Appendix A. Search Strategy

DATABASE SEARCHED & TIME PERIOD COVERED:
PUBMED – 1/1/2014-12/11/2014

SEARCH STRATEGY:
(hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan) AND (osteoarthritis, knee OR (knee* AND osteoarthritis) OR (knee* AND arthrit*) OR gonarthrosis)
OR
(hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan) AND degenerative joint disease AND (knee OR knees)
OR
((viscosupplement* OR visco-supplement*) AND (osteoarthritis, knee OR (knee* AND osteoarthritis) OR (knee* AND arthrit*) OR gonarthrosis))

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DATABASE SEARCHED & TIME PERIOD COVERED:
Web of Science Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH – 1/1/2014-12/11/2014

SEARCH STRATEGY:
TS=(hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan) AND TS=(knee OR knees) AND TS=(osteoarthritis OR arthrit* OR gonarthrosis)
OR
TS=(hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan) AND TS=(knee OR knees) AND TS=(degenerative joint disease)
OR
TS=(viscosupplement* OR visco-supplement*) AND TS=(knee OR knees) AND TS=(osteoarthritis OR arthrit* OR gonarthrosis)

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DATABASE SEARCHED & TIME PERIOD COVERED:
SCOPUS – 1/1/2014-12/12/2014

SEARCH STRATEGY:
TITLE-ABS-KEY (hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan) AND TITLE-ABS-KEY (knee OR knees)
OR
TITLE-ABS-KEY (hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan) AND TITLE-ABS-KEY (knee OR knees) AND ALL ("degenerative joint disease")
OR
TITLE-ABS-KEY (viscosupplement* OR visco-supplement*) AND TITLE-ABS-KEY (knee OR knees) AND TITLE-ABS-KEY (osteoarthritis OR arthrit* OR gonarthrosis)

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DATABASE SEARCHED & TIME PERIOD COVERED:

Cochrane – 1/1/2014-12/12/2014

SEARCH STRATEGY:
SEARCH 1:
hyaluronic acid or hyaluronate* or hyaluronan or hylan:ti,ab,kw (Word variations have been searched)
AND
osteoarthritis, knee or (knee* and osteoarthritis) or (knee* and arthrit*) or gonarthrosis

All Results (17)
Cochrane Reviews (0)
All Review Protocol
Other Reviews (2)
Trials (14)
Methods Studies (0)
Technology Assessments (0)
Economic Evaluations (1)
Cochrane Groups (0)

SEARCH 2:
hyaluronic acid or hyaluronate* or hyaluronan or hylan:ti,ab,kw (Word variations have been searched)
AND
degenerative joint disease
AND
knee or knees

All Results (2)
Cochrane Reviews (0)
All Review Protocol
Other Reviews (0)
Trials (2)
Methods Studies (0)
Technology Assessments (0)
Economic Evaluations (0)
Cochrane Groups (0)

SEARCH 3:
viscosupplement* or visco-supplement*:ti,ab,kw (Word variations have been searched)
AND
osteoarthritis, knee or (knee* and osteoarthritis) or (knee* and arthrit*) or gonarthrosis

All Results (5)
Cochrane Reviews (0)
All Review Protocol
Other Reviews (0)
Trials (4)
Methods Studies (0)
Technology Assessments (1)
Economic Evaluations (0)
Cochrane Groups (0)

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DATABASE SEARCHED & TIME PERIOD COVERED:
Embase– 1/1/2014-12/12/2014

SEARCH STRATEGY:
SEARCH 1:
hyaluronic NEAR/2 acid* OR hyaluronate* OR 'hyaluronan' OR 'hyaluronan'/exp OR hyaluronan OR hylan AND
'osteoarthritis' OR 'osteoarthritis'/exp OR osteoarthritis AND ('knee' OR 'knee'/exp OR knee OR knees) OR (knee* AND arthrit*) OR 'gonarthrosis' OR 'gonarthrosis'/exp OR gonarthrosis
AND
Humans/lim

SEARCH 2:
hyaluronic NEAR/2 acid* OR hyaluronate* OR 'hyaluronan' OR 'hyaluronan'/exp OR hyaluronan OR hylan
AND
degenerative AND ('joint' OR 'joint'/exp OR joint) AND ('disease' OR 'disease'/exp OR disease)
AND
'knee' OR 'knee'/exp OR knee OR knees
AND
Humans/lim

SEARCH 3:
viscosupplement* OR 'visco supplement' OR 'visco supplements' OR 'visco supplemental'
AND
'osteoarthritis' OR 'osteoarthritis'/exp OR osteoarthritis OR arthrit* OR 'gonarthrosis' OR 'gonarthrosis'/exp OR gonarthrosis
AND
'knee' OR 'knee'/exp OR knee OR knees
AND
Humans/lim

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DATABASE SEARCHED & TIME PERIOD COVERED:
New York Academy of Medicine Grey Literature Report – 1/1/2014-12/12/2014

SEARCH STRATEGY:
Hyaluronic OR hyaluronate OR hyaluronan OR hylan OR viscosupplement OR visco-supplement

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DATABASE SEARCHED & TIME PERIOD COVERED:
Canadian Agency for Drugs and Technologies in Health (CADTH) – 1/1/2014-12/12/2014

SEARCH STRATEGY:
hyaluronic OR hyaluronate OR hyaluronan OR hylan OR viscosupplement OR visco-supplement

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 1/1/1990-10/30/2013

SEARCH STRATEGY:
(1a)
hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan
AND
osteoarthritis, knee OR (knee* AND osteoarthritis) OR (knee* AND arthrit*) OR gonarthrosis

OR

(1b)
hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan
AND
degenerative joint disease
AND
knee OR knees

OR

(1c)
viscosupplement* OR visco-supplement*
AND
osteoarthritis, knee OR (knee* AND osteoarthritis) OR (knee* AND arthrit*) OR gonarthrosis

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DATABASE SEARCHED & TIME PERIOD COVERED:
Cochrane Databases – 1/1/1990-11/21/13

SEARCH STRATEGY 1a:
hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan
AND
osteoarthritis, knee OR (knee* AND osteoarthritis) OR (knee* AND arthrit*) OR gonarthrosis

All Results (216)
Cochrane Reviews (5)
Other Reviews (14)
Trials (184)
Methods Studies (1)
Technology Assessments (7)
Economic Evaluations (5)

SEARCH STRATEGY 1b:
hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan
AND
degenerative joint disease
AND

knee OR knees

All Results (8)
Cochrane Reviews (4)
Other Reviews (0)
Trials (4)
Methods Studies (0)
Technology Assessments (0)
Economic Evaluations (0)

SEARCH STRATEGY 1c:
viscosupplement* OR visco-supplement*
AND
osteoarthritis, knee OR (knee* AND osteoarthritis) OR (knee* AND arthrit*) OR gonarthrosis

All Results (57)
Cochrane Reviews (2)
Other Reviews (4)
Trials (45)
Methods Studies (0)
Technology Assessments (5)
Economic Evaluations (1)

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DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 1/1/1990-11/22/2013

SEARCH STRATEGY:
(1a)
hyaluronic NEAR/2 acid* OR hyaluronate* OR 'hyaluronan'/exp OR hyaluronan OR hylan
AND
osteoarthritis, AND ('knee'/exp OR knee) OR (knee* AND ('osteoarthritis'/exp OR osteoarthritis)) OR (knee* AND arthrit*) OR 'gonarthrosis'/exp OR gonarthrosis
AND
[humans]/lim
(EXCLUDE MEDLINE RESULTS)

(1b)
'degenerative joint disease'/exp OR 'degenerative joint disease' OR 'degenerative joint diseases'
AND
'knee'/exp OR knee OR knees
AND
[humans]/lim
(EXCLUDE MEDLINE RESULTS)

(1c)
viscosupplement* OR 'visco supplement' OR 'visco supplements' OR 'visco supplementation'

AND
(knee* AND ('osteoarthritis'/exp OR osteoarthritis)) OR (knee* AND arthrit*) OR 'gonarthrosis'/exp OR gonarthrosis
AND
[humans]/lim
(EXCLUDE MEDLINE RESULTS)

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DATABASE SEARCHED & TIME PERIOD COVERED:
Web of Science Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH – 1/1/1990-11/22/2013

SEARCH STRATEGY:
Topic=(hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan) AND Topic=(knee OR knees) AND Topic=(osteoarthritis OR arthrit* OR gonarthrosis)

OR

Topic=(hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan) AND Topic=(knee OR knees) AND Topic=(degenerative joint disease)

OR

Topic=(viscosupplement* OR visco-supplement*) AND Topic=(knee OR knees) AND Topic=(osteoarthritis OR arthrit* OR gonarthrosis)

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DATABASE SEARCHED & TIME PERIOD COVERED:
SCOPUS – 1/1/1990-11/25/2013

SEARCH STRATEGY:
(1a)
hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan
AND
knee OR knees
AND
osteoarthritis OR arthrit* OR gonarthrosis
1481

(1b)
TITLE-ABS-KEY(hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan)
AND
knee OR knees
AND
degenerative joint disease
AND

SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal)
65

(1c)
TITLE-ABS-KEY((viscosupplement* OR visco-supplement*)
AND
knee OR knees
AND
osteoarthritis OR arthrit* OR gonarthrosis
AND
SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal)
337

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DATABASE SEARCHED & TIME PERIOD COVERED:
NEW YORK ACADEMY OF MEDICINE GREY LITERATURE REPORT – Earliest dates to 11/26/2013

SEARCH STRATEGY:
Hyaluronic OR hyaluronate OR hyaluronan OR hylan OR viscosupplement OR visco-supplement OR knee OR knees

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DATABASE SEARCHED & TIME PERIOD COVERED:
CANADIAN AGENCY FOR DRUGS AND TECHNOLOGIES IN HEALTH (CADTH) GREY MATTERS DATABASE – Earliest to 11/26/2013

SEARCH STRATEGY:
hyaluronic OR hyaluronate OR hyaluronan OR hylan

viscosupplement OR visco-supplement

knee OR knees

Appendix B. List of Excluded Studies

Not English – N=8

1. Auerbach B, Melzer C. [Cross-linked hyaluronic acid in the treatment of osteoarthritis of the knee--results of a prospective randomized trial]. Zentralbl Chir. 2002 Oct;127(10):895-9. PMID: 12410458.

