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OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines

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Summary

Purpose: To develop concise, patient-focussed, up to date, evidence-based, expert consensus recommendations for the management of hip and knee osteoarthritis (OA), which are adaptable and designed to assist physicians and allied health care professionals in general and specialist practise throughout the world.

Methods: Sixteen experts from four medical disciplines (primary care, rheumatology, orthopaedics and evidence-based medicine), two continents and six countries (USA, UK, France, Netherlands, Sweden and Canada) formed the guidelines development team. A systematic review of existing guidelines for the management of hip and knee OA published between 1945 and January 2006 was undertaken using the validated appraisal of guidelines research and evaluation (AGREE) instrument. A core set of management modalities was generated based on the agreement between guidelines. Evidence before 2002 was based on a systematic review conducted by European League Against Rheumatism and evidence after 2002 was updated using MEDLINE, EMBASE, CINAHL, AMED, the Cochrane Library and HTA reports. The quality of evidence was evaluated, and where possible, effect size (ES), number needed to treat, relative risk or odds ratio and cost per quality-adjusted life years gained were estimated. Consensus recommendations were produced following a Delphi exercise and the strength of recommendation (SOR) for propositions relating to each modality was determined using a visual analogue scale.

Results: Twenty-three treatment guidelines for the management of hip and knee OA were identified from the literature search, including six opinion-based, five evidence-based and 12 based on both expert opinion and research evidence. Twenty out of 51 treatment modalities addressed by these guidelines were universally recommended. ES for pain relief varied from treatment to treatment. Overall there was no statistically significant difference between non-pharmacological therapies [0.25, 95% confidence interval (CI) 0.16, 0.34] and pharmacological therapies (ES = 0.39, 95% CI 0.31, 0.47). Following feedback from Osteoarthritis Research International members on the draft guidelines and six Delphi rounds consensus was reached on 25 carefully worded recommendations. Optimal management of patients with OA hip or knee requires a combination of non-pharmacological and pharmacological modalities of therapy. Recommendations cover the use of 12 non-pharmacological modalities: education and self-management, regular telephone contact, referral to a physical therapist, aerobic, muscle strengthening and water-based exercises, weight reduction, walking aids, knee braces, footwear and insoles, thermal modalities, transcutaneous electrical nerve stimulation and acupuncture. Eight recommendations cover pharmacological modalities of treatment including acetaminophen, cyclooxygenase-2 (COX-2) non-selective and selective oral non-steroidal anti-inflammatory drugs (NSAIDs), topical NSAIDs and capsaicin, intra-articular injections of corticosteroids and hyaluronates, glucosamine and/or chondroitin sulphate for symptom relief; glucosamine sulphate, chondroitin sulphate and diacerein for possible structure-modifying effects and the use of opioid analgesics for the treatment of refractory pain. There are recommendations covering five surgical modalities: total joint replacements, unicompartmental knee replacement, osteotomy and joint preserving surgical procedures; joint lavage and arthroscopic debridement in knee OA, and joint fusion as a salvage procedure when joint replacement had failed. Strengths of recommendation and 95% CIs are provided.

Conclusion: Twenty-five carefully worded recommendations have been generated based on a critical appraisal of existing guidelines, a systematic review of research evidence and the consensus opinions of an international, multidisciplinary group of experts. The recommendations may be adapted for use in different countries or regions according to the availability of treatment modalities and SOR for each modality of therapy. These recommendations will be revised regularly following systematic review of new research evidence as this becomes available.

Key words: OARSI, Treatment guidelines, Hip and knee osteoarthritis.

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Osteoarthritis (OA) is the most common type of arthritis and the major cause of chronic musculoskeletal pain and mobility disability in elderly populations worldwide[1]. Knee and hip pain are the major causes of difficulty in walking and climbing stairs in the elderly in Europe[2] and the USA[3] and as many as 40% of people over the age of 65 in the community in the United Kingdom suffer symptoms associated with knee or hip OA[2].

Treatment of OA of the knee and hip is directed towards

- Reducing joint pain and stiffness.
- Maintaining and improving joint mobility.
- Reducing physical disability and handicap.
- Improving health-related quality of life.
- Limiting the progression of joint damage.
- Educating patients about the nature of the disorder and its management.

More than 50 modalities of non-pharmacological, pharmacological and surgical therapy for knee and hip OA are described in the medical literature[4].

Over the years a number of National and Regional Guidelines have been developed to assist physicians, allied health professionals and patients in their choice of therapy for the management of knee and hip OA, but internationally agreed and universally applicable guidelines for the management of these global disorders have been lacking.

In September 2005 the Osteoarthritis Research International (OARSI) appointed an international, multidisciplinary committee of experts with a remit to produce up to date, evidence-based, globally relevant, consensus recommendations for the management of knee and/or hip OA in 2007. The first part of the work of this committee was to undertake a critical appraisal of all existing evidence-based and consensus guidelines for the treatment of knee and/or hip OA and a systematic review of the recent research evidence. The results of this critical appraisal and systematic review were published recently[4]. This second part of the report contains the current OARSI evidence-based, expert consensus recommendations for the treatment of knee and/or hip OA.

Scope and purpose

The guidelines are intended to provide concise, patient-focussed, up to date, evidence-based, expert consensus recommendations for the management of hip and knee OA, which are globally relevant.

Target users

The guidelines have been developed to provide assistance to physicians and allied health care professionals who deal with patients with OA hip and knee in both primary and secondary (specialist) care settings. The guidelines should also provide a helpful resource for patients with OA hip or knee, patient representative groups and health care funders and administrators. It is anticipated that these OARSI international core recommendations will be modified and adapted as appropriate for National and Regional use.

Stakeholder involvement

The guideline development committee was composed of 16 experts from four medical disciplines (primary care 2, rheumatology 11, orthopaedics 1, and evidence-based medicine 2) and six countries in Europe and North America (France, Netherlands, Sweden, UK, Canada and USA). All members of the development team participated in (1) a critical appraisal of existing treatment guidelines[4]; (2) a Delphi exercise to generate consensus recommendations; and (3) an exercise to grade the strength of recommendation (SOR) for all modalities of therapy recommended.

Rigour of development

CRITICAL APPRAISAL OF EXISTING GUIDELINES

Methodological details of the *systematic literature search*, the *inclusion/exclusion criteria*, the *quality and content assessment* and the *data analyses* of all existing guidelines for the management of hip and/or knee OA published between 1945 and October 2005 can be found in the first part of this report[4]. The quality of the guidelines was assessed using the AGREE instrument[5] and standardised percent scores (0–100%) for scope, stakeholder involvement, rigour, clarity, applicability and editorial independence, as well as overall quality, were calculated. Treatment modalities addressed and recommended by the guidelines were summarised. Agreement (%) was estimated and the best level of evidence (LoE) to support each recommendation was extracted.

SYSTEMATIC REVIEW OF THE MORE RECENT EVIDENCE

Systematic reviews of research evidence for the treatment of hip and/or knee OA up to January 2002 were available from the systematic literature review undertaken by the European League against Rheumatism (EULAR). Methodological details of the *systematic literature search*, the *inclusion/exclusion criteria*, the *quality assessments* and *outcome measures (efficacy, side effects and cost-effectiveness)* for research evidence relating to the treatment of OA hip and/or knee published between 31st January 2002 and 31st January 2006 can also be found in the first part of this report[4]. The quality of evidence was evaluated using the Oxman and Guyatt method for systematic reviews[6] and the Jadad scale for randomised controlled trials (RCTs)[7]. Where possible, effect size (ES)[8], number needed to treat (NNT)[9], relative risk (RR) or odds ratio (OR)[10] and cost per quality-adjusted life year (QALY) gained[4] were estimated. Sensitivity analyses[11] were undertaken to determine whether selected RCTs published after January 31st 2006 would alter any of the evidence-based conclusions from the critical appraisal of existing guidelines and the systematic review of the recent research evidence significantly.

DELPHI EXERCISE TO GENERATE CONSENSUS RECOMMENDATIONS

Concise propositions relating to all aspects of non-pharmacological, pharmacological and surgical treatments of OA hip and/or knee were generated as follows.

The committee of experts was divided into three subgroups:

- Non-pharmacological: Altman, Brandt, Croft, and Doherty.
- Pharmacological: Abramson, Bierma-Zeinstra, Dougados, and Hochberg.
- Surgical: Arden, Hunter, Kwoh, Lohmander, and Tugwell.

Each expert was provided with a comprehensive table of 51 potential treatment modalities together with a summary of recommendations from the critical appraisal of existing guidelines[4] (percentage of guidelines addressing modality, AGREE instrument score for quality[5], the LoE[12] and ES

for pain[8]) and a summary of the systematic analysis of the research evidence from 2002 to 2006[4] (Quality scores[6,7], ES[8] for pain, function and stiffness, the NNT[9], the RR/OR[10] and the cost per QUALY[4]). A full list of references from which the summary data had been extracted was also provided. With the exception of the co-chairs (RM and GN) and the lead researcher (WZ), who did not contribute to the primary generation of propositions in order to avoid administrative bias, each committee expert was asked to generate a *comprehensive* list of propositions relating to modalities of treatment in the group to which they were assigned, based on the available *research evidence* and their own *clinical expertise*. There was no limit to the number of propositions proposed for the initial master list.

After elimination of closely similar or overlapping propositions a master list of 110 propositions relating to 54 non-pharmacological modalities of treatment, 37 pharmacological, 18 surgical and one combining non-pharmacological and pharmacological modalities was circulated to all members of the guideline development group apart from RM, GN and WZ for acceptance or rejection. The experts were also given the opportunity to suggest amalgamations and rewording of individual propositions. After four rounds of the Delphi exercise in which propositions with >60% of votes were accepted, those with <20% were rejected and those attracting between 20% and 60% of votes were taken forward for consideration following further amalgamations and minor rewording, provisional consensus was reached on 34 propositions. These were posted on the OARSI website and presented for comments and suggestions by OARSI members at a plenary session of the World Congress on OA in Prague in December 2006. After further additions, amalgamations, minor rewording and two further Delphi rounds, consensus was reached on accepting 25 carefully worded propositions (Table I). All eligible members of the committee voted at each step of the Delphi exercise.

STRENGTH OF RECOMMENDATION (SOR)

The SOR for each treatment proposition was based on the opinions of the guideline development group after taking into consideration the research evidence for efficacy, safety and cost-effectiveness of each treatment proposed, and the clinical expertise of the members of the guideline committee including such considerations as the experts' experience and perception of patient tolerance, acceptability and adherence to the treatment in question and their expert knowledge of any logistic issues involved in the administration of the treatment.

Each member of the guideline development committee, except for RM, GN and WZ, was asked to indicate their SOR for each accepted proposition on a 0–100 mm visual analogue scale (VAS) after being provided with

(a) the list of accepted propositions in which the level of the research evidence for each proposition was indicated (Table I) according to the evidence hierarchy[12] (Table II),
(b) the results of the critical appraisal of existing guidelines[4],
(c) a summary of the systematic analysis of the research evidence from 2002 to 2006 (Ref. 4, Table 5) including details of quality scores, ES for pain, function and stiffness, the NNT, the RR or OR and the cost per QALY for each modality of treatment proposed where these were available, and
(d) a first draft of this manuscript.

Mean and standard error of the mean (S.E.M.) for the SOR for each proposition were calculated, with and without recusals for voting on individual propositions by individual members of the committee, where there was any possibility of a potential conflict of interest, and the results were expressed as means with 95% confidence limits.

OARSI recommendations

After six rounds of the Delphi exercise there was expert consensus for 25 recommendations for the treatment of hip and knee OA. These are summarised in Table I together with the level of evidence (LoE) supporting them, the ES for pain relief [ES_{pain} 95% confidence interval (CI)], the extent of consensus (%) and the SOR (mean $\pm$ 2 S.E.M.) for each proposition. The treatment propositions recommended in Table I are grouped as general, non-pharmacological, pharmacological and surgical without ranking the recommendations for the order in which the treatments should be offered.

General recommendations

1. Optimal management of OA requires a combination of non-pharmacological and pharmacological modalities.
SOR: 96% (95% CI 93–99)

Combination of pharmacological and non-pharmacological treatments is frequently employed in clinical practise and is universally recommended in 12/12 existing guidelines for the management of hip and/or knee OA[4]. Although there was 100% consensus and strong recommendation for combining pharmacological and non-pharmacological therapies following the Delphi exercise, this recommendation lacks evidence from RCTs with appropriate factorial design. It is largely based on expert opinion (LoE IV) and uncontrolled observations of additional benefit in RCTs and meta-analyses (MAs) of trials of non-pharmacological modalities of therapy (e.g., exercise[13,14], weight reduction[15,16], and education[17]) where all patients were receiving pharmacological treatment with analgesics or non-steroidal anti-inflammatory drugs (NSAIDs).

Non-pharmacological modalities of treatment

2. All patients with hip and knee OA should be given information access and education about the objectives of treatment and the importance of changes in lifestyle, exercise, pacing of activities, weight reduction, and other measures to unload the damaged joint(s). The initial focus should be on self-help and patient-driven treatments rather than on passive therapies delivered by health professionals. Subsequently emphasis should be placed on encouraging adherence to the regimen of non-pharmacological therapy.
SOR: 97% (95% CI 95–99)

Provision of information and overall patient education about the objectives of treatment and the importance of changes in lifestyle, exercise, pacing of activities, weight reduction and other measures to unload damaged joints is supported by two MAs[17,18] (LoE Ia), but the ES for pain relief is small (0.06 95% CI 0.02, 0.10)[18] and RCTs with an appropriate factorial design to assess the efficacy of individual components of the education programme have not been undertaken. Attempts to identify which components of self-management programmes contribute most to their efficacy

Table I
OARSI recommendations and research evidence

Proposition	LoE	ES for pain (95% CI)	Frequency recommended in existing guidelines	Level of consensus (%)	SOR (%) (95% CI)
General					
1. Optimal management of OA requires a combination of non-pharmacological and pharmacological modalities.	IV		12/12	100	96 (93–99)
Non-pharmacological modalities of treatment					
2. All patients with hip and knee OA should be given information access and education about the objectives of treatment and the importance of changes in lifestyle, exercise, pacing of activities, weight reduction, and other measures to unload the damaged joint(s). The initial focus should be on self-help and patient-driven treatments rather than on passive therapies delivered by health professionals. Subsequently emphasis should be placed on encouraging adherence to the regimen of non-pharmacological therapy.	Ia (education) IV (adherence)	0.06 (0.02, 0.10)	8/8	92	97 (95–99)
3. The clinical status of patients with hip or knee OA can be improved if patients are contacted regularly by phone.	Ia	0.12 (0.00, 0.24)	2/2	77	66 (57–75)
4. Patients with symptomatic hip and knee OA may benefit from referral to a physical therapist for evaluation and instruction in appropriate exercises to reduce pain and improve functional capacity. This evaluation may result in provision of assistive devices such as canes and walkers, as appropriate.	IV		5/5	100	89 (82–96)
5. Patients with hip and knee OA should be encouraged to undertake, and continue to undertake, regular aerobic, muscle strengthening and range of motion exercises. For patients with symptomatic hip OA, exercises in water can be effective.	Ia (knee) IV (hip) Ib (hip, water based)	0.52 (0.34, 0.70) aerobic 0.32 (0.23, 0.42) strength 0.25 (0.02, 0.47) water based	21/21 21/21 8/8	85	96 (93–99)
6. Patients with hip and knee OA, who are overweight, should be encouraged to lose weight and maintain their weight at a lower level.	Ia	0.13 (−0.12, 0.38)	13/14	100	96 (92–100)
7. Walking aids can reduce pain in patients with hip and knee OA. Patients should be given instruction in the optimal use of a cane or crutch in the contralateral hand. Frames or wheeled walkers are often preferable for those with bilateral disease.	IV		11/11	100	90 (84–96)
8. In patients with knee OA and mild/moderate varus or valgus instability, a knee brace can reduce pain, improve stability and diminish the risk of falling.	Ia		8/9	92	76 (69–83)
9. Every patient with hip or knee OA should receive advice concerning appropriate footwear. In patients with knee OA insoles can reduce pain and improve ambulation. Lateral wedged insoles can be of symptomatic benefit for some patients with medial tibio-femoral compartment OA.	IV (footwear) Ia (insole)		12/13	92	77 (66–88)
10. Some thermal modalities may be effective for relieving symptoms in hip and knee OA.	Ia	0.69 (−0.07, 1.45)	7/10	77	64 (60–68)
11. TENS can help with short-term pain control in some patients with hip or knee OA.	Ia		8/10	69	58 (45–72)
12. Acupuncture may be of symptomatic benefit in patients with knee OA.	Ia	0.51 (0.23, 0.79)	5/8	69	59 (47–71)

