OsteoArthritis and Cartilage (2007) **15,** 981–1000

doi:10.1016/j.joca.2007.06.014

Osteoarthritis and Cartilage

International Cartilage Repair Society

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

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

W. Zhang Ph.D., R. W. Moskowitz M.D., G. Nuki M.B., F.R.C.P.*, S. Abramson M.D., R. D. Altman M.D., N. Arden M.Sc., M.R.C.P., S. Bierma-Zeinstra Ph.D., K. D. Brandt M.D., P. Croft M.D., M. Doherty M.D., F.R.C.P., M. Dougados M.D., M. Hochberg M.D., D. J. Hunter M.B.B.S., Ph.D., K. Kwoh M.D., L. S. Lohmander M.D., Ph.D. and P. Tugwell M.D.

University of Edinburgh, Osteoarticular Research Group, The Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ, United Kingdom

Summary

Purpose: As a prelude to developing updated, evidence-based, international consensus recommendations for the management of hip and knee osteoarthritis (OA), the Osteoarthritis Research Society International (OARSI) Treatment Guidelines Committee undertook a critical appraisal of published guidelines and a systematic review (SR) of more recent evidence for relevant therapies.

Methods: Sixteen experts from four medical disciplines (primary care two, rheumatology 11, orthopaedics one and evidence-based medicine two), two continents and six countries (USA, UK, France, Netherlands, Sweden and Canada) formed the guidelines development team. Three additional experts were invited to take part in the critical appraisal of existing guidelines in languages other than English. MEDLINE, EMBASE, Science Citation Index, CINAHL, AMED, Cochrane Library, seven Guidelines Websites and Google were searched systematically to identify guidelines for the management of hip and/or knee OA. Guidelines which met the inclusion/exclusion criteria were assigned to four groups of four appraisers. The quality of the guidelines was assessed using the AGREE (Appraisal of Guidelines for Research and Evaluation) instrument 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 to support each recommendation was extracted. Evidence for each treatment modality was updated from the date of the last SR in January 2002 to January 2006. The quality of evidence was evaluated using the Oxman and Guyatt, and Jadad scales for SRs and randomised controlled trials (RCTs), respectively. Where possible, effect size (ES), number needed to treat, relative risk (RR) or odds ratio and cost per quality-adjusted life year gained (QALY) were estimated.

Results: Twenty-three of 1462 guidelines or consensus statements retrieved from the literature search met the inclusion/exclusion criteria. Six were predominantly based on expert opinion, five were primarily evidence based and 12 were based on both. Overall quality scores were 28%, 41% and 51% for opinion-based, evidence-based and hybrid guidelines, respectively ($P = 0.001$). Scores for aspects of quality varied from 18% for applicability to 67% for scope. Thirteen guidelines had been developed for specific care settings including five for primary care (e.g., Prodigy Guidance), three for rheumatology (e.g., European League against Rheumatism recommendations), three for physiotherapy (e.g., Dutch clinical practice guidelines for physical therapy) and two for orthopaedics (e.g., National Institutes of Health consensus guidelines), whereas 10 did not specify the target users (e.g., Ontario guidelines for optimal therapy). Whilst 14 guidelines did not separate hip and knee, eight were specific for knee but only one for hip. Fifty-one different treatment modalities were addressed by these guidelines, but only 20 were universally recommended. Evidence to support these modalities ranged from Ia (meta-analysis/SR of RCTs) to IV (expert opinion). The efficacy of some modalities of therapy was confirmed by the results of RCTs published between January 2002 and 2006. These included exercise (strengthening ES 0.32, 95% confidence interval (CI) 0.23, 0.42, aerobic ES 0.52, 95% CI 0.34, 0.70 and water-based ES 0.25, 95% CI 0.02, 0.47) and nonsteroidal anti-inflammatory drugs (NSAIDs) (ES 0.32, 95% CI 0.24, 0.39). Examples of other treatment modalities where recent trials failed to confirm efficacy included ultrasound (ES 0.06, 95% CI −0.39, 0.52), massage (ES 0.10, 95% CI −0.23, 0.43) and heat/ice therapy (ES 0.69, 95% CI −0.07, 1.45). The updated evidence on adverse effects also varied from treatment to treatment. For example, while the evidence for gastrointestinal (GI) toxicity of non-selective NSAIDs (RR = 5.36, 95% CI 1.79, 16.10) and for increased risk of myocardial infarction associated with rofecoxib (RR = 2.24, 95% CI 1.24, 4.02) were reinforced, evidence for other potential drug related adverse events such as GI toxicity with acetaminophen or myocardial infarction with celecoxib remained inconclusive.