2. Bingol U, Yurtkuran M. Comparison of the clinical efficacy and adverse effects of two hyaluronan preparations with different molecular weights and a methyl prednisolone acetate in knee osteoarthritis ORIGINAL (NON-ENGLISH) TITLE Diz Osteoartritinde Iki Farkli{dotless} Molekul Agi{dotless}rli{dotless}kli{dotless} Hyaluronik Asit Preparati{dotless} ve Metil Prednisolon Asetat Preparati{dotless}ni{dotless}n Etki ve Yan Etkilerinin Klinik Olarak Karsi{dotless}lasti{dotless}ri{dotless}lmasi{dotless}. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi. 2013 2013;59(3):189-200. PMID: 2013594380 FULL TEXT LINK http://dx.doi.org/10.4274/tftr.72687.

3. Bingöl Ü, Yurtkuran M. Comparison of the clinical efficacy and adverse effects of two hyaluronan preparations with different molecular weights and a methyl prednisolone acetate in knee osteoarthritis. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi. 2013;59(3):189-200.

4. Hashemi SM, Madadi F, Razavi S, et al. Intra-articular hyaluronic acid injections Vs. dextrose prolotherapy in the treatment of osteoarthritic knee pain. Tehran University Medical Journal. 2012 May;70(2):119-25. PMID: 2012213013.

5. Ostalowska A, Nowak D, Swiechowicz S, et al. Assessment of knee function and biochemical parameters of articular fluid and peripheral blood in gonarthrosis patients following intra-articular administration of hyaluronic acid. Pol Orthop Traumatol. 2013;78:173-81. PMID: 23959433.

6. Oswald A, Gachter A. [Acute local reaction after intra-articular injection of HYALAN G-F 20 (Synvisc) for treatment of gonarthrosis onset]. Praxis (Bern 1994). 2000 Nov 16;89(46):1929-31. PMID: 11111412.

7. Pavelka K, Trc T, Karpas K, et al. [Intra-articular treatment with Hyalgan in osteoarthrosis of the knee joint: experience in clinical practice in the Czech Republic]. Acta Chir Orthop Traumatol Cech. 2002;69(5):302-7. PMID: 12557601.

8. Swiechowicz S, Ostalowska A, Kasperczyk A, et al. Evaluation of hyaluronic acid intra-articular injections in the treatment of primary and secondary osteoarthritis of the knee. Pol Orthop Traumatol. 2012;77:105-9. PMID: 23306296.

Study Design – N=124

1. How effective are Hyalgan injections for arthritis? Johns Hopkins Med Lett Health After 50. 1998 Mar;10(1):8. PMID: 9600056.

2. How do the new injections for arthritis of the knee work, and who is a good candidate for this treatment? Johns Hopkins Med Lett Health After 50. 2000 Jul;12(5):8. PMID: 10879156.

3. . Intra-articular injections for osteoarthritis of the knee. Med Lett Drugs Ther. 2006 Mar 27;48(1231):25-7. PMID: 16554699.

4. I've read that hyaluronic acid knee injections can be used to postpone knee surgery. Can hyaluronic acid in pill form provide the same relief? Health News. 2006 Apr;12(4):16. PMID: 16583498.

5. Summaries for patients. Viscosupplementation for knee osteoarthritis. Ann Intern Med. 2012 Aug 7;157(3):I-36. PMID: 22868857.

6. Knee injections offer minimal relief from arthritis pain. Harv Mens Health Watch. 2012 Sep;17(2):8. PMID: 23050288.

7. Abate M, Schiavone C, Di Gregorio P, et al. Comparison between hyaluronic acid and platelet rich plasma in the treatment of hip and knee osteoarthritis: Preliminary results. Journal of Orthopaedics and Traumatology. 2013 October;14(1 SUPPL. 1):S17.

8. Abbott T, Altman RD, Dimeff R, et al. Do hyaluronic acid injections delay total knee replacement surgery? Arthritis and Rheumatism. 2013 October;65 SUPPL. 10:S910-S1.

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10. Adams ME. Acute local reactions after intraarticular hylan for osteoarthritis of the knee. J Rheumatol. 1996 May;23(5):944-5; author reply 6. PMID: 8724316.

11. Ahadi T, Abtahi M. Platelet-rich plasma versus hyaluronic Acid. Arthroscopy. 2012 Nov;28(11):1585; author reply -6. PMID: 23107248.

12. Allam A, El-Gazzar NM, El Sergany MAS, et al. Clinical and radiologic assessment of intra-articular hyaluronic acid injection versus ultrasound in management of primary osteoarthritis of the knee (a prospective study). Annals of the Rheumatic Diseases. 2013;72 SUPPL. Date of Publication: June 2013 CONFERENCE NAME Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR 2013 CONFERENCE LOCATION Madrid, Spain CONFERENCE DATE 12 to 2013-06-15(3):2013-06.

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22. Bruyere O, Collette JH, Ethgen O, et al. Biochemical markers of bone and cartilage remodeling in prediction of longterm progression of knee osteoarthritis. J Rheumatol. 2003 May;30(5):1043-50. PMID: 12734904.

23. Brys DA. Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee. J Bone Joint Surg Am. 2004 Apr;86-A(4):874; author reply -5. PMID: 15069162.

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25. Campos GC, Rezende MU, Fruchi R, et al. Adding triamcinolone to viscosupplementation: One year outcome of randomized trial. Osteoarthritis and Cartilage. 2014 April;22 SUPPL. 1:S198.

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41. Felson DT. Clinical practice. Osteoarthritis of the knee. N Engl J Med. 2006 Feb 23;354(8):841-8. PMID: 16495396.

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44. Gokmen F, Akbal A, Komurcu E, et al. Comparison of effects of combined physical therapy program and intra-articular treatment of hyaluronic acid on pain, balance and quality of life in patients with knee osteoarthritis ORIGINAL (NON-ENGLISH) TITLE Diz Osteoartritli Hastalarda Intraartikuler Hyaluronik Asit Tedavisi ile Kombine Fizik Tedavi Uygulamalarinin Anullri, Denge ve Yasam Kalitesi Uzerine Etkisinin Karsilastirilmasi. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi. 2013 April;59 SUPPL. 1:483.

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55. Henrotin Y, Hauzeur JP, Bruel P, et al. Intra-articular use of a medical device composed of hyaluronic acid and chondroitin sulfate (Structovial CS): effects on clinical, ultrasonographic and biological parameters. BMC Res Notes. 2012;5:407. PMID: 22862789.

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58. Huskisson E, Donnelly S. Is hyaluronic acid effective in patients with osteoarthritis of the knee? West J Med. 2000 Oct;173(4):252. PMID: 11017989.

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Appendix C. Evidence Table

Appendix Table C1. Evidence Table of all included studies

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Altman et al., 1998[69]	US <1998 RCT/CCT parallel Funding: Industry	Age Range: 40-90 Mean age: 64 SD controls: 10 (whole group) Number of participants enrolled: 495 Number of participants in analysis: 333 Number of knees: NR Mean BMI: NR % Female: 57	Diagnosis of osteoarthritis of the knee: ACR(NR) Knee radiograph(Kellgren-Lawrence grade 2 or 3, >=1 osteophyte) Duration of symptoms Knee pain 1 year or more Score(s) on OA assesments VAS for pain on a 50 foot walk: >=20mm WOMAC pain subscale: >=20 on >=1 item out of 5 6-point categorical scale: moderate or marked main Minimum age: 40 Maximum age: 80 No prior IA HA injection within one year No other IA injections, including corticosteroids within preceding 3 months If both knees affected, more serious one was used	NR	NR	Arm 1: N = 115 Mean age: 65 (10) Placebo/sham Acetaminophen up to 4000mg /day permitted as rescue Arm 2: N = 105 Mean age: 62(10) Hyalgan 20mg/2ml Molecular weight: 500-730kD Oral placebo for naproxen twice daily and Acetaminophen up to 4000mg /day permitted as rescue Arm 3: N = 113 Mean age: 63(9) NSAID Total treatments: 5 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Berenbaum et al., 2012[70]	France, Germany 2008-2009 EudraCt no 2008-003875-35 RCT/CCT parallel Funding: Industry	Age Range: NR Mean age: 67 SD controls: NR Number of participants enrolled: 426 Number of participants in analysis: 426 Number of knees: NR Mean BMI: 27.7 (3.1) for Hyalgan % Female: 63	Diagnosis of osteoarthritis of the knee: ACR(NR) Radiologic(Kellgren-Lawrence stage II or III within past 12 months) Duration of symptoms At least 6 months Failure of another treatment modality: Analgesics and/or regular NSAIDs Score(s) on OA assesments Global knee pain VAS: 40mm/100mm WOMAC pain subscale score: 25 or greater on the 0-100 normalized scale Lequesne Index: 4 or greater Minimum age: 49 Maximum age: 81 Intolerance to NSAIDs or weak opioids Radiologic evidence of bilateral OA if global pain VAS in contralateral knee<30mm	Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Use of certain analgesics: Opioids within past month of baseline Other musculoskeletal or joint disease or condition that limits mobility: Inflammatory or other rheumatic diseases Patelofemoral symptomatic OA Secondary OA Symptomatic hip OA ipsilateral to target knee Clinical joint effusion Excessive varus or valgus knee deformity (on physical exam, confirmed radiographically		Arm 1: N = 209 Mean age: 66.1 (8.1) Hyalgan Molecular weight: 500 kD-730 kD NSAID or paracetamol up to 4g/d as rescue medication Arm 2: N = 217 Mean age: 67.2 (7.8) GO-ON (2.5 ml, 10mg/ml) Molecular weight: 800 kD-1500 kD NSAID or paracetamol up to 4g/d as rescue medication Total treatments: 3 Time between treatment: 3 weeks