Pharmacological modalities of treatment					
13. Acetaminophen (up to 4 g/day) can be an effective initial oral analgesic for treatment of mild to moderate pain in patients with knee or hip OA. In the absence of an adequate response, or in the presence of severe pain and/or inflammation, alternative pharmacologic therapy should be considered based on relative efficacy and safety, as well as concomitant medications and co-morbidities.	Ia (knee) IV (hip)	0.21 (0.02, 0.41)	16/16	77	92 (88–99)
14. In patients with symptomatic hip or knee OA, non-steroidal anti-inflammatory drugs (NSAIDs) should be used at the lowest effective dose but their long-term use should be avoided if possible. In patients with increased GI risk, either a COX-2 selective agent or a non-selective NSAID with co-prescription of a PPI or misoprostol for gastroprotection may be considered, but NSAIDs, including both non-selective and COX-2 selective agents, should be used with caution in patients with CV risk factors.	Ia (knee) Ia (hip)	0.32 (0.24, 0.39)	NSAID + PPI 8/8 NSAID + misoprostol 8/8 COX-2 inhibitors 11/11	100	93 (88–99)
15. Topical NSAIDs and capsaicin can be effective as adjunctives and alternatives to oral analgesic/anti-inflammatory agents in knee OA.	Ia (NSAIDs) Ia (capsaicin)	0.41 (0.22, 0.59)	7/9 8/9	100	85 (75–95)
16. IA injections with corticosteroids can be used in the treatment of hip or knee OA, and should be considered particularly when patients have moderate to severe pain not responding satisfactorily to oral analgesic/anti-inflammatory agents and in patients with symptomatic knee OA with effusions or other physical signs of local inflammation.	Ib (hip) Ia (knee)	0.72 (0.42, 1.02)	11/13	69	78 (61–95)
17. Injections of IA hyaluronate may be useful in patients with knee or hip OA. They are characterised by delayed onset, but prolonged duration, of symptomatic benefit when compared to IA injections of corticosteroids.	Ia (knee) Ia (hip)	0.32 (0.17, 0.47)	8/9	85	64 (43–85)
18. Treatment with glucosamine and/or chondroitin sulphate may provide symptomatic benefit in patients with knee OA. If no response is apparent within 6 months treatment should be discontinued.	Ia (glucosamine) Ia (chondroitin)	0.45 (0.04, 0.86) 0.30 (−0.10, 0.70)	6/10 2/7	92	63 (44–82)
19. In patients with symptomatic knee OA glucosamine sulphate and chondroitin sulphate may have structure-modifying effects while diacerein may have structure-modifying effects in patients with symptomatic OA of the hip.	Ib (knee) Ib (hip)			69	41 (20–62)
20. The use of weak opioids and narcotic analgesics can be considered for the treatment of refractory pain in patients with hip or knee OA, where other pharmacological agents have been ineffective, or are contraindicated. Stronger opioids should only be used for the management of severe pain in exceptional circumstances. Non-pharmacological therapies should be continued in such patients and surgical treatments should be considered.	Ia (week opioids) IV (strong opioids) IV (others)		9/9	92	82 (74–90)
Surgical modalities of treatment					
21. Patients with hip or knee OA who are not obtaining adequate pain relief and functional improvement from a combination of non-pharmacological and pharmacological treatment should be considered for joint replacement surgery. Replacement arthroplasties are effective, and cost-effective interventions for patients with significant symptoms, and/or functional limitations associated with a reduced health-related quality of life, despite conservative therapy.	III		14/14	92	96 (94–98)

(*continued on next page*)

Table I (*continued*)

Proposition	LoE	ES for pain (95% CI)	Frequency recommended in existing guidelines	Level of consensus (%)	SOR (%) (95% CI)
22. Unicompartmental knee replacement is effective in patients with knee OA restricted to a single compartment.	IIb			100	76 (64–88)
23. Osteotomy and joint preserving surgical procedures should be considered in young adults with symptomatic hip OA, especially in the presence of dysplasia. For the young and physically active patient with significant symptoms from unicompartmental knee OA, high tibial osteotomy may offer an alternative intervention that delays the need for joint replacement some 10 years.	IIb		10/10	100	75 (64–86)
24. The role of joint lavage and arthroscopic debridement in knee OA are controversial. Although some studies have demonstrated short-term symptom relief, others suggest that improvement in symptoms could be attributable to a placebo effect.	Ib (lavage) Ib (debridement)	0.09 (−0.27, 0.44) −0.01 (−0.37, 0.35)	3/3 5/6	100	60 (47–82)
25. In patients with OA of the knee, joint fusion can be considered as a salvage procedure when joint replacement has failed.	IV		2/2	100	69 (57–82)

LoE: Ia: meta-analysis of RCTs; Ib: RCT; IIa controlled study without randomisation; IIb: quasi-experimental study (e.g., uncontrolled trial, one arm dose-response trial, etc.); III: observational studies (e.g., case–control, cohort, and cross-sectional studies); and IV: expert opinion. ES is the standard mean difference, i.e., the mean difference between a treatment and a control group divided by the SD of the difference. ES = 0.2 is considered small, ES = 0.5 is moderate, and ES > 0.8 is large.

Table II
Level of Evidence (LoE)

LoE	Type of evidence
Ia	Metaanalysis of Randomized Controlled Trials
Ib	At least one Randomized Controlled Trial
IIa	At least one well-designed controlled study, but without randomisation
IIb	At least one well-designed quasi-experimental study
III	At least one non-experimental descriptive study (e.g., comparative, correlation or case–controlled study)
IV	Expert committee reports, opinions and/or experience of respected authorities

by meta-regression analysis were unsuccessful[18–20]. The recommendation that initial focus should be on self-help and patient-driven treatments rather than on passive therapies delivered by health professionals is based on expert opinion, common sense and economic considerations alone (LoE IV). There is, however, evidence from a number of RCTs of exercise therapy[21–25] (LoE Ib) to support the recommendation that subsequent emphasis should be placed on encouraging adherence to the regimen of non-pharmacological therapy.

3. The clinical status of patients with hip or knee OA can be improved if patients are contacted regularly by phone.
SOR: 66% (95% CI 57–75)

The best evidence to suggest that monthly telephone contact by lay personnel aimed at promoting self-care for patients with OA knee could be associated with improvements in joint pain and physical function for up to a year comes from an RCT in 439 OA patients[26]. Subsequent subgroup analysis showed that regular telephone contact was associated with pain relief (ES = 0.65, $P < 0.01$) even in a small group of 40 patients whose medical treatment with drugs and physical therapy remained stable[27], and telephone contact did not influence psycho-social outcomes such as morale, satisfaction with care, adherence to medication or social support[28]. Overall the ES for pain relief and maintenance of physical function may be much smaller. While there are no published MAs of trials of telephone intervention alone, Warsi's MA of arthritis self-management programmes[17] included three trials in patients with knee OA in which telephone contact was part of the package[21,29,30]. Notwithstanding the difficulty of assessing the efficacy of individual components of the self-management strategy, two of these studies[29,30] demonstrated much smaller, non-significant, effects on pain. The estimated ES[4] for the three trials was similar to the pooled ES for pain relief in 17 self-management programmes (ES = 0.12, 95% CI 0.00–0.24)[17]. The proposition that the clinical status of patients with *hip* OA can be improved if patients are contacted regularly by phone is based on expert opinion alone (LoE IV).

4. Patients with symptomatic hip and knee OA may benefit from referral to a physical therapist for evaluation and instruction in appropriate exercises to reduce pain and improve functional capacity. This evaluation may result in provision of assistive devices such as canes and walkers, as appropriate.
SOR: 89% (95% CI 82–96)

The recommendation to refer patients with symptomatic hip or knee OA to a physical therapist is mainly supported by expert opinion (LoE IV). Referral to a physical therapist

was strongly recommended by 100% of the expert panel and is also recommended in 5/5 of existing guidelines where referral for physiotherapy was considered[4]. The recommendation to refer patients with symptomatic knee OA for physical therapy is supported by the results of three RCTs[31–33]. One demonstrated significant short-term (8 weeks) improvements in pain, physical function and health-related quality of life[31]. Another showed improvements in WOMAC indices up to 1 year after referral for a 4 week treatment programme by a physical therapist[32]; and a third demonstrated improved clinical outcomes over and above a programme of home exercises[33] (LoE Ib). However two other RCTs of multimodal physiotherapy programmes, including patellar taping and exercises, showed no persistent benefits when compared with standard treatment without physical therapy[34] or simulated placebo physical therapy treatment modalities[35]. There are no published RCTs of referral of patients with symptomatic hip OA for multimodal physical therapy.

5. Patients with hip and knee OA should be encouraged to undertake, and continue to undertake, regular aerobic, muscle strengthening and range of motion exercises. For patients with symptomatic hip OA, exercises in water can be effective.
SOR: 96% (95% CI 93–99)

The recommendation that patients with OA knee should be encouraged to undertake regular aerobic walking exercises and home-based quadriceps muscle strengthening exercises is a core recommendation in 21/21 published guidelines[4] and is supported by a systematic review and MA of 13 RCTs[14] (LoE Ia). Pooled ESs for pain relief are in the moderate range for both aerobic (ES = 0.52, 95% CI 0.34, 0.70) and muscle strengthening exercises (ES = 0.32, 95% CI 0.23, 0.42) and pooled ESs for self-reported disability are 0.46 (95% CI 0.25, 0.67) for aerobic exercise and 0.32 (95% CI 0.23, 0.41) for quadriceps strengthening exercises. By contrast the recommendation that patients with hip OA continue to undertake regular aerobic, muscle strengthening and range of motion exercises is largely based on clinical expertise (LoE IV)[36]. Evidence for pain relief (ES = 0.25, 95% CI 0.02, 0.47)[37] and improvement in stiffness (ES = 0.17, 95% CI 0.05, 0.39)[37] in patients with symptomatic hip OA following exercise in water comes from two RCTs[37,38] (LoE Ib).

6. Patients with hip and knee OA, who are overweight, should be encouraged to lose weight and maintain their weight at a lower level.
SOR: 96% (95% CI 92–100)

Encouragement to lose weight and maintain weight at a lower level in overweight patients with lower limb OA was strongly recommended by all members of the guideline development group (100% Table I) and is a core recommendation in 13/14 existing guidelines for the management of lower limb OA where this modality of therapy was considered[4]. At the time of completing the systematic review of the published research evidence before 31st January 2006 the recommendation was supported by the results of two high quality RCTs[15,16] (LoE Ib). In patients with knee OA the ESs for relief of pain (ES = 0.13, 95% CI −0.12, 0.38)[15,16], stiffness (0.36 95% CI −0.08, 0.80)[15] and functional improvement (0.69 95% CI 0.24, 1.14)[15] were small to moderate with an NNT of 3 (95% CI 2, 9)[15] for a decrease in WOMAC scores of >50%, 8 weeks after commencing a low energy diet (3.4 MJ/day). The recommendation is further supported by the publication of a recent systematic review and MA[39] of four RCTs with data on 454 patients with OA knee (LoE Ia). The pooled ESs for improvements in pain and physical disability are confirmed as small (0.20 95% CI 0, 0.39 and 0.23 95% CI 0.04, 0.42, respectively), with a mean weight reduction of 6.1 kg (range 4.7–7.6 kg). Meta-regression analysis demonstrated significant improvement in disability with weight loss > 5% or at a rate of >0.24%/week. There are no published RCTs to confirm comparable benefits from weight loss in patients with hip OA. The recommendation that patients with hip OA should be encouraged to lose weight and maintain their weight at a lower level is based on expert opinion (LoE IV) and evidence of a relationship between obesity and hip OA in case–control studies[40].

7. Walking aids can reduce pain in patients with hip and knee OA. Patients should be given instruction in the optimal use of a cane or crutch in the contralateral hand. Frames or wheeled walkers are often preferable for those with bilateral disease.
SOR: 90% (95% CI 84–96)

Although there are no RCTs to support their use there was complete expert consensus for the proposition that walking aids can reduce pain in patients with hip and knee OA (LoE IV), and for the recommendation that patients should be given instruction in the optimal use of a cane or crutch in the contralateral hand. This is supported by kinematic studies of knee moments of force following the use of a cane in the contralateral hand in patients with knee OA[41], and earlier studies of the biomechanics of the hip following the use of a stick in the contralateral hand in patients with hip OA[42].There are data that show that up to 40% of patients with hip or knee OA own a cane[43] and sticks or canes are recommended for patients with symptomatic knee OA in 11/11 existing guidelines[4].

8. In patients with knee OA and mild/moderate varus or valgus instability, a knee brace can reduce pain, improve stability and diminish the risk of falling.
SOR: 76% (95% CI 69–83)

Evidence that pain, stiffness and physical function are significantly improved using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the McMaster Toronto arthritis patient preference questionnaire (MACTAR) with knee braces in patients with knee OA comes from a Cochrane review[44] (LoE Ia) and a single RCT[45] which compared the use of a valgus brace + medical treatment with a neoprene sleeve + medical treatment and medical treatment alone. Assessment at 6 months showed greater improvement in WOMAC scores with use of the valgus brace than the neoprene sleeve. Knee braces are recommended in 8/9 existing guidelines for the management of knee OA where this modality of treatment was considered[4].

9. Every patient with hip or knee OA should receive advice concerning appropriate footwear. In patients with knee OA insoles can reduce pain and improve ambulation. Lateral wedged insoles can be of symptomatic benefit for some patients with medial tibio-femoral compartment OA.
SOR: 77% (95% CI 66–88)

The use of lateral wedged insoles for patients with medial tibio-femoral compartment OA is recommended in 12/13 existing guidelines for the management of knee OA[4]. The proposition that lateral wedged insoles can provide symptomatic benefit for patients with medial tibio-femoral compartment OA, as well as decreasing lateral thrust in the knee[46], is supported by three observational studies[46–48], but not by three RCTs[49–51]. Despite the fact that there was no symptomatic benefit (WOMAC pain, joint stiffness, and physical functioning subscales) at 6 months[50] or 2 years[51] in a prospective RCT of laterally wedged insoles in 156 patients with medial femoro-tibial OA, NSAID usage was reduced and compliance was better in the treatment group. This was accepted by the investigators[50,51] and a systematic review[44] as evidence supporting clinical benefit (LoE Ia). No structural protection was observed in this study after 2 years[51]. The recommendation that every patient with hip or knee OA should receive advice concerning appropriate footwear is based on expert opinion alone (LoE IV). There have been no controlled trials of footwear in patients with hip OA and no controlled trials to support the hypothesis[52] that sports shoes or other footwear with shock absorbing soles provide symptomatic benefit in patients with lower limb OA (hip or knee) by reducing impact loads.

10. Some thermal modalities may be effective for relieving symptoms in hip and knee OA.
SOR: 64% (95% CI 60–68)

Heat and cryotherapy are used very widely in the management of patients with OA. Heat can be administered by a variety of techniques including diathermy and the application of heat packs or immersion in warm water or wax baths, while cryotherapy is usually administered by application of ice packs or massage with ice. Thermotherapy of one kind or another is recommended in 7/10 existing guidelines where these modalities were considered[4]. Supporting evidence is very limited. A single systematic review[53] (LoE Ia) analysed two RCTs of ice massage in 100 patients with knee OA[54] and ice packs or short wave diathermy in two groups of 15 and 17 patients with knee OA[55]. Massaging with ice for 20 min × 5/week for 2 weeks resulted in clinically significant (29%) improvement in quadriceps strength (ES = 1.03, 95% CI 0.44, 1.62) but had no clinically significant effect on the range of movement or on walking[54]. Application of ice packs × 3/week for 3 weeks was followed by some improvement in pain (weighted mean difference, WMD −2.70 95% CI −5.52, 0.12)[55], but this was not statistically significant. Short wave diathermy was not followed by any improvement in pain after 3 weeks and there was no evidence of clinical benefit following either modality of thermotherapy after 3 months[55]. There have been no controlled trials of thermotherapy for patients with hip OA.

11. Transcutaneous electrical nerve stimulation (TENS) can help with short-term pain control in some patients with hip or knee OA.
SOR: 58% (95% CI 45–72)

TENS is a recommended treatment for relief of pain in 8/10 existing guidelines for the management of knee OA[4]. Evidence for efficacy available to the OARSI treatment guidelines development group was summarised in a Cochrane systematic review published in 2000[56] and a systematic review published in 2004[57] (NNT = 2, 95% CI 1, 5) (LoE Ia). The short-term efficacy of 2–4 weeks treatment with TENS in providing clinically significant pain relief in patients with knee OA has been subsequently confirmed in a recent systematic review and MA of seven RCTs involving 425 patients[58]. Dose-dependent inhibition of nociceptive nerve transmission at a segmental level may provide a physiological rationale[59] for the efficacy of TENS, and no serious adverse effects of therapy have been reported[58].

12. Acupuncture may be of symptomatic benefit in patients with knee OA.
SOR: 59% (95% CI 47–71)

Acupuncture is recommended as a modality of therapy for the symptomatic treatment of patients with OA knee or hip in 5/8 existing guidelines in which it was considered[4], and its recommendation achieved a 69% consensus following the Delphi exercise. A summary of the evidence for its clinical efficacy in lower limb joint OA which was available to the OARSI treatment guideline development group showed moderate ESs for pain (ES = 0.51, 95% CI 0.23, 0.79), stiffness (ES = 0.41, 95% CI 0.13, 0.69) and function (ES = 0.51, 95% CI 0.23, 0.79) with an NNT of 4 (95% CI 3, 9) for clinically significant relief of pain[60] (LoE Ib). An earlier (2001) systematic review of the evidence for the efficacy of acupuncture in OA knee which included seven RCTs and 393 patients suggested that real acupuncture was more effective than sham acupuncture for relief of pain (LoE Ia) but the evidence with regard to improvement in function was inconclusive[61]. A very recent RCT in 352 patients with knee OA showed very small, statistically significant, improvements in pain intensity in patients 2 and 6 weeks following true acupuncture but the addition of acupuncture to a course of advice and exercises delivered by physiotherapists provided no additional improvement in the WOMAC index pain subscale at 6 months[62].

