared to NSAIDs only, from baseline to 12 weeks follow-up

Study	Quality	Outcomes	Treatment group				Mean difference		P value
			Hylan G-F 20 and NSAIDs		NSAID				
			mean (n=32)	SD	mean (n=32)	SD	mean difference	95% CI	
Adams (1995)	22/27	Pain on motion (100 mm VAS) 12 weeks	26	22.6	19	22.6	7.0	-4.3-18.3	0.2
		Pain at rest (100 mm VAS) 12 weeks	12	22.6	9	22.6	3.0	-8.3-14.3	0.6
		Pain at night (100 mm VAS) 12 weeks	10	22.6	13	28.3	-3.0	-15.8-9.8	0.6
		Overall assessment of pain (100 mm VAS) 12 weeks	26	22.6	19	28.3	7.0	-5.8-19.8	0.3

Table 25 Mean pain scores for hylan G-F 20 and NSAIDs at 26 weeks

Study	Quality	Outcomes	Treatment group				Mean difference		P value
			Hylan G-F 20		NSAIDs				
			mean (n=27)	SD	mean (n=31)	SD	mean difference	95% CI	
Adams (1995)	22/27	Pain on motion (100 mm VAS) 26 weeks	40	22.3	52	26.0	-12.0	-24.8-0.8	0.07
		Pain at rest (100 mm VAS) 26 weeks	25	16.7	22	15.6	3.0	-5.5-11.5	0.5
		Pain at night (100 mm VAS) 26 weeks	25	22.3	28	26.0	-3.0	-15.8-9.8	0.6
		Overall assessment of pain (100 mm VAS) 26 weeks	47	20.8	52)	22.3	-5.0	-16.4-6.4	0.4

Table 26 Mean pain scores for combined hylan G-F 20 and NSAIDs vs NSAIDs only, at 26 weeks

Study	Quality	Outcomes	Treatment group				Mean difference		P value
			Hylan G-F 20 and NSAIDs		NSAIDs				
			mean (n=32)	SD	mean (n=31)	SD	mean difference	95% CI	
Adams (1995)	22/27	Pain on motion (100 mm VAS) 26 weeks	37	22.6	52	26.0	-15.0	-27.3- -2.7	0.02
		Pain at rest (100 mm VAS) 26 weeks	11	17.0	22	15.6	-11.0	-19.2- -2.8	0.01
		Pain at night (100 mm VAS) 26 weeks	9	22.6	28	26.0	-19.0	-31.3- -6.7	0.003
		Overall assessment of pain (100 mm VAS) 26 weeks	37	22.6	52	22.3	-15.0	-26.3- -3.7	0.01

Patients were defined as symptom free if their VAS score for a particular pain outcome was below 20 mm. For the primary outcome measure of pain with motion, significantly more patients treated with hylan G-F 20 were assessed to be symptom free at 26 weeks follow-up compared to NSAID treated patients (Table 27). A relative risk ratio of 4.6 indicates that patients in the hylan G-F 20 group were 4.6 times more likely to be symptom free of pain on motion than their NSAID treated counterparts. A NNT of 4 indicates that for every four patients treated with hylan G-F 20, one additional patient would benefit compared to treating with NSAIDs only. No other pain measure showed any significant differences in the number of patients who were symptom free between the two treatment groups. However, significantly more patients given combined therapy were determined to be symptom free at 26 weeks for pain on motion, pain at night and pain at rest compared to patients treated with NSAIDs only (Table 28).

Table 27 Number of patients who were symptom free at 26 weeks (hylan G-F 20 vs NSAIDs)

Study	Quality	Outcomes	Treatment group				Relative risk		Number needed to treat	
			Hylan G-F 20		NSAID					
			r/n[a]	%	r/n	%	RR	95% CI	NNT	95% CI
Adams (1995)	22/27	No pain on motion	8/27	29.6	2/31	6.4	4.6	1.1-19.8	4	2-25
		No pain at rest	13/27	48.1	15/31	48.4	1.0	0.6-1.7	NNH 500	NNTH 4 to ∞ to NNTB 4
		No pain at night	17/27	63.0	15/31	48.4	1.3	0.8-2.1	7	NNTH 9 to ∞ to NNTB 2
		Overall assessment of pain (no pain)	5/27	18.5	3/31	9.7	1.9	0.5-7.3	11	NNTH 11 to ∞ to NNTB 4

[a] r/n = number of subjects with condition / number of subjects in intervention group.

Table 28 Number of patients who were symptom free at 26 weeks (hylan G-F 20 and NSAIDs vs NSAIDs only)

Study	Quality	Outcomes	Treatment group				Relative risk		Number needed to treat	
			Hylan G-F 20 and NSAID		NSAID					
			r/n[a]	%	r/n	%	RR	95% CI	NNT	95% CI
Adams (1995)	22/27	No pain on motion	9/32	28.1	2/31	6.4	4.4	1.02-18.6	4	2-25
		No pain at rest	26/32	81.2	15/31	48.4	1.7	1.1-2.5	3	2-9
		No pain at night	25/32	78.1	15/31	48.4	1.6	1.1-2.4	3	2-14
		Overall assessment of pain (no pain)	8/32	25.0	3/31	9.7	2.6	0.7-8.8	7	NNTH 33 to ∞ to NNTB 3

[a] r/n = number of subjects with condition / number of subjects in intervention group.

Physical function

Dickson (Dickson et al 2001) assessed physical function using the WOMAC C physical function subscale while Adams (Adams et al 1995) provided a measure of the restriction of activity scored on a 100 mm VAS. Neither study found any significant difference in either improvement of functional activity or restriction of activity scores at any assessed time point (Table 29). Adams also found no difference between treatment groups in the proportion of patients determined to be symptom free for this outcome (scores of less than 20 mm on VAS) at 26 weeks follow-up for either hylan G-F 20 alone or combined treatment when compared with NSAIDs alone (Table 30).

Table 29 Physical function scores (hylan G-F 20 vs NSAIDs)

Study	Quality	Outcomes	Treatment group				Mean difference		P value
			Hylan G-F 20		NSAID[a]				
			mean (n)	SD	mean (n)	SD	mean difference	95% CI	
Dickson (2001)	24/27	Mean change in WOMAC C (functional ability subscale) score at 12 weeks from baseline	16 (53)	21.8	14 (55)	14.8	2.0	-5.1-9.1	0.6
Adams (1995)	22/27	Restriction of activity (100 mm VAS)							
		Mean improvement (12 weeks)	13 (25)	30	14 (32)	28.3	-1.0	-16.5-14.5	0.9
		Mean score (26 weeks)	41 (27)	26.0	52 (31)	27.8	-11.0	-25.2-3.2	0.1

[a] NSAID used in Dickson et al (2001) study was diclofenac, NSAID used in Adams et al (1995) study was NSAID of choice by treating medical practitioner.

Table 30 Proportion of patients free of activity restriction

Study	Quality	Outcomes	Treatment group				Relative risk		Number needed to treat	
			r/n[a]	%	r/n	%	RR	95% CI	NNT	95% CI
			Hylan G-F 20		NSAIDs					
Adams (1995)	22/27	Symptom free at 26 weeks	7/27	25.9	3/31	9.7	2.7	0.8-9.3	6	NNTH 33 to ∞ to NNTB 3
			Hylan G-F 20 and NSAIDs		NSAIDs only					
		Symptom free at 26 weeks	8/32	25.0	3/31	9.7	2.6	0.7-8.8	7	NNTH 33 to ∞ to NNTB 3

[a] r/n = number of subjects with condition / number of subjects in intervention group.

Stiffness

Dickson (Dickson et al 2001) examined the degree of stiffness experienced in the affected knee joint using the WOMAC B stiffness subscale. No significant difference in mean change in stiffness scores was found between the two treatment groups from baseline to 12 weeks follow-up (Table 31).

Table 31 Mean change in stiffness scores (hylan G-F 20 vs NSAID diclofenac)

Study	Quality	Outcomes	Treatment group				Mean difference		P value
			Hylan G-F 20		Diclofenac				
			mean (n)	SD	mean (n)	SD	mean difference	95% CI	
Dickson (2001)	24/27	Mean change in WOMAC B (stiffness subscale) score at 12 weeks from baseline	18 (53)	29.1	16 (55)	29.7	2	-9.2-13.2	0.7

Other measures

Overall opinion of treatment at 12 weeks was also evaluated in one study (Dickson et al, 2001) using a 5-category ordinal scale of very poor to very good. No significant differences in opinion were found between the two treatment groups (Table 32) and a test for trend showed no linear relationship between treatment category and response to global assessment (χ^2 = 0.01, p = 0.9). The mean number of paracetamol used by patients in either treatment arm did not differ over any time period up to 12 weeks follow-up (Table 33). However, these results are based on the evaluable population and therefore should be regarded with caution.

Table 32 Overall opinion of treatment at 12 weeks (hylan G-F 20 vs NSAID diclofenac)

Study	Quality	Outcomes	Treatment group				Relative risk		Number needed to treat	
			Hylan G-F 20		NSAID					
			r/n[a]	%	r/n	%	RR	95% CI	NNT	95% CI
Dickson (2001)	24/27	Very poor	4/42	9.5	3/42	7.1	1.3	0.3-5.6	50	NNTH 11 to ∞ to NNTB 7
		Poor	4/42	9.5	4/42	9.5	1.0	0.3-3.7	NE	
		Fair	5/42	11.9	11/42	26.2	0.4	0.2-1.2	NNH 7	NNTH 11 to ∞ to NNTB 7
		Good	20/42	47.6	13/42	30.9	1.5	0.9-2.7	6	
		Very good	9/42	21.4	11/42	26.2	1.0		NNH 20	NNTH 11 to ∞ to NNTB 7

[a] r/n = number of subjects with condition / number of subjects in intervention group.

Table 33 Mean number of paracetamol used (hylan G-F 20 vs NSAID diclofenac)

Study	Quality	Outcomes	Treatment group				Mean difference		P value
			Hylan G-F 20		Diclofenac				
			mean (n)	SD	mean (n)	SD	mean difference	95% CI	
Dickson (2001)	24/27	Paracetamol use							
		Weeks 1-4	36 (38)	37.0	36 (39)	43.7	0.0	-1.8-1.8	1.0
		Weeks 5-8	45 (35)	53.2	41 (36)	42.0	4.0	-18.6-26.6	0.7
		Weeks 9-12	41 (34)	46.6	33 (35)	41.4	8.0	-13.2-29.2	0.4

Summary: The effectiveness of hylan G-F 20 vs NSAIDs

In a comparison of hylan G-F 20 with NSAIDs the study by Dickson et al (2001) found greater improvement in scores for pain at night, walking on a flat surface and pain sitting or lying at 12 weeks follow-up. No other pain measures, physical function, stiffness or overall assessment of treatment scores, or paracetamol use was found to be different between the two treatment groups. Adams et al (1995) compared combined hylan G-F 20 and NSAID treatment to NSAID treatment only and found significantly reduced mean pain scores in the combined therapy arm at 26 weeks follow-up. However, both of these studies were underpowered.