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Blanco et al., 2008[51]	Spain <2008 RCT/CCT parallel Funding: Industry	Mean age: 68.3 SD controls: (9.1) Number of participants enrolled: 42 Mean BMI: 33 % Female: 76	Diagnosis of osteoarthritis of the knee: WOMAC pain(>/=150mm) ACR Kellgren-Lawrence(IV) Minimum age: 40 Waiting list for knee replacement	Prior surgical procedure on affected knee Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Other musculoskeletal or joint disease or condition that limits mobility Use of glucosamine within prior 3 months Use of an investigational drug within 30 days of study entry CNS impairment, impaired coagulation Known sensitivity to HA, paracemtamol, or diclofenac Immune-comprised or receiving immuno-suppressive therapy or considered unable to complete treatment or followup	NR	Arm 1: N = 20 Mean age: 68.3(9.1) Placebo/sham Paracetamol and/or dicofenac as rescue analgesics Arm 2: N = 22 Mean age: 67.5(8.1) Adant Molecular weight: 900 kDa Total treatments: 10 (2 cycles of 5 weekly injections, separated by 24 weeks) Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Brandt et al., 2001[71]	US 1996-1997 RCT/CCT parallel Funding: Industry	Age Range: NR Mean age: NR SD controls: NR Number of participants enrolled: 226 Number of participants in analysis: 226 and 135 Number of knees: NR Mean BMI: HA: 32(6); Saline: 30.1(6.2) % Female: 63	Diagnosis of osteoarthritis of the knee: Kellgren-Lawrence(Grade II or III) Score(s) on OA assesments WOMAC: pain score 13 or greater in knee to be treated knee and less than 13 in contralateral knee Minimum age: 50 Willing to d/c other analgesics and NSAIDs for 5 half-lives of the relevant drug Able to walk 50 feet unassisted Not pregnant or planning pregnancy	Prior surgical procedure on affected knee: Arthroplasty Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Initiation of quadriceps exercise program within 4 months of screening Kellgren-Lawrence Grade IV radiographic changes in either knee Tx with anticoagulants, immunosuppressives, or muscle relaxants Inability to tolerate acetaminophen Clinically significant comorbidity (renal or hepatic disease) or abnormality in routine lab tests or allergy to lidocaine	Involvement of both knees: HA: 78% Saline: 88%	Arm 1: N = 112 Mean age: 67(8.4) Placebo/sham Arm 2: N = 114 Mean age: 65(8.4) Orthovisc (2 mL, 15mg/mL) Molecular weight: 1000-2900 kD (considered high MW) Total treatments: 3 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
DeCaria et al., 2012[72]	Ontario Canada <2012 RCT/CCT parallel Funding: Non-industry	Age Range: 60-80 Mean age: NR SD controls: NR Number of participants enrolled: 30 Number of participants in analysis: na Number of knees: na Mean BMI: HA: 30.48(6.16) Placebo: 29.40(4.11) % Female: 47	Diagnosis of osteoarthritis of the knee: ACR: Kellgren-Lawrence(Grade II-III) ACR clinical criteria for knee pain(NR) Failure of another treatment modality: Multiple years Minimum age: 60 Maximum age: 80	Prior surgical procedure on affected knee: Except for arthroscopy 18 months or more before study commencement Other musculoskeletal or joint disease or condition that limits mobility: Non OA arthritis (e.g., RA, gout), OA in other lower limbs, end-stage knee OA; lower back pathology that limited walking, leg length differential>2cm A neurological or cardiovascular condition that could impair gait function Cognitive impairment Intraarticular injection within 6 months prior to study commencement Chronic use of oral corticosteroids	NR	Arm 1: N = 15 Mean age: 72.93 (5.48) 500 mg acetaminophen to be taken up to 4g/day as rescue medication Placebo/sham 1.2 ml 0.001 mg/ml inert HA Arm 2: Hyaluronic acid (2 ml, 20 mg/ml) Molecular weight: 730 kD 500 mg acetaminophen to be taken up to 4g/day as rescue medication Total treatments: 3 Time between treatment: 1 week
Dixon et al., 1988[68]	UK <1988 RCT/CCT parallel Funding: Industry	Age Range: 43-85 Mean age: 68.5 SD controls: NR Number of participants enrolled: 63 Number of participants in analysis: 53 Number of knees: NR Mean BMI: NR % Female: 54	Diagnosis of osteoarthritis of the knee: Symptomatic OA NR	Use of certain analgesics: If other than for OA Other musculoskeletal or joint disease or condition that limits mobility: Hip OA; primary inflammation of the knee (e.g., RA, psoriatic arthropathy, pseudogout, joint infection) Skin conditions overlying the joint Poor general health	NR	Arm 1: N = 33 Mean age: nr Hyalgan 0.2mg/2 ml Molecular weight: NR Placebo/sham Arm 2: N = 30 Mean age: nr Hyalgan 20mg/2 ml Molecular weight: NR Paracetamol was permitted but NSAIDS, corticosteroids, and strong analgesics were not Total treatments: Varied 1 for first 3 weeks and then 2

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Dougados et al., 1993[49]	France <1993 RCT/CCT parallel Funding: NR	Mean age: 69.0 SD controls: 10.6 Number of participants enrolled: 110 Number of participants in analysis: 95 (ITT also done) Mean BMI: NR % Female: 71.0	Diagnosis of osteoarthritis of the knee: ACR Score(s) on OA assesments VAS for pain: >=40 out of 100 Femorotibial localization Knee effusion	Prior surgical procedure on affected knee: Prosthesis or any intra-articular surgery during the preceding 2 years Use of certain analgesics: Dose of NSAIDS or analgesics stable during previous month Other musculoskeletal or joint disease or condition that limits mobility: Secondary osteoarthritis of the knee Serious concomitant medical illness Any arthrocentesis during prior 3 months Stable dose of any basic OA therapy stable for prior 3 months; Stable use of any physiotherapy during the previous month and first 7 weeks of study	NR	Arm 1: Placebo/sham Arm 2: Hyalectin (Hyalgan) Molecular weight: 500-730 kDa Total treatments: 4 Time between treatment: 1 week
Forster et al., 2003[50]	UK <2002 RCT/CCT parallel Funding: NR	Age Range: NR Mean age: 61.5 SD controls: NR Number of participants enrolled: 38 Number of participants in analysis: 32 Mean BMI: NR % Female: NR	Diagnosis of osteoarthritis of the knee: On waiting list for arthroscopic washout Fitness for general or local anesthesia	Prior surgical procedure on affected knee Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Mechanical symptoms	NR	Arm 1: N = 19 Mean age: 63 Arthroscopic washout Arm 2: N = 19 Mean age: 60 Hyalgan Molecular weight: 500-730 kD Total treatments: 5 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Grecomoro et al., 1987[83]	Italy <1987 RCT/CCT parallel Funding: NR	Age Range: 43-92 Mean age: 64.88 SD controls: 10.94 Number of participants enrolled: 34 Number of knees: 40 % Female: 19/34	Diagnosis of osteoarthritis of the knee: Not reported Knee pain with movement	NR	Involvement of both knees: 6/34	Arm 1: N = 20 knees Mean age: NR Placebo/sham Arm 2: N = 20 knees Mean age: NR Hyalgan Molecular weight: 500K-750K Total treatments: 3 Time between treatment: 1 week
Henderson et al., 1994[84]	UK <1994 RCT/CCT parallel Funding: NR	Age Range: NR Mean age: NR SD controls: NR Number of participants enrolled: 91 Number of participants in analysis: 84 Number of knees: NR Mean BMI: NR % Female: 69	Diagnosis of osteoarthritis of the knee: Clinical history and radiological evidence Kellgren-Lawrence(Grades I and II: severity group 1; Grades III and IV: severity group 2) Score(s) on OA assesments VAS scale for pain evoked by activities: minimum score of 30 mm out of 100mm	Other musculoskeletal or joint disease or condition that limits mobility: Inflammatory joint disease, metabolic bone disease, anserine bursitis, pain referred from other structures	Involvement of both knees: >99%	Arm 1: N = 20 (Severity group I) Mean age: 60.0(1.9) Placebo/sham Arm 2: N = 26 Severity Group 2 Second placebo group Arm 3: N = 18 Severity Group 1 Mean age: 63.9(1.9) Hyalgan (20mg/2mL) Molecular weight: NR Arm 4: N = 26 Severity Group 2 Mean age: 67.0(1.7) Hyalgan Total treatments: 5 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Huang et al., 2011[73]	Taiwan <2011 RCT/CCT parallel Funding: Industry	Age Range: nr Mean age: 65.0 SD controls: 8.3 Number of participants enrolled: 200 Number of participants in analysis: 198 Number of knees: NR Mean BMI: 25.6(3.6) % Female: 76	Diagnosis of osteoarthritis of the knee: ACR (knee pain with one or more of the following conditions: age>50, crepitus, or morning stiffness<30 minutes duration Radiographic evidence(Kellgren Lawrence score II and III, predominance in tibio-femoral compartment) VAS pain scores on 50-foot walking test(>=40mm) Minimum age: 50 Any acute disease or trauma leading to secondary OA had to have occurred at least 5 years before study entry	Current or prior receipt of glucocorticoids in affected knee Other musculoskeletal or joint disease or condition that limits mobility Severe degeneration of knee joint with marked joint narrowing, varus, or valgus deformity of the knee (>12") or other joint deformities or other joint disorders Joint or skin infections Joint prostheses of lower limb or symptomatic hip Inflammatory joint disease, specific arthropathy, severe axis deviations or instabilities,	NR	Arm 1: N = 100 Mean age: 64.2(8.4) Placebo/sham Arm 2: N = 100 Mean age: 65.9(8.1) Hyalgan (20mg/2ml) Total treatments: 5 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Huskisson et al., 1999[74]	United Kingdom <1997 RCT/CCT parallel Funding: NR	Age Range: nr Mean age: nr SD controls: nr Number of participants enrolled: 100 Number of participants in analysis: 81 Number of knees: NR Mean BMI: nr % Female: 67	Diagnosis of osteoarthritis of the knee: ARA Criteria Kellgren-Lawrence(II or III) Consistent pain for 3 months Moderate to severe pain on walking	Current or prior receipt of glucocorticoids in affected knee Other musculoskeletal or joint disease or condition that limits mobility: Serious functional impairment at the knee, hip OA, other related joint OA, psoriasis, sacroiliitis, painful knee conditions other than OA Kellgren Lawrence IV Known or suspected joint infection Poor general health or other conditions which would prevent regular hospital attendance Skin conditions overlying the joint Severe intercurrent hepatic or renal disease or major general medical conditions		Arm 1: N = 50 Mean age: 64.8 (9.3) Placebo/sham Arm 2: N = 50 Mean age: 65.8 (8.8) Hyalgan Molecular weight: 500-730 kDa Total treatments: 5 Time between treatment: 1 week
Kahan et al., 2003[75]	France 10/1998-2/2000 RCT/CCT parallel Funding: NR	Mean age: 66 SD controls: 10 Number of participants enrolled: 506 Number of participants in analysis: 506 Mean BMI: 28 % Female: 67.5	Diagnosis of osteoarthritis of the knee: ACR Kellgren-Lawrence(any) Failure of another treatment modality: Two courses of NSAID therapy, each at least 10 d long, within the last 3 months and/or a symptomatic slowacting drug taken continuously during the last 2 months Score(s) on OA assesments Pain VAS: >= 40 mm / 100 mm Minimum age: 18	Prior surgical procedure on affected knee: Arthroscopy, lavage, meniscectomy, etc.) within the last year; TKR ever Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Inflammatory flare in the target knee (effusion with nocturnal pain, local heat or redness, morning stiffness for longer than 45 min or greater than 50% increase in the VAS pain score as compared to the previous week) Synovectomy, tibial osteotomy Surgery scheduled within last 9 months	Involvement of both knees: 74	Arm 1: N = 253 Mean age: 66 (10) Conventional treatment Arm 2: N = 253 Mean age: 66 (10) Synvisc Molecular weight: NR Total treatments: 3 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Karlsson et al., 2002[76]	Sweden <2002 RCT/CCT parallel Funding: Industry	Age Range: NR Mean age: reported by arm below SD controls: reported by arm below Number of participants enrolled: 246 Number of participants in analysis: ITT: 246 PP: 210 Number of knees: NR Mean BMI: 28 % Female: 61	Score(s) on OA assesments Lequesne algofunctional index: >=10 Weight-bearing pain VAS: >=40mm Minimum age: 60 Normal general physical exam	Prior surgical procedure on affected knee: Arthroscopy, arthrography, surgery less than 6 months prior to inclusion Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Other musculoskeletal or joint disease or condition that limits mobility: RA or other inflammatory joint disease (ACR criteria) Any disabling problem of the musculoskeletal system or other organ system which could interfere with the assessment of efi¬ □cacy Bone attrition in either knee (Ahlback III or IV), previous intra-articular fracture of the knee Alcohol or drug abuse Known allergy to any substance related to the study Clinically relevant hematological of known clinical chemistry values outside the reference values at the time of inclusion Any disabling problem with any other organ system that could interfere with the assessment of efficacy	NR	Arm 1: N = 66 (57 PP) Mean age: 71(6) Placebo/sham Arm 2: N = 92 (76 PP) Mean age: 72(7) Artzal (2.5 ml 1% hyaluronan) Molecular weight: 1,000 kDa Arm 3: N = 88 (77 PP) Mean age: 70(7) Synvisc (2 ml 0.8%) Molecular weight: 7,000 kDa Total treatments: 3 Time between treatment: 1 day