Pharmacological modalities of treatment

13. Acetaminophen (paracetamol) (up to 4 g/day) can be an effective initial oral analgesic for treatment of mild to moderate pain in patients with knee or hip OA. In the absence of an adequate response, or in the presence of severe pain and/or inflammation, alternative pharmacologic therapy should be considered based on relative efficacy and safety, as well as concomitant medications and comorbidities.
SOR: 92% (95% CI 88–99)

Acetaminophen (paracetamol) is a core recommendation for use as an analgesic in 16/16 existing guidelines for the management of hip or knee OA[4]. Current European (EULAR) recommendations for the management of hip[63] and knee[64] OA suggest that, because of its safety and efficacy, doses of up to 4 g/day should be the oral analgesic of first choice for mild/moderate pain, and if successful, should be used as the preferred long-term oral analgesic. However, in recent years both the efficacy[65] and the safety[66,67] of long-term use of acetaminophen at this dose have been questioned. Evidence for efficacy available to the OARSI treatment guideline development committee was summarised in a Cochrane systematic review[68] largely based on a single RCT published before July 2002 and an MA of 10 RCTs published in 2004[69] with data from 1712 OA patients (LoE Ia). Efficacy was confirmed but the ES was small (ES = 0.21, 95% CI 0.02, 0.4)[69]. A more recently updated Cochrane systematic review published in 2006[70] included

data from 5986 patients in 15 RCTs (7 vs placebo and 10 vs NSAIDs). Acetaminophen was superior to placebo in 5/7 trials and pooled analysis of data on overall pain using multiple methods showed a statistically significant, but very small, reduction in pain (ES = 0.13, 95% CI 0.04, 0.22) which is of questionable clinical significance. The NNT to achieve an improvement in pain ranged from 2 (1, 2)[68] in the earlier systematic review to 4–16[70] in the later MA. There was no significant difference in toxicity between acetaminophen and placebo in these short-term trials (RR = 1.02, 95% CI 0.89, 1.87)[70]. The evidence for possible gastrointestinal (GI) and renal toxicity with long-term treatment with acetaminophen 4 g/day, reviewed in the first part of this report[4], remains equivocal. The RR for upper GI bleeding or perforation ranged from RR 1.2 (95% CI 0.8, 1.7)[71] in a MA of three case–control studies with individual patient data to RR 3.6 (95% CI 2.60, 5.10)[66] in a case–control study using the UK General Practice Research Database; and the RR of renal insufficiency ranged from RR 0.83 (95% CI 0.50, 1.39) in one cohort study (CS)[72] to RR 2.5 (95% CI 1.7, 2.6) in a case–control comparison[73].

14. In patients with symptomatic hip or knee OA, non-steroidal anti-inflammatory drugs (NSAIDs) should be used at the lowest effective dose but their long-term use should be avoided if possible. In patients with increased GI risk, either a COX-2 selective agent or a non-selective NSAID with co-prescription of a proton pump inhibitor (PPI) or misoprostol for gastroprotection may be considered, but NSAIDs, including both non-selective and COX-2 selective agents, should be used with caution in patients with cardiovascular (CV) risk factors.

SOR: 93% (95% CI 88–99)

The use of oral NSAIDs with misoprostol or a PPI for gastroprotection is recommended in 8/8 existing guidelines for the management of hip or knee OA[4] and the use of selective COX-2 inhibitors is recommended in all 11 of the guidelines where this modality of therapy was considered[4]. A telephone survey of 1149 patients with OA in the UK in 2003 revealed that only 15% were taking paracetamol, while 32% were taking non-selective NSAIDs and 18% COX-2 selective drugs for analgesia[74]. There is evidence that NSAIDs can be effective in reducing pain in patients with OA knee and hip (LoE Ia). A 2004 MA of 23 short-term, placebo-controlled RCTs of NSAIDs, including COX-2 selective agents in >10000 patients with knee OA, showed that the ES for pain reduction was 0.32 (95% CI 0.24, 0.39)[75]. However in 10 trials that did not exclude non-responders where the outcomes were more homogeneous the ES for pain reduction was smaller (ES = 0.23, 95% CI 0.15, 0.31)[75]. Evidence that NSAIDs are superior to acetaminophen for pain relief in patients with lower limb joint OA is available from another 2004 MA of RCTs[69] (ES = 0.20, 95% CI 0.10, 0.30). The clinical response rate was higher (RR = 1.24, 95% CI 1.08, 1.41) and the number of patients preferring NSAIDs to acetaminophen was considerably greater (RR = 2.46, 95% CI 1.51, 4.12)[69]. The ESs for pain relief in short-term trials are, however, less than 0.4, which has been suggested as the minimum to be of any clinical importance[76].

There is abundant evidence that NSAIDs are associated with more adverse effects than acetaminophen in short-term trials. The 2004 MA[69] showed that NSAIDs were associated with GI discomfort more frequently than acetaminophen (RR = 1.35, 95% CI 1.05, 1.75) and this was confirmed in the more recent Cochrane systematic review of short-term RCTs (RR = 1.47, 95% CI 1.08, 2.00)[70]. More importantly NSAIDs can cause serious GI complications such as peptic ulcers, perforations and bleeds (PUBS) and this risk increases with age, concurrent use of other medications, and probably with the duration of therapy[77]. A MA of severe upper GI complications of NSAIDs showed an OR of 5.36 (95% CI 1.79, 16.1) in 16 NSAID vs placebo trials in 4431 patients and a pooled OR for PUBS of 3.0 (95% CI 2.5, 3.7) in 23 case–control studies in 25,732 patients[78]. The pooled RR of PUBS from nine cohort studies representing >750,000 person years of drug exposure was 2.7 (95% CI 2.1, 3.5)[78]. The recommendation that in patients with increased GI risk, either a COX-2 selective agent or a non-selective NSAID with co-prescription of a PPI or misoprostol for gastroprotection should be considered is supported by evidence from a systematic review of 112 RCTs which included nearly 75,000 patients[79] (LoE Ia). The RRs for symptomatic ulcers and serious GI complications with these different strategies are shown in Table III. There was no evidence for similar gastroprotection with H2 receptor antagonists and treatment with misoprostol is associated with an increased risk of diarrhoea (RR = 1.81, 95% CI 1.52, 2.61)[80] and the GI protection that is associated with the use of COX-2 selective agents is largely lost when low-dose aspirin is administered concurrently for CV prophylaxis[81].

What is the evidence to support the recommendation that NSAIDs, including both non-selective and COX-2 selective agents, should be used with caution in patients with CV risk factors? Following the withdrawal of the COX-2 selective NSAID rofecoxib in 2004 because of an increased RR of thrombotic CV events including myocardial infarction and stroke in a colorectal adenoma chemoprevention trial[82] a number of RCTs and systematic reviews of the CV safety of other COX-2 selective and non-selective NSAIDs have been undertaken[83–86]. Table IV shows the RRs for CV events in patients treated with COX-2 selective and non-selective NSAIDs. While the increased risk of CV adverse events with rofecoxib was confirmed, similar CV toxicity was not seen consistently with celecoxib or valdecoxib and the overall CV risk associated with COX-2 selective inhibitors was not significantly greater than that associated with conventional non-selective NSAIDs (RR = 1.19, 95% CI 0.80, 1.75)[79]. This has been borne out in the more recent 2006 systematic review and MA of atherothrombotic complications of COX-2 selective and non-selective NSAIDs[87]. The incidence of serious vascular events was 1% per annum in patients treated with COX-2 selective agents compared with 0.9% in those on traditional NSAIDs (RR = 1.16, 95% CI 0.97, 1.38)[87]. There was, however, some heterogeneity in risk among the traditional NSAIDs with a modest increase in risk of CV events with ibuprofen (RR =1.51, 95% CI 0.96, 2.37) and diclofenac (RR = 1.63, 95% CI 1.12, 2.37) but not with naproxen (RR = 0.92, 95% CI 0.67, 1.26)[87]. The current advice[88] from the European Agency for the Evaluation of Medicinal Products (EMEA) is that COX-2 selective NSAIDs are contraindicated in patients with ischaemic heart disease or stroke and that prescribers should exercise caution when prescribing COX-2 inhibitors for patients with risk factors for heart disease, such as hypertension, hyperlipidaemia, diabetes and smoking, as well as for patients with peripheral arterial disease. In the USA all marketed prescription NSAIDs, both non-selective and COX-2 selective carry a boxed warning about their potential for causing CV events and GI bleeding.

Table III
Relative risk of GI adverse events associated with NSAIDs and strategies for their prevention

Intervention*	Adverse events	RR/OR (95% CI)	Evidence
Acetaminophen	GI discomfort	0.80 (0.27, 2.37)	MA of RCTs[69]
	GI perforation/bleed	3.60 (2.60, 5.10)	CC[66]
	GI bleeding	1.2 (0.8, 1.7)	MA of CCs[71]
NSAIDs	GI perforation/ulcer/bleed	5.36 (1.79, 16.10)	MA of RCTs[78]
		2.70 (2.10, 3.50)	MA of CSs[78]
		3.00 (2.70, 3.70)	MA of CCs[78]
Topical NSAIDs	GI events	0.81 (0.43, 1.56)	MA of RCTs[89]
	GI bleed/perforation	1.45 (0.84, 2.50)	CC[92]
H2 blocker + NSAID vs NSAID	Serious GI complications	0.33 (0.01, 8.14)	MA of RCTs[79]
	Symptomatic ulcers	1.46 (0.06, 35.53)	
PPI + NSAID vs NSAID	Serious GI complications	0.46 (0.07, 2.92)	MA of RCTs[79]
	Symptomatic ulcer	0.09 (0.02, 0.47)	
Misoprostol + NSAID vs NSAID	Serous GI complications	0.57 (0.36, 0.91)	MA of RCTs[79]
	Symptomatic ulcers	0.36 (0.20, 0.67)	
	Diarrhoea	1.81 (1.52, 2.61)	MA of RCTs[80]
COX-2 inhibitors vs NSAID	Serious GI complications	0.55 (0.38, 0.80)	MA of RCTs[79]
	Symptomatic ulcers	0.49 (0.38, 0.62)	

RR: relative risk; OR: odds ratio; CI: confidence interval; GI: gastrointestinal; NSAID: non-steroidal anti-inflammatory drug; H2 blockers: histamine type 2 receptor antagonists.
*Compared with placebo/non-exposure unless otherwise stated.

The EMEA also advises

- Prescribers and patients should continue to use NSAIDs at the lowest effective dose for the shortest duration to control symptoms.
- Prescribers should continue to chose any NSAID on the basis of the overall safety profile of the product, as set out in the product information, and the patient's individual risk factors.
- Prescribers should not switch between NSAIDs without careful consideration of the overall safety profile of the products and the patient's individual risk factors, as well as the patient's preferences.

15. Topical NSAIDs and capsaicin can be effective as adjunctives and alternatives to oral analgesic/anti-inflammatory agents in knee OA.
SOR: 85% (95% CI 75−95)

Topical NSAIDs are widely used as adjunctive or alternative therapy by patients with OA knee and are recommended in 7/9 existing guidelines where this modality of therapy was considered[4]. A MA of 13 RCTs, including 1983 patients with hand as well as knee OA, undertaken in 2004 confirmed that topical NSAIDs were superior to placebo in relieving pain and stiffness and in improving function (LoE Ia)[89]. Efficacy for pain relief was only apparent in the first 2 weeks of treatment with ESs of 0.41 (95% CI 0.16, 0.66) in week 1 and 0.40 (95% CI 0.15, 0.65) in week 2 but topical NSAIDs are less effective than oral NSAIDs in the first week of treatment. The NNT for topical NSAIDs was only 3 (95% CI 2, 4) but placebo effects may be large with all topical therapies. The ESs for improvement in stiffness and in function were 0.49 (95% CI 0.17, 0.80) and 0.36 (95% CI 0.24, 0.48), respectively. However the MA showed evidence of statistically significant asymmetry of a funnel plot[90] suggesting the possibility of publication

Table IV
Relative risks of CV and renal adverse events associated with COX-2 selective and non-selective NSAIDs

Intervention*	Adverse events	RR/OR (95% CI)	Evidence
Acetaminophen	Renal failure	0.83 (0.50, 1.39)	CS[72]
		2.5 (1.7, 3.6)	CC[73]
NSAIDs	Myocardial infarction	1.09 (1.02, 1.15)	MA of CSs[83]
H2 blocker + NSAID vs NSAID	Serious CV or renal events	0.53 (0.08, 3.46)	MA of RCTs[79]
PPI + NSAID vs NSAID	Serious CV or renal events	0.78 (0.10, 6.26)	MA of RCTs[79]
Misoprostol + NSAID vs NSAID	Serious CV or renal events	1.78 (0.26, 12.07)	MA of RCTs[79]
COX-2 inhibitors			
Coxibs vs NSAID	Serious CV or renal events	1.19 (0.80, 1.75)	MA of RCTs[79]
Celecoxib	Myocardial infarction	2.26 (1.0, 5.1)	MA of RCTs[84]
		0.97 (0.86, 1.08)	MA of CSs & CCs[83]
Rofecoxib	Myocardial infarction	2.24 (1.24, 4.02)	MA of RCTs[85]
		1.27 (1.12, 1.44)	MA of CSs and CCs[83]
Valdecoxib	CV events	2.3 (1.1, 4.7)	MA of RCTs[86]

CV: cardiovascular; please see the footnotes of Table III for other abbreviations.
*Compared with placebo/non-exposure unless otherwise stated.

bias with under reporting of negative studies and consequent overestimation of the benefits of topical NSAIDs. This MA provided no trial evidence to support long-term use of topical NSAIDs in knee OA but there was some heterogeneity of efficacy between preparations and a more recent MA did demonstrate a small pooled effect ($ES_{pain} = 0.28$, 95% CI 0.14, 0.42)[91]. Overall topical NSAIDs are safe with no more side effects than placebo[89]. GI side effects are less likely than they are with oral NSAIDs[89,90] and there was no evidence that they could be a cause of upper GI perforation or bleeds in a large case–control study[92] (Table III). However local reactions such as itching, burning and rashes are more frequent[89].

Topical capsaicin creams contain a lipophilic alkaloid extracted from chilli peppers which activates and sensitises peripheral c-nociceptors by binding and activating the transient receptor potential vanilloid type 1 (TRPV1) cation channel[93]. Paradoxically, although the application of capsaicin to the skin causes burning pain at the site of application, it can also be an effective topical analgesic which is recommended as an alternative or adjunctive treatment for knee OA in 8/9 existing treatment guidelines where this modality of therapy was considered[4]. Evidence for the efficacy of topical capsaicin (0.025% cream × 4 daily) in patients with knee OA is supported by an MA of RCTs of topical capsaicin in the treatment of chronic painful conditions[94] (LoE Ia). This included a single placebo-controlled trial in 70 patients with knee OA[95] as well as two RCTs in patients with hand OA. The mean reduction in pain was 33% with an NNT of 4 (95% CI 3, 5) after 4 weeks of therapy but adequate blinding is not possible in trials with this agent. Treatment with topical capsaicin is safe but 40% of patients are troubled by local burning, stinging or erythema.

16. Intra-articular (IA) injections with corticosteroids can be used in the treatment of hip or knee OA, and should be considered particularly when patients have moderate to severe pain not responding satisfactorily to oral analgesic/anti-inflammatory agents and in patients with symptomatic knee OA with effusions or other physical signs of local inflammation.

SOR: 78% (95% CI 61–95)

IA injections of corticosteroids have been widely used as adjunctive therapy in the treatment of patients with knee OA for more than 50 years[96], and are recommended as a treatment option in 11/13 of existing treatment guidelines where this modality of therapy was considered[4]. The efficacy of IA steroid injections in patients with knee OA is well supported by evidence from a 2005 Cochrane systematic review[97] (LoE Ia), subsequently updated in 2006[98], which examined data from 13 placebo-controlled RCTs. The ES for relief of pain was in the moderate range (ES = 0.72, CI 0.42, 1.02) with an NNT of 4 (95% CI 2, 11) at 2 and 3 weeks after injection but function was not significantly improved (ES = 0.06, 95% CI −0.17, 0.30) and evidence for relief of pain 4 and 24 weeks post-injection was lacking[97]. Some RCTs have demonstrated better outcomes in patients with synovial effusions[99] but others have not found that clinical signs of inflammation or the presence of a joint effusion[100,101] are predictors of a good clinical response; suggesting that IA steroid injections should not be restricted to patients with physical signs of inflammation and/or joint effusion. A single RCT[102] in 42 patients with knee OA with signs of inflammation showed that IA injections of 20 mg of triamcinolone hexacetonide were superior to 6 mg of a betamethasone acetate/bisodium phosphate combination for the number of patients reporting pain reduction up to 4 weeks after injection (RR = 2, 95% CI 1.10, 3.63) but the number of head to head comparisons between different IA corticosteroid preparations is too few to support any evidence-based recommendations for a particular preparation.

By contrast the evidence to support the recommendation for IA steroid injection in patients with OA hip is mainly limited to two RCTs[103,104] (LoE Ib) and two uncontrolled cohort studies[105,106]. In one RCT an IA injection combining bupivacaine and triamcinolone did not give better pain relief than IA injections of saline after 1 month (RR = 1.18, 95% CI 0.68, 2.15) or after 3 months (RR = 0.61, CI 0.23, 1.60); and the combination containing IA steroid was not better than injections of local anaesthetic alone in patients with OA awaiting hip joint replacement[103]. A second RCT in 80 patients with severe symptomatic OA hip compared the effects of fluoroscopically controlled IA injection of 80 mg triamcinolone hexacetonide or 1% mepivacaine and demonstrated significant reduction in pain and improved mobility after 3 weeks and 3 months in the steroid treated patients but not in those treated with IA injections of local anaesthetic[104].

No serious adverse events were reported as a consequence of IA steroid injections in 1973 patients in 28 controlled trials in patients with OA knee[98]. Potential side effects include post-injection flares of pain, crystal synovitis, haemarthrosis, joint sepsis and steroid articular cartilage atrophy, as well as systemic corticosteroid effects such as fluid retention or aggravation of hypertension or diabetes mellitus. Emphasis has been placed on the importance of accurate placement of IA injections to maximise benefit and reduce the risk of adverse effects such as fat necrosis and para-articular tissue atrophy[107]. There are limited data at present to indicate how frequently it is safe to administer IA steroid injections to patients with OA hip or knee. Most experts recommend caution regarding too-frequent use; repeat injections more than four times annually are generally not recommended.

17. Injections of IA hyaluronate may be useful in patients with knee or hip OA. They are characterised by delayed onset, but prolonged duration, of symptomatic benefit when compared to IA injections of corticosteroids.