Hylan G-F 20 vs hyaluronic acid

Pain

In an effort to make a direct comparison in the effectiveness of hylans and HA, Wobig performed a 12-week multicentre trial treating 38 patients (38 knees) with hylan G-F 20 and another 32 patients (35 knees) with a lower MW HA (750 kDa) (Wobig et al 1999). The primary outcome measure in this study was the change in patient assessed VAS pain scores during weight bearing from baseline to 12 weeks follow-up. Results were presented in graphical form with only the mean values expressed; therefore, independent assessment was not possible (Table 34). However, the authors claim that patients treated with hylan G-F 20 displayed significantly greater improvement in VAS scores for weight-bearing pain and overall pain compared to patients treated with the lower MW HA.

Table 34 Change in weight-bearing pain score or overall improvement in patient pain (baseline to week 12)

Study	Quality[a]	Outcomes	Treatment group				Mean difference		P value
			Hylan G-F 20		Diclofenac				
			mean (n=38)	SD	mean (n=35)	SD	mean difference	95% CI	
Wobig (1999)	QS: 19/27 CI: NE from primary outcome P: NE from primary outcome	Weight-bearing pain (patient assessed) reduction in VAS score (mm)	38	-	25	-	13		NE
		Overall improvement (reduction) in pain VAS (mm, patient assessed)	67	-	51	-	16		NE

[a] Quality score (QS) determined from checklist created by Downs and Black (Downs & Black 1998); clinical importance (CI) scored from 1 to 4 with 1 = clinically important benefit for the full range of plausible estimates, 2 = point effect clinically important but confidence interval includes clinically unimportant effects, 3 = confidence interval does not include any clinically important effects, 4 = range of estimates include clinically important effects but range of estimates compatible with no effect or harmful effect (National Health and Medical Research Council 2000); power (P).

The percentage of patients determined to be symptom free at 12 weeks was also determined. Symptom free was defined as a VAS score below 20 mm. The authors claim that significantly more patients in the hylan G-F 20 arm were symptom free at 12 weeks compared to HA treated patients for measures of patient and evaluator rated weight-bearing pain and overall pain assessment. However, these data were not presented.

Other outcomes

No other outcomes such as patient global assessment or stiffness were reported in this study.

Summary: Effectiveness of hylan G-F 20 vs HA

Only one study looked at the comparative effectiveness of hylan G-F 20 vs HA (Wobig et al 1999). Due to deficiencies in the reporting of data, no conclusions could be drawn from this study.

Hylan G-F 20 combined with appropriate care vs appropriate care only

A comparison of the effectiveness of patients treated with hylan G-F 20 combined with appropriate care (n=127) and patients treated with appropriate care only (n=128) was performed in an unpublished study in 2000 (Raynauld et al 2000). Appropriate care was defined as 'the preferred management strategy of a treating physician who was encouraged to follow the Recommendations for the Medical Management of Osteoarthritis of the Hip and Knee proposed by the American College of Rheumatology'. This study was performed without blinding of the patient. As the outcome measures are based on a subjective interpretation by the patient, this lack of blinding leads to serious issues of reporting bias that put the following results into some doubt. Further, the promise of compensation of a free course of the hylan G-F 20 at the completion of the experiment for patients in both control and experimental groups insinuates that the product is superior from the outset.

Pain

The primary outcome measure was the mean change in the WOMAC Likert pain score from baseline to 1 year follow-up. For the assessment of pain the WOMAC Likert pain score ranged from a minimum of 0 to a maximum of 20. The definition of an improved patient was a 20 per cent or greater improvement in the WOMAC Likert pain score from baseline to 1 year follow-up. The authors defined a significant clinical improvement of hylan G-F 20 over appropriate care as a least a 20 per cent difference in mean change in WOMAC Likert pain scores from baseline to 1 year, between the two treatment arms. Results show that both treatment arms significantly decreased mean WOMAC Likert pain scores from baseline to 1 year (Table 35). When mean change in WOMAC Likert pain scores were expressed as a percentage of baseline and compared, the hylan G-F 20 plus appropriate care group had a 25 per cent greater improvement in change over appropriate care only. Therefore the authors concluded that hylan G-F 20 plus appropriate care produced a clinically significant improvement over appropriate care alone.

Table 35 Mean WOMAC Likert pain scores at baseline and 1 year

Study	Quality[a]	Outcomes	Treatment group				Mean difference		P value
			Hylan G-F 20 plus appropriate care		Appropriate care only				
			mean (n=127)	SD	mean (n=127)	SD	mean difference	95% CI	
Raynauld (2000)	QS: 23/27 CI: 1 P: 100%	Mean WOMAC Likert pain score baseline	11.35	2.71	11.94	2.89	-0.6	-1.3-0.1	0.09
		Mean WOMAC Likert pain score 1 year	6.94	3.97	10.10	4.24	-3.2	-4.2--2.1	<0.001

[a] Quality score (QS) determined from checklist created by Downs and Black (Downs & Black 1998); clinical importance (CI) scored from 1 to 4 with 1 = clinically important benefit for the full range of plausible estimates, 2 = point effect clinically important but confidence interval includes clinically unimportant effects, 3 = confidence interval does not include any clinically important effects, 4 = range of estimates include clinically important effects but range of estimates compatible with no effect or harmful effect (National Health and Medical Research Council 2000); power (P).

Patients were almost two times more likely to have improved when treated with hylan G-F 20 in addition to appropriate care, compared to treatment with appropriate care alone (Table 36). NNT analysis suggests that only three patients would have to be treated with hylan G-F 20 in addition to appropriate care in order to have one additional patient improver compared to treatment with appropriate care alone.

Table 36 Number of patients improved from baseline and 1 year (≥20% improvement in WOMAC Likert pain score)

Study	Quality	Outcomes	Treatment group				Relative risk		Number needed to treat	
			Hylan G-F 20 plus appropriate care		Appropriate care only					
			r/n[a]	%	r/n	%	RR	95% CI	NNT	95% CI
Raynauld (2000)	23/27	Number of improvers at 1 year	87/127	68.5	51/127	40.1	1.7	1.3-2.2	3	2-5

[a] r/n = number of subjects with condition / number of subjects in intervention group.Physical function

Physical function was measured using the WOMAC C physical function subscale. Patients receiving combined treatment of hylan G-F 20 and appropriate care were found to have significantly lower (ie better) physical function scores at 12 months than patients on appropriate care only (Table 37).

Table 37 Mean WOMAC C physical function scores at baseline and 1 year (combined treatment vs appropriate care only)

Study	Quality	Outcomes	Treatment group				Mean difference		P value
			Hylan G-F 20 plus appropriate care		Appropriate care only				
			mean (n=127)	SD	mean (n=128)	SD	mean difference	95% CI	
Raynauld (2000)	23/27	Mean WOMAC C score baseline	39.54	9.27	40.20	9.26	-0.7	-2.9-1.6	0.6
		Mean WOMAC C score 1 year	24.26	12.95	33.87	13.88	-9.6	-12.9--6.3	<0.001

Patient global assessment

Patient global assessment in this study was assessed using a 5-category ordinal scale rating treatment effectiveness from very poor to very good. Patient assessment of overall health at baseline and at 12 months showed no significant differences for any of the ratings (Table 38). However, a test for trend showed a significant linear relationship between treatment arm and the rating given in a global assessment of overall health (χ^2 = 7.86, p = 0.005). In other words, patients in the combined treatment arm were more likely to give a better rating for overall health than patients with appropriate care only.

Table 38 Patient global assessment of overall health at baseline and 1 year (hylan G-F 20 plus appropriate care vs appropriate care only)

Study	Quality	Outcomes	Treatment group				Relative risk		Number needed to treat	
			Hylan G-F 20 plus appropriate care		Appropriate care only					
			r/n[a]	%	r/n	%	RR	95% CI	NNT	95% CI
Raynauld (2000)	23/27	Baseline								
		Very poor	1/126	0.8	2/127	1.6	0.5	0.1-5.5	143	NNTH 50 to ∞ to NNTB 33
		Poor	11/126	8.7	13/127	10.2	0.8	0.4-1.8	100	NNTH 17 to ∞ to NNTB 11
		Fair	30/126	23.6	33/127	25.8	0.9	0.6-1.4	50	NNTH 7 to ∞ to NNTB 12
		Good	61/126	48.0	61/127	47.7	1.0	0.8-1.3	250	NNTH 10 to ∞ to NNTB 8
		Very good	23/126	18.1	18/127	14.1	1.3	0.7-2.3	25	NNTH 20 to ∞ to NNTB 8
		1 year								
		Very poor	0/124	0	4/107	3.8	NE			
		Poor	6/124	4.8	12/107	11.2	0.4	0.2-1.1	17	NNTH 50 to ∞ to NNTB 8
		Fair	37/124	29.8	34/107	31.8	0.9	0.6-1.4	50	NNTH 10 to ∞ to NNTB 7
		Good	60/124	48.4	46/107	43.0	1.1	0.8-1.5	20	NNTH 14 to ∞ to NNTB 5
		Very good	21/124	16.9	11/107	10.3	1.6	0.8-3.2	14	NNTH 50 to ∞ to NNTB 7

[a] r/n = number of subjects with condition / number of subjects in intervention group.

At 12 months the proportion of patients rating their treatment knee as good or very good was significantly higher in the combined treatment arm compared to appropriate care only (Table 39). Conversely, the proportion of patients rating their treatment knee as poor or very poor was significantly lower in the combined treatment arm compared to appropriate care only. A test for trend indicated a significant correlation between treatment group and patient rating of study knee at 1 year ($\chi^2 = 30.8$, $p<0.001$). In other words there was an association between combined hylan G-F 20 and appropriate care treatment and favourable assessment of the knee treatment.