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Khanasuk et al., 2012[77]	Thailand 2011-2012 RCT/CCT parallel Funding: NR	Mean age: NR SD controls: NR Number of participants enrolled: 32 Number of participants in analysis: 30 Number of knees: NR Mean BMI: 26 % Female: 80	Diagnosis of osteoarthritis of the knee: ACR for primary OA of the knee(NR) Pain VAS(>=3/10) Kellgren-Lawrence radiological grading(>=Grade II) Minimum age: 45	Current or prior receipt of HA in affected knee Intention to take pain medication after injection History of allergy to avian products	NR	Arm 1: N = 15 Mean age: 65.1(9.6) Hylan GF-20 (Synvisc)(single 6 ml injection) Molecular weight: Reported as High Arm 2: N = 15 Mean age: 67.0(9.5) Hyalgan (single injection Molecular weight: Reported as Low Total treatments: 1
Leopold et al., 2003[87]	US 2000-2002 RCT/CCT parallel Funding: Non-industry	Age Range: 39-83 Mean age: NR SD controls: NR Number of participants enrolled: 100 Number of participants in analysis: 80 Number of knees: NR Mean BMI: CS: 29.3 HA:28.8 % Female: CS: 56 HA: 52	Diagnosis of osteoarthritis of the knee: Radiographic evidence of symptomatic knee OA(NR) Minimum age: 18 Dissatisfaction with prior attempts at nonoperative management modalities	Current or prior receipt of HA in affected knee Other musculoskeletal or joint disease or condition that limits mobility Pregnant or lactating Radiographic evidence of bone on bone arthritis or Chodrocalcinosis Insufficiency of the collateral ligament, of the ACL or PCL with concomitant symptomatic giving way of the affected extremity or a current infection in the affected extremity as demonstrated on physical exam History of crystalline arthropathy or neuropathic arthropathy Allergy or hypersensitivity to any of the study medications or to poultry products	NR	Arm 1: N = 42 Mean age: 64 Arm 2: N = 38 Mean age: 66 Hylan G-F 20 (16mg/2ml) Total treatments: 3 HA 1CS Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Lundsgaard et al., 2008[81]	Denmark <2008 NCT00144820 RCT/CCT parallel Funding: Non-industry	Age Range: NR Mean age: 69.6 SD controls: 7.27 Number of participants enrolled: 251 Number of participants in analysis: 243 Mean BMI: 29.3 % Female: 52.4	Score(s) on OA assesments Daily knee pain on VAS (that did not respond to analgesics): 20mm/100mm Minimum age: 59 Daily	Prior surgical procedure on affected knee: Invasive procedures within past 6 months Current or prior receipt of glucocorticoids in affected knee Other musculoskeletal or joint disease or condition that limits mobility: RA or other inflammatory arthritis Contra-indication to hyaluronate Contra-indication to knee injection Medications that could interfere with intervention Comorbidity, e.g. psychosis or dementia that could interfere Knee infection or uric acid crystals	NR	Arm 1: Saline 2ml Arm 2: Saline 20 mL, no hyaluronate Arm 3: Hyalgan Molecular weight: NR Total treatments: 4 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Pavelka et al., 2011[78]	Czech Republic, France, Italy, Switzerland, the Slovak Republic and Germany November 2007 - January 2009 NCT00556608 RCT/CCT parallel Funding: Industry	Age Range: 41-80 Mean age: 65 SD controls: 9 Number of participants enrolled: 381 Number of participants in analysis: 354 Mean BMI: 27 % Female: 72.9	Diagnosis of osteoarthritis of the knee: ACR Kellgren-Lawrence(2 or 3) Duration of symptoms 3 months Failure of another treatment modality: NSAIDS Score(s) on OA assesments WOMAC pain: include 40 - 80 Minimum age: 40	Prior surgical procedure on affected knee: TKR, arthroplasty Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Use of certain analgesics: Chronic use of NSAIDS, analgesics or narcotics Other musculoskeletal or joint disease or condition that limits mobility: Pain mainly related to femoral patellar syndrome at the target knee, no remaining joint space width at the target knee, symptomatic hip osteoarthritis or other condition that would interfere with study assessments, severe varus/valgus deformity in the target knee, history or current evidence of other joint diseases, such as inflammatory, infective or metabolic joint disease, concomitant rheumatic disease, significant injur Lymphatic stasis in the relevant limb, skin infection, disease or trauma at the injection site Initiation of target knee physical therapy in the past 3 months, initiation/ change in dose of symptomatic slow-acting drugs for osteoarthritis BMI >=32	Involvement of both knees: 66%	Arm 1: N = 192 Mean age: 65.1 (9.1) Synovial Molecular weight: 800 - 1,200 kD Arm 2: N = 188 Mean age: 64.9 Synvisc Molecular weight: 6,000 kD Total treatments: 3 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Petrella et al., 2002[79]	Canada < 2002 RCT/CCT parallel Funding: Industry	Age Range: NR Mean age: 65.5 SD controls: 9.5 Number of participants enrolled: 120 Number of participants in analysis: 108 Mean BMI: 30.7 % Female: 45.8	Diagnosis of osteoarthritis of the knee: Kellgren-Lawrence(1 to 3 included) Score(s) on OA assesments VAS pain 0-10 scale: 3+ Unilateral OA	Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee NSAID intolerance Bilateral symmetric inflammatory reaction	Involvement of both knees: 0%	Arm 1: N = 28 Mean age: 62.6 (9.5) Placebo/sham Arm 2: N = 25 Mean age: 67.3 (8.9) Suplasyn Molecular weight: NR Placebo pill Arm 3: N = 29 Mean age: 65.0 (9.7) Suplasyn Molecular weight: NR NSAID Arm 4: N = 26 Mean age: 66.3 (8.8) NSAID Total treatments: 3 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Petrella et al., 2008[88]	Canada <2008 RCT/CCT parallel Funding: Non-industry	Age Range: nr Mean age: 71 SD controls: 8 Number of participants enrolled: 200 Number of participants in analysis: nr Mean BMI: 27.2 % Female: 30	Diagnosis of osteoarthritis of the knee: Medial compartment OA Radiographic grade(1-3) Did not exhibit non-arthritis-related disease	Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee End-stage OA in affected knee	NR	Arm 1: N = 50 Mean age: 71+/-8 Placebo/sham Arm 2: N = 50 Mean age: 68+/-6 HA dual molecular weight Molecular weight: 580–780 kDa+1.2 to 2.0 million kDa Arm 3: N = 50 Mean age: 69+/-5 HA low molecular weight Molecular weight: 500–730 kDa Arm 4: N = 50 Mean age: 71+/9 HA high molecular weight Molecular weight: 6 million kDa Total treatments: 3 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Petrella et al., 2011[89]	Canada < 2011 ISRCTN98630331 RCT/CCT parallel Funding: NR	Age Range: NR Mean age: 70 SD controls: 8 Number of participants enrolled: 200 Number of participants in analysis: Unclear Mean BMI: 27 % Female: 57	Diagnosis of osteoarthritis of the knee: Kellgren-Lawrence(1 to 3 included) Score(s) on OA assesments VAS pain: 45+	Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Use of certain analgesics: Dosage of glucosamine and/or chondroitin sulfate, and/or NSAIDs that has been stable over the preceding three months with the dosage remaining constant during the study Other musculoskeletal or joint disease or condition that limits mobility: End stage OA Active skin disease or infection in the area of the injection site Any condition/ disease which in the opinion of the investigator could interfere with patient compliance and/ or interfere with the interpretation of the treatment results Contra-indication to intra-articular injection or known hypersensitivity to Sodium Hyaluronate Planned surgery on knee	NR	Arm 1: N = 50 Mean age: 71 (8) Placebo/sham Arm 2: N = 50 Mean age: 68 (6) sodium hyaluronate Molecular weight: Combined high & low weight Arm 3: N = 50 Mean age: 69 (5) sodium hyaluronate - low weight Molecular weight: 500-730 KDa Arm 4: N = 50 Mean age: 71 (9) sodium hyaluronate - high weight Molecular weight: 6000 KDa Total treatments: 3 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Pham et al., 2004[82]	France <2004 RCT/CCT parallel Funding: NR	Age Range: 50+ Mean age: 64.9 SD controls: 7.7 Number of participants enrolled: 301 % Female: 65 average	Diagnosis of osteoarthritis of the knee: Presence of a symptomatic primary painful medial femorotibial knee OA defined by a daily pain visual analogue scale (VAS) score .30 mm in the previous month VAS for pain(>30mm in prior month) Joint space(>2mm)	Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Use of certain analgesics: Diacerein or other antiinflammatories Other musculoskeletal or joint disease or condition that limits mobility: Severe OA (jpint space <2mm), secondary knee OA, Paget's Contraindications to HA Need for surgery	NR	Arm 1: N = 85 Mean age: 64.9 (7.7) Placebo/sham Arm 2: N = 131 Mean age: 71.0 NRD101 Molecular weight: 1.900 kDa Arm 3: N = 85 Mean age: 64.5 Diacerein Total treatments: 12? (3 course every 3 months for a year) Time between treatment: 1 week
Raman et al., 2008[80]	UK < 2008 RCT/CCT parallel Funding: Non-industry	Age Range: 42-82 Mean age: 67.2 SD controls: NR Number of participants enrolled: 392 Number of participants in analysis: 380 Mean BMI: NR % Female: 68	Diagnosis of osteoarthritis of the knee: Score(s) on OA assesments VAS (10 point scale): 6+ Preferred tx strategy was viscosupplementation	Prior surgical procedure on affected knee Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Bilateral OA	NR	Arm 1: N = 199 Mean age: NR Synvisc (Hylan GF 20) Molecular weight: 6000 kD Arm 2: N = 193 Mean age: NR Hyalgan Molecular weight: 500 - 730 kD Total treatments: 3 for Synvisc, 5 for Hyalgan Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Roman et al., 2000[85]	Spain < 2000 RCT/CCT parallel Funding: NR	Age Range: 41-86 Mean age: 65.14 SD controls: 9.77 Number of participants enrolled: 49 Mean BMI: NR % Female: 83.7	Diagnosis of osteoarthritis of the knee: Kellgren-Lawrence(2 or 3 included)	NR	NR	Arm 1: N = 30 Mean age: NR Adant Molecular weight: 900 kD Arm 2: N = 19 Mean age: NR Hyalgan Molecular weight: 800 kD Total treatments: 5 Time between treatment: 1 week
Tamir et al., 2001[86]	Israel < 2001 RCT/CCT parallel Funding: NR	Age Range: NR Mean age: 71 SD controls: NR Number of participants enrolled: 49 Number of participants in analysis: Unclear Mean BMI: NR % Female: 73.5	Diagnosis of osteoarthritis of the knee: Altman Kellgren-Lawrence(2 to 4 included) Minimum age: 60 Maximum age: 85	Prior surgical procedure on affected knee: No surgery ever, no arthroscopy within 6 months Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Other musculoskeletal or joint disease or condition that limits mobility: RA, other inflammatory arthritis, OA of hip, OA from fracture of knee Skin conditions on knee	NR	Arm 1: N = 24 Mean age: 70 Placebo/sham Arm 2: N = 25 Mean age: 71 Bio-Hy Molecular weight: 3000 kDa Total treatments: 5 Time between treatment: 1 week