SOR: 64% (95% CI 43–85)

Hyaluronic acid is a large molecular weight glycosaminoglycan which is a constituent of synovial fluid in normal and osteoarthritic joints. IA injection of hyaluronan (HA), with relatively high and low molecular weight averages, is widely used, and recommended in 8/9 existing guidelines as a useful therapeutic modality for treating patients with OA knee as a viscosupplement or pharmaceutical[4], despite considerable ongoing controversy with regard to its efficacy, cost-effectiveness and benefit to risk ratio. The evidence available to the OARSI treatment guidelines development group from the critical appraisal of existing guidelines and the systematic review of the research evidence from 2002 to January 2006 was derived from two systematic reviews published in 2003[108] and 2005[109] (LoE Ia). The pooled ES for reduction in pain at 2–3 months following at least three IA injections at weekly intervals in 22 placebo-controlled RCTs was 0.32 (95% CI 0.17, 0.47). There was, however, significant heterogeneity between studies with inconclusive data to suggest that the higher molecular weight HA preparations may be more effective[108]. An asymmetric funnel plot and a positive Egger test also suggested the

possibility of publication bias; and the identification of two unpublished trials with a pooled ES of 0.07 (95% CI −0.15, 0.28) further suggested that the overall ES might have been overestimated[108]. The 2005 MA found no evidence of improvement in function in pooled results from nine placebo-controlled RCTs which included joint function as an outcome (ES = 0.00, 95% CI −0.23, 0.23) and no effects on pain during movement compared with saline injections that were judged to be clinically meaningful at any time point after treatment[109]. Two further systematic reviews of IA injections of HA in patients with OA knee were published in 2006[110,111]. One MA of seven placebo-controlled RCTs which used the WOMAC or Lequesne indexes as outcome measurements found small but significant improvements in the Lequesne index, but not in the WOMAC scales for self-reported pain or disability up to 6 months after treatment[110]. A more comprehensive industry-sponsored Cochrane review which included an MA of 40 placebo-controlled trials with five different commercially available HA products found statistically significant improvements in pain on weight bearing when results were pooled (WMDs of −8, −13, −9 and −3 at 1–4, 5–13, 14–26 and 45–52 weeks, respectively), but improvements from baseline to the maximum at 5–13 weeks varied from 28% to 54% for pain and from 9% to 32% for function with different products[111]. In 10 trials comparing IA HA injections with IA corticosteroids there were no significant differences 4 weeks after injection but IA HA was shown to be more effective 5–13 weeks post-injection for one or more of a number of outcome variables (WOMAC OA index, Lequesne index, pain, range of flexion, and number of responders)[98,111]. No major safety issues were detected[111] but in placebo-controlled trials minor adverse events such as transient pain at the injection site occurred slightly more frequently in patients treated with IA HA (RR = 1.08, 95% CI 1.01, 1.15)[109]. A recent study[112] used the decision algorithm proposed by Jadad *et al.*[113] and the GRADE (Grades of Recommendation Assessment, Development and Evaluation)[114] system to explore the reasons for discordant conclusions in six published systematic reviews of IA HA for the treatment of OA knee[108–111,115,116]. The reasons for inconsistency identified included inclusion of different controlled trials as a result of different search strategies and selection criteria, differences in the outcome measures and time points selected for extraction; and different statistical methods for data synthesis, which resulted in conflicting estimates of therapeutic effect[112]. There is much less research evidence to support the proposition that IA injections of HA can be a useful treatment in patients with hip OA. Three quasi systematic reviews have examined the results of a number uncontrolled clinical trials and case series[117–119], a single comparison of injection of a low or high molecular weight HA[120], and a single, double blind, three armed RCT in 101 patients with hip OA in which IA injections of a low molecular weight HA preparation were compared with IA saline and IA corticosteroid injections[121]. In the randomised comparison of three injections of high and low molecular weight HA given at weekly intervals under fluoroscopic control there were significant improvements of approximately 40% in VAS, WOMAC and Lequesne index scores 1, 3 and 6 months after treatment but no significant differences at any of the time points between the two groups[120]. However in the placebo-controlled trial in which three injections of HA, corticosteroid or saline were given with ultrasound guidance at 2 weekly intervals, there were no significant differences between the HA treated, corticosteroid treated or saline treated groups in pain on walking, WOMAC or Lequesne indices 14, 28 or 90 days after the course of injections[121]. Responses at 14 days applying OARSI response criteria were 53% in patients treated with HA, 56% in the corticosteroid treated group and 33% in the placebo-treated patients. At 28 days 53% responded to HA, 66% to corticosteroids and 44% to placebo[121].

18. Treatment with glucosamine and/or chondroitin sulphate may provide symptomatic benefit in patients with knee OA. If no response is apparent within 6 months treatment should be discontinued. SOR: 63% (95% CI 44–82)

The aminosugar glucosamine and the glycosaminoglycan chondroitin sulphate are both naturally occurring constituents of cartilage proteoglycans that are very widely used as 'nutritional supplements' by patients with OA[122]. A crystalline preparation of glucosamine sulphate is approved as a medicinal product for the treatment of OA in many countries in Europe, Asia and Latin America. Glucosamine sulphate is recommended in 6/10 existing guidelines for the management of hip or knee OA, but chondroitin sulphate in only 2/7 guidelines where these modalities of therapy were considered[4], and there is continuing controversy as to the efficacy of these agents as symptom modifying drugs.

Evidence available to the guideline development committee concerning the efficacy and safety of glucosamine was mainly derived from the 2005 update of the Cochrane systematic review and MA[123] and an earlier MA published in 2003[124] (LoE Ia). In comparisons with placebo, pooled analysis of 20 RCTs involving 2570 patients with knee OA showed a 28% improvement in pain (ES = 0.61, 95% CI 0.28, 0.95) and a 21% improvement in function using the Lequesne index (ES = 0.51, 95% CI 0.96, 0.05)[123]. However WOMAC pain, stiffness and function were not significantly changed and there was considerable heterogeneity of outcomes in different trials. With such marked heterogeneity, pooling of results may not be appropriate and estimates of overall ESs may be misleading. The possible reason(s) for the variation in outcomes also requires an explanation. In 10 placebo-controlled RCTs in which the Rottapharm preparation of glucosamine sulphate 1500 mg daily was used there were significant improvements in pain (ES = 1.31, 95% CI 0.64, 1.99) and function (ES = 0.51, 95% CI 0.05, 0.96) while there were no significant improvements in WOMAC pain or function indices in the pooled results of RCTs that used other glucosamine formulations[123]. Analysis of the eight RCTs in which allocation concealment was considered adequate also failed to show drug efficacy for relief of pain or improvement in function using the WOMAC index[123]. A more recent systematic review was undertaken specifically to try and identify the factors that might be responsible for the heterogeneity of outcomes in trials of glucosamine[125]. In 15 RCTs which met the inclusion criteria the summary of ES for pain relief was 0.35 (95% CI 0.14, 0.56) but there was a considerable variation in outcomes attributable to differences between studies, rather than to chance[126], with an I^2 of 80%[125] (i.e., 80% of the inconsistency could be attributed to the true differences between studies). An Egger test and funnel plot[90] did not suggest publication bias and there were no clear indications that the heterogeneity was attributable to differences in trial design, trial quality, the number of drop-outs or differences in intention to treat analyses, but the differences in adequacy of the allocation concealment detected in the Cochrane review[123] were confirmed. The

most striking differences, however, seemed to be related to the glucosamine preparation that was used. The ES for trials which used glucosamine sulphate was 0.44 (95% CI 0.18, 0.70) compared with 0.06 (95% CI −0.08, 0.20) for those that used glucosamine hydrochloride, and the ES for trials utilising the Rottapharm preparation of glucosamine sulphate was 0.55 (95% CI 0.29, 0.82) compared with an ES of 0.11 (95% CI −0.16, 0.38) for trials with other products. The possibility of industry bias as an additional or alternative explanation for the heterogeneity of outcomes between glucosamine trials was also suggested, but not substantiated[125]. In the first part of this report it was shown that sensitivity analysis following addition of the data from two large multicentre RCTs which were published after the close of the systematic review in January 2006; the NIH sponsored Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)[127] in which glucosamine hydrochloride was used, and the Glucosamine Unum in Die Efficacy (GUIDE) trial[128] in which glucosamine sulphate 1500 mg daily was employed, to the main body of trial outcomes, did not alter the ESs for pain efficacy significantly[4]. The NNT for treatment of knee OA with glucosamine sulphate is 5 (95% CI 4, 7)[124] and treatment is not associated with any serious adverse effects[123].

The evidence supporting the recommendation that chondroitin sulphate may provide symptomatic benefit in patients with knee OA is also conflicting. At the time of the Delphi exercise the evidence for efficacy of chondroitin sulphate was supported by two MAs published in 2000[129,130] and a third one in 2003[124] (LoE Ia). Analysis of eight RCTs involving 755 patients showed a moderate ES for pain reduction (ES = 0.52, 95% CI 0.37, 0.67) with an NNT of 5 (4, 7) and no evidence of serious side effects[124]. However, as shown in the first part of this report[4], sensitivity analysis following addition of the data from the GAIT study[127] to the main body of trial outcomes reduced the ES for pain reduction significantly (ES = 0.30, 95% CI −0.10, 0.70) and suggested that treatment with chondroitin sulphate was not significantly more effective than placebo. This was also the conclusion of the most recent systematic review and MA[131]. In their analysis of 20 trials involving 3846 patients the ES for pain relief was large (ES = 0.75, 95% CI 0.50, 0.99) but they identified very marked heterogeneity of outcomes between trials with an I^2 of 92%. Small trials with poor quality features such as uncertain concealment of allocation and a failure to analyse results on an intention to treat basis showed larger effects in favour of chondroitin than did the remaining trials[131]. Similar caveats had been raised in one of the earlier MAs[130]. When Reichenbach *et al.* restricted the analysis to three recent trials with large sample sizes and an intention to treat analysis[127,132,133]; the ES for pain reduction was only 0.03 (95% CI −0.07, 0.13) with an I^2 of 0%[131]. However this restricted analysis included one study with an exceptionally high placebo response rate[127], one study that was only published as an abstract[132] and only 40% of all trial patients. The pooled RR for adverse events in an MA of 12 placebo-controlled trials was 0.99 (95% CI 0.76, 1.21)[131].

19. In patients with symptomatic knee OA glucosamine sulphate and chondroitin sulphate may have structure-modifying effects while diacerein may have structure-modifying effects in patients with symptomatic OA of the hip.

SOR: 41% (95% CI 20−62)

Evidence that glucosamine sulphate 1500 mg/day may have structure-modifying effects in patients with knee OA comes from two placebo-controlled RCTs involving 414 patients[134,135] and two systematic reviews and MAs[123,124] (LoE Ia). In one trial there was no radiographic loss of joint space width (JSW) in the medial compartment of the tibiofemoral joint after 3 years (mean −0.06 mm, 95% CI −0.22, 0.09) in the treated patients compared with progressive loss in the placebo group (mean −0.31 mm, 95% CI −0.48, −0.13)[134]. The pooled results of both trials showed an ES = 0.24 (95% CI 0.04, 0.43)[123].

The proposition that chondroitin sulphate (800 mg/day) may also have structure-modifying effects is supported by an MA of five placebo-controlled RCTs. The difference in changes over 2 years between chondroitin and placebo demonstrated a small effect in favour of chondroitin: 0.16 mm on minimum JSW (95% CI 0.08, 0.24) and 0.23 mm on mean JSW (95% CI 0.09, 0.37)[131] (LoE Ia).

The evidence to support the proposition that diacerein may have structure-modifying effects in patients with hip OA comes from a single 3-year placebo-controlled RCT in 507 patients with primary hip OA[136] and a systematic review and MA[137] (LoE Ia). In patients who completed 3 years of therapy with diacerein 50 mg twice daily the rate of joint space narrowing was [mean ± standard deviation (SD)] 0.18 ± 0.25 mm/year vs 0.23 ± 0.23 mm/year with placebo ($P = 0.042$)[136]. Similar structure-modifying effects were not evident in a 1-year placebo-controlled RCT in patients with knee OA[138].

20. The use of weak opioids and narcotic analgesics can be considered for the treatment of refractory pain in patients with hip or knee OA, where other pharmacological agents have been ineffective, or are contraindicated. Stronger opioids should only be used for the management of severe pain in exceptional circumstances. Non-pharmacological therapies should be continued in such patients and surgical treatments should be considered.

SOR: 82% (95% CI 74−90)

The use of opioid analgesics is recommended in 9/9 existing treatment guidelines for the management of hip or knee OA[4]. A number of systematic reviews and MAs of the use of opioids for chronic non-cancer pain[139,140], musculoskeletal pain[141] and more recently OA[142] have provided evidence of efficacy and acceptable safety in short-term trials (LoE Ia). Analysis of 18 placebo-controlled RCTs including 3244 patients with OA showed a moderate ES for reduction in pain intensity (ES = 0.78, 95% CI 0.59, 0.98) but there was substantial heterogeneity between studies which was not obviously related to the opioid preparation that was used or the methodological quality of the RCTs[142]. The median duration of trials was 12 weeks (range 1.4−72 weeks)[142]. Analysis of five placebo-controlled RCTs which included 1429 OA patients receiving opioids showed a small effect on improvement in physical function (ES = 0.31, 95% CI 0.24, 0.39)[142]. Benefits associated with the use of opioids were, however, limited by frequent side effects; nausea (30%), constipation (23%), dizziness (20%), somnolence (18%) and vomiting (13%)[142]. Overall 25% of patients treated with opioids withdrew from studies compared with 7% of placebo-treated patients with a number needed to harm (NNH) of 5. The withdrawal rate for strong opioids (oxymorphone, oxycodone, oxytrex, fentanyl, morphine sulphate) was 31% (NNH 4) compared with a withdrawal rate of 19% and an NNH of 9 for the weaker opioids (tramadol, tramadol/paracetamol, codeine

and propoxyphene)[142]. This MA[142] did not allow any conclusions concerning comparisons of the efficacy or safety of opioids and other available analgesics such as paracetamol or NSAIDs because of the very limited number of head to head trials. However, another MA of opioids for chronic non-cancer pain, including OA, demonstrated that only strong opioids were significantly more effective than paracetamol or NSAIDs (ES = 0.34, 95% CI 0.01, 0.67)[140]. A systematic review conducted a decade earlier had, however, confirmed that paracetamol–codeine combinations did provide a small (approximately 5%) but statistically significant analgesic benefit when compared with paracetamol alone, but adverse effects were more frequent (RR = 2.5, 95% CI 1.5, 4.2)[143]. All the systematic reviews highlight the fact that there have been no long-term trials of the use of opiates for treating patients with OA[139–142]. This is obviously relevant because of ongoing concerns about the risks of dependence or addiction to opiates[144]. While in the USA there is evidence that the use of opioids for the management of chronic musculoskeletal pain doubled (RR = 2.0, 95% CI 1.52, 2.48) and the use of potent opioids more than quadrupled (RR = 4.5, 95% CI 2.18, 6.87) between 1980 and 2000[145], a survey of primary care physicians in the UK published in 2006 suggested that as many as 25% never prescribed opioids for patients with persistent non-cancer related pain[146] and this was mainly determined by personal beliefs about the appropriateness of prescribing opioids in these circumstances, rather than evidence-based guidelines[146].

21. Patients with hip or knee OA who are not obtaining adequate pain relief and functional improvement from a combination of non-pharmacological and pharmacological treatment should be considered for joint replacement surgery. Replacement arthroplasties are effective, and cost-effective interventions for patients with significant symptoms, and/or functional limitations associated with a reduced health-related quality of life, despite conservative therapy.

SOR: 96% (95% CI 94–98)

Total hip arthroplasty (THA) and knee joint arthroplasty (TKA) are universally recommended in 14/14 existing treatment guidelines[4], and generally accepted as reliable and appropriate surgical procedures to restore function and improve health-related quality of life in patients with hip and knee OA who are not obtaining adequate pain relief and functional improvement with a combination of pharmacological and non-pharmacological treatments[147,148]. As ethical and methodological considerations have precluded evaluation of total joint replacement with RCTs, evidence to support their efficacy is based substantially on numerous uncontrolled observational studies and a very small number of cohort studies where outcomes have been compared with standard medical care (LoE III). These are well summarised in a 2004 qualitative and systematic review of the scientific literature relating to health-related quality of life outcomes following THA and TKA[149]. This analysed the outcomes in 74 arthroplasty studies (32 hip and knee, 26 THA and 16 TKA alone) involving many thousands of patients with OA. The Short Form-36 (SF-36) (40 studies) and the WOMAC index (28 studies) were the instruments most frequently employed. Most studies reported on post-operative outcomes up to 6 or 12 months but there were some data on clinical outcomes up to 7 years following surgery. All studies reported substantial improvements in pain and physical functioning but the effects on mental health and social functioning were more variable[149]. Pain scores improved more quickly and more dramatically than physical functional outcomes with maximal improvements in the first 3–6 months[149]. An earlier systematic review of outcomes following THR with different types of prosthesis in 118 uncontrolled studies involving 77,375 patients with a mean follow up of 9.4 years (range 2–20 years) found that 43% (95% CI 34, 49) to 84 (95% CI 46, 100) were free from pain, depending on the type of prosthesis used. Revision rates ranged from 0.18 (S.E.M. 0.04) to 2.04 (S.E.M. 0.19)/100 person years[150]. MA of functional outcomes following unicompartmental[151], bicompartmental[151] and tricompartmental[152] knee arthroplasty showed mean improvements in a global knee score, incorporating pain, function and range of motion, of 63%, 93%, and 100%, respectively, 4–6 years after surgery. Cumulative revision rates at 10 years following THA and TKA for OA hip and knee were 7%[153] and 10%[154], respectively.

A number of studies have shown that quality of life indices following THA approximate to those in the age and gender matched population[155–157] a year after surgery. Overall THA is more effective than TKA in restoring patients with hip or knee OA to normal function and age is not an obstacle to effective surgery[149]. However higher age, more preoperative pain, musculoskeletal co-morbidities such as low back pain, and OA in the non-operated hip, predict a poorer outcome following THA[158]. More severe pain, functional limitation, low mental health scores and medical co-morbidities have also been shown to predict a poorer outcome following TKA[159]. Following development and evaluation of explicit criteria for the appropriateness of indications for THA[160] and TKA[161], based on a method that combines expert opinion with available scientific evidence[162], it has recently been demonstrated that physical and social functions as assessed by the SF-36 and WOMAC instruments improved to a significantly greater extent following THA and TKA in patients where the indications for surgery were appropriate[163]. THA and TKA were shown to be more cost-effective treatments for the management of hip and knee OA than current pharmacological modalities of therapy in the first part of this report[4]. The most recently published data suggest that the cost per QUALY gained from TKA (13995 Euros) is twice that gained from THA (6710 Euros)[164].