Table 39 Patient global assessment of treatment knee at baseline and 1 year (hylan G-F 20 plus appropriate care vs appropriate care only)

Study	Quality	Outcomes	Treatment group				Relative risk		Number needed to treat	
			Hylan G-F 20 plus appropriate care		Appropriate care only					
			r/n[a]	%	r/n	%	RR	95% CI	NNT	95% CI
Raynauld (2000)	23/27	Baseline								
		Very poor	23/127	18.1	38/127	29.7	0.6	0.4-0.9	8	4-100
		Poor	58/127	45.7	57/127	44.5	1.0	0.8-1.3	125	NNTH 8 to ∞ to NNTB 9
		Fair	44/127	34.6	31/127	24.2	1.4	1.0-2.1	10	NNTH 111 to ∞ to NNTB 5
		Good	2/127	1.6	1/127	0.8.	2.0	0.2-21.8	125	NNTH 50 to ∞ to NNTB 3
		Very good								
		1 year								
		Very poor	4/123	3.2	19/107	17.8	0.2	0.1-0.5	7	5-14
		Poor	25/123	20.2	42/107	39.2	0.5	0.3-0.8	5	3-14
		Fair	43/123	34.7	28/107	26.2	1.3	0.9-2.0	11	NNTH 33 to ∞ to NNTB 5
		Good	39/123	31.4	15/107	14.0	2.3	1.3-3.9	5	3-14
		Very good	12/123	9.7	3/107	2.8	3.5	1.0-12.0	14	8-100

[a] r/n = number of subjects with condition / number of subjects in intervention group.Stiffness

In measurement of stiffness using the WOMAC B stiffness subscale, patients treated with hylan G-F 20 plus appropriate care showed significantly lower (ie better) scores at 12 months compared to patients treated with appropriate care only (Table 40).

Table 40 Mean WOMAC B stiffness scores at baseline and 1 year (combined treatment vs appropriate care only)

Study	Quality	Outcomes	Treatment group				Mean difference		P value
			Hylan G-F 20 plus appropriate care		Appropriate care only				
			mean (n=127)	SD	mean (n=128)	SD	mean difference	95% CI	
Raynauld (2000)	23/27	Mean WOMAC B score baseline	5.06	1.51	5.10	1.42	-0.04	-0.4-0.3	0.8
		Mean WOMAC B score 1 year	3.22	1.74	4.31	1.56	-1.09	-1.5- -0.7	<0.001

Summary: Effectiveness of hylan G-F 20 and appropriate care vs appropriate care only

The results of this study show significant improvement in mean pain score, physical function and patient global assessment at 1 year when hylan G-F 20 used in conjunction with appropriate care is compared to appropriate care only. However, as most of the outcome measures are based on a subjective interpretation by the patient, the lack of blinding leads to serious issues of reporting bias that put these results into some doubt. The promise of compensation of a free course of hylan G-F 20 at the completion of the experiment for patients in both control and experimental groups suggests that the product is superior from the outset. Therefore, the results of this study should be treated with caution.

Summary: The overall effectiveness of hylan G-F 20

In conclusion, hylan G-F 20 was associated with some level of improvement in measures such as mean pain scores at 26 weeks when blinding was instituted and only in combination with NSAID therapy. However, this result is found in a single study of relatively small size. Therefore, treatment with hylan G-F 20 alone is, with one exception, no more effective in improving outcome measures of pain, global assessment, physical function or stiffness than treatment with NSAIDs. Comparison with a lower MW HA is inconclusive due to poor data reporting. The combination of hylan G-F 20 with appropriate care has produced significant improvements in pain, global assessment, physical function and stiffness compared to appropriate care alone. However, these results are questionable due to potential bias inherent in the study design.

What are the economic considerations?

The purpose of economic evaluation is to assist decision-makers in ensuring that society's ultimately scarce resources are allocated to those activities from which we will get the most value. That is, it seeks to enhance economic efficiency.

Economic evaluation under the MSAC process focuses on the scarce resources available within the Australian health system. It asks whether these scarce resources would be better spent on producing the amount of health gain obtainable through the intervention in question or through the identified comparator intervention.

The aim of the present economic evaluation was to systematically review the evidence for the costs and effectiveness of hyaluronic acid compounds and hylans respectively, compared to the three comparators NSAIDs, IA corticosteroids and COX-2 inhibitors, when these interventions are provided under Australian conditions, and to provide an indication of the extent of uncertainty entailed.

The perspective for the present evaluation was that of the Australian health system overall. Cost data therefore covered all non-trivial health system resources directly used in providing the intervention. Neither direct costs for patients and their families / carers nor indirect costs, also known as productivity costs, were considered due to the paucity of information about these in the literature on viscosupplementation.

It was intended that, where a single unequivocal outcome indicator could be identified, the result would be expressed in terms of the incremental cost-effectiveness ratio (ICER), which is calculated as shown below:

$$\text{ICER} = \frac{\text{increment in cost}}{\text{increment in effectiveness}}$$

$$= \frac{\text{cost of viscosupplementation} - \text{cost of comparator treatment}}{\text{health outcome from viscosupplementation} - \text{Health outcome from comparator treatment}}$$

Commentary on the economic evaluation submitted with the application

An extensive search failed to find any economic evaluation of viscosupplementation for OA of the knee in the published literature. The unpublished economic evaluation submitted by the applicant (Raynauld et al 2000) has been reviewed using the NHMRC checklist for appraising economic evaluation studies (see Appendix G, NHMRC 2001)

The study question was well defined, and the study employed both cost-effectiveness and cost-utility analysis, using clinical and quality of life outcomes (Raynauld et al 2000). Counts of resource use were based on the Canadian clinical trial data, but prices were adapted using Australian sources. A 1-year horizon was adopted, and thus no discounting of future costs or consequences was undertaken. Both incremental and sensitivity analysis were reported, with estimates of incremental cost per patient improved in the first year to be $3,322, and the incremental cost per Quality Adjusted Life Year (QALY) gained in that time to be $13,260. Sensitivity analysis suggested an upper bound on the incremental cost of $5,672 per patient improved, and of $55,381 per QALY gained. In

terms of ability to generalise, the patient group reflected the known population prevalence of known risk factors for knee OA. The original RCT was conducted in Canada, a nation whose health system shares many characteristics with that of Australia. Further, experimental and control treatments were provided by rheumatologists and orthopaedic surgeons in accordance with the Guidelines for the Medical Management of Osteoarthritis issued by the American College of Rheumatology. These guidelines are compatible with Australian practice for the management of OA. Finally, Canadian estimates of costs were itemised and converted into equivalent Australian dollars and expressed as average cost, which is appropriate in assessing a national policy for a service that may be provided in a large number of facilities across the country.

However, as was highlighted in the review of the effectiveness measurement in this study (pg 55), blinding of patients to treatment groups was not done, and an incentive of free hylan G-F 20 after study completion was given prior to the beginning of the study. The intention-to-treat protocol was not followed, with dropouts in both groups not being included in the analysis. Although mentioned in the exclusion criteria, some grade IV OA sufferers as determined by radiographic methods were included in both treatment groups, perhaps contributing to increased pain scores and reduced effectiveness in the appropriate care only group. Therefore, based on this one study against the comparator of appropriate care, the accuracy of the resulting cost-effectiveness and cost-utility information for hylan G-F 20 must be questioned.

Determining the cost-effectiveness of viscosupplementation from the identified literature

Therefore, the second step in this economic analysis was to use available research in an attempt to determine the ICER of using viscosupplementation in preference to NSAIDs, IA corticosteroids or COX-2 inhibitors.

Effectiveness studies identified in the literature search were deemed suitable for incorporation into a cost-effectiveness analysis if they were of sufficient quality to have reported a credible estimate of effectiveness in a format suitable for economic evaluation, and if they had reported sufficient information to deduce the costs incurred. Five studies were candidates for inclusion in the cost-effectiveness analysis (Table 41). Three were trials of the HA Hyalgan® (Altman & Moskowitz 1998; Leardini et al 1991; Pietrogrande et al 1991). Two were trials of hylan G-F 20 (Adams et al 1995; Raynauld et al 2000). Studies of Supartz™, the only other available viscosupplementation product available for use in Australia besides hylan G-F 20, did not satisfy the inclusion criteria for this aspect of the review.

Outcome measures of interest in the five studies under review described the number of patients who improved from baseline to the end of the study, or experienced little or no pain at the final evaluation period of the study. However, wide variations in the incremental effectiveness of the interventions led to different incremental cost-effectiveness ratios even between studies making identical comparisons of treatment. The majority of these five studies were underpowered, some were unblinded, and only one had a time horizon that extended past six months (Raynauld et al 2000), although, even this study suffered from methodological flaws. Further, no studies compared viscosupplementation with COX-2 inhibitors and there is no data comparing hylan G-F 20 with IA corticosteroids. Therefore, little valid information on outcomes and their relationship to costs was obtained from the existing literature.

Table 41 Studies evaluated for cost-effectiveness of viscosupplements vs comparators

Study	Comparison	Outcome measure	Point estimate of cost-effectiveness	Comments
Altman (1998)	HA vs NSAIDs	Number of improvers	$19,575/ patient improved	Underpowered, no significant difference in number of improvers between treatments
Leardini (1991)	HA vs IA corticosteroids	Number of patients with little or no pain at rest	$750/ patient with little or no pain	Significant difference in effectiveness of t2 treatments but unblinded study
Pietrogrande (1991)	HA vs IA corticosteroids	Number of patients with little or no pain at rest	$7,704/ patient with no pain at rest	No significant difference in effectiveness of 2 treatments, unblinded study
Adams (1995)	Hylan G-F 20 vs NSAIDs	Number of patients symptom free	$2,300/ patient symptom free	Significant difference in effectiveness of 2 treatments, based on small sample size, underpowered
Raynauld (2000)	Hylan G-F 20 plus appropriate care vs appropriate care only	Number of improvers	$3,000/ patient improved	Significant difference in effectiveness of 2 treatments but unblinded study

Comparative costs of different treatments

Since there is insufficient evidence to conclude that viscosupplementation with HA is more effective for the treatment of knee OA than its identified comparators, a cost-effectiveness analysis was not appropriate. Further, due to the nature of the available literature, a credible estimate of the cost-effectiveness of hylan G-F 20 against its comparators could not be made. Therefore, the remaining relevant information is the relative cost of providing viscosupplementation or its comparators to the population of Australians with knee OA.