Appendix D. Data Abstraction Tools

1. **DJD Data Abstraction Tool**
2. **Cochrane Risk of Bias Tool for Randomized Controlled Trials, Adapted**
3. **Ottawa-Newcastle Risk of Bias Assessment for Observational Studies, Adapted**
4. **Assessment of Reporting of Adverse Events (Questions from McHarms)**
5. **AMSTAR Assessment of Reporting Quality for Systematic Reviews**

1. DJD Data Abstraction Tool

Should this article have been previously excluded based on the exclusion criteria?

Do you need another article to complete this form?

- Yes (stop until Aneesa links the article; specify reference number)
- No

Clear Response

Does this article report on part of a larger study or a follow-up to a previous study?

- Yes
- No

Clear Response

Does the larger study have a name?

- Yes
- No

Clear Response

When did this study occur? (e.g. dates or year of recruitment to date of completion)

- Years (specify)
- NR

Clear Response

Location(s):

- US
- Not US (specify country)
- Multi-country

Clear Response

Study Design (choose one):

- RCT/CCT parallel
- RCT/CCT crossover
- Open or uncontrolled trial
- Population-based prospective cohort study
- Case control study
- Case study
- Case series
- Database analysis

Clear Response

Does this study report on AE outcomes?

- Yes
- No

Clear Response

Participants:

If not reported, please indicate "NR"

- ☐ Age range: ___ to ___ (specify range)
- ☐ Mean age (whole group if reported) (specify mean)
- ☐ Standard Deviation (SD) controls (specify SD)
- ☐ Number of participants enrolled (specify number)
- ☐ Number of participants in analysis if different from enrolled (specify number)
- ☐ Number of knees if reported that way (specify)
- ☐ Mean BMI (specify)
- ☐ % female (specify %)
- ☐ Not Reported

Inclusion criteria for participation in the study:

- ☐ Diagnosis of osteoarthritis of the knee (specify diagnostic modality and cutoff scores, if relevant)
- ☐ Duration of symptoms
- ☐ Failure of another treatment modality (specify)
- ☐ Score(s) on OA assesments
- ☐ Age >= ___ (specify inclusion of age)
- ☐ Age < ___ (specify inclusion of age)
- ☐ Other 1 (specify)
- ☐ Other 2 (specify)
- ☐ Other 3 (specify)
- ☐ Other 4 (specify)
- ☐ Other 5 (specify)
- ☐ Not Reported

Exclusion criteria for the study:

- ☐ Prior surgical procedure on affected knee (specificy type) ☐
- ☐ Current or prior receipt of HA in affected knee
- ☐ Current or prior receipt of glucocorticoids in affected knee
- ☐ Use of certain analgesics (specify the analgesics) ☐
- ☐ Other musculoskeletal or joint disease or condition that limits mobility (rheumatoid arthritis, osteoporosis, hip OA)(specify) ☐
- ☐ Other chronic disease that limits mobility (advanced CVD, advanced COPD, Parkinsons...) ☐
- ☐ Obesity
- ☐ Age > ___ (specify exclusion of age) ☐
- ☐ Age < ___ (specify exclusion of age) ☐
- ☐ Other 1 (specify) ☐
- ☐ Other 2 (specify) ☐
- ☐ Other 3 (specify) ☐
- ☐ Other 4 (specify) ☐
- ☐ Other 5 (specify) ☐
- ☐ Not Reported

Comorbidities:

- ☐ Obesity (specify % of participants) ☐
- ☐ Involvement of both knees (specify % of participants) ☐
- ☐ Diabetes (specify % of participants) ☐
- ☐ Other 1 (specify) ☐
- ☐ Other 2 (specify) ☐

☐ Other 3 (specify) _____

☐ Not Reported

Intervention

How many arms are there?

_____

Control group (Arm 1)

☐ Number of participants (specify number) _____

☐ Mean age (SD) (specify number) _____

☐ HA Brand or chemical name [indicate name] _____

☐ Additional treatment

☐ None

☐ Placebo/sham

☐ NSAID

☐ Opioid pain medications

☐ Corticosteroid injection

☐ Corticosteroid oral

☐ Plasma enriched with growth factors

☐ Other (specify) _____

Intervention (Arm 2)

☐ Number of participants (specify number) _____

☐ Mean age (SD) (specify number) _____

☐ HA Brand or chemical name [indicate name] _____

☐ Additional treatement

Intervention (Arm 3)

- ☐ Number of participants (specify number) ☐
- ☐ Mean age (SD) (specify number) ☐
- ☐ HA Brand or chemical name [indicate name] ☐
- ☐ Additional treatement

Intervention (Arm 4)

- ☐ Number of participants (specify number) ☐
- ☐ Mean age (SD) (specify number) ☐
- ☐ HA Brand or chemical name [indicate name] ☐
- ☐ Additional treatement

Intervention (Arm 5)

- ☐ Number of participants (specify number) ☐
- ☐ Mean age (SD) (specify number) ☐
- ☐ HA Brand or chemical name [indicate name] ☐
- ☐ Additional treatement

How many total treatments did participants receive?

☐

If more than one treatment, how far apart?

Number Unit

☐

Outcomes (choose all that apply):

☐ Arthroplasty (or time to arthroplasty or delay to arthroplasty or avoidance of...)

☐ Function:

☐ Quality of life:

☐ Adverse events/harms

☐ Other included outcomes 1 (specify outcome) ☐

☐ Other included outcomes 2 (specify outcome) ☐

☐ Other included outcomes 3 (specify outcome) ☐

☐ Other included outcomes 4 (specify outcome) ☐

☐ Other included outcomes 5 (specify outcome) ☐

☐ Other included outcomes 6 (specify outcome) ☐

Funding:

☐ Industry

☐ Non Industry

☐ Not Reported

Did the authors have any conflict of interest?

● Yes

● No

● NR

Clear Response

Does this article need another form to be completed for the same article (i.e., article reports more than one study)?

● Yes (please complete another form) ● No Clear Response

Reference Mining

● Yes (specify reference number) [ ] ● No Clear Response

Needs to discuss

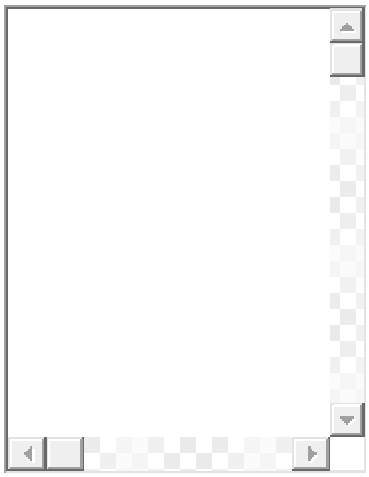
● Yes ● No Clear Response

Has this form been reconciled?*

*Indicate "yes" only if this form has been reconciled. Programmer will pull data from this form.

● Yes ● No Clear Response

Comments



2. Cochrane Risk of Bias Tool for Randomized Controlled Trials, Adapted

1. **Sequence Generation:** Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

Was the participant recruitment and assignment to condition (allocation sequence) adequately generated? (a "no" would mean, e.g., that care providers assigned patients to treatment arms or allowed patients to self-select treatment arms).

- Low risk (yes)
- High risk (no)
- Unclear

Clear Response

2. **Allocation concealment:** Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.

Did the study report a reasonable plan for concealment of allocation? (e.g., use of an opaque envelope to store the allocation key).

- Low risk
- High risk
- Unclear

Clear Response

3. **Blinding of participants, personnel and outcome assessors** ***Assessments should be made for each main outcome (or class of outcomes)*****:** Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective

3a. Did the study report adequate blinding of participants (was the control group appropriate for the intervention)?

- Low risk
- High risk
- Unclear

Clear Response

3b. Did the study report adequate blinding of care providers (if different from outcome assessors)

(including assessors of AEs)?

- Low risk
- High risk
- Unclear

Clear Response

3c. Did the study report adequate blinding of outcome assessors (including assessors of AEs)?

- Low risk
- High risk
- Unclear

Clear Response

4. **Incomplete outcome data** *Assessments should be made for each main outcome (or class of outcomes)*

4a. Was the loss to follow-up less than 20%?

- Low risk
- High risk
- Unclear

Clear Response

4b. Were loss-to-follow-up or other missing data explained?

- Low risk
- High risk
- Unclear

Clear Response

4c. Did the analysis include:

- a) all participants randomized to particular groups
- b) only those who completed the treatment regimen
- c) were crossovers counted as participants in the group they crossed into

- N/A
- Unclear

Clear Response

5. **Selective outcome reporting:** Did the authors describe measuring outcomes for which they then reported no actual results?