22. Unicompartmental knee replacement is effective in patients with knee OA restricted to a single compartment.

SOR: 76% (95% CI 64–88)

Approximately one third of patients with knee OA have unicompartmental disease that is largely restricted to a single compartment[165]. In approximately 30% of these patients with unicompartmental knee OA the medial compartment is affected, in 3% it is the lateral compartment and in 69% the disease predominantly involves the patello-femoral joint[165]. Evidence supporting the efficacy of unicompartmental knee arthroplasty (UKA) in patients with knee OA restricted to a single compartment is summarised in a recent systematic review of nine studies comparing UKA with TKA[166]. This included one RCT[167] (LoE Ib), six concurrent non-randomised trials (LoE IIa) and two retrospective comparative studies with historical controls (LoE III). Knee pain and function were comparable 5 years after UKA and TKA but range of movement was better after UKA[166]. Complication rates were similar following both procedures but prosthesis

survival following UKA was 85–90% at 10 years compared with >90% for TKA[166].

23. Osteotomy and joint preserving surgical procedures should be considered in young adults with symptomatic hip OA, especially in the presence of dysplasia. For the young and physically active patient with significant symptoms from unicompartmental knee OA, high tibial osteotomy may offer an alternative intervention that delays the need for joint replacement some 10 years.

SOR: 75% (95% CI 64–86)

Osteotomy is recommended as a modality of treatment in 10/10 existing guidelines for the management of hip or knee OA where this was considered[4]. Intertrochanteric varus or valgus osteotomy has been used as a treatment for hip OA for nearly a century[168] and pelvic or femoral osteotomies are widely advocated to correct the biomechanics and joint congruency in young patients with hip dysplasias before the development of symptomatic hip OA[169]. Evidence to support the efficacy of these procedures is limited to analysis of clinical outcomes in three uncontrolled prospective[170–172] and nine retrospective cohort studies[63] (LoE III). High tibial osteotomy was promulgated as a treatment for knee OA in the 1960s[173]. The biomechanical rationale for the operation, that realignment of the varus deformity would reduce stress on the medial compartment of the knee by redistributing the weight of the body from the arthrotic medial compartment to the healthy lateral one[174], was challenged by a study that demonstrated that while 25° of valgus angulation were required to unload the medial compartment of the joint[175] optimal clinical results were associated with corrections of only 6–14°[176]. The proposition that high tibial osteotomy may offer an alternative intervention that can delay the need for joint replacement for some 10 years is supported to some extent by an MA of 2406 osteotomies in 19 uncontrolled cohort studies[176] (LoE III). Good or excellent outcomes, defined as less pain and improved walking ability or >70 points on the Hospital for Special Surgery (HSS) knee rating system[177] were achieved in 75% of patients at 60 months and 60% of patients at 100 months[176]. The overall failure rate at 10 years was 25% but the average time between high tibial osteotomy and arthroplasty was 6 years[176].

24. The roles of joint lavage and arthroscopic debridement in knee OA are controversial. Although some studies have demonstrated short-term symptom relief, others suggest that improvement in symptoms could be attributable to a placebo effect.

SOR: 60% (95% CI 47–82)

Arthroscopic debridement, a procedure that variably includes joint lavage, the removal of loose bodies, debris, mobile fragments of articular cartilage, unstable torn menisci and impinging osteophytes, has been extensively used in the treatment of OA knee for more than 70 years[178]; and joint lavage is currently recommended as useful treatment for patients with knee OA in 3/3 treatment guidelines where this modality of therapy was considered[4]. However, controversy regarding the efficacy and indications for these procedures in the management of knee OA continues. For many years evidence for the efficacy of arthroscopic joint lavage and debridement in knee OA rested on the clinical outcomes observed in uncontrolled cohorts[179–183] as is the case for the majority of surgical interventions (LoE III). In such studies 50–80% of patients were typically recorded as having decreases in knee pain lasting from 1 to 5 years[184]. One RCT, which compared articular debridement and lavage alone in 76 knees with medial compartment knee OA, found that 80% of the debridement group and 14% of the washout group were pain free at 1 year, with 59% of the debridement group and 12% of the washout group remaining free from knee pain after 5 years[185] (LoE Ib). A second prospective comparative study compared arthroscopic debridement with non-operative medical treatment in 70 patients[186]. After 2 years 75% of the operated patients and 16% of the medically treated patients had improvements using the HSS[177] knee rating score[186]. RCTs comparing tidal knee irrigation with standard medical therapy[187], and joint lavage plus physiotherapy with physiotherapy alone[188] both demonstrated statistically significant reduction in pain in the lavage groups at 3 months[187,188], and this was still evident at 1 year in the latter trial[188] (LoE Ib). However a good quality, placebo-controlled RCT in which 180 patients with knee OA were randomly assigned to receive arthroscopic debridement, arthroscopic lavage or placebo (sham) surgery with a skin incision and simulated arthroscopy showed no significant differences between the groups in the primary end point (pain on a self-reported 12-item knee specific pain scale) at 24 months, or in any of the other secondary outcome measures of pain and function at any time point[189]. The ESs for pain and function were 0.09 (95% CI −0.27, 0.44) and −0.10 (95% CI −0.45, 0.26) for arthroscopic lavage, and −0.01 (95% CI −0.37, 0.35) and −0.09 (95% CI −0.27, 0.45) for arthroscopic debridement. This is one of only a very few placebo-controlled RCTs of surgical procedures in which sham surgery has been undertaken. Clearly surgery does have very powerful placebo effects and the investigators emphasised, as have others[190], that the power of placebos should never be underestimated. Although much of the controversy that followed the publication of this study related to the ethical and practical issues of undertaking blinded placebo-controlled trials of surgical procedures, it was also criticised on methodological grounds relating to the design of the study, the documentation of clinical and operative features, the outcome measures employed and the statistical analysis[191], as well as a failure to undertake a subset analysis to see whether any subgroups of patients who were deriving benefit from arthroscopic debridement were being lost in the pooled analysis. A recent review of published studies concluded that there was some evidence to suggest that arthroscopic debridement of meniscus tears in patients with OA and arthroscopic debridement of knees with low-grade OA may have limited utility[192] (LoE III).

25. In patients with OA of the knee, joint fusion can be considered as a salvage procedure when joint replacement has failed.

SOR: 69% (95% CI 57–82)

The most common indication for knee arthrodesis in patients with knee OA is severe pain and instability in an unreconstructable knee following an infection at the site of a previous knee arthroplasty[193]. Although success rates with primary and revision arthroplasty have improved considerably in the last two decades knees with substantial metaphyseal bone loss, inadequate ligamentous restraints, multiple failed revisions, inadequate soft-tissue coverage with loss of extensor mechanism and infection with virulent organisms should also be considered[193], as should patients with serious medical co-morbid disease (LoE IV). Knee

fusion is recommended as a salvage procedure when joint replacement has failed in both the existing guidelines that considered this modality of treatment[4]. Evidence of outcomes following knee arthrodesis is largely based on information from uncontrolled retrospective cohort studies[194–198] (LoE III). However a comprehensive review and MA of studies published in 1995 reported successful fusions in 94.6% of cases following intramedullary nailing compared with 63.6% when external fixators were used[199]. In one small comparison of nine OA patients who had undergone knee arthrodesis with nine who had had a primary TKA, SF-36 scores for pain, health, vitality, social and emotional well-being were similar in the two groups, although the arthroplasty treated patients scored higher for physical functioning[200]. The Arthritis Impact Measurement Score (AIMS) was also better after arthroplasty because of increased mobility (0.97 vs 2.5 points) and physical activity (4 vs 6.3 points) but patients with an arthrodesis had a better mean score on the pain scale (3.3 vs 3.9)[200]. In general following knee arthrodesis patients can expect a stable painless leg with some functional difficulties with climbing stairs and with sitting in a theatre or an aeroplane[193].

Contraindications to knee arthrodesis include an arthrodesis of the contralateral hip or knee and significant OA in the ipsilateral hip or ankle[199]. All patients can expect some shortening of the leg (2.5–6.4 cm)[193] and complications may occur in up to 50% of patients. These include peroneal nerve palsy, pain associated with migration of the metal nail, thrombophlebitis and, rarely, non-union[193].

Discussion

SCOPE AND PURPOSE

The OARSI treatment guidelines have been developed to provide evidence-based, expert consensus recommendations for the management of hip and knee OA, which are current, patient-focussed, and globally relevant. Although their primary purpose is to provide assistance to physicians and allied health care professionals in both general and specialist practise, it is anticipated that the recommendations will also provide an authoritative source of information about options for the management of OA hip or knee for patients, and for those involved in the funding and administration of health care. It is also anticipated that these OARSI international core recommendations will be modified and adapted as appropriate for National and Regional application, and for use by health care professionals in different specialist settings.

The systematic review of existing guidelines and recent research evidence for the treatment of OA of the hip and/or knee, which formed the first part of the OARSI exercise, identified a 'core set' of 20 treatment modalities which were universally recommended in 23 evidence-based and/or expert consensus guidelines from around the world[4]. Critical appraisal of these guidelines suggested that overall quality was sub-optimal and that consensus recommendations were not always supported by the best available clinical evidence[4]. The appraisal suggested that there was a need for updated guidelines; and that hybrid guidelines combining expert opinion with research evidence were most likely to fulfil high quality standards[4,5]. However the quality of such hybrid guidelines ultimately reflects not only the quality of the systematic review of the research evidence, but also the experience, expertise and judgement of the experts charged with producing them. It has been suggested that treatment guideline development groups should be multidisciplinary, and ideally should include representatives from all stakeholder groups whose professional activities or interests are under consideration[12]. In order to approach this requirement the OARSI Treatment Guideline Committee was made up of 16 experts from four medical disciplines (primary care 2, rheumatology 11, orthopaedic surgery 1 and evidence-based medicine 2) from two continents and six countries (Canada, France, Netherlands, UK and USA). ACR guidelines for the medical management of OA of the hip or knee[201] were developed by four US rheumatologists, and the most recent EULAR recommendations for the management of hip OA were developed by 23 experts from departments of rheumatology and orthopaedics from 14 countries limited to Europe[63]. These and other existing guidelines[4] have been variously criticised for lack of methodological rigour, editorial independence and applicability as well as for inadequate stakeholder involvement[202–204]. Details of the methodology for undertaking the systematic search for existing guidelines, and the quality and content assessment and data analyses that led to the critical appraisal of the 23 existing guidelines have been presented and discussed in detail in the first part of this report[4], as have the methodological details of the systematic review of the scientific evidence from 2002 to 2006 and the quality and outcome assessments for efficacy, side effects and cost-effectiveness[4]. So too have the sensitivity analyses that were undertaken to determine whether selected RCTs published after January 31st 2006 would alter any of the evidence-based conclusions from the critical appraisal of existing guidelines and the systematic review of the recent research evidence significantly[4].

A Delphi exercise was undertaken to generate consensus recommendations. This followed the approach pioneered during the development of the EULAR guidelines for the treatment of knee[64] and hip[63] OA with some important differences. In the development of the EULAR recommendations expert consensus on only 10 key treatment propositions, preceded the systematic search for research evidence; a process that we have characterised as *clinically driven and evidence-supported*[4]. By contrast during the development of the OARSI recommendations the results of the systematic review of the research evidence and the critical appraisal of existing guidelines were made available to the guideline development committee before they embarked on the Delphi exercise, a process that we have characterised as *evidence-driven and clinically supported*[4]. No restriction was placed on the number of treatment propositions or recommendations to be considered and eventual consensus was reached on the recommendation of 25 carefully worded propositions after six Delphi rounds. These treatment propositions encompass all of the 20 modalities of therapy which were universally recommended in existing guidelines[4(Table 4)] and all but four of the modalities of treatment for which there was agreement in between 25% and 100% of existing guidelines[4(Table 4)].

STAKEHOLDER CONSULTATION

Stakeholder involvement is one of the key criteria in the appraisal of clinical guidelines[5]. In order to obtain feedback and suggestions from potential users of the recommendations during the process of guideline development two consultation steps were included. Such consultation with potential guideline users, which is, for example, always included during the development of treatment guidelines by the Scottish Intercollegiate Guidelines Network (SIGN)[205], serves to help generate a sense of involvement and ownership among potential users as well as generating valuable feedback and suggestions for the committee concerning

alternative interpretations of the research evidence. The first of these consultation steps, described in detail in the first part of this report[4], was a pilot survey of the perceived usefulness of the treatment modalities addressed in existing guidelines among physicians and other health care professionals attending a New York University – OARSI Rheumatology Symposium in New York City in 2006. Although the number of participants was small, the range of health professionals limited and the majority of those surveyed were from the USA, the views expressed concerning the usefulness of various modalities of treatment were found to be consistent with those generated by the critical appraisal of the existing guidelines that led to the definition of a core set of recommended treatment modalities[4]. The second and more comprehensive public consultation step was conducted after four rounds of the Delphi exercise had generated provisional consensus on 34 propositions. These were posted on the OARSI website and presented for comment and discussion by OARSI members at a plenary session of the World Congress on OA in Prague in December 2006. Suggestions from OARSI members were considered by the guideline committee prior to further additions, amalgamations, minor rewording and two final Delphi rounds, which ultimately led to consensus on the 25 carefully worded propositions.

INTERPRETATION OF LOE, ES AND SOR

The type of research evidence that is considered optimal or admissible when undertaking systematic reviews varies according to the type of clinical question that is being addressed. While a prospective cohort study may be the most appropriate type of study to assess the importance of a risk factor for disease causation or progression, RCTs are regarded as the gold standard for assessing the efficacy of therapeutic interventions[206]. Evidence hierarchies, such as the one used in this study (Table II), are recommended[12], and widely used, to grade the level of evidence during the development of treatment guidelines. Such methods for grading strength of recommendations are however, problematic. Although they do allow guideline developers to include consideration of the research evidence, they are strongly driven by the evidence hierarchy for efficacy and always downgrade highly effective treatments such as total joint replacements, which are not readily assessable by RCT, because of practical and ethical considerations. To overcome this problem, the EULAR OA task force[64,210] and a multidisciplinary UK panel[211] developed an integrated approach in which SOR, based on both the LoE and clinical expertise is recorded on a VAS[64,211]. This approach, which was adopted in the development of the OARSI recommendations, allows decision-making based on the balance between research evidence and clinical practise, so that the SOR reflects the overall *clinical effectiveness* of the therapy in question. Secondly, SORs which are predominantly based on an evidence hierarchy for *clinical efficacy* may not adequately encompass adverse effects or truly reflect the trade-off between risk and benefit which is fundamental for making clinical decisions. In addition, traditionally graded SORs are recorded on categorical scales[12,207–209]. The use of a VAS based SOR[64,211] has the advantage of allowing the calculation of 95% CIs as well as mean values, so enabling users to better estimate the precision of the SOR for any particular recommendation.

The value of using the VAS SOR with 95% CI to reflect the balance between research evidence and clinical expertise is well illustrated in two of the OARSI recommendations. The SOR for joint replacement in patients with hip and knee OA (proposition 21) was 96% with very narrow 95% CI (94–98) despite only grade III research evidence, reflecting the excellent trade-off between harms and benefits for these procedures, and the strong consensus among the experts. By contrast the SOR for IA injections of hyaluronate in patients with OA knee or hip (proposition17) was only 64% with wide 95% CI (43–85), despite Ia evidence for efficacy of pain relief from some published metaanalyses. Presumably this reflected a range of expert opinion as a consequence of conflicting evidence of efficacy in RCTs and MAs of this modality of therapy, as well as consideration of the cost, convenience and overall risk/benefit ratio.

Effect size is a measure of standard mean difference between treatments (e.g., treatment vs placebo) in units of the SD of the difference[212]. When conducting MAs it is common practise to normalise the same, or different outcome measures, across different studies. This allows cross-study comparisons and statistical pooling of the results from different studies. However, ES is a *derived* outcome developed for research purposes which reflects change as an SD of change, but lacks the numerical measurement of the outcome that was actually assessed (e.g., % pain reduction on a 0–100 mm VAS). Unlike outcome measures themselves or the NNT, the interpretation of ES in clinical practise is not an easy one to communicate clearly to health administrators, health professionals or patients. Great care must be taken when attempting to compare ES across treatments, e.g., electromagnetic therapy (ES = 0.77, 95% CI 0.36, 1.17) vs NSAIDs (ES = 0.32, 95% CI 0.24, 0.39) for osteoarthritic pain[4]. Conclusions based on such comparisons of ES may be dangerous and invalid without further examination of some of the details of the studies, such as the number of studies included in the MAs, the characteristics of the patients included and the comparators that have been used. Potential users of the OARSI guidelines are, therefore, strongly advised to examine the 95% CIs between treatments before coming to any conclusions about comparisons of ESs.