The number of potential recipients of treatment (ie sufferers of OA of the knee) was established from numbers obtained from the Burden of Disease study by Mathers (Mathers et al 1999). This study estimated that there were 625,090 Australians suffering from OA in 1996. This number was assumed to be conservative, with a projected increase by 2001. However, not all of these people would be suffering OA of the knee. The relative proportion of OA sufferers who had OA of the knee compared to all other sites was determined from the Hospital Morbidity Database (AIHW 2001). Sixty-three per cent of all hospital admissions with a primary diagnosis of OA were classified as suffering from OA of the knee. Using this proportion as an estimate of the percentage of knee OA sufferers in the total OA patient population suggests that 393,806 Australians suffer from OA of the knee in a typical year. From this number were subtracted the 33,571 patients admitted to hospital with a primary diagnosis of OA of the knee (AIHW 2001). These hospitalised patients are assumed to be likely to receive more invasive treatment, such as total knee replacement, and thus unlikely to receive viscosupplementation. It is impossible to estimate the number of patients who would be receiving non-pharmacological or simple analgesic treatment in order to eliminate them from the calculation. Therefore, the final working estimate of Australians suffering knee OA who could possibly be eligible for viscosupplementation in any one year would be approximately 360,235. All costs of treatment are based on this estimate.

Cost data were converted to the single year 2001, and expressed in Australian dollars. The unit cost of Hyalgan® was only available in United States dollars, and was converted to Australian dollars using Purchasing Power Parities. The unit cost of hylan G-F 20

entered into this analysis was that supplied by Bayer Australia Limited. The unit cost of Supartz™ that was included in this analysis was supplied by Smith and Nephew, Australia. The unit costs of other items in this analysis were obtained from either the Medicare Benefits Schedule (MBS), the Schedule of Pharmaceutical Benefits (PBS) or derived from the Australian Refined Diagnosis Related Groups (Department of Health 2001). These unit costs are set out in Table 42.

Table 42 Unit costs in year 2001 Australian dollars of items considered in the economic evaluation

Item description (quantity)	Cost (year 2001 Australian dollars)	Source
Viscosupplements		
Hylan G-F 20 (3 syringes of 2 mL each)	444.50	Bayer
Hyalgan® (per syringe 2 mL each)	120.20	PBM (US)[a] 8024
Supartz™ (5 syringes, 2.5 mL each)	445.00	Smith and Nephew Australia
NSAIDs		
Ibuprofen 400 mg tabs (100)	12.32	PBS 3190X
Naproxen 500 mg tablets (50)	13.30	PBS 1659H
H_2 antagonists		
Misoprostol 200 μg tab (120)	51.42	PBS 1648R
Omeprazole 20 mg capsule (30)	46.11	PBS 1326T
COX-2 inhibitors		
Celecoxib 100 mg caps (60)	32.05	PBS 8439E
200 mg caps (30)	32.05	PBS 8440F
Rofecoxib 12.5 mg tabs (30)	29.44	PBS 8471W
25 mg tabs (30)	42.75	PBS 8472X
Analgesic		
Acetaminophen 500 mg tablets (100)	7.68	PBS 1746X
Corticosteroid		
Methyl prednisolone acetate, 40 mg in 1 mL injection (5)	21.52	PBS 1928L
Betamethasone acetate/betamethasone sodium phosphate 3 mg/3.9 mg in 1 mL (5)	23.73	PBS 2694T
Consultations		
Rheumatologist initial consult	117.45	MBS 110
Subsequent visits	58.80	MBS 116
Orthopaedic surgeon initial consult	66.60	MBS 104
Subsequent visits	33.40	MBS 105
Radiologist	66.60	MBS 104
General practitioner	28.75	MBS 23
Procedure		
Injection into or arthrocentesis of synovial cavity	25.40	MBS 50124
Second injection as part of the same consultation	15.20	MBS 50124
Diagnostic		
Haematology white blood cell count	16.70	MBS 65070
Synovial fluid white blood cell count	12.20	MBS 69300
Synovial fluid gram stain	12.20	MBS 69300
Synovial fluid bacterial culture	47.00	MBS 69321
Knee x-ray	40.90	MBS 57521
Treatment		
Gastrointestinal haemorrhage age<65 without catastrophic or severe complications	1,136.16	AR-DRG G61B (version 4.1)[b]
Gastrointestinal haemorrhage age<65 plus catastrophic or severe complications or age>64	2,434.32	AR-DRG G61A (version 4.1)[b]

a PBM: Pharmacy Benefits Management. The prices of Hyalgan® and SupartzTM in American dollars were converted to Australian dollars using 2001 Purchasing Power Parities (conversion factor 1.34 available at www.oecd.org), ie for Hyalgan® US$89.70 per 2 mL syringe (10 mg/mL) x 1.34 = A$120.20. [b] Adjusted by the Consumer Price Index (CPI).

The cost of treatment

Initially, the costs of treatment were ascertained for a single patient receiving one course of viscosupplementation to one knee or a single course of one of the comparators (COX-2 inhibitors, NSAIDs or IA corticosteroids) (Table 43). A single course of viscosupplementation was defined as either a 3 or 5 injection (one per week) regimen of Hyalgan®, a 5 injection (one per week) regimen of Supartz™ or a 3 injection (also one per week) regimen of hylan G-F 20. One course of IA corticosteroid (specifically Triamcinolone acetonide) was either a single injection, or the maximum of 4 injections, per year. One course of COX-2 inhibitor or NSAID was defined as the daily prescribed intake for a 1-year duration. All costings included the initial visit to a rheumatologist and the resulting cost of the medication/treatment. For IA injections and viscosupplementation, costs also included subsequent visits to the rheumatologist for further injection procedures as well as the cost of the injection procedure itself (local anaesthetic included).

Average costs per patient were also calculated for multiple courses of viscosupplements or IA corticosteroids, in one or both knees, for the period of one year (Table 43). The calculations of these costs can be found in Appendix H. The number of patients receiving multiple courses of viscosupplements was estimated from the study by Raynauld (Raynauld et al 2000). In this study it was found that, of the population provided with viscosupplementation over the period of 1 year, 60 per cent received one course of treatment, 38 per cent two courses and 2 per cent three courses.

Therefore, in determining the cost of providing viscosupplementation to the total population of knee OA patients, it was assumed that 215,102 of 358,504 (60%) had one course of viscosupplementation, 136,232 (38%) had two courses and 7,170 (2%) had three courses. Costs of a first course included the initial rheumatologist visit followed by the three or five subsequent visits to perform the procedure, the viscosupplement itself and the costs of the injection procedure. Second and third courses were somewhat less expensive with the initial consult not included. Therefore, the population values were multiplied by the cost of either a single course; or the sum of a single and second courses; or the sum of a single, second and third courses, to give costs of viscosupplementation for the total population.

Cost per patient per year for the provision of COX-2 inhibitors and NSAIDs to the entire population of knee OA sufferers are compared to the yearly costs per patient of viscosupplementation in one knee. This is despite the acknowldgement that COX-2 inhibitors and NSAIDs act holistically and would therefore provide relief to both knees.

Downstream costs were not considered in these calculations for any intervention.

Table 43 Cost of one course of the defined intervention per patient per year

	Cost per year in Australian dollars			
Treatment	**Per patient, one course, one knee[a]**	**Per patient, multiple courses, one knee [a,b]**	**Per patient, multiple courses, two knees [a,b]**	**All patients, multiple courses, one knee (in millions) [b,c]**
Hyalgan® 5 injections	$1,139.45	$1,568.69	$2,530.03	$562
Hyalgan® 3 injections	$730.65	$988.19	$1,565.00	$354
Supartz™ 5 injections	$983.45	$1,347.17	$2,086.99	$483
Hylan G-F 20 3 injections	$814.55	$1,107.33	$1,803.27	$397
IA corticosteroid TA injections	$223.38	$541.17[d]	$446.76/$1,082.34[e]	$80/$194[e]
Celecoxib	$502.05			$180
Rofecoxib	$630.45			$226
NSAID (naproxen)	$316.95			$114

[a] The calculations pertaining to these costs are provided in Appendix H. [b] For viscosupplements assumed that 60% receive one course, 38% two courses and 2% three courses in the first year. [c] Calculation based on all patients with knee OA receiving respective treatment. [d] Cost of 4 injections per year. [e] Cost of 1 injection per year / cost of 4 injections per year.

Per patient, viscosupplementation is a more expensive treatment than its comparators (Table 43). The costs range from $730–1140 per patient per year to treat one knee compared with $220–630 per patient per year for the comparative treatments. The cost of the viscosupplementation product and the extra visits to the rheumatologist are the major reasons for this observation.

Viscosupplementation with Hyalgan® or Supartz™ (both HA compounds), allowing for multiple courses per year for the entire population of knee OA sufferers in the Australian population, would cost three to five times more per year than NSAID treatment ($350–560 million vs $114 million) (Table 43). In the case of Hyalgan®, pricing is dependent upon the number of injections provided in one course. Hylan G-F 20 would cost three times more per year than NSAIDs ($397 million). IA corticosteroids would be 30 per cent less costly than NSAIDs if only one injection per patient per year was provided but 60 per cent more expensive if the maximum of four injections per year were given. The cost of providing COX-2 inhibitors is higher than for NSAIDs but still half the cost of viscosupplementation.

Conclusions

Safety

Studies included in this review are limited in their assessment of adverse events. The majority of studies provided very little information on the process for adverse event collection and all but one study failed to include a definition of what was considered an adverse event. Numerous studies were small, some were unblinded and others were of short duration. Therefore, the conclusions made concerning the safety of hyaluronic acid (HA) in relation to identified comparators should be regarded with some caution. What is suggested by the available data, however, is that viscosupplementation with HA compounds has similar incidence of local adverse events (ie at the level of the knee) as intra-articular (IA) corticosteroid injections but greater incidence than non-steroidal anti-inflammatory drugs (NSAIDs). Conversely, IA injection of HA produces fewer systemic adverse events (specifically gastrointestinal upset) than NSAID treatment.

Studies showed that viscosupplementation with hylan G-F 20 produces a similar incidence of local adverse events as injection with lower MW hyaluronic acid viscosupplement and with NSAIDs. Hylan G-F 20 combined with appropriate care showed a higher incidence of local adverse events when compared with appropriate care only. Conversely, hylan G-F 20 was found to have a lower incidence of systemic adverse events than NSAIDs. There was no difference in systemic adverse events when hylan G-F 20 combined with appropriate care was compared with appropriate care only. However, hylan G-F 20 plus appropriate care was found to be associated with a lower risk of side effects and gastrointestinal adverse events when compared with appropriate care only. As the research design allowed for the possibility of significant bias in this final study, care should be taken when interpreting these results.

No studies were found that compared safety, effectiveness or cost-effectiveness of HA or hylans with COX-2 inhibitors.