- Low risk
- High risk
- Unclear

Clear Response

6. **Other sources of bias:** State any important concerns about bias not addressed in the other domains in the tool

6a. Were findings reported as percent who responded (vs. change in assessment score from baseline)?

- Yes
- No
- Unclear
- N/A

Clear Response

6b. Was a **standardized measurement tool** used (i.e., WOMAC, IALs/ADLs, etc)

- Low risk
- High risk
- Unclear

Clear Response

6c. Did the authors describe a **washout period** of at least 3 months for steroid injections or 6 months for Hyaluronic acid?

- Low risk
- High risk
- Unclear

Clear Response

6d. Were co-interventions either avoided in the trial design or did the authors ensure that they were similar between the index and control groups?

- Low risk
- High risk
- Unclear

Clear Response

Have you reconciled this form with the second reviewer?

- Yes
- No

Clear Response

3. Ottawa-Newcastle Risk of Bias Assessment for Observational Studies, Adapted

Risk of Bias Assessment for Observational Studies

1. Representativeness/appropriateness of participant selection
Random or consecutive recruitment=Y
Convenience sample=N
Not reported or unclear

2. Control for baseline differences in cohorts
Similarity of groups at baseline or adjustment in analyses=Y
No attempt to control or adjust=N
Not reported=NR

3. Loss to followup
Explanation provided for loss of participants and/or intention to treat=Y
No explanation or no mention of original number=N

4. Masking of exposure to outcomes assessor
Description of masking=Y
No masking or no description =N

5. Ascertainment of condition
Description of ascertainment/diagnostic criteria=Y
No description or patient self-report=N

6. Documentation of other treatment modalities
Documentation=Y
No documentation=N

7. Extent to which valid outcomes are described
Adequate description of outcome=Y
Insufficient detail regarding outcome or follow-up time=N

8. Prespecification of harms, mode of harms collection
Description of a list of harms assessed or monitoring=Y
No such description or passive harms collection=N
No AE collection=NA

9. Financial COI
Funding source described and not manufacturer=Y
Funding source described as manufacturer=N
No funding source mention=NR

10 Investigator COI reported?
No COI=Y
COI=N
Not reported=NR

4. Adverse Events (Questions from McHarms)

1. Were the harms PRE-DEFINED using standardized or precise definitions?

Harms can be defined as the totality of adverse consequences of an intervention or therapy. Harms are the opposite of benefits, against which they are directly compared. The balance between the benefit(s) and harm(s) of an intervention (i.e. drug or surgery) is ideally used to determine its efficacy or effectiveness.

Pre-defined indicates that the harms that were expected are explicitly defined prior to the collection of these expected events. For example, if bleeding is listed as a harmful event, the criteria by which they determine the bleeding (i.e. body location, type, or amount of blood loss that counts as an event, etc) should be specified.

Standardized classification of harms can be derived from any of the following:

1) reference to standard terminology or classifications of harms from a recognized external organization(s)(such as government regulatory or health agencies. Examples of standardized terminology for harms includes, WHO-ART, MEDra, HTA report on the Measurement and Monitoring of Surgical Adverse Events)

2) previously explicitly defined classifications of harms in the literature, or

3) based on pre-specified clinical criteria, or

4) pre-specified laboratory test (may not need to have a specific cut-off level specified in all cases)

In some instances only some of the harms identified in a study will be precisely defined. In

this case, there must be some judgement.

- Yes
- No
- Unclear

Clear Response

2. Was the mode of harms collection specified as ACTIVE?

Active ascertainment of harms indicates that participants are asked about the occurrence of specific harms in structured questionnaires or interviews or pre-defined laboratory or diagnostic tests and usually performed at pre-specified time intervals.

Passive ascertainment of harms indicates that study participants spontaneously report (on their own initiatives) or are allowed to report harmful events not probed with active ascertainment.

- Yes
- No
- Unclear

Clear Response

3. Was the potential occurrence of harmful events collected at pre-specified intervals; for example, the occurrence of post-operative complications were evaluated on a daily basis within 30 days of the surgery?

- Yes
- No
- Unclear

Clear Response

4. Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?

For example, the study reported 3 types of harmful events (nausea, vomiting, and bleeding); for each of these events the frequency was reported for each study group.

- Yes
- No
- Unclear

Clear Response

5. Was the TOTAL NUMBER of participants affected by harms specified for each study arm?

- Yes
- No
- Unclear

Clear Response

6. If the study reported that there were no serious AE's reported did they define serious AEs?

- Yes
- No
- Unclear
- N/A

Clear Response

Have you reconciled this form with the second reviewer?

- Yes
- No

Clear Response

5. AMSTAR Assessment of Reporting Quality for Systematic Reviews

1. Was an 'a priori' design provided?
The research question and inclusion criteria should be established before the conduct of the review.

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."
□ Yes
□ No
□ Can't answer
□ Not applicable

2. Was there duplicate study selection and data extraction?
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.
□ Yes
□ No
□ Can't answer
□ Not applicable

3. Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).
□ Yes
□ No
□ Can't answer
□ Not applicable

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.
□ Yes
□ No
□ Can't answer
□ Not applicable

5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided.

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."
□ Yes
□ No
□ Can't answer
□ Not applicable

6. Were the characteristics of the included studies provided?
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

Note: Acceptable if not in table format as long as they are described as above.
□ Yes
□ No
□ Can't answer
□ Not applicable
7. Was the scientific quality of the included studies assessed and documented?
'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).

□ Yes
□ No
□ Can't answer
□ Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.
□ Yes
□ No
□ Can't answer
□ Not applicable

9. Were the methods used to combine the findings of studies appropriate?
For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2
). If heterogeneity
exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.
□ Yes
□ No
□ Can't answer
□ Not applicable

10. Was the likelihood of publication bias assessed?
An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.
□ Yes
□ No
□ Can't answer
□ Not applicable

11. Was the conflict of interest included?
Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

Note: To get a "yes," must indicate source of funding or support for the systematic

review AND for each of the included studies.
□ Yes
□ No
□ Can't answer
□ Not applicable

Shea et al. BMC Medical Research Methodology 2007 7:10 doi:10.1186/1471-2288-7-10

Additional notes (in italics) made by Michelle Weir, Julia Worswick, and Carolyn Wayne based on conversations with
Bev Shea and/or Jeremy Grimshaw in June and October 2008 and July and September 2010.

Appendix E. Non-English Language Article Abstracts Reviewed

Table E1. Non-English Language Articles with English Abstracts: Assessment of a Random Selection

ID/ Author, year, language	Design	Intervention	N, participant demographics	Outcomes
161/Not reported, 2012, Finnish	Care guidelines	Multiple	Not applicable (NA)	NA
180/Alhoff, 1998, German	CCT	HA vs. std care, 6 months	179 gonarthrosis patients	Cost-effectiveness in terms of treatment cost and productivity, Lequesne and Euroquol for pain and mobility 92.4% of all patients under HYA achieved optimum values of Euroquol for general satisfaction vs. 42.9% in the reference group
254/Borras-Verdera, 2012, Spanish	Open uncontrolled trial	1 injection HA + mannitol, periodic followup (FU) for 6 months	79 pts. with painful knee OA	VAS WOMAC for pain and joint function, safety, need for rescue medication: % of patients who improved + effect A significant reduction in joint pain, stiffness and functional disability compared with baseline was observed at every follow-up visit (P<.001). Joint function improved by 38.7% on Day 30, reaching 47.5% on Day 180
296/Chen, 2002, Chinese	Open uncontrolled trial	3 weekly HA injections, 1-6 month FU	96 pts	Lysholm scoring, clinical signs, mobility, safety: % of patients who improved + outcome obvious improvements in the signs and function of knee in 39 patients (40.6%), only some improvements in 48 patients (50.0%),

ID/ Author, year, language	Design	Intervention	N, participant demographics	Outcomes
				and no obvious improvements in other 9 patients (9.4%). The total effectiveness rate was 74.0%
335/Dai, 2002, Chinese	controlled trial	Weekly HA injections, variable number	310 postop pts (arthroscopy or open)	Average VAS score for pain, time to maximum painless ROM **after arthroscopy** + effect: The VAS score of patients in the treatment group was significant lower than that of the control group. The period to the maximal painless ROM of the joint was 6 days in the treatment group after open operation, while 9 days in the control group
342/Diehl, 2013, German	review	Knee OA: Multiple treatment modalities	NA	NA (no real conclusions except that HA is safe and provide shortterm symptom relief)
348/Dougados, 1994/French	Evaluation of arthroscopy to assess cartilage lesions and changes due to treatment (chondroscopy)	Preliminary study of repeated HA injections to test applicability, sensitivity of chondroscopy to visualize changes in cartilage	Not reported	Not relevant
379/Fukuda, 2004, Japanese	Non-systematic review	HA injection	Findings suggest HA effective for joint cellular and immune function but insufficient evidence on its effect on progression	
380/Gadek, 2011, Polish	No study details	HA injection (Suplasyn)	Not reported	Study "reconfirmed effectiveness and safety..." No data in abstract
381/Galus, 2006, Polish	Non-systematic review on uses of HA			No mention of efficacy
409/Gu, 2011, Chinese	Non-systematic review on use of HA			Mentions evidence from insurers
422/He, 2012	Case control study (really a trial) of HA + exercise vs. HA			No useful findings for this report, as HA was control
431/Heybeli 2008	Post arthroscopic HA vs. no	Post-surgical Orthovisc injection	67 patients 40-65 years of age	Improvement in pain scores at 6 weeks

ID/ Author, year, language	Design	Intervention	N, participant demographics	Outcomes
	treatment			did not differ between the two groups (HA 21%, control 16%; p=0.478), whereas improvement in function scores was significantly higher in the HA group (23% vs 9.2%; p=0.018)
443/ Hu 2006	RCT	HA vs. ligustrazine, 5 tx, 63 month followup	71 cases (82 knees)	There was significant decrease in Lequesneos index in SH group after the treatment (P<0.01), but not in LI group (P>0.05). Three weeks later, there was significant decrease in Lequesneos index in both groups after the treatment (P<0.01), with no significant difference between SH and LI group (P>0.05). After the 5-week treatment, the efficacy rate of the LI group was 82.1%, and that of the SH group was 87.2%
466/ Ishikawa 2002 japanese	NSR on HA for knee and shoulder			NR
517/Krocker 2006 German	Uncontrolled trial	Single injection of Durolane, synthetic HA, 24 weeks followup	50 patients with primary OA	KOOS, VAS, and EQ-5D, as well as motion of the knee. At 2 wks: the subjective function of knee and quality of life had increased significantly. At 24 wks, all parameters increased significantly (quality of life and activity +19%; range of motion active 109 vs. 115 degrees ; pain, 55 vs. 41 mm (VAS); all p<0.01)
520/Kuiper-Geertsma 2000 Dutch	NSR			NR
542/Li 2011Chinese	RCT	Comparison of PRP and HA: 3 injections at 3-week intervals, 6-month followup	30 patients	International Knee Documentation Committee (IKDC) score, WOMAC score, and