THE CONCEPT OF A CORE SET OF RECOMMENDATIONS: COMPARISON WITH OTHER GUIDELINES

Attempts have been made to define core sets for OA[213] within the International Classification of Functioning, Disability and Health (ICF)[214] and an International Classification of Health Interventions has been proposed by the World Health Organisation (WHO)[215]. There are, however, currently no generally accepted core sets of treatments for patients with OA. In the first part of this report we were able to identify 20 modalities of therapy for OA hip and/or knee which were universally recommended in existing guidelines[4]. These comprised eight non-pharmacological modalities (education, self-management, regular telephone contact, aerobic, muscle strengthening and water-based exercises, referral to a physical therapist and the use of a cane or stick); six pharmacological modalities (acetaminophen, NSAIDs, both non-selective with co-prescription of a PPI or misoprostol and selective COX-2 inhibitors, opioids and herbal preparations); five surgical modalities (total joint replacements, osteotomy, knee fusion and knee aspiration/joint lavage) as well as the combination of non-pharmacological and pharmacological treatments. With some carefully worded caveats all of these modalities of therapy are included in the current OARSI recommendations which have been developed by a multinational, multidisciplinary group of experts from primary and secondary care after evaluation of the critical appraisal of existing treatment guidelines and a systematic review of the recent research evidence, with the exception of herbal

treatments (Table I). In addition there was a consensus for treatment recommendations, with caveats, based on four non-phamacological modalities (weight loss, shoe insoles, knee braces, TENs), four pharmacological (oral and topical NSAIDs, topical capsaicin and IA injections of corticosteroids and hyaluronate) and one surgical modality (arthroscopic debridement) which are recommended in 75% of existing guidelines; for acupuncture, thermal modalities and glucosamine sulphate recommended in 50%, and for chondroitin sulphate recommended in 25%. However, the SOR was only >90% in 8/25 of the carefully worded treatment propositions relating to five non-pharmacological modalities of therapy (education/self-help, exercise, weight reduction and the use of walking aids); one pharmacological modality (acetaminophen) and one surgical modality of treatment (total joint replacement) in addition to the general recommendation to combine pharmacological and non-pharmacological treatments.

LIMITATIONS

The OARSI guidelines have some limitations. Although the guideline development committee was multinational and multidisciplinary it only included experts from Europe and North America and 11/16 of its members were rheumatologists. Primary care physicians and orthopaedic surgeons were underrepresented. Although there were no experts from allied health professions such as nursing or physiotherapy, efforts were made to obtain the views of other health professionals through the questionnaire survey at the New York – OARSI Symposium and the collection of comments from the wider OARSI membership through posting the draft recommendations on the OARSI website and public presentation and discussion of the draft guidelines at the World Congress on OA in December 2006. Unfortunately patients' perspectives on the recommendations remain unknown. Secondly, due to time constraints, only the scientific literature from 2002 to 2006 was systematically reviewed. Evidence before 2002 was obtained from the EULAR systematic review, and it was not possible to combine the data from the two systematic reviews because of discrepancies in methodology and the scope of the guidelines. Thirdly, a number of new studies have been published after the closing date of our literature search (Jan 2006). These include some studies of chondroitin sulphate[131,133], weight reduction[39], diacerein[137,216] and vascular risk of NSAIDs and coxibs[87,217–219]. Whether any of this more recently published data would change the calculated evidence parameters significantly and whether they will have any impact on the current OARSI recommendations remains to be determined. Finally, the Delphi exercise had to be arbitrarily terminated after the sixth round when it had become clear that consensus to accept or reject two propositions [one for diacerein and the other for avocado-soybean unsaponifiables (ASU)] was not possible despite attempts at rewording or amalgamation with treatment propositions that had already been accepted. There was limited support (>20% but <60% voting) for propositions stating that diacerein and ASU may provide slow acting symptomatic benefit in patients with knee or hip OA.

The evidence for symptomatic efficacy of diacerein in patients with OA hip or knee available to the OARSI Treatment Guidelines Development group from the systematic review of the research evidence from 2002 to January 2006 came from four RCTs with heterogeneous results[138,220–222] (LoE Ib). The ES_{pain} was small (0.22, 95% CI 0.01, 0.42) and the RR for diarrhoea was 3.98 (95% CI 2.90, 5.47)[4]. Some symptomatic efficacy of diacerein was suggested by a more recently published RCT[223] and two MAs[137,216], but the first of these raised concerns about the heterogeneity of outcomes and the possibility of publication bias[137], and the latter[216] was criticised for omitting the results of analyses for heterogeneity and for possible bias resulting from industry support[224].

The evidence for symptomatic efficacy of ASU in patients with OA hip or knee available to the OARSI Treatment Guidelines Development group from the systematic review of the research evidence from 2002 to January 2006 came from a systematic review of four RCTs, three out of four of which showed some evidence of efficacy for relief of pain in OA hip and knee[225] (LoE 1a) and treatment with ASU was recommended in 3/4 existing guidelines[4].

Table V
Research evidence for efficacy of modalities of therapy not included in OARSI recommendations

Modality	Frequency of recommendation in other guidelines	LoE	Research evidence ES_{pain} (95% CI)
Non-pharmacological			
Spa/sauna	1 Guideline only	Ib	0.46 (0.17, 0.75)
Laser	1 of 6	Ia	–
Ultrasound	1 of 5	Ia	0.06 (−0.39, 0.52)
Radiotherapy	1 Guideline only	IIb	–
Electrotherapy/EMG	1 of 8	Ia	0.77 (0.36, 1.17)
Pharmacological			
Diacerein	1 of 2	Ib	0.22 (0.01, 0.42)
SAM-e	–	Ia	0.22 (−0.25, 0.69)
ASU	3 of 4	Ia	–
Herbal remedy	–	Ia	–
Oestrogen	1 Guideline only	IV	–
Bisphosphonates	–	IV	–
Antidepressants	1 Guideline only	IV	–
Surgical			
Patellar resurfacing	1 Guideline only	Ib	–
Joint distraction	–	IV	–
Knee aspiration	–	IV	–

ES = 0.2 is considered small, ES = 0.5 is moderate, and ES > 0.8 is large. SAM-e: S-adenosylmethionine. LoE: Ia: meta-analysis of RCTs; Ib: RCT; IIa: controlled study without randomisation; IIb: quasi-experimental study (e.g., uncontrolled trial, one arm dose-response trial,); III: observational studies (e.g., case–control, cohort, cross-sectional studies); and IV: expert opinion.

Other modalities of therapy for hip and/or knee OA for which there is some published suggestion of efficacy, but for which no current recommendations are made in the OARSI guidelines are listed in Table V together with the LoE for efficacy, the ES (95% CI) where this could be calculated and the frequency with which the therapeutic modality is recommended in other guidelines.

UTILITY AND APPLICABILITY

These are OARSI international core recommendations for the treatment of OA of the hip and knee. It is anticipated that they will need to be adapted, and possibly modified, for National and Regional application, where individual modalities of therapy are not available or where there are other organisational barriers to introducing the core recommendations into primary care and specialist practise. In order to facilitate dissemination and implementation the guideline development committee recommends

- Publication of the guidelines in *Osteoarthritis and Cartilage* accompanied by a commentary to assist with interpretation.
- Delivery of the document to all OARSI members with encouragement to translate the guidelines into different languages.
- Posting the guidelines with open access on the public section of the OARSI website.
- Fostering contact and liaison with other societies and professional groups representing stakeholders in primary and secondary care worldwide.
- Encouraging other professional and multidisciplinary groups concerned with the management of patients with OA knee and hip in primary and secondary care settings throughout the world to consider using the OARSI recommendations as a starting point for developing their own guidelines.
- Fostering consultation with and feedback from patient representative organisations.
- Encouraging presentation and discussion of the recommendations at National and International conferences and seminars.

RECOMMENDATIONS FOR AUDIT

OARSI recommends audit to assess current treatment of OA of the hip and knee in primary care and specialist practise throughout the world and audits to assess the impact of implementation of the guidelines on clinical outcomes.

UPDATING

OARSI plans to update research evidence annually and the guidelines as appropriate every 3–5 years.

Conflicts of interest

Full final disclosure statements from all members of the OARSI treatment guidelines committee are shown in Appendix 2. Disclosure statements were reviewed by the OARSI ethics committee at the beginning of the guideline development process and again prior to voting on the SOR for each proposition. No potential conflict of interest was identified by the ethics committee that would necessitate the exclusion of any member of the committee or preclude any member from voting on the SOR for any specific treatment proposition. A policy of self-recusal was, however, instituted: "Should a committee member feel that they may be unduly influenced in their vote, based on a consulting or ownership relationship with a particular industrial entity that produces a drug in the class being voted upon, they should recuse themselves from voting on that item in the treatment guidelines". MH recused himself from voting on the SOR for propositions 13–20 and PT from voting on proposition 15. Subsequent sensitivity analysis, however, showed that inclusion of members' votes on the propositions from which they were recused would not have altered the SOR on any of the recommendations significantly, with overlapping 95% CIs. The recommendations are endorsed by the OARSI Board, but were developed independently by the OARSI Treatment Guidelines Committee.

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Appendix 1. Members of the OARSI treatment guidelines committee

Chair	George Nuki, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK
Co-chair	Roland W. Moskowitz, University Hospitals, Case Western Reserve University, Cleveland, OH, USA
Lead investigator	Weiya Zhang, Academic Rheumatology, Nottingham City Hospital, University of Nottingham, Nottingham, UK
Members	Steve Abramson, Hospital for Joint Diseases, New York University School of Medicine, New York, NY, USA
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	Nigel K. Arden, Medical Research Council, Southampton General Hospital, Southampton, UK
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	Peter Croft, Keele University, Keele, UK
	Michael Doherty, Academic Rheumatology, Nottingham City Hospital, University of Nottingham, Nottingham, UK
	Maxime Dougados, Hopital Cochin, Paris, France
	Marc Hochberg, University of Maryland School of Medicine, Baltimore, MD, USA
	David J. Hunter, Boston University School of Medicine, Boston, MA, USA
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	Stefan Lohmander, Department of Orthopaedics, Clinical Sciences, Lund University, Lund, Sweden
	Peter Tugwell, Institute of Population Health, University of Ottawa, Ottawa, Canada

Appendix 2. Committee members disclosures

Name	Consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses	Ownership interest	Business relationship	Service with organisation with interests comparable to OARSI	Nothing to declare
W. Zhang	Nil	Nil	Nil	Leader EULAR OA task force	
R.W. Moskowitz	Adolor Anesiva Bioiberica Bionicare Endo Merck Novartis Pfizer Rottapharm Sanofi-Aventis	Nil	Nil	Nil	
G. Nuki	AstraZeneca Savient	Nil	Nil	Nil	
S. Abramson	Amgen GlaxoSmithKline Merck Novartis Pfizer	Amgen BMS Merck Pfizer Resolvyx	Nil	Nil	
R.D. Altman	Abbott Anesiva Ferring Kinicure McNeil Negma Novartis Pfizer Proprius Reliant Rottapharm Sanofi-Aventis	Nil	Nil	Nil	
N. Arden	Merck Sharp & Dohme Novartis Pfizer Proctor & Gamble Q-Med Roche Rottapharm Schering-Plough Servier	Nil	Nil	Nil	
S. Bierma-Zeinstra	Nil	Nil	Nil	Nil	✓
K.D. Brandt	Anesiva Genzyme Novartis Pfizer	Pfizer	Nil	Nil	
P. Croft	Nil	Nil	Nil	Nil	✓
M. Doherty	AstraZeneca GlaxoSmithKline IDEA technology Ipsen Novartis Reckitt	Nil	Nil	EULAR OA task force	

Appendix 2 (*continued*)

Name	Consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses	Ownership interest	Business relationship	Service with organisation with interests comparable to OARSI	Nothing to declare
M. Dougados	Abbott AstraZeneca BMS CombinatoRx Merck Negma Novartis Pfizer Pharmasciences Proctor & Gamble Roche Wyeth	Nil	Nil	Nil	
M. Hochberg	Amgen AstraZeneca Bayer Biogen idec Bionicare Bristol Myers Squibb Chugai CombinatoRx Dainippon Sumitomo Ferring Genzyme GlaxoSmithKline Merck NicOx Novartis Proctor & Gamble Proprius Roche Sanofi-Aventis Wyeth	Nil	Nil	Nil	
D.J. Hunter	AstrZeneca Donjoy Merck Pfizer Stryker	Nil	Nil	Nil	
K. Kwoh	Beveridge Inst GlaxoSmithKline Novartis TAP	Cartesia	Nil	Nil	
L.S. Lohmander	AstraZeneca Centocor GlaxoSmithKline Pfizer	Nil	Nil	Nil	
P. Tugwell	Abbott Almirall AstraZeneca Aventis Berlex Biomatrix Bristol Myers Squibb Cadeuceus Centocor CIGNA Dimedix Dimethaid IDRC Eli Lilly				

(*continued on next page*)

Appendix 2 (*continued*)

Name	Consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses	Ownership interest	Business relationship	Service with organisation with interests comparable to OARSI	Nothing to declare
	Genzyme Glaxo-Welcome GlaxoSmithKline Hoechst Marion Roussel Innovus Johnson&Johnson Lilley Medicus Merck Merck Frost Novartis Novopharm Ortho McNeil Parke Davis Pennside Pfizer Rhone-Poulenc Roche Sandoz Scios Searle SmithKline Beecham Teva Wyeth Ayerst	Nil	Nil	Nil	

References

1. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann Rheum Dis 2001 Feb;60:91–7 (See comment, Review, 45 refs).
2. Dawson J, Linsell L, Zondervan K, Rose P, Randall T, Carr A, *et al*. Epidemiology of hip and knee pain and its impact on overall health status in older adults. Rheumatology 2004;43:497–504.
3. Dunlop DD, Manheim LM, Song J, Chang RW. Arthritis prevalence and activity limitations in older adults. Arthritis Rheum 2001;44:212–21.
4. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, *et al*. OARSI recommendations for the management of hip and knee osteoarthritis, Part I: Critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthritis Cartilage 2007;15:981–1000.
5. The AGREE Collaboration. Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument. Available from: www agreecollaboration org; 2006.
6. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. J Clin Epidemiol 1991;44:1271–8.
7. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
8. Hedges LV. Fitting continues models to effect size data. J Educ Stat 1982;7:245–70.
9. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. BMJ 1995;310:452–4.
10. Kleinbaum DG, Kuppler LL, Morgenstern H. Epidemiologic Research – Principles and Quantitative Methods. John Willey & Sons, Inc. 1982.
11. Lau J, Ioannidis JPA, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997;1(127):820–6.
12. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. BMJ 27 Feb 1999;318(7183):593–6 (Review, 17 refs).
13. Petrella RJ, Bartha C. Home based exercise therapy for older patients with knee osteoarthritis: a randomised controlled trial. J Rheumatol 2000;27:2215–21.
14. Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. Ann Rheum Dis 2005;64:544–8.
15. Christensen R, Astrup A, Bliddal H. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. Osteoarthritis Cartilage 2005;13:20–7.
16. Messier SP, Loeser RF, Miller GD, Morgan TM, Rejeski WJ, Sevick MA, *et al*. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the arthritis, diet, and activity promotion trial. Arthritis Rheum 2004;50:1501–10.
17. Warsi A, LaValley MP, Wang PS, Avorn J, Solomon DH. Arthritis self-management education programs: a meta-analysis of the effect on pain and disability. Arthritis Rheum 2003;48:2207–13.
18. Chodosh J, Morton SC, Mojica W, Maglione M, Suttorp MJ, Hilton L, *et al*. Meta-analysis: chronic disease self-management programs for older adults. Ann Intern Med 2005;143:427–38.
19. Warsi A, Wang PS, LaValley MP, Avorn J, Solomon DH. Self-management education programs in chronic disease: a systematic review and methodological critique of the literature. Arch Intern Med 2004;164:1641–9.
20. Chodosh J, Morton SC, Suttorp MJ, Shekelle PJ. Self-management education for osteoarthritis. Ann Intern Med 2006;144:618.
21. WH Ettinger Jr, Burns R, Messier SP, Applegate W, Rejeski WJ, Morgan T, *et al*. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. The Fitness, Arthritis and Seniors Trial (FAST). JAMA 1997;277:25–31.
22. Rejeski WJ, Brawley LR, Ettinger W, Morgan T, Thompson C. Compliance to exercise therapy in older participants with knee osteoarthritis: implications for treating disability. Med Sci Sports Exerc 1997;29:977–85.
23. O'Reilly SC, Muir KR, Doherty M. Effectiveness of home exercise on pain and disability from osteoarthritis of the knee: a randomised, controlled trial. Ann Rheum Dis 1999;58:15–9.
24. Belza B, Topolski T, Kinne S, Patrick DL, Ramsey SD. Does adherence make a difference? Results from a community-based aquatic exercise program. Nurse Res 2002;51:285–91.
25. Thomas KS, Muir KR, Doherty M, Jones AC, O'Reilly SC, Bassey EJ. Home-based exercise programme for knee pain and knee osteoarthritis: randomised controlled trial. BMJ 2002;325:752–5.
26. Weinberger M, Tierney WM, Booher P, Katz BP. Can the provision of information to patients with osteoarthritis improve functional status? A randomized, controlled trial. Arthritis Rheum 1989;32:1577–83.
27. Rene J, Weinberger M, Mazzuca SA, Brandt KD, Katz BP. Reduction of joint pain in patients with knee osteoarthritis who have received monthly telephone calls from lay personnel and whose medical treatment regimens have remained stable. Arthritis Rheum 1992;35:511–5.
28. Weinberger M, Tierney WM, Booher P, Katz BP. The impact of increased contact on psychosocial outcomes in patients with