Effectiveness

The majority of RCTs uncovered in the search for viscosupplements for osteoarthritis (OA) of the knee have been performed using a placebo treated group as the control. As this placebo is generally a saline solution that is not part of the treatment pathway for OA, legitimate comparators were identified that are part of the existing clinical pathway for treatment of OA. Studies comparing the effectiveness of HA or hylan to IA corticosteroids or NSAIDs were few. No studies comparing COX-2 inhibitors were found. The design and heterogeneity of the studies included in this review provided for few strong conclusions of the effectiveness of viscosupplementation with HA or hylan.

From the limited evidence available, HA was found to be as effective as, but no more effective than, NSAIDs at improving patient perceived pain scores, physical function, patient global assessment or stiffness scores. HA was found to be as effective as, but no more effective than, IA corticosteroids for alleviating night, rest and touch pain, but found to show a trend for reduced risk of pain under load. HA improved physical functioning and patient global assessment scores in comparison to IA corticosteroids.

Results of stiffness scores and analgesic use when comparing HA to IA corticosteroids were inconclusive and contradictory.

Overall, hylan G-F 20 was associated with some level of improvement in measures such as mean pain scores at 26 weeks when blinding was instituted, particularly in combination with NSAID therapy. However, these results were found in a single study of relatively small size. Therefore, treatment with hylan G-F 20 alone is, with one exception, no more effective in improving outcome measures of pain, global assessment, physical function or stiffness than treatment with NSAIDs. Comparison with a lower MW HA was inconclusive due to poor data reporting. The combination of hylan G-F 20 with appropriate care produced significant improvements in pain, global assessment, physical function and stiffness compared to appropriate care alone. However, these results were questionable due to potential bias inherent in the study design.

Cost-effectiveness

Only one identified study performed cost-effectiveness and cost-utility analysis. This study compared combined treatment of viscosupplementation plus appropriate care with appropriate care only. The authors reported the incremental cost per patient improved in the first year to be $3,322, and the incremental cost per Quality Adjusted Life Year (QALY) gained in that time to be $13,260. Sensitivity analysis suggested an upper bound on the incremental cost of $5,672 per patient improved and of $55,381 per QALY gained. However, critical appraisal uncovered numerous flaws in the research design, which impacted on the economic analysis. Therefore, based on this one study against the comparator of appropriate care, the evidence for the comparative cost-effectiveness of hylan G-F 20 specifically must be regarded with caution.

A cost-effectiveness analysis was attempted from the results of existing literature. However, wide variations in the incremental effectiveness of these interventions led to different incremental cost-effectiveness ratios, even between studies making identical comparisons of treatment. Issues of study quality make the resulting data even less reliable. The majority of studies were underpowered, some were unblinded, and only one had a time horizon that extended past six months. Further, no studies compared viscosupplementation with COX-2 inhibitors and there was no data comparing hylan G-F 20 with IA corticosteroids. Therefore, little valid information on the cost-effectiveness of viscosupplementation products could be obtained from the existing literature.

An estimate was calculated of the cost that could be expected over a 1-year time period if any of the four identified comparators (NSAIDs, COX-2, viscosupplements or IA corticosteroids) were provided to the identified population of knee OA sufferers. Initially, the cost per patient per year to receive one course of any treatment was determined. One course of NSAID treatment was least expensive at $316 per patient per year. Conversely, one course of viscosupplements was most expensive, in the range $700–1140 per patient per year depending on the product and the number of injections per course. The cost difference between the two treatments was due to the extra visits to the clinician to administer the product, and the cost of the product itself.

When the costs of providing the entire population of knee OA sufferers in Australia with one or more courses of viscosupplementation or one of its comparators for 1 year were calculated, NSAIDs were the least expensive treatment option at $114 million per year. Comparatively, viscosupplements were the most expensive treatment option costing

$390 million for 1 year of hylan G-F 20 and up to $480 million per year for Supartz™. The disparity in the costs between the two viscosupplements is largely due to the two extra injections required for one course of Supartz™. While a single injection per course per year of the IA corticosteroid triamcinolone acetonide was 30 per cent cheaper in price to NSAID treatment ($80 million), a four-injection course of IA corticosteroid per year increased the price to 60 per cent higher than that of NSAIDs ($190 million). This was again due to the extra clinical visits and injection required. COX-2 inhibitors were up to two times more expensive to provide than NSAIDs ($180–230 million) due to the expense of the drugs themselves.

Recommendation

MSAC recommended that on the strength of evidence pertaining to intra-articular viscosupplementation for the treatment of osteoarthritis of the knee, public funding should not be supported for this procedure.

- The Minister for Health and Ageing accepted this recommendation on March 9, 2003.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumer health issues, and health administration and planning:

Member	**Expertise or affiliation**
Dr Stephen Blamey (Chair)	general surgery
Professor Bruce Barraclough	general surgery
Professor Syd Bell	pathology
Dr Paul Craft	clinical epidemiology and oncology
Associate Professor Jane Hall	health economics
Dr Terri Jackson	health economics
Ms Rebecca James	consumer health issues
Professor Brendon Kearney	health administration and planning
Associate Professor Richard King	internal medicine
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Mr Lou McCallum	consumer health issues
Dr Ewa Piejko	general practice
Mr Chris Sheedy	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Ageing
Professor John Simes	clinical epidemiology and clinical trials

Professor Richard Smallwood	Chief Medical Officer, Commonwealth Department of Health and Ageing
Dr. Robert Stable	representing the Australian Health Ministers' Advisory Council
Professor Bryant Stokes	neurological surgery,
Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Supporting committee

Supporting committee for MSAC application 1045
Intra-articular viscosupplementation for the treatment of osteoarthritis of the knee

Dr Terri Jackson (Chair) BA, MA, PhD (Health Policy) Health Economist Senior Research Fellow, Monash University Health Economics Unit	Member of MSAC
Associate Professor Leslie Barnsley BMed (Hons), GradDipEpidemiology (Clinical), PhD, FRACP, FAFRM (RACP) Department of Rheumatology, Concord Hospital	Australian Rheumatology Association
Professor Bruce Barraclough MB BS FRACS FACS DDU Professor of Cancer Services, University of Sydney and Northern Sydney Health	Member of MSAC
Mr David Marshall MB BS, (Adel), FRACS (Orth), FAORTHA	Royal Australasian College of Surgeons
Ms Anne Oldridge (deceased)	Consumers' Health Forum
Dr Jitendra Parikh MB BS (Calcutta), MD Obst and Gynaec (Bombay), MPM (NSW), Master Family Medicine (Monash)	Royal Australian College of General Practitioners
Dr Kevin Pile MB, ChB, MD, FRACP Department of Rheumatology, Queen Elizabeth Hospital	Royal Australasian College of Physicians

Appendix C Electronic database search strategy

The following search strategy was developed for Medline on a SilverPlatter platform. Similar strategies were used for the different bibliographic databases, with the same text words being used along with the relevant alternatives to MeSH (ie EmTree headings).

#36 #35 and #31 (1231 records)

#35 viscosuppl* or #34 (6797 records)

#34 #32 or #33 (6792 records)

#33 explode "Hyaluronic-Acid" / all SUBHEADINGS in MIME,MJME (6766 records)

#32 hylan (77 records)

#31 #30 not #29 (2050321 records)

#30 #27 or #28 (2642128 records)

#29 (TG=ANIMAL) not ((TG=HUMAN) and (TG=ANIMAL)) (2527344 records)

#28 explode "COHORT-STUDIES" / WITHOUT SUBHEADINGS in MIME,MJME (411851 records)

#27 #20 or #21 or #22 or #23 or #24 or #26 (2617905 records)

#26 (#25 in ti) or (#25 in ab) (1218914 records)

#25 control* or prospectiv* or volunteer* (1718471 records)

#24 PROSPECTIVE-STUDIES (139575 records)

#23 FOLLOW-UP-STUDIES (245355 records)

#22 explode "EVALUATION-STUDIES" / all SUBHEADINGS in MIME,MJME (404147 records)

#21 TG=COMPARATIVE-STUDY (964932 records)

#20 #18 not #19 (505319 records)

#19 (TG=ANIMAL) not ((tg=HUMAN) and (tg=ANIMAL)) (2527344 records)

#18 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 (540436 records)

#17 RESEARCH-DESIGN (24582 records)

#16 (random* in ti) or (random* in ab) (231276 records)

#15 (#14 in ti) or (#14 in AB) (65767 records)

#14 (singl* or doubl* or trebl* or tripl*) near (blind* or mask*) (89505 records)

#13 (clin* near trial*) in ab (58153 records)

#12 (clin* near trial*) in ti (17920 records)

#11 explode "CLINICAL-TRIALS" / all SUBHEADINGS in MIME,MJME (125907 records)

#10 CLINICAL-TRIAL in PT (319570 records)

#9 #7 not #8 (243901 records)

#8 (TG=ANIMAL) not ((TG=HUMAN) and (TG=ANIMAL)) (2527344 records)

#7 #1 or #2 or #3 or #4 or #5 or #6 (255912 records)

#6 SINGLE-BLIND-METHOD (6214 records)

#5 DOUBLE-BLIND-METHOD (66635 records)

#4 RANDOM-ALLOCATION (43701 records)

#3 RANDOMIZED-CONTROLLED-TRIALS (18421 records)

#2 CONTROLLED-CLINICAL-TRIAL in PT (58359 records)

#1 RANDOMIZED-CONTROLLED-TRIAL in PT (151738 records)

Appendix D Health technology assessment internet sites

AUSTRALIA

- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) http://www.surgeons.org/open/asernip-s.htm
- Centre for Clinical Effectiveness (Monash University, Australia) http://www.med.monash.edu.au/healthservices/cce/evidence/
- Health Economics Unit, Monash University http://chpe.buseco.monash.edu.au

AUSTRIA

- Institute of Technology Assessment / HTA unit http://www.oeaw.ac.at/ita/e1-3.htm

CANADA

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/en/index.htm
- Alberta Heritage Foundation for Medical Research (AHFMR) http://www.ahfmr.ab.ca/publications.html
- Canadian Coordinating Office for Health Technology Assessment (CCOHTA) http://www.ccohta.ca/newweb/pubapp/pubs.asp
- Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database http://www.mycabot.ca
- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org
- Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca
- Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm
- Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca

DENMARK

- Danish Institute for Health Technology Assessment (DIHTA) http://www.dihta.dk/publikationer/index_uk.asp

FINLAND

- FINOHTA http://www.stakes.fi/finohta/e/

FRANCE

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) http://www.anaes.fr/

GERMANY

- German Institute for Medical Documentation and Information (DIMDI) / HTA http://www.dahta.dimdi.de/

- German Scientific Working Group of Technology Assessment

  http://www.epi.mh-hannover.de/(eng)/hta.html

THE NETHERLANDS

- Health Council of the Netherlands Gezondheidsraad http://www.gr.nl/engels/welcome/frameset.htm