ID/ Author, year, language	Design	Intervention	N, participant demographics	Outcomes
				Lequesne index significant differences in IKDC score, WOMAC score, and Lequesne index between pre- and post-injection in 2 groups (P < 0.05); no significant difference was found between different time points (3, 4, and 6 months) in test group (P > 0.05), while significant differences were found between the postoperative 6th month and the postoperative 3rd and 4th months in control group (P < 0.05). There was no significant difference in IKDC score, WOMAC score, and Lequesne index between 2 groups within 4 months (P > 0.05), but the effectiveness of test group was significantly better than that of control group at 6 months after injection (P < 0.05)
544/ Li 2009, Chinese	Uncontrolled trial of acupuncture effect on HA			NR
545/Liang 2010	Double blind placebo controlled RCT	HA vs. CS? , duration not reported	Sample size unknown	Findings unclear: HA better than CS?
ID #546 Ling 2002,	NSR			NA
IDs #563, 568,	NSRs			
ID#578 Mar 2013 Spanish	Dataset analysis and modeling of 10-year budget impact	HA injection	Patients awaiting knee replacement	Modeling estimates that HA can delay TKR by 2.67 years. Leading to significant cost saving
ID# 587 Marson 2007 Italian	NSR			
ID# 602 Menshikova 2007 Russian	Uncontrolled trial	ostenil (HA)	60 OA patients, mean age 65	Significant improvement was seen in 60% patients. Pain and stiffness in the knee

ID/ Author, year, language	Design	Intervention	N, participant demographics	Outcomes
				joint relieved 2-fold. The function improved less. OA severity by Leken's index decreased by two degrees. 20% patients stopped intake of NAD, 32% had no need in taking NAD regularly. Subjective and objective assessment (by the patient and by the doctor) of the symptoms severity improved twice. Twelve months later the
ID# 616 Mitner 2001 German	Controlled trial (patients were own controls: blinding unclear)	HA, 5 weekly injections	43 patients with bilateral knee OA	In knees treated with hyaluronic acid the mean peak torque of the knee extensor was 57 +/- 26.15/32 +/- 19.63 Nm vs. 77.17 +/- 32.54/47.83 +/- 21.43 Nm after ($p < 0.01$), the mean peak torque of the knee flexor was 40.44 +/- 21.58/22.89 +/- 16.64 Nm vs. 53.55 +/- 24.26/34.05 +/- 17.37 Nm after treatment ($p < 0.01$) at the angular velocities of 60 degrees/s and 180 degrees/s. Significant differences ($p > 0.01$) between treated and untreated knee were found for total work of the extensor and flexor of the knee. The pain at rest decreased from 3.83 +/- 1.72 cm to 1.36 +/- 1.42 cm and the pain under load decreased from 7.57 +/- 1.34 cm to 3.75 +/- 1.32 cm in the treated knee group ($p < 0.01$)
634/Navarro 2006	Uncontrolled trial	HA, 5 weekly injections	111 patients	Significant

ID/ Author, year, language	Design	Intervention	N, participant demographics	Outcomes
Spanish				improvement in all efficacy variables
642/Noain 2002 Spanish	Case reports			2 reports of acute local reactions
644/Nozaki 2002 Japanese	NSR			
647/Okuda 1994 Japanese	Not OA, not study of HA			

Appendix F. Table Hyaluronic Acid Products Indicated for Treatment of OA of the Knee but Not Approved in the US

Table F1. Hyaluronic Acid Products Indicated for Treatment of OA of the Knee but Not Approved in the US

Product Name	Molecular Weight	Source	US Equivalent	Manufacturer
Adant	900 kD	Synthetic *	None	Meiji Seika Pharma Co., Ltd. Japan
Artz	620-1170kD	Avian	Supartz	Seikagaku Corporation Japan
BioHy	600-3000kD	Synthetic	Euflexxa	Biotechnology General Corp./Savient
Durolane	1000kD	Avian	None	Q-Med
Go-on	800-1500kD	Synthetic	None	Rottapharm|Madaus, Monza, Italy
Hyaject	1500kD	Synthetic	Unclear	Ormed Gmbh Germany
Hyalart	750kD	Avian	Hyalgan?	MEDA Manufacturing GmbH
Hyalubrix	1500-3200kD	Synthetic	None	Fidia
Hylan GF-20	600kD	Avian	Synvisc	
Hyruan	3000kD	n/a	None	LG Life Science
Ostenil	1200-1400kD	Synthetic	None	TRB Chemedica Ltd. UK
Sinovial	800-1200kD	Avian	None	IBSA Gulf Kingdom of Saudi Arabia
Suplasyn	500-730kD	Synthetic	Hyalgan	Alveda/Mylan

*Purified from a cultured strain of Streptococcus via fermentation

Appendix G. Required Domains: Definitions and Scores

Table G1. Grading the strength of a body of evidence: Required domains and their definitions*

Domain	Definition and Elements	Score and Application
Study Limitations	Study limitations are the degree to which the included studies for a given outcome or comparison have a high likelihood of adequate protection against bias (i.e., good internal validity), assessed through two main elements: • Study design (e.g., RCTs or observational studies) • Aggregate quality of the studies under consideration. Information for this determination comes from the rating of quality (good/fair/poor) done for individual studies	Use one of three levels of, separately by type of study design: • Low level of study limitations • Medium level of study limitations • High level of study limitations
Consistency	The principal definition of consistency is the degree to which reported effect sizes from included studies appear to have the same direction of effect. This can be assessed through two main elements: • Effect sizes have the same sign (that is, are on the same side of "no effect") • The range of effect sizes is narrow.	Use one of three levels of consistency: • Consistent (i.e., no inconsistency) • Inconsistent • Unknown or not applicable (e.g., single study) As noted in the text, single-study evidence bases (even mega-trials) cannot be judged with respect to consistency. In that instance, use "Consistency unknown (single study)."

Domain	Definition and Elements	Score and Application
Directness	The rating of directness relates to whether the evidence links the interventions directly to health outcomes. For a comparison of two treatments, directness implies that head-to-head trials measure the most important health or ultimate outcomes. Two types of directness, which can coexist, may be of concern: Evidence is indirect if: • It uses intermediate or surrogate outcomes instead of health outcomes. In this case, one body of evidence links the intervention to intermediate outcomes and another body of evidence links the intermediate to most important (health or ultimate) outcomes. • It uses two or more bodies of evidence to compare interventions A and B -- e.g., studies of A vs. placebo and B vs. placebo, or studies of A vs. C and B vs. C but not A vs. B. Indirectness always implies that more than one body of evidence is required to link interventions to the most important health outcomes. Directness may be contingent on the outcomes of interest. EPC authors are expected to make clear the outcomes involved when assessing this domain.	Score dichotomously as one of two levels directness • Direct • Indirect If indirect, specify which of the two types of indirectness account for the rating (or both, if that is the case) -- namely, use of intermediate/ surrogate outcomes rather than health outcomes, and use of indirect comparisons. Comment on the potential weaknesses caused by, or inherent in, the indirect analysis. The EPC should note if both direct and indirect evidence was available, particularly when indirect evidence supports a small body of direct evidence.
Precision	Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome (i.e., for each outcome separately) If a meta-analysis was performed, this will be the confidence interval around the summary effect size.	Score dichotomously as one of two levels of precision: • **Precise** • **Imprecise** A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions. For example, results may be statistically compatible with both clinically important superiority and inferiority (i.e., the direction of effect is unknown), a circumstance that will preclude a valid conclusion.
	Reporting bias results from selectively publishing or reporting research findings based on the favorability of direction or magnitude of effect. It includes: • Study publication bias, i.e., nonreporting of the full study. • Selective outcome reporting bias, i.e., nonreporting (or incomplete reporting) of planned outcomes or reporting of unplanned outcomes. • Selective analysis reporting bias, i.e., reporting of one or more favorable analyses for a given outcome while not reporting other, less favorable analyses. Assessment of reporting bias for individual studies depends on	Score as one of two levels: • **Suspected** • **Undetected** Reporting bias is suspected when: • Testing for funnel plot asymmetry demonstrates a substantial likelihood of bias, And/or • A qualitative assessment suggests the likelihood of missing studies,

Domain	Definition and Elements	Score and Application
	many factors–e.g. availability of study protocols, unpublished study documents, and patient-level data. Detecting such bias is likely with access to all relevant documentation and data pertaining to a journal publication, but such access is rarely available. Because methods to detect reporting bias in observational studies are less certain, this guidance does not require EPCs to assess it for such studies	analyses, or outcomes data that may alter the conclusions from the reported evidence. Undetected reporting bias includes all alternative scenarios

*Adapted from Berkman, N. D., et al. (2008). Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD).

Appendix H. Metrics and Tools Used to Assess Progression and Response to Treatment for Osteoarthritis of the Knee and Health-related Quality of Life

1. WOMAC Index
2. LeQuesne Index
3. SF-36
4. EuroQuol-5D™

Figure H1. The Womac Osteorthritis Index

WOMAC OSTEOARTHRITIS INDEX VERSION LK3.0

INSTRUCTIONS TO PATIENTS

In sections A, B, and C questions will be asked in the following format and you should give your answers by putting an "X" in one of the boxes.

NOTE:

1. If you put your "X" in the left-hand box, i.e.

None	Mild	Moderate	Severe	Extreme
☒	☐	☐	☐	☐

then you are indication that you have no pain.

2. If you put your "X" in the right-hand box, i.e.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☒

then you are indication that your pain is extreme.

3. Please note:
   a). that the further to the right you place your "X" the more pain you are experiencing.

   b) that the further to the left you place your "X" the less pain you are experiencing.

   c) please do not place your "X" **outside** the box.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have experience in the last 48 hours. ☐

Remember the further you place your "X" to the right, the more pain, stiffness or disability you are indicating that you experienced. Finally, please note that you are to complete the questionnaire with respect to your study joint(s). You should think about your study joint(s) when answering the questionnaire, i.e., you should indicate the severity of your pain, stiffness and physical disability that you feel is caused by arthritis in your study joint(s). Your study joint(s) has been identified for you by your health care professional. If you are unsure which joint(s) is your study joint, please ask before completing the questionnaire.