osteoarthritis: a randomized, controlled trial. J Rheumatol 1991;18: 849–54.
29. Mazzuca SA, Brandt KD, Katz BP, Chambers M, Byrd D, Hanna M. Effects of self-care education on the health status of inner city patients with osteoarthritis of the knee. Arthritis Rheum 1997;40:1466–74.
30. Keefe FJ, Caldwell DS, Williams DA, Gil KM, Mitchell D, Martinez S, *et al*. Pain coping skills training in the management of osteoarthritis knee pain. II Follow-up results. Behav Ther 1990;21:435–47.
31. Fransen M, Crosbie J, Edmonds J. Physical therapy is effective for patients with osteoarthritis of the knee: a randomized controlled clinical trial. J Rheumatol 2001;28:156–64.
32. Deyle GD, Henderson NE, Matekel RL, Ryder MG, Garber MB, Allison SC. Effectiveness of manual physical therapy and exercise in osteoarthritis of the knee. A randomized, controlled trial. Ann Intern Med 2000;132:173–81.
33. Deyle GD, Allison SC, Matekel RL, Ryder MG, Stang JM, Gohdes DD, *et al*. Physical therapy treatment effectiveness for osteoarthritis of the knee: a randomized comparison of supervised clinical exercise and manual therapy procedures versus a home exercise program. Phys Ther 2005;85:1301–17.
34. Quilty B, Tucker M, Campbell R, Dieppe P. Physiotherapy, including quadriceps exercises and patellar taping, for knee osteoarthritis with predominant patello-femoral joint involvement: randomized controlled trial. J Rheumatol 2003;30:1311–7.
35. Bennell KL, Hinman RS, Metcalf BR, Buchbinder R, McConnell J, McColl G, *et al*. Efficacy of physiotherapy management of knee joint osteoarthritis: a randomized, double-blind, placebo controlled trial. Ann Rheum Dis 2005;64:906–12.
36. Roddy E, Zhang W, Doherty M, Arden NK, Barlow J, Birrell F, *et al*. Evidence-based recommendations for the role of exercise in the management of osteoarthritis of the hip or knee—the MOVE consensus. Rheumatology (Oxford) 2005;44:67–73.
37. Cochrane T, Davey RC, Matthes Edwards SM. Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis. Health Technol Assess 2005;9(31):iii–iiv.
38. Stener-Victorin E, Kruse-Smidje C, Jung K. Comparison between electro-acupuncture and hydrotherapy, both in combination with patient education and patient education alone, on the symptomatic treatment of osteoarthritis of the hip. Clin J Pain 2004;20: 179–85.
39. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis 2007;66:433–9.
40. Lievense AM, Bierma-Zeinstra SM, Verhagen AP, van Baar ME, Velhaar JA, Koes BW. Influence of obesity on the development of osteoarthritis of the hip: a systematic review. Rheumatology (Oxford) 2002;41:1155–62.
41. Chan GNY, Smith AW, Kirtley C, Tsang WWN. Changes in knee moments with contralateral versus ipsilateral cane usage in females with knee osteoarthritis. Clin Biomech 2005;20:396–404.
42. Blount WP. Don't throw away the cane. J Bone Joint Surg Am 1956; 38-A:695–708.
43. Van der Esch M, Heijmans M, Dekker J. Factors contributing to the possession and use of walking aids among persons with rheumatoid arthritis and osteoarthritis. Arthritis Rheum 2003;49:838–42.
44. Brouwer RW, Jakma TS, Verhagen AP, Verhaar JA, Bierma-Zeinstra SM. Braces and orthoses for treating osteoarthritis of the knee. Cochrane Database Syst Rev Jan 2005;25(1):CD004020.
45. Kirkley A, Webster-Bogaert S, Litchfield R, Amendola A, Macdonald A, McCalden R, *et al*. The effect of bracing on varus gonarthrosis. J Bone Joint Surg Am 1999;81:539–48.
46. Ogata K, Yasunaga M, Nomiyama H. The effect of wedged insoles on the thrust of osteoarthritic knees. Int Orthop 1997;21:308–12.
47. Sasaki T, Yasuda K. Clinical evaluation of the treatment of osteoarthritic knees using a newly designed wedged insole. Clin Orthop Relat Res 1987;221:181–7.
48. Keating EM, Faris PM, Ritter MA, Kane J. Use of lateral heel and sole wedges in the treatment of medial osteoarthritis of the knee. Orthop Rev 1993;22:921–4.
49. Toda Y, Segal N, Kato A, Yamamoto S, Irie M. Effect of a novel insole on the subtalar joint of patients with medial compartment osteoarthritis of the knee. J Rheumatol 2001;28:2705–10.
50. Maillefert JF, Hudry C, Baron G, Kieffert P, Bourgeois P, Lechevalier D, *et al*. Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis: a prospective randomized controlled study. Osteoarthritis Cartilage 2001;9:738–45.
51. Pham T, Maillefert JF, Hudry C, Kieffert P, Bourgeois P, Lechevalier D, *et al*. Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis. A two-year prospective randomized controlled study. Osteoarthritis Cartilage 2004;12:46–55.
52. Dieppe P, Buckwalter JA. Management of limb joint osteoarthritis. In: Klippel JH, Dieppe PA, Eds. Rheumatology. 2nd edn. London, Philadelphia, St Louis, Sydney, Tokyo: Mosby 1998:8.9.1.
53. Brosseau L, Yonge KA, Robinson V, Marchand S, Judd M, Wells G, *et al*. Thermotherapy for treatment of osteoarthritis. Cochrane Database Syst Rev 2003;(4):CD004522.
54. Yurtkuran M, Kocagil T. TENS, electroacupuncture and ice massage: comparison of treatment for osteoarthritis of the knee. Am J Acupunct 1999;27:133–40.
55. Clarke RG, Willis LA, Stenner L, Nichols PJR. Evaluation of physiotherapy in the treatment of osteoarthritis of the knee. Rheumatol Rehabil 1974;13:190–7.
56. Osiri M, Welch V, Brosseau L, Shea B, McGowan J, Tugwell P, *et al*. Transcutaneous electrical nerve stimulation for knee osteoarthritis. Cochrane Database Syst Rev 2000;(4):CD002823.
57. Brosseau L. Efficacy of transcutaneous electrical nerve stimulation for osteoarthritis of the lower extremities: a meta-analysis. Phys Ther Rev 2004;9:213–33.
58. Bjordal JM, Johnson MI, Lopes-Martins RAB, Bogen B, Chow R, Llunggren AE. Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and meta-analysis of randomised placebo-controlled trials. BMC Musculoskelet Disord 2007;8: 51. doi:10.1186/1471-2474/8/51.
59. Sluka KA, Walsh D. Transcutaneous electrical nerve stimulation: basic science mechanisms and clinical effectiveness. Pain 2003;4: 109–21.
60. Witt C, Selim D, Reinhold T, Jena S, Brinkhaus B, Liecker B, *et al*. Cost-effectiveness of acupuncture in patients with headache, low back pain and osteoarthritis of the hip and the knee. Focus Alternative Compl Ther 2005;10(Suppl 1):57–8 (12th Annual Symposium on Complementary Health Care – Abstracts, 19–21 September 2005, Exeter, UK).
61. Ezzo J, Hadhazy V, Birch S, Lixing L, Kaplan G, Hochberg M, *et al*. Acupuncture for osteoarthritis of the knee: a systematic review. Arthritis Rheum 2001;44:819–25.
62. Foster NE, Thomas E, Barlas P, Hill JC, Young J, Mason E, *et al*. Acupuncture as an adjunct to exercise based physiotherapy for osteoarthritis of the knee: randomised controlled trial. BMJ 2007; doi: 10.1136/bmj.39280.509803.BE (On line).
63. Zhang W, Doherty M, Arden N, Bannwarth B, Bijlsma J, Gunther KP, *et al*. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2005;64: 669–81.
64. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, *et al*. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003;62:1145–55 (Review, 82 refs).
65. Case JP, Baliunas AJ, Black JA. Lack of efficacy of acetaminophen in treating symptomatic knee osteoarthritis: a randomized, double-blind, placebo controlled comparison trial wit diclofenac sodium. Arch Intern Med 2003;163:169–78.
66. Garcia Roderiguez LA, Hernandez-Diaz S. Risk of upper gastrointestinal complications among users of acetaminophen and non-steroidal anti-inflammatory drugs. Epidemiology 2001;12:570–6.
67. Rahme E, Pettitt D, LeLorier J. Determinants and sequelae associated with utilization of acetaminophen versus traditional nonsteroidal antiinflammatory drugs in an elderly population. Arthritis Rheum 2002;46: 3046–54.
68. Towheed TE, Hochberg MC, Judd MG, Wells G. Acetaminophen for osteoarthritis. The Cochrane Libr (Oxford) 2002;(4): ID #CD004257.
69. Zhang W, Jones A, Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? A meta-analysis of randomised controlled trials. Ann Rheum Dis 2004;63:901–7.
70. Towheed TE, Maxwell L, Judd MG, Catton M, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2006;(1):CD004257.
71. Lewis SC, Langman MJS, Laporte J-R, Matthres NS, Rawlins MD, Wiholm B-E. Dose–response relationships between individual nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) and serious upper gastrointestinal bleeding: a meta-analysis based on individual patient data. Br J Clin Pharmacol 2002;54:320–6.
72. Rexrode KM, Buring JE, Glynn RJ, Stampfer MJ, Youngman LD, Gaziano JM. Analgesic use and renal function in men. JAMA 2001; 286(3):315–21.
73. Fored CM, Ejerblad E, Lindblad P, Fryzek JP, Dickman PW, Signorello LB, *et al*. Acetaminophen, aspirin, and chronic renal failure. N Engl J Med 2001;345:1801–8.
74. TNS/arthritis care survey. Available from: www.arthritiscare.org.uk/OANation; 2003.
75. Bjordal JM, Ljunggren AE, Klovning A, Slordal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. BMJ 2004;329:1317–20.

76. Angst F, Aesclimann A, Michel BA, Stucki G. Minimal clinically important rehabilitation effects in patients with osteoarthritis of the lower extremities. J Rheumatol 2002;29:131–8.
77. Tramer MR, Moore RA, Reynolds DJ, McQuay HJ. Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. Pain 2000;85:169–82.
78. Ofman JJ, MacLean CH, Straus WL, Morton SC, Berger ML, Roth EA, *et al.* A metaanalysis of severe upper gastrointestinal complications of nonsteroidal antiinflammatory drugs. J Rheumatol 2002;29:804–12.
79. Hooper L, Brown TJ, Elliott R, Payne K, Roberts C, Symmons D. The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review. BMJ 2004;329:948–52.
80. Capurso L, Koch M. Prevention of NSAID-induced gastric lesions: H2 antagonists or misoprostol? A meta-analysis of controlled clinical studies (In Italian). Clin Ter 1991;139:179–89.
81. Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E, , *et al*TARGET Study Group. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. Lancet 2004;364:665–74.
82. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, *et al.* Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005; 352:1092–102.
83. Hernandez-Diaz S, Varas-Lorenzo C, Garcia Rodriguez LA. Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. Basic Clin Pharmacol Toxicol 2006;98:266–74.
84. Caldwell B, Aldington S, Weatherall M, Shirtcliffe P, Beasley R. Risk of cardiovascular events and celecoxib: a systematic review and meta-analysis. J R Soc Med 2006;99:132–40.
85. Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Lancet 2004;364:2021–9.
86. Aldington S, Shirtcliffe P, Weatherall M, Beasley R. Increased risk of cardiovascular events with parecoxib/valdecoxib: a systematic review and meta-analysis. N Z Med J 2005;118:U1766.
87. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono P. Do selective cyclo-oxygenase inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ 2006;332:1302–8.
88. EMEA/CHMP/410051/2006.
89. Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical NSAIDs in the treatment of osteoarthritis: a meta-analysis of randomized controlled trials. Chin J Evid Based Med 2005;5(9):667–74.
90. Egger M, Smith JD, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. BMJ 1997;315:629–34.
91. Biswal S, Medhi B, Panhi P. Long-term efficacy of nonsteroidal anti-inflammatory drugs in knee osteoarthritis: meta-analysis of randomized placebo controlled trials. J Rheumatol 2006;33:1841–4.
92. Evans JMM, McMahon AD, McGilchrist MM, White G, Murray FE, McDevitt DG, *et al.* Topical non-steroidal anti-inflammatory drugs and admission to hospital for upper gastrointestinal bleeding and perforation: a record linkage case–control study. BMJ 1995;311:22–6.
93. Baron R. Capsaicin and nociception: from basic mechanisms to novel drugs. Lancet 2000;356:785–7.
94. Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin. A meta-analysis. Eur J Clin Pharmacol 1994;46:517–22.
95. Deal CL, Schnitzer TJ, Lipstein E, Seibold JR, Stevens RM, Levy MD, *et al.* Treatment of arthritis with topical capsaicin: a double-blind trial. Clin Ther 1991;13:383–95.
96. Miller JH, White J, Norton TH. The value of intra-articular injections in osteoarthritis of the knee. J Bone Joint Surg Br 1958;40:636–43.
97. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intra-articular corticosteroid for treatment of osteoarthritis of the knee. The Cochrane Libr (Oxford) 2005;(4):ID #CD005328.
98. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intra-articular corticosteroid for treatment of osteoarthritis of the knee. The Cochrane Libr (Oxford) 2006;(2):ID #CD005328.
99. Gaffney K, Ledingham J, Perry JD. Intra-articular triamcinolone hexacetonide in knee osteoarthritis: factors influencing the clinical response. Ann Rheum Dis 1995;54:379–81.
100. Dieppe PA, Sathapatayavongs B, Jones HE, Bacon PA, Ring EF. Intra-articular steroids in osteoarthritis. Rheumatol Rehabil 1980;19:212–7.
101. Jones A, Doherty M. Intra-articular corticosteroids are effective in osteoarthritis but there are no clinical predictors of response. Ann Rheum Dis 1996;55:829–32.
102. Valtonen EJ. Clinical comparison of triamcinolonehexacetonide and betamethasone in the treatment of osteoarthrosis of the knee joint. Scand J Rheumatol Suppl 1981;41:1–7.
103. Flanagan J, Casale FF, Thomas DL, Desai KB. Intra-articular injection for pain relief in patients awaiting hip replacement. Ann R Coll Surg Engl 1988;70:156–7.
104. Kullenberg B, Runesson R, Tuvhag R, Olsson C, Resch S. Intra-articular corticosteroid injection: pain relief in osteoarthritis of the hip? J Rheumatol 2004;31:2265–8.
105. Plant MJ, Borg AA, Dziedzic K, Saklatvala J, Dawes PT. Radiographic patterns and response to corticosteroid hip injection. Ann Rheum Dis 1997;56:476–80.
106. Robinson P, Keenan AM, Conaghan PG. Clinical effectiveness and dose–response of image-guided intra-articular corticosteroid injection for hip osteoarthritis. Rheumatology (Oxford) 2007;46:285–91.
107. Jones A, Regan M, Ledingham J, Pattrick M, Manhire A, Doherty M. Importance of placement of intra-articular steroid injections. BMJ 1993;307:1329–30.
108. Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. JAMA 2003; 290:3115–21.
109. Arrich J, Piribauer F, Mad P, Schmid D, Klaushofer K, Mullner M. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. CMAJ 2005;172:1039–43.
110. Medina JM, Thomas A, Denegar CR. Knee osteoarthritis: should your patient opt for hyaluronic acid injection? J Fam Pract 2006;58: 669–75.
111. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006 April 19th;(2):CD005321.
112. Campbell J, Bellamy N, Gee T. Differences between systematic reviews/meta-analyses of hyaluronic acid/hyaluronan//hylan in osteoarthritis of the knee. Osteoarthritis Cartilage 2007;15:1424–36.
113. Jadad AR, Cook DJ, Browman GP. A guide to interpreting discordant systematic reviews. CMAJ 1997;156:1411–6.
114. The GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490–4.
115. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. J Bone Joint Surg Am 2004;86:538–45.
116. Modowai A, Ferrer M, Choi HK, Castle JA. Hyaluronic acid injections relieve knee pain. J Fam Pract 2005;54:758–67.
117. Conrozier T, Vignon E. Is there evidence to support the inclusion of viscosupplementation in the treatment paradigm for patients with hip osteoarthritis? Clin Exp Rheumatol 2005;23:711–6.
118. Fernandez Lopez JC, Ruana-Ravina A. Efficacy and safety of intraarticular hyaluronic acid in the treatment of hip osteoarthritis: a systematic review. Osteoarthritis Cartilage 2006;14:1306–11.
119. Van den Bekerom MPJ, Lamme B, Sermon A, Mulier M. What is the evidence for viscosupplementation in the treatment of patients with hip osteoarthritis? Systematic review of the literature. Arch Orthop Trauma Surg 2007; doi:10.1007/s00402-007-0447-z
120. Tikiz C, Unlu Z, Sener A, Efe M, Tuzun C. Comparison of the efficacy of lower and higher molecular weight viscosupplementation in the treatment of hip osteoarthritis. Clin Rheumatol 2005;24:244–50.
121. Quistgaard E, Christensen R, Torp-Pedersen S, Bliddal H. Intra-articular treatment of hip osteoarthritis: a randomized trial of hyaluronic acid, corticosteroid and isotonic saline. Osteoarthritis Cartilage 2006;14: 163–70.
122. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States 2002. Adv Data May 27 2004;(343):1–19.
123. Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, *et al.* Glucosamine therapy for treating osteoarthritis. The Cochrane Libr (Oxford) 2005;(4):ID #CD002946.
124. Richy F, Bruyere O, Ethgen O, Cucherat M, Henrotin Y, Reginster J-Y. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. Arch Intern Med 2003;163:1514–22.
125. Vlad SC, La Valley MP, McAlindon TE, Felson DT. Glucosamine for pain in osteoarthritis. Why do trial results differ? Arthritis Rheum 2007;56:2267–77.
126. Higgins JP, Simon GT, Deeks JJ, Altman RD. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
127. Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, *et al.* Glucosamine, chondroitin sulphate and the two in combination for painful knee osteoarthritis. N Engl J Med 2006;354: 795–808.
128. Herrero-Beaumont G, Roman Ivorra JA, del Carmen Trabado MC, Blanco FJ, Benito P, Martin-Mola E, *et al.* Glucosamine sulphate in the treatment of knee osteoarthritis symptoms: a randomized, double-blind, placebo-controlled study using acetaminophen as a side comparator. Arthritis Rheum 2007;56:555–67.
129. Leeb BF, Schweizer M, Montag K, Smolen J. A meta-analysis of chondroitin sulphate in the treatment of osteoarthritis. J Rheumatol 2000; 27:205–11.
130. McAlindon TE, La Valley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. JAMA 2000;283:1469–75.