NEW ZEALAND

- New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/

NORWAY

- Norwegian Centre for Health Technology Assessment (SMM) http://www.oslo.sintef.no/smm/Publications/Engsmdrag/FramesetPublications.htm

SPAIN

- Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS) http://www.isciii.es/aets/cdoc.htm

- Catalan Agency for Health Technology Assessment (CAHTA) http://www.aatm.es/cgi-bin/frame.pl/ang/pu.html

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU) http://www.sbu.se/admin/index.asp

SWITZERLAND

- Swiss Network on Health Technology Assessment (SNHTA) http://www.snhta.ch/

UNITED KINGDOM

- Health Technology Board for Scotland http://www.htbs.org.uk/
- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.hta.nhsweb.nhs.uk/
- University of York NHS Centre for Reviews and Dissemination (NHS CRD) http://www.york.ac.uk/inst/crd/
- National Institute for Clinical Excellence (NICE) http://www.nice.org.uk/index.htm

UNITED STATES

- Agency for Healthcare Research and Quality (AHRQ) http://www.ahrq.gov/clinic/techix.htm
- Harvard Center for Risk Analysis – Cost-Utility Analysis Database Project [comprehensive league table] http://www.hcra.harvard.edu/tablesdata.html
- U.S. Dept. of Veterans Affairs Technology Assessment Program (VATAP) http://www.va.gov/resdev/prt/pubs_individual.cfm?webpage=pubs_ta_reports.htm

Appendix E Critical appraisal checklist

STUDY QUALITY ASSESSMENT CHECKLIST

Suitable for trials, cohorts and case-control studies

(Downs & Black (1998) – adapted for this MSAC assessment)

Viscosupplementation

Author(s):
Institution(s):
Year:
Study Design:
Comparators:

Reporting

1. *Is the hypothesis/aim/objective of the study clearly described?*

yes	1
no	0

2. *Are the main outcomes to be measured clearly described in the Introduction or Methods section?*

   If the main outcomes are first mentioned in the Results section, the question should be answered 'no'.

yes	1
no	0

3. *Are the characteristics of the patients included in the study clearly described?*

   In cohort studies and trials, inclusion and/or exclusion criteria should be given.

yes	1
no	0

4. *Are the interventions of interest clearly described?*

   Interventions that are to be compared should be clearly described.

yes	1
no	0

5. *Are the distributions of principal confounders in each group of subjects to be compared clearly described?*

   Confounders = age, gender, obesity, trauma.

yes	2
partially	1
no	0

6. *Are the main findings of the study clearly described?*

   Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions (This question does not cover statistical tests which are considered below).

yes	1
no	0

7. *Does the study provide estimates of the random variability in the data for the main outcomes?*

   In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered 'yes'.

yes	1
no	0

8. *Have all important adverse events that may be a consequence of the intervention been reported?*

   This should be answered 'yes' if the study demonstrates that there was a comprehensive attempt to measure adverse events.

   Adverse events = systemic effects, injection site pain, swelling, infiltration, infection, chondrocalcinosis, fever, headache, GI complaints (for NSAIDS).

yes	1
no	0

9. *Have the characteristics of patients lost to follow-up been described?*

   This should be answered 'yes' where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered 'no' where a study does not report the number of patients lost to follow-up.

yes	1
no	0

10. *Have the actual probability values been reported (eg 0.035 rather than <0.05) for the main outcomes, except where the probability value is less than 0.001?*

yes	1
no	0

External validity

All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.

11. *Were the subjects asked to participate in the study representative of the entire population from which they were recruited?*

    The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as 'unable to determine'.

yes	1
no	0
unable to determine	0

12. *Were those subjects who were prepared to participate representative of the entire population from which they were recruited?*

    The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

yes	1
no	0
unable to determine	0

13. *Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?*

    For the question to be answered 'yes' the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered 'no' if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

yes	1
no	0
unable to determine	0

Internal validity - bias

14. *Was an attempt made to blind study subjects to the intervention they have received?*

    For studies where the patients would have no way of knowing which intervention they received, this should be answered 'yes'.

yes	1
no	0
unable to determine	0

15. *Was an attempt made to blind those measuring the main outcomes of the intervention?*

yes	1
no	0
unable to determine	0

16. *If any of the results of the study were based on "data dredging", was this made clear?*

    Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer 'yes'.

yes	1
no	0
unable to determine	0

17. *In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients?*

    Where follow-up was the same for all study patients the answer should be 'yes'. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be 'yes'. Studies where differences in follow-up are ignored should be answered 'no'.

yes	1
no	0
unable to determine	0

18. *Were the statistical tests used to assess the main outcomes appropriate?*

    The statistical techniques used must be appropriate to the data. For example non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered 'yes'. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered 'yes'.

yes	1
no	0
unable to determine	0

19. *Was compliance with the intervention(s) reliable?*

    Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered 'no'. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered 'yes'.

yes	1
no	0
unable to determine	0

20. *Were the main outcome measures used accurate (valid and reliable)?*

    For studies where the outcome measures are clearly described, the question should be answered 'yes'. For studies which refer to other work or which demonstrate that the outcome measures are accurate, the question should be answered 'yes'.

yes	1
no	0
unable to determine	0

Internal validity – confounding (selection bias)

21. *Were the patients in different intervention groups (trials and cohort studies) recruited from the same population?*

    For example, patients for all comparison groups should be selected from the same hospital. The question should be answered 'unable to determine' where there is no information concerning the source of patients included in the study.

yes	1
no	0
unable to determine	0

22. *Were study subjects in different intervention groups (trials and cohort studies) recruited over the same period of time?*

    For a study which does not specify the time period over which the patients were recruited, the question should be answered 'unable to determine'.

yes	1
no	0
unable to determine	0

23. *Were study subjects randomised to intervention groups?*

    Studies which state that subjects were randomised should be answered 'yes' except where method of randomisation is unknown or would not ensure random allocation. For example, alternate allocation would score 'no' because it is predictable.

yes	1
no	0
unable to determine	0

24. *Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?*

    All non-randomised studies should be answered 'no'. If assignment was concealed from patients but not from staff, it should be answered 'no'.

yes	1
no	0
unable to determine	0

25. *Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?*

    This question should be answered 'no' for trials if: the main conclusions of the study were based on analyses of treatment rather than intention-to-treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomised studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered 'no'.

yes	1
no	0
unable to determine	0

26. *Were losses of patients to follow-up taken into account?*

    If the number of patients lost to follow-up are not reported, the question should be answered as 'unable to determine'. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered 'yes'.

yes	1
no	0
unable to determine	0

Subscale Scores

Reporting =	/11
External validity =	/3
Bias =	/7
Confounding =	/6

Total Quality Index Score = /27

Appendix F Studies included in the review

Level of evidence	Quality score[a]	Study	Location	Study design	Study population	Intervention	Outcomes(s) assessed	Length of follow-up
II	QS: 15/27 CI: 4 P: under-powered	(Leardini et al 1987)	Italy	Single blind RCT	36 patients, 40 knees HA (Hyalgan®) group 63.5±5.8 years 4 males/ 16 females Corticosteroid (Methyl prednisolone acetate, MPA) 64.7±7.0 years 3 males/ 13 females Active gonarthrosis, Grades II and III on Kellgren's scoring Washout period of 6 months for any IA treatment, 30 days for systemic corticosteroids, 15 days for NSAIDs	**HA**: 20 joints injected with 2 mL of 10 mg/mL Na Hyaluronate, (Hyalgan®) , one injection per week for 3 weeks **Corticosteroid**: 20 joints injected with 1 mL of 40 mg/mL MPA, 1 injection per week for 3 weeks No NSAIDs for first 2 months of study, then allowed for ≤ 2 weeks duration.	**Pain and function:** pain assessed by the Scott and Huskisson VAS (1= absent, 5= very severe). Active and passive movement measured in degrees, ring size in cm. **Adverse events:** no mention of how collected, assumed simple monitoring. Assessment at 0, 1, 2 and 3 weeks, 60 days and 1 year. Outcomes assessed on 20 joints in each group for all time points but 1 year (15 joints in HA, 17 joints in MPA).	1 year
II	QS: 18/27 CI: NE for primary outcome P: NE for primary outcome, 70% for secondary outcomes	(Leardini et al 1991)	Italy	RCT un-blinded	Ideopathic OA of the knee based on American Rheumatology Association criteria and radiologically assessed according to the Kellgren classification Previous failure of NSAID treatment **Exclusions:** treatment in past 3 months of any IA drug, serious concomitant disorders, ongoing infections, pregnancy, history of allergy or hypersensitivity to drugs	**HA**: 20 joints injected with 2 mL of 10 mg/mL Na Hyaluronate, (Hyalgan®), 1 injection per week for 3 weeks **Corticosteroid**: 20 joints injected with 1 mL of 40 mg/mL MPA, 1 injection per week for 3 weeks **Arthrocentesis:** performed prior to each injection if effusion present. Patients kept at rest for 2 days after injection.	**Pain and function:** pain assessed by a VAS (0-100 cm), duration of morning stiffness in minutes and joint flexion in degrees. Night pain, rest pain, pain under load and touch pain scored as (0= none, 1= slight, 2= moderate, 3= strong, 4= very strong). NSAID consumption scored as (0= none, 1= occasional low doses, 2= regular low doses, 3= regular high doses) **Adverse events:** assessment at 0, 1, 2, 3, 4 and 5 weeks, 60 days. Blood pressure, heartbeat, and laboratory tests were carried out to assess changes in blood chemistry, liver and kidney function and carbohydrate metabolism.	60 days

[a] QS = quality score out of 27, see Appendix E; CI = clinical importance; P = power.