Section A

INSTRUCTIONS TO PATIENTS

The following questions concern the amount of pain you have experienced due to arthritis in your study joint(s).For each situation please enter the amount of pain experienced in the last 48 hours (Please mark your answers with an “X”.)

1. Walking on a flat surface.

None	Mild	Moderate	Severe	Extreme	
☐	☐	☐	☐	☐	**PAIN 1**

2. Going up or down stairs.

None	Mild	Moderate	Severe	Extreme	
☐	☐	☐	☐	☐	**PAIN 2**

3. At night while in bed.

None	Mild	Moderate	Severe	Extreme	
☐	☐	☐	☐	☐	**PAIN 3**

4. Sitting or lying.

None	Mild	Moderate	Severe	Extreme	
☐	☐	☐	☐	☐	**PAIN 4**

5. Standing upright.

None	Mild	Moderate	Severe	Extreme	
☐	☐	☐	☐	☐	**PAIN 5**

Section B

INSTRUCTIONS TO PATIENTS

The following questions concern the amount of joint stiffness (not pain) you have experienced in the last 48 hours in your study joint(s). Stiffness is a sensation of restriction or slowness in the ease with which you move your joints. (Please mark your answers with an “X”.)

6. How sever is your stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme	
☐	☐	☐	☐	☐	**STIFF6**

7. How severe is your stiffness after sitting, lying, or resting later in the day?

None	Mild	Moderate	Severe	Extreme	
☐	☐	☐	☐	☐	**STIFF7**

Section C

INSTRUCTIONS TO PATIENTS

The following questions concern YOUR PHYSICAL FUNCTION. By this we mean your ability to move around and to look after yourself. For each of the following activities, please indicate the degree of difficulty you have experienced in the last 48 hours due to arthritis in your study joint(s). (Please mark your answers with an "X".)

QUESTION: What degree of difficulty do you have?

8. Descending stairs.

None	Mild	Moderate	Severe	Extreme	
☐	☐	☐	☐	☐	**PFTN8**

9. Ascending stairs.

None	Mild	Moderate	Severe	Extreme	
☐	☐	☐	☐	☐	**PFTN9**

10. Rising from sitting.

None	Mild	Moderate	Severe	Extreme	
☐	☐	☐	☐	☐	**PFTN10**

11. Standing.

None	Mild	Moderate	Severe	Extreme	
☐	☐	☐	☐	☐	**PFTN11**

12. Bending to floor.

None	Mild	Moderate	Severe	Extreme	
☐	☐	☐	☐	☐	**PFTN12**

13. Walking on flat

None	Mild	Moderate	Severe	Extreme	
☐	☐	☐	☐	☐	**PFTN13**

14. Getting in/out of car.

None	Mild	Moderate	Severe	Extreme	
☐	☐	☐	☐	☐	**PFTN14**

15. Going shopping.

None	Mild	Moderate	Severe	Extreme	
☐	☐	☐	☐	☐	**PFTN15**

16. Putting on socks/stockings.

None	Mild	Moderate	Severe	Extreme	**PFTN16**
☐	☐	☐	☐	☐	

17. Rising from bed.

None	Mild	Moderate	Severe	Extreme	**PFTN17**
☐	☐	☐	☐	☐	

18. Taking off socks/stockings.

None	Mild	Moderate	Severe	Extreme	**PFTN18**
☐	☐	☐	☐	☐	

19. Lying in bed.

None	Mild	Moderate	Severe	Extreme	**PFTN19**
☐	☐	☐	☐	☐	

20. Getting in/out of bath.

None	Mild	Moderate	Severe	Extreme	**PFTN20**
☐	☐	☐	☐	☐	

21. Sitting.

None	Mild	Moderate	Severe	Extreme	**PFTN21**
☐	☐	☐	☐	☐	

22. Getting on/off toilet.

None	Mild	Moderate	Severe	Extreme	**PFTN22**
☐	☐	☐	☐	☐	

23. Heavy domestic duties.

None	Mild	Moderate	Severe	Extreme	**PFTN23**
☐	☐	☐	☐	☐	

24. Light domestic duties.

None	Mild	Moderate	Severe	Extreme	**PFTN24**
☐	☐	☐	☐	☐	

THANK YOU FOR COMPLETING THE QUESTIONNAIRE

Figure H2. Lequesne Index

Index of Severity for Osteoarthritis of the Knee by Lequesne et al

Overview:

Lequesne et al developed an index of severity for osteoarthritis for the knee (ISK). This can be used to assess the effectiveness of therapeutic interventions.

Sections for index:

(1) pain or discomfort

(2) maximum distance walked

(3) activities of daily living

I Pain or Discomfort

Parameter	Finding	Points
pain or discomfort during nocturnal bedrest	none	0
	only on movement or in certain positions	1
	without movement	2
duration of morning stiffness or pain after getting up	none	0
	< 15 minutes	1
	>= 15 minutes	2
remaining standing for 30 minutes increases pain	no	0
	yes	1
pain on walking	none	0
	only after walking some distance	1
	early after starting	2
pain or discomfort after getting up from sitting without use of arms	no	0
	yes	1

where:

- A change in a 1991 version was to have the duration of morning stiffness scored 0 if it was 1 minute or less and 1 if it was from 1 to less than 15 minutes.

- Pain on walking in a 1991 version expanded "early after starting" to "after initial ambulation and increasingly with continued ambulation"

II. Maximum Distance Walked

Parameter	Finding	Points
maximum distance walked	unlimited	0
	> 1 kilometer but limited	1
	about 1 kilometer (about 15 minutes)	2
	about 500 - 900 meters (about 8-15 minutes)	3
	from 300 - 500 meters	4
	from 100 - 300 meters	5
	< 100 meters	6
walking aids required	None	0
	1 walking stick or crutch	1
	2 walking sticks or crutches	2

III. Activities of Daily Living

Parameter	Finding	Points
able to climb up a standard flight of stairs	easily	0
	with mild difficulty	0.5
	with moderate difficulty	1.0
	with marked difficulty	1.5
	impossible	2.0
able to clumb down a standard flight of stairs	easily	0
	with mild difficulty	0.5
	with moderate difficulty	1.0
	with marked difficulty	1.5
	impossible	2.0
able to squat or bend at the knee	easily	0
	with mild difficulty	0.5
	with moderate difficulty	1.0
	with marked difficulty	1.5
	impossible	2.0
able to walk on uneven ground	easily	0

	with mild difficulty	0.5
	with moderate difficulty	1.0
	with marked difficulty	1.5
	impossible	2.0

index of severity =

= SUM(points for all parameters)

Interpretation:

• minimum points for each section: 0

• maximum points for each section: 8

• minimum index score: 0

• maximum index score: 24

Index Score	Handicap
0	none
1 - 4	mild
5 - 7	moderate
8 - 10	severe
11 - 13	very severe
>= 14	extremely severe

Modifications

The index was modified in 1997 with some minor changes to morning stiffnes and termed the "algofunctional index".

References:

Lequesne M Mery C et al. Indexes of severity for osteoarthritis of the hip and knee. Scand J Rheumatology. 1987; Supplement 65: 85-89.

Lequesne M. Indices of severity and disease activity for osteoarthritis. Seminars in Arthritis and Rheumatism. 1991; 20 (supplement 2): 48-54.

Lequesne MG. The algofunctional indices for hip and knee osteoarthritis. J Rheumatol. 1997; 24: 779-781.

Figure H3. The RAND Medical Outcomes Study Short Form (SF)–36

RAND HEALTH

RAND > RAND Health > Surveys > Medical Outcomes Study >

Medical Outcomes Study: 36-Item Short Form Survey Instrument

RAND 36-Item Health Survey 1.0 Questionnaire Items

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. **Compared to one year ago,** how would your rate your health in general **now**?	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

(Circle One Number on Each Line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not limited at All
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
5. Lifting or carrying groceries	[1]	[2]	[3]
6. Climbing **several** flights of stairs	[1]	[2]	[3]
7. Climbing **one** flight of stairs	[1]	[2]	[3]
8. Bending, kneeling, or stooping	[1]	[2]	[3]
9. Walking **more than a mile**	[1]	[2]	[3]
10. Walking **several blocks**	[1]	[2]	[3]
11. Walking **one block**	[1]	[2]	[3]
12. Bathing or dressing yourself	[1]	[2]	[3]

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Circle One Number on Each Line)

	Yes	No
13. Cut down the amount of time you spent on work or other activities	1	2
14. **Accomplished less** than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2

16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

(Circle One Number on Each Line)

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2
18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

20. During the **past 4 weeks,** to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(Circle One Number)

Not at all 1

Slightly 2

Moderately 3

Quite a bit 4

Extremely 5

21. How much **bodily** pain have you had during the **past 4 weeks**?

(Circle One Number)

None 1

Very mild 2

Mild 3

Moderate 4

Severe 5

Very severe 6

22. During the **past 4 weeks,** how much did **pain** interfere with your normal work (including both work outside the home and housework)?

(Circle One Number)

Not at all 1

A little bit 2

Moderately 3

Quite a bit 4

Extremely 5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks** . . .

(Circle One Number on Each Line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and	1	2	3	4	5	6

peaceful?						
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks,** how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

(Circle One Number)

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

How TRUE or FALSE is each of the following statements for you.

(Circle One Number on Each Line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get	1	2	3	4	5

worse					
36. My health is excellent	1	2	3	4	5

ABOUT

The RAND Corporation is a research organization that develops solutions to public policy challenges to help make communities throughout the world safer and more secure, healthier and more prosperous. RAND is nonprofit, nonpartisan, and committed to the public interest.

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Figure H4. EURO-QUOL (EQ)-5D-3L™

Health Questionnaire

English version for the UK

(Validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑

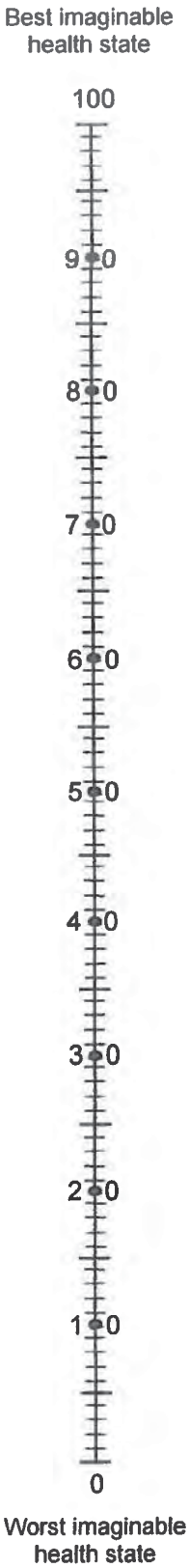
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