131. Reichenbach S, Sterchi R, Scherer M, Trelle S, Burgi E, Burgi U, *et al*. Meta-analysis: chondroitin for osteoarthritis of the knee or hip. Ann Intern Med 2007;146:580–90.
132. Kahan A. STOPP (study on osteoarthritis progression prevention): a new two year trial with chondroitin 4 & 6 sulphate (CS). www.ibsa-ch.com/eular 2006 amsterdam vignon-2pdf (accessed on 18 September 2006).
133. Mazieres B, Hucher MMH, Zam MMZ. Chondroitin sulphate in the treatment for knee osteoarthritis: a randomized, double-blind, multi center, placebo-controlled trial. Ann Rheum Dis 2006;65(Suppl II):398.
134. Reginster JY, Deroisy R, Rovati LC. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo-controlled clinical trial. Lancet 2001;357:251–6.
135. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giocovelli G, Rovati LC. Glucosamine sulphate use and delay of progression of knee osteoarthritis. Arch Intern Med 2002;162:2113–23.
136. Dougados M, Nguyen M, Berdah L, Mazieres B, Vignon E, Lequesne M. Evaluation of the structure-modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three year, placebo-controlled trial. Evaluation of the chondromodulating effect of diacerein in OA of the hip. Arthritis Rheum 2001;44:2539–47.
137. Fidelix TS, Soares BG, Treviani VF. Diacerein for osteoarthritis. Cochrane Database Syst Rev 2006 Jan 25;(1):CD005117.
138. Pham T, Le Henanff A, Ravaud P, Dieppe P, Paolozzi L, Dougados M. Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD 101, in comparison with diacerein and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis. Ann Rheum Dis 2004;63:1611–7.
139. Kalso E, Edwards JE, Moore RA, McQuay H. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain 2004; 112:372–80.
140. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic non-cancer pain: a meta-analysis of effectiveness and side effects. CMAJ 2006;174:1589–94.
141. Abasolo L, Carmona L. Systematic review: are major opioids effective in the treatment of musculoskeletal pain? Med Clin (Barc) 2007;128: 291–301.
142. Avouac J, Gossec L, Dougados M. Efficacy and safety of opioids for osteoarthritis: a meta-analysis of randomized controlled trials. Osteoarthritis Cartilage 2007;15:957–65.
143. De Craen AJM, Di Giulio G, Lampe-Schoenmaeckers AJEM, Kessels AGH, Kleijnen J. Analgesic efficacy and safety of paracetamol–codeine combinations versus paracetamol alone: a systematic review. BMJ 1996;313:321–5.
144. Von Korff M, Deyo RA. Potent opioids for chronic musculoskeletal pain: flying blind? Pain 2004;109:207–9.
145. Caudill-Slosberg MA, Schwartz LM, Woloshin S. Office visits and analgesic prescriptions for musculoskeletal pain in US: 180 vs. 2000. Pain 2004;109:514–9.
146. Hutchinson K, Moreland AME, Williams AC de C, Weinman J, Horne R. Exploring beliefs and practice of opioid prescribing for persistent non-cancer pain by general practitioners. Eur J Pain 2007;11:93–8.
147. Harris WH, Sledge CB. Total hip and total knee replacement (1). N Engl J Med 1990;323:725–31.
148. Harris WH, Sledge CB. Total hip and total knee replacement (2). N Engl J Med 1990;323:801–7.
149. Ethgen O, Bruyere O, Richy F, dardennes C, Reginster J-Y. Health-related quality of life in total hip and total knee arthroplasty: a qualitative and systematic review of the literature. J Bone Joint Surg Am 2004;86:963–74.
150. Fitzpatrick R, Shortall E, Sculpher M, Murray D, Morris R, Lodge M, *et al*. Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prostheses. Health Technol Assess 1998;2:1–64.
151. Callahan CM, Drake BG, Heck DA, Dittus RS. Patient outcomes following unicompartmental or bicompartmental knee arthroplasty. A meta-analysis. J Arthroplasty 1995;10:141–50.
152. Callahan CM, Drake BG, Heck DA, Dittus RS. Patient outcomes following tricompartmental knee arthroplasty. A meta-analysis. JAMA 1994; 271:1349–57.
153. Soderman P, Malchau H, Herberts P, Zugner R, Regner H, Garellick G. Outcome after total hip arthroplasty: Part II. Disease-specific follow-up and the Swedish National Total Hip Arthroplasty Register. Acta Orthop Scand 2001;72:113–9.
154. Rand JA, Trousdale RT, Ilstrup DM, Harmsen WS. Factors affecting the durability of primary total knee prostheses. J Bone Joint Surg Am 2003;85:259–65.
155. Wiklund I, Romanus B. A comparison of quality of life before and after arthroplasty in patients who had arthrosis of the hip joint. J Bone Joint Surg Am 1991;73:765–9.
156. O'Boyle CA, McGee H, Hickey A, O'malley K, Joyce CR. Individual quality of life in patients undergoing hip replacement. Lancet 1992; 339:1088–91.
157. Nilsdotter AK, Aurell Y, Siosteen AK, Lohmander LS, Roos HP. Radiographic stage of osteoarthritis or sex of the patient does not predict 1-year outcome after total hip arthroplasty. Ann Rheum Dis 2001; 60:228–32.
158. Nilsdotter AK, Petersson IF, Roos EM, Lohmander LS. Predictors of patient-relevant outcome after total hip replacement for osteoarthritis: a prospective study. Ann Rheum Dis 2003;62:923–30.
159. Lingard EA, Katz JN, Wright EA, Sledge CB, Kinemax Outcomes Group. Predicting the outcome of total knee arthroplasty. J Bone Joint Surg Am 2004;86:2179–86.
160. Quintana JM, Arostegui I, Azkarate J, Goenaga JI, Elexpe X, Letona J, *et al*. Evaluation of explicit criteria for total hip replacement. J Clin Epidemiol 2000;53:1200–8.
161. Escobar A, Quintana JM, Arostegui I, Azkarate J, Guenaga JI, Arenaza JC, *et al*. Development of explicit criteria for total knee replacement. Int J Technol Assess Health Care 2003;19:57–70.
162. Park RE, Fink A, Brook RH, Chassin MR, Kahn KL, Merrick NJ, *et al*. Physician ratings of appropriate indications for six medical and surgical procedures. Am J Public Health 1986;76:766–72.
163. Quintana JM, Escobar A, Arostegui I, Bilbao A, Azkarate J, Goenaga JI, *et al*. Health-related quality of life and appropriateness of knee or hip joint replacement. Arch Intern Med 2006;166:220–6.
164. Rasanen P, Paavolainen P, Sintonen H, Koivisto A-M, Blom M, Ryynanen O-P, Chassin MR, Kahn KL, Merrick NJ, *et al*. Effectiveness of hip or knee replacement surgery in terms of quality-adjusted life years and costs. Acta Orthop 2007;78:108–15.
165. Ledingham J, Regan M, Jones A, Doherty M. Radiographic patterns and associations of osteoarthritis of the knee in patients referred to hospital. Ann Rheum Dis 1993;52:520–6.
166. Griffin T, Rowden L, Morgan D, Atkinson R, Woodruff P, Maddern G. Unicompartmental knee arthroplasty for the treatment of unicompartmental osteoarthritis: a systematic study. ANZ J Surg 2007;77:214–21.
167. Weale AE, Murray DW, Newman JH, Ackroyde CE. The length of the patellar tendon after unicompartmental and total knee replacement. J Bone Joint Surg Br 1999;81:790–5.
168. Brand RA. Hip osteotomies: a biomechanical consideration. J Am Acad Orthop Surg 1997;5:282–91.
169. Millis MB, Kim YJ. Rationale for osteotomy and related procedures for hip preservation: a review. Clin Orthop Relat Res 2002;405:108–21.
170. Hasegawa Y, Iwase T, Kitamura S, Yamauchi KK, Sakano S, Iwata H. Eccentric rotational acetabular osteotomy for acetabular dysplasia: follow up of one hundred and thirty two hips for five to ten years. J Bone Joint Surg Am 2002;84:404–10.
171. Siebenrock KA, Leunig M, Ganz R. Periacetabular osteotomy: the Bernese experience. J Bone Joint Surg Am 2001;83:449–55.
172. Koulouvaris P, Stafylas K, Aznaoutoglou C, Zacharis K, Xenakis T. Isolated varus intertrochanteric osteotomy for hip dysplasia in 52 patients: long-term results. Int Orthop (SICOT) 2007;31:193–8.
173. Jackson JP, Waugh W. Tibial osteotomy for osteoarthritis of the knee. J Bone Joint Surg Br 1961;43:746–51.
174. Harris WR, Kostiuk JP. High tibial osteotomy for osteoarthritis of the knee. J Bone Joint Surg Am 1970;52:330–6.
175. Shaw JA, Moulton MJ. High tibial osteotomy: an operation based on a spurious mechanical concept. Am J Orthop 1996;25:429–36.
176. Virolainen P, Aro HT. High tibial osteotomy for the treatment of osteoarthritis of the knee: a review of the literature and a meta-analysis of follow-up studies. Arch Orthop Trauma Surg 2004;124:258–61.
177. Insall JN, Dorr D, Scott RD, Scott WN. Rationale of the knee society clinical rating system. Clin Orthop 1999;248:13–4.
178. Burman MS, Finkelstein H, Mayer L. Arthroscopy of the knee joint. J Bone Joint Surg Am 1934;16:255–68.
179. Rand JA. Arthroscopic management of degenerative meniscus tears in patients with degenerative arthritis. Arthroscopy 1985;1:253–8.
180. Baumgaetner MR, Cannon WD Jr, Vittori JM, Schmidt ES, Maurer RC. Arthroscopic debridement of the arthritic knee. Clin Orthop Relat Res 1990;253:197–202.
181. Mclaren AC, Blokker CP, Fowler PJ, Roth JN, Rock MG. Arthroscopic debridement of the knee for osteoarthrosis. Can J Surg 1991;34: 595–8.
182. Ogilvie-Harris DJ, Fitzialos DP. Arthroscopic management of the degenerative knee. Arthroscopy 1991;7:161–7.
183. Yang SS, Nisonson B. Arthroscopic surgery of the knee in the geriatric patient. Clin Orthop Relat Res 1995;316:50–8.
184. Day B. The indications for arthroscopic debridement for osteoarthritis of the knee. Orthop Clin North Am 2005;36:413–7.
185. Hubbard MJ. Articular debridement versus washout for degeneration of the medial femoral condyle. J Bone Joint Surg Br 1996;78:217–9.
186. Merchan EC, Galindo E. Arthroscope-guided surgery versus nonoperative treatment for limited degenerative osteoarthritis of the femorotibial joint over 50 years of age: a prospective comparative study. Arthroscopy 1993;9:663–7.
187. Ike RW, Arnold WJ, Rothschild EW, Shaw HL. Tidal irrigation versus conservative medical management in patients with osteoarthritis of

the knee: a prospective randomized study. Tidal Irrigation Cooperating Group. J Rheumatol 1992;19:772–9.
188. Livesley PJ, Doherty M, Needoff M, Moulton A. Arthroscopic lavage of osteoarthritic knees. J Bone Joint Surg Br 1991;73:922–6.
189. Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykenall DH, *et al*. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002;347:81–8.
190. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med 2001;344:1594–602.
191. Chambers K, Schulzer M, Sobelov B. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. Arthroscopy 2002;18:683–7.
192. Siparsky P, Ryzewicz M, Peterson B, Bartz R. Arthroscopic treatment of osteoarthritis of the knee: are there any evidence-based indications? Clin Orthop Relat Res 2007;455:107–12.
193. Conway JD, Mont MA, Bezwada HP. Arthrodesis of the knee. J Bone Joint Surg Am 2004;86:835–48.
194. Wasielewski RC, Barden RM, Rosenberg AG. Results of different surgical procedures on total knee arthroplasty infections. J Arthroplasty 1996;11:931–8.
195. Wilde AH, Stearns KL. Intramedullary fixation for arthrodesis of the knee after infected total knee arthroplasty. Clin Orthop Relat Res 1989;24:887–92.
196. Behr JT, Chmell SJ, Schwartz CM. Knee arthrodesis for failed knee arthroplasty. Arch Surg 1985;120:350–4.
197. Hak DJ, Lieberman JR, Finerman GA. Single plane and biplane external fixators for knee arthrodesis. Clin Orthop Relat Res 1995;316:134–44.
198. Knutson K, Hovelius L, Lindstrand A, Lidgren L. Arthrodesis after failed knee arthroplasty. A nationwide multicenter investigation of 91 cases. Clin Orthop Relat Res 1984;191:202–11.
199. Damron TA, McBeath AA. Arthrodesis following failed total knee arthroplasty: comprehensive review and meta-analysis of recent literature. Orthopedics 1995;18:361–8.
200. Benson ER, Resine ST, Lewis CG. Functional outcome of arthrodesis for failed total knee arthroplasty. Orthopedics 1998;21:875–9.
201. Altman RD, Hochberg MC, Moskowitz RW, Schnitzer TJ. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum 2000;43:1905–15.
202. Pencharz JN, Grigoriadis E, Jansz GF, Bombardier C. A critical appraisal of clinical practice guidelines for the treatment of lower-limb osteoarthritis. Arthritis Res 2002;4:36–44 (Review, 33 refs).
203. Roddy E, Doherty M. Guidelines for management of osteoarthritis published by the American College of Rheumatology and the European League Against Rheumatism: why are they so different? Rheum Dis Clin North Am 2003;29:717–31.
204. Wegman A, van der WD, van Tulder M, Stalman W, de Vries T. Nonsteroidal antiinflammatory drugs or acetaminophen for osteoarthritis of the hip or knee? A systematic review of evidence and guidelines. J Rheumatol 2004;31:344–54.
205. Scottish Intercollegiate Guidelines Network. SIGN 50; A Guideline Developers' Handbook. Edinburgh: SIGN. Available from: http://www.sign.ac.uk/guidelines/fulltext/50/section7.html; 2001.
206. Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ, Evidence-Based Medicine Working Group. Users' guides to the medical literature. IX. A method for grading health care recommendations. JAMA 1995;274:1800–4 (Erratum appears in JAMA 1996 Apr 24; 275(16):1232).
207. United States Department of Health and Human Services Agency for Health Care Policy and Research. Acute Pain Management; Operative or Medical Procedures and Trauma. Rockville, MD: AHCPR 1993. p. 107 (Clinical practice guideline no. 1, AHCPR publication no. 92-0023).
208. Hadorn DC, Baker D, Hodges JS, Hicks N. Rating and quality of evidence for clinical practice guidelines. J Clin Epidemiol 1996;49:749–54.
209. Harbour R, Miller J. A new system for grading recommendations in evidence-based guidelines. BMJ 2001;323:334–6.
210. Pendleton A, Arden N, Dougados M, Doherty M, Bannwarth B, Bijlsma JW, *et al*. EULAR recommendations for the management of knee osteoarthritis; report of a task force of the Standing Committee for International Clinical Studies Including Clinical Trials (ESCISIT). Ann Rheum Dis 2000;59:936–44.
211. Roddy E, Zhang W, Doherty M, Arden NK, Barlow J, Birrell F, *et al*. Evidence-based clinical guidelines: a new system to better determine true strength of recommendation. J Eval Clin Pract 2005;12:347–52.
212. Glass GV. Primary, secondary, and meta-analysis of research. Educ Res 1976;3:3–8.
213. Dreinhofer K, Stucki G, Ewert T, Huber E, Ebenbichier G, Gutenbrunner C, *et al*. ICF core sets for osteoarthritis. J Rehabil Med 2004;(Suppl 44):75–80.
214. Boonen A, Rasker JJ, Stucki G. The international classification for functioning, disability and health. Clin Rheumatol 2007;26:1803–8.
215. WHO. WHO Business Plan for Classifications. Building Blocks of Health Information. Report no. v. 1.0. Geneva: World Health Organisation 2005.
216. Rintelen B, Neumann K, Leeb BF. A meta-analysis of controlled clinical studies with diacerein in the treatment of osteoarthritis. Arch Intern Med 2006;166:1899–906.
217. Krueger K, Lino L, Dore R, Radominski S, Zhang Y, Kaur A, *et al*. Gastrointestinal tolerability of etoricoxib in rheumatoid arthritis patients: results of the etoricoxib vs diclofenac sodium gastrointestinal tolerability and effectiveness trial (EDGE-II). Ann Rheum Dis 2007 Oct 27 (Epub ahead of print).
218. Nielsen OH, Ainsworth M, Csillag C, Rask-Madsen J. Systematic review: coxibs, non-steroidal anti-inflammatory drugs or no cyclooxygenase inhibitors in gastroenterological high-risk patients? Aliment Pharmacol Ther 2006;23:27–33.
219. Scott PA, Kingsley GH, Smith CM, Choy EH, Scott DL. Non-steroidal anti-inflammatory drugs and myocardial infarctions: comparative systematic review of evidence from observational studies and randomised controlled trials. Ann Rheum Dis 2007;66:1296–304.
220. Lequesne M, Berdah L, Gerentes I. Efficacy and tolerance of diacerhein in the treatment of gonarthrosis and coxarthrosis. Rev Prat 1998;48(17 Suppl):S31–5.
221. Nguyen M, Dougados M, Berdah L, Amor B. Diacerein in the treatment of osteoarthritis of the hip. Arthritis Rheum 1994;37:529–36.
222. Pelletier J-P, Yaron M, Haraoui B, Cohen P, Nahir MA, Choquette D, *et al*. Efficacy and safety of diacerein in osteoarthritis of the knee: a double-blind, placebo-controlled trial. Arthritis Rheum 2000;43:2339–48.
223. Louthrenoo W, Nilganuwong S, Aksaranugraha S, Asananatanabodee P, Saengnipanthkul S, Thai Study Group. The efficacy, safety, and carry over effect of diacerein in the treatment of painful knee osteoarthritis: a randomised, double-blind, NSAID-controlled trial. Osteoarthritis Cartilage 2007;15:605–14.
224. Hunter DJ, Wise B. Review: diacerein is more effective than placebo and is as effective as NSAIDs for knee and hip osteoarthritis. Evid Based Med 2007;12:74; doi:10.1136/ebm.12.3.74.