II	QS: 26/27 CI: 4 P: under-powered	(Altman & Moskowitz 1998)	Academic and private practice centres United States	Double blind RCT	Consecutive patients at 15 academic or private practice centres HA (n=164) NSAID (n=163) Clinically diagnosed with OA, ≥40 years of age, knee pain ≥1 year and ≥20 mm on 100 mm VAS after 50-ft walk, knee pain ≥ 20 mm on ≥ 1 item on the WOMAC pain subscale, moderate or marked pain on 6 point categorical scale (none, slight, mild, moderate, marked, severe), knee radiograph showing ≥1 osteophyte and rated grade II to III on the Kellgren-Lawrence scale **Exclusions:** no IA injections of HA in last year, no IA injections of other treatments within past 3 months	2-week washout for all patients **HA (Hyalgan®) :** arthrocentesis if necessary then 20 mg/ 2 mL HA injection, one injection per week for 5 weeks, oral placebo 2 tablets daily for 26 weeks **Naproxen (NSAID):** sham injection, lidocaine local only once per week for 5 weeks, arthrocentesis if effusion present, 500 mg tablet Naproxen, 2 tablets/day for 26 weeks **Placebo**: arthrocentesis if necessary, injection of 2 mL saline vehicle, 1 injection per week for 5 weeks, oral placebo 2 tablets/day for 26 weeks Rescue therapy 500 mg tablets of acetominophen up to 4,000 mg /day.	**Primary outcome measure**: patient recorded pain after 50-foot walk 100 mm VAS. Assessed at baseline, weeks 1-5, 9, 12, 16, 21, 26 **Secondary measures**: patient and assessor global assessment of pain during previous 48 hours- 6 point categorical scale, time in seconds to complete 50-ft walk, WOMAC–VAS, heel to buttock distance (cm), knee range of motion by goniometer in degrees, mid patellar knee circumference in mm, clinical estimate of knee effusion (present/absent), acetominophen tablet count. Assessed at baseline, weeks 1-5, 9, 12, 16, 21, 26 Overall evaluation of treatment effectiveness (patient and assessor) Assessed at weeks 9, 16 and 26 **Adverse events:** any reported adverse event, lab and haematological assessments, synovial fluid analysis recorded at baseline, weeks 1-5, 9, 12, 16, 21, 26	26 weeks
II	QS: 22/27 CI: 4 P: under-powered	(Petrella et al 2002)	Primary care referral centre, Canada	Double blind RCT	Patients recruited from large primary care referral centre for assessment of knee OA, radiographic evidence of grade I-III medial compartment, unilateral knee OA[b]	4 treatment groups **HA plus placebo (Suplasyn):** 2 mL of 10 mg/mL injection, 1 injection per week for 3 weeks plus placebo tablet 2 daily for 12 weeks	**Pain:** self-report pain 10 cm VAS after sitting 10 minutes, pain subscale of WOMAC (on 10 cm VAS) **Activity related pain:** VAS after self-paced stepping (SPS) or walking (SPW)	12 weeks

[b] Grading based on the study by Altman

					Exclusions: non-OA arthritides, previous NSAID intolerance, gastrointestinal haemorrhage, peptic ulcer disease, avian allergy, regular consumption of 'herbal' products (eg glucosamine sulphate) IA injection of HA or corticosteroid within previous 6 months **Final baseline inclusion criteria:** grade I to III OA on radiograph, ≥3 cm on 10 cm VAS for current pain HA plus placebo (n=25) HA plus NSAID (n=29) Placebo injection plus NSAID (n=26) Placebo injection plus placebo tablets (n=28)	**HA plus NSAID (Suplasyn):** 2 mL of 10 mg/mL injection, 1 injection per week for 3 weeks plus 75 mg diclofenac + 200 µg misoprostol twice daily for 12 weeks **Placebo injection plus NSAID:** saline vehicle 2 mL 1 injection per week for three weeks plus 75 mg diclofenac + 200 µg misoprostol twice daily for 12 weeks **Placebo injection plus placebo tablets:** saline vehicle 2 mL 1 injection per week for three weeks plus placebo tablet 2 daily for 12 weeks **Rescue therapy:** 650 mg acetominophen 4 times daily when required All groups also given resistance exercise program 10 minutes 3 days per week	**Physical functioning:** stiffness and disability subscales of WOMAC, time to complete (sec) and heart rate all after SPS and SPW **Adverse events:** No mention of the method for collection **Outcomes:** measured at baseline, week 4 and at week 12	
II	QS: 19/27 CI: 1 P: 93%	(Tekeoglu et al 1998)		RCT un-blinded	40 female patients with Kellgren-Lawrence graded OA with presence of pain **Exclusions:** knee joint disease other than OA, history of allergy, skin infections HA (Orthovisc™) (n=20) Bexamethasone (corticosteroid) (n=20)	**HA (Orthovisc™):** 20 mg/2 mL injection once weekly for 3 weeks **Bexamethasone (corticosteroid):** 3 mg/mL injection once weekly for 3 weeks Both groups of patients rested for 1 day after injection **Rescue medications:** paracetamol only, no NSAIDs Arthrocentesis performed on	**Intensity of pain**: assessed at baseline only: 1= slight pain, 2= moderate pain, 3= severe pain **Clinical severity of activities of daily living:** WOMAC function measures, 17 different activities, scored on Likert scale; 1= none, 2= mild, 3= moderate, 4= severe, 5= extreme **Joint flexion:** measured in degrees **Patient and assessor determination of treatment efficacy:** 0= unsatisfactory, 1= poor, 2= fair, 3= good, 4= excellent	15 weeks

						either group when effusion present	Assessments performed at baseline, week 3 and week 15 **Adverse events:** Blood pressure and heart rate measured at each clinical evaluation, blood and urine collected for lab analysis at baseline and 15 weeks, measurement of liver and kidney function, carbohydrate metabolism	
II	QS: 18/27 CI: NE for primary outcome, 2 for no pain under load P: NE from primary outcome, under-powered for pain under load	(Pietrogrande et al 1991)	Multi-centre orthopaedic and trauma units, Italy	Multi-centre RCT un-blinded	90 patients (24 males/ 66 females), confirmed knee OA by Kellgren scale **Exclusions:** knee joint diseases not associated with OA, any severe concomitant diseases or diseases interfering with an evaluation of knee OA, pregnancy, history of allergy, skin infections, IA treatments within 3 months of study start HA (Hyalgan®) (n=45) Methyl prednisolone acetate (MPA) (n=45)	**HA (Hyalgan®):** 20 mg/2 mL injected once per week for 5 weeks **Methyl prednisolone acetate (MPA)**: 40 mg/ mL injected once per week for 3 weeks Rescue analgesics or NSAIDs allowed in both groups	**Primary measures:** **Daytime spontaneous pain:** (pain felt during normal activities of daily living) measured by 0-100 mm VAS, unsure if patient assessed. **Morning stiffness:** in minutes **Joint motion:** degrees of flexion and extension **Treatment efficacy:** patient and assessor measured, 0= unsatisfactory, 1= poor, 2= fair, 3= good, 4= excellent **Secondary measures:** **Night pain, rest pain, pain under load, touch pain:** 0= absent, 1= slight, 2= moderate, 3= strong, 4= very strong Unsure if patient assessed **NSAID consumption:** 0= none, 1= occasional, 2= continuous low doses, 3= continuous high doses **Volume of effusate:** in mL Above outcomes all measured at baseline, 7, 14, 21, 28, 35 and 60 days **Adverse events:** Type, duration and severity of any	60 days

							reported adverse event noted, blood pressure, heart rate at each clinical exam, blood and urine sampled for routine laboratory safety screen at baseline and at 60 days	
II	QS: 19/27 CI: NE from primary outcome P: NE from primary outcome	(Wobig et al 1999)	Germany	Multi-centre double blind RCT	>18 years, primary OA of the knee, Larsen grade I-III, ESR<40 mm/h, rheumatoid factor <1:160 daily persistent pain **Exclusions:** Free of pain, detectable effusion, considered by investigators to be unreliable	**LMW Hyaluronic acid:** (0.75 KD, n=32), 2 mL once per week for 3 weeks **Hylan G-F 20:** (6 KD, n=38) 2 mL once per week for 3 weeks **Protocol:** 2-week washout period baseline clinical assessment after washout arthrocentesis before each injection injections at weeks 0, 1 and 2 follow-up at weeks 3, 8 and 12 concomitant medications and rescue therapy permitted	**Weight-bearing pain:** VAS (0-100 mm), patient and evaluator measured- at baseline and all other time points **Overall treatment response:** VAS (0-100 mm), patient and evaluator measured- at weeks 3, 8 and 12 **Improvement in most painful knee movement:** VAS (0-100 mm), patient measured only at weeks 3, 8 and 12 Symptom free = VAS scores ≤20 mm or improvement in overall treatment or knee movement ≥80 mm **Adverse events:** Interview of patient at each visit, investigator determined whether reported or observed adverse events were: likely, possibly, unlikely to be related to treatment	12 weeks

II	QS: 22/27 CI: 4 P: under-powered	(Adams et al 1995)		Double blind RCT	18-75 years, chronic ideopathic OA on radiographic exam, Kellgren-Lawrence radiographical grade I-III (in no more than 2 compartments-not grade III in patellofemoral compartment) Also had to satisfy 4 of the following 6 criteria: ESR<30 mm/h, Rheumatoid factor titre <1:160, morning stiffness ≤30 min, crepitus on active motion, tenderness of the bony margins, physician determination of the absence of RA **Exclusions:** Any other serious systemic disease, depression, neuroses, acute synovitis or excessive effusion, clinically obese >30% above normal body weight, varus or valgus deformity >15°, pregnant, not using effective form of contraception, chronic daily steroid therapy, surgery or joint injection ≤3 months previously	**Group 1:** NSAID only continuous for all 26 weeks of study, arthrocentesis at weeks 1, 2 and 3 (n=32) **Group 2:** hylan G-F 20 only, one 2 mL injection at weeks 1, 2 and 3, any effusion in the joint was removed (n=28) **Group 3:** hylan G-F 20 and NSAID Effusion in the joint was removed (n=33) Rescue analgesia can be acetominophen but no other meds can be taken Evaluations at weeks 1 (baseline), 2, 3, 7, 12 and the 26 weeks follow-up.	**Patient assessed outcomes**: By VAS (100 mm) pain on motion[c], pain at rest, pain at night, restriction of activity Overall assessment of arthritic pain By ordinal scale (1= never able to perform, 2 = occasionally able, 3= frequently able) For : level of activity when: standing, sitting, walking, climbing, running By ordinal scale (1 = none, 2= pain only on starting activity after rest, 3= pain during day when active, 4= pain during day at rest, 5= pain all day and waking patient at night) For: severity of pain **Evaluator assessed outcomes:** By VAS (100 mm) Medial joint tenderness, lateral joint tenderness, pain during 50-ft walk, overall assessment of clinical condition **Adverse events:** interview of patient at each study visit	26 weeks
II	QS: 24/27 CI: 4 P: under-powered	(Dickson et al 2001)	18 GP offices in the UK	Multi-centre double blind RCT	35-80 years, radiologically confirmed OA predominant in the tibio-femoral compartment with no other OA joint that might require escape analgesia (ie knee most painful joint) X-ray indicative of OA taken less than 2	**All patients:** washout of 3-7 days (no NSAIDs, analgesics, with exception of 500 mg paracetamol– to 3 g/day). At end of washout patients assessed by VAS to have score >40 mm on	**Efficacy:** WOMAC pain questionnaire (section A only) 5 categories each measured by 10 cm horizontal VAS. Pain with walking on flat surface, going up or down stairs, at night while in bed, sitting or lying,	12 weeks

[c] primary measure

					years. **Exclusions:**patient is bedridden, in a wheelchair, unable to walk 50 steps unaided. Patient has joint disease (RA, crystalline or other systemic inflammatory arthropathy) Clinically significant renal, hepatic or haematological disorders. Arthrocentesis and hylan G-F 20 (n=53) Arthrocentesis (1x3 weeks) and diclofenac capsules (n=55)	at least 2 of 5 of the WOMAC pain scales randomised to one of 3 groups: **Arthrocentesis and hylan G-F 20:** (2 mL, 1x 3 weeks) **Arthrocentesis (1x3 weeks) and diclofenac capsules:** (100 mg/day for 12 weeks) **Arthrocentesis (1x3 weeks) and placebo capsules:** (1/day for 12 weeks) Intervention begins at week 0. Injections and arthrocentesis at weeks 0, 1, and 2. Blinded observer evaluation and patient reported evaluation at weeks 0, 1, 2, 3, 4, 8, 12.	standing upright At baseline and at the final visit (12 weeks) full WOMAC questionnaire (sections A, B and C) and the Lequesne index administered. Finally, patients asked to rate overall opinion of the treatment on a 5-category verbal scale. **Adverse events:** at each visit, open ended questions asked of each patient regarding any local or systemic adverse events since the previous visit. Blood samples taken at start and finish to monitor for any changes in haematology and biochemistry tests.	
II	QS: 23/27 CI: 1 P: 100%	(Raynauld et al 2000)	Multi-centre	RCT	**Inclusion criteria:** primary diagnosis of OA grades I-III (Larsen?), ≥40 years of age, ambulatory, previous history of OA on study knee with pain most days for the previous 3 months. WOMAC–VAS total pain score >175 mm on 5 visual VAS (100 cm scales). OA in study knee (verified by x-ray taken within last year). Willing and able to understand English or French and able to complete questionnaire and memory aid. **Exclusion criteria:** corticosteroid injections in the study knee in the previous 3 months. Prior viscosupplementation therapy. Patients with a hypersensitivity to avian protein. Venous or lymphatic stasis	After inclusion in the study patients were randomised to one of 2 treatment groups: **Synvisc + appropriate care:** (n=127**)** initial injection at baseline (2 mL) followed by a further 2 injections over the next 2 weeks. If pain persisted, a minimum of 4 weeks from the last injection was required before a second set of injections could be instigated. Appropriate care described as below. **Appropriate care only**: (n=128) Following the American College of Rheumatology (ACR) Guidelines	**Effectiveness:** **Primary measure:** mean change in WOMAC Likert pain score from baseline to termination. Measured at baseline, months 1, 2, 4, 6, 8, 10 and 12. Recall was for the period 4 weeks prior to the assessment. **Secondary measures:** % of patients improved. An improved patient was defined as ≥20% improvement in WOMAC Likert pain score. % of patients improved. In this instance an improved patient was defined as ≥20% improvement in WOMAC Likert pain score and either 20%	12 months

					present in the leg. Infected knee(s) or a history of. Grade IV OA of the study knee (verified by x-ray taken in past year). Isolated patella-femoral involvement in the study knee. Secondary forms of OA in the study knee. Chondrocalcinosis in the study knee. Varus or valgus deformity >12º. Concomittant inflammatory arthritis or metabolic arthritis. Morbidity in joints that would impede measurements in the study knee. Any other morbidity (uncontrolled) that required > 3 visits to the physician in the past 3 months. Pregnancy, breast-feeding or women of childbearing potential who are not practicing an acceptable method of birth control.	(ie investigators encouraged at all times to reduce medication dose, or move to a lower intensity intervention, in patients whose symptoms sufficiently improve). Appropriate care left to the discretion of the treating physician, again encouraged to follow ACR guidelines.	improvement in function or stiffness score. **Patient global assessment:** measured in 2 ways. Continuously (at each measurement point: baseline, months 1, 2, 4, 6, 8, 10 and 12). Patient asked to rate OA in study knee, all joints and overall health as very good, good, fair, poor, or very poor. And once at end of study, asking patient to rate OA in study knee, all joints and overall health for past 48 hours compared to baseline. **Safety:**two methods – asking patients to complete global assessments of side effects and to report any adverse events. **Global assessment:** at each time point (months 1, 2, 4, 6, 8, 10 and 12), patients asked to rate side effects experienced in the last 4 weeks as none, mild, moderate or severe. At study completion patient asked to consider any side effects experienced since the baseline visit as none, mild, moderate or severe. **Adverse events:** at each time point (months 1, 2, 4, 6, 8, 10 and 12), information on any adverse event was collected. Severity (mild, moderate, severe), outcome (resolved, improved, death), and action taken (none, dose reduced,	

							discontinued) were assessed Relationship of adverse event to Synvisc determined by investigator as none, remote, possible, probable, not assessable. History of the adverse event categorised as: never experienced before, occasionally experienced, often or experienced all the time. Any serious adverse events were reported to investigators within 24 hours.	

Appendix G Checklist for appraising economic evaluation studies

Appraisal items for internal validity

1. Was the study question well defined?
2. Were appropriate health care options chosen and clearly described?
3. Was an appropriate study type used?
4. Was the effectiveness of the health care options established?
5. Were the cost estimates related to baseline population risk?
6. Were all the relevant costs and consequences identified for each health care option?
7. Were costs and consequences measured accurately?
8. Were costs and consequences valued credibly?
9. Was differential timing considered?
10. Was an incremental analysis performed?
11. Was a sensitivity analysis performed?
12. Were modelling techniques used in a clear and reasonable way?

Criteria for assessing the ability to generalise in economic evaluation studies

1. Patient group
2. Health system setting
3. Health care option
4. Resource costs
5. Marginal versus average cost
6. Other specific issues

Source:(National Health and Medical Research Council 2001)

Appendix H Costing calculations for interventions in treatment of knee OA

Costs of treatments per patient per year

hylan G-F 20 3 injections one course per year						
Rheumatologist- initial visit	$117.45	1	$117.45	$814.55	$1,511.65	
Rheumatologist-subsequent visit	$58.80	3	$176.40	$176.40	$176.40	
hylan GF-20	$444.50	1	$444.50	$444.50	$444.50	
Injection into synovial cavity	$25.40	3	$76.20	$76.20	$76.20	
total cost			$814.55	$1,511.65	$2,208.75	$1,107.33
hylan G-F 20 3 injections two knees one course per year						
Rheumatologist- initial visit	$117.45	1	$117.45	$1,304.65	$2,491.85	
Rheumatologist-subsequent visit	$58.80	3	$176.40	$176.40	$176.40	
Supartz 1st knee	$444.50	1	$444.50	$444.50	$444.50	
Injection into synovial cavity 1st knee	$25.40	3	$76.20	$76.20	$76.20	
Supartz 2nd knee	$444.50	1	$444.50	$444.50	$444.50	
Injection into synovial cavity 2nd knee	$15.20	3	$45.60	$45.60	$45.60	
total cost			$1,304.65	$2,491.85	$3,679.05	$1,803.27
Triamcinolone acetonide (IA corticosteroid) 1 injection one course per year						
Rheumatologist- initial visit	$117.45	1	$117.45			
Rheumatologist-subsequent visit	$58.80	1	$58.80			
Triamcinolone acetonide	$23.73	1	$23.73			
Injection into synovial cavity	$25.40	1	$25.40			
total cost			$225.38			
Triamcinolone acetonide (IA corticosteroid) 4 injection one course per year						
Rheumatologist- initial visit	$117.45	1	$117.45			
Rheumatologist-subsequent visit	$58.80	4	$235.20			
Triamcinolone acetonide	$23.73	4	$94.92			
Injection into synovial cavity	$25.40	4	$101.60			
total cost			$549.17			
COX-2 Celecoxib 200 mg/day per year						
Rheumatologist- initial visit	$117.45	1	$117.45			
Celecoxib 200 mg 30 tabs	$32.05	12	$384.60			
total cost			$502.05			
COX-2 Rofecoxib 25 mg/day per year						
Rheumatologist- initial visit	$117.45	1	$117.45			
Rofecoxib 25 mg 30 tabs	$42.75	12	$513.00			
total cost			$630.45			
NSAID Naproxen 1000 mg/day per year						
Rheumatologist- initial visit	$117.45	1	$117.45			
Naproxen 500 mg 50 tabs	$13.30	15	$199.50			
total cost			$316.95			

* For viscosupplements assumed that 60% receive one course, 38% two courses and 2% three courses in one year

Appendix I Abbreviations

AIHW: Australian Institute for Health and Welfare

AR-DRG: Australian Refined – Diagnosis Related Groups

ARTG: Australian Registry for Therapeutic Goods

CI: confidence intervals

COX-2: cyclo-oxygenase

cm: centimetre

HA: hyaluronic acid

HAQ: health assessment questionnaire

HRQOL: health related quality of life

HTA: Health Technology Assessment

HUI: Health Utility Index

Hylan G-F 20: hylan Gel Fluid 20

IA: intra-articular

ICER: incremental cost-effectiveness ratio

IL-1: interleukin – 1

ITT: intention to treat

KDa: kiloDalton (1,000 Daltons)

MBS: Medicare Benefits Schedule

MIMS: Monthly Index of Medical Specialties

mm: millimetre

MPA: methyl prednisolone acetate

MSAC: Medical Services Advisory Committee

MW: molecular weight**n:** number

NA: not applicable

NE: not estimable

NHMRC: National Health and Research Council

NNH: numbers needed to harm

NNT: numbers needed to treat

NNTB: numbers needed to treat to benefit

NNTH: numbers needed to treat to harm

NSAID: non-steroidal anti-inflammatory drug

OA: osteoarthritis

OMERACT: outcome measures in arthritis clinical trials

P: probability

PBS: Pharmaceutical Benefits Schedule

QALY: quality adjusted life years

QS: quality score

RCT: randomised controlled trial

r/n: number of subjects with condition / number of subjects in intervention group

RR: relative risk

SD: standard deviation

SF-36: Short Form-36

SPS: self-paced stepping

SPW: self-paced walking

VAS: visual analogue scale

WOMAC: Western Ontario and McMaster Universities Arthritis Index

χ^2: chi-squared

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