Conclusion: Twenty-three guidelines have been developed for the treatment of hip and/or knee OA, based on opinion alone, research evidence or both. Twenty of 51 modalities of therapy are universally recommended by these guidelines. Although this suggests that a core set of recommendations for treatment exists, critical appraisal shows that the overall quality of existing guidelines is sub-optimal, and consensus recommendations are not always supported by the best available evidence. Guidelines of optimal quality are most likely to be achieved by combining research evidence with expert consensus and by paying due attention to issues such as editorial independence, stakeholder involvement and applicability. This review of existing guidelines provides support for the development of new guidelines cognisant of the limitations in existing guidelines. Recommendations should be revised regularly following SR of new research evidence as this becomes available.

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

*Address correspondence and reprint requests to: Prof. George Nuki, Emeritus Professor of Rheumatology, University of Edinburgh, Osteoarticular Research Group, The Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ, United Kingdom. E-mail: g.nuki@ed.ac.uk
Received 16 June 2007; revision accepted 16 June 2007.

Introduction

Osteoarthritis (OA) is the most common form of arthritis and a major contributor to functional impairment and reduced independence in older adults[1]. The hip and knee are the principal large joints affected by OA. Although estimates of the prevalence of hip and knee OA vary considerably depending on whether the disease is defined by both symptoms and radiographic changes, or by radiographic criteria alone, knee OA is more prevalent[2–6] than hip OA[7–11]. Overall, as many as 40% of those aged over 65 in the community may have symptomatic OA of the knee or hip[12,13]. Current treatment strategies with both non-pharmacologic and pharmacologic therapies aim to reduce pain, physical disability and handicap, and some of them attempt to limit structural deterioration in affected joints. Surgical therapies are available for patients who fail to respond to more conservative measures[14,15]. In recent years, both the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) have developed recommendations to optimise the treatment of hip and/or knee OA based on a variable combination of expert consensus and systematic review (SR) of research evidence[16–18]. Although these guidelines are used by physicians, funding authorities and government agencies in order to try and improve the quality of care of patients with knee and hip OA, they have been criticised for lack of methodological rigour, stakeholder involvement and applicability[19–21]; and the recommendations for certain modalities of treatment that they contain may require modification following publication of more recent randomised controlled trials (RCTs) and meta-analyses (MAs). The Osteoarthritis Research Society International (OARSI) therefore appointed an international, multidisciplinary committee of experts in September 2005 with the remit of producing up to date, evidence-based, globally relevant consensus recommendations for the management of hip and/or knee OA in 2007. The committee undertook a critical appraisal of existing evidence-based and consensus guidelines and an SR of the current research evidence; as a prelude to developing consensus recommendations following a Delphi exercise. This paper reports the results of the critical appraisal of existing treatment guidelines and the SR of the more recent research evidence. The purpose of this study was to identify the evidence available, assess its quality and to use this knowledge to develop a new guideline. Part II of this document: "The OARSI evidence-based consensus recommendations for the treatment of OA of the hip and knee" will be published separately in *Osteoarthritis and Cartilage*.

Methods

PARTICIPANTS

The guideline development committee was composed of 16 experts from four medical disciplines (primary care two, rheumatology 11, orthopaedics one, and evidence-based medicine two) and six countries in Europe and North America (France, Netherlands, Sweden, UK, Canada and the USA). All members of this guideline development team participated in: (1) a critical appraisal of existing treatment guidelines; (2) a Delphi exercise to generate consensus recommendations; and (3) an exercise to grade the strength of recommendation for all modalities of therapy recommended. Three additional experts were invited to undertake critical appraisals of existing guidelines in languages other than English.

CRITICAL APPRAISAL OF EXISTING GUIDELINES

Systematic literature search

A systematic literature search for existing guidelines for the management of hip and/or knee OA published in any language between 1945 and October 2005 was undertaken using MEDLINE (1966–), EMBASE (1980–), CINAHL (1980–), AMED (1985–) and the Science Citation Index (1945–). The search strategy consisted of two basic components: guidelines in any term (e.g., guidelines, recommendations, standards, algorism, or expert consensus, etc.) and hip or knee OA in any possible terms in the databases (Appendix 1). In addition, Google (the first 100 hits) and seven Guideline Websites were searched, including the National Guideline Clearinghouse http://www.guidelines.gov/, Primary Care Clinical Practice Guidelines http://medicine.ucsf.edu/resources/guidelines/, the Scottish Intercollegiate Guidelines Network http://www.sign.ac.uk/, the Canadian Medical Association Infobase for Clinical Practice Guidelines http://mdm.ca/cpgsnew/cpgs/index.asp, the Guidelines International Network http://www.g-i-n.net/, Evidence Based Medicine Guidelines http://www.ebm-guidelines.com/, and the National Institute for Clinical Excellence http://www.nice.org.uk/.

Inclusion/exclusion criteria

Guidelines developed for the management of hip and/or knee OA using consensus or evidence-based methods were included. The latest version was included if the guidelines had been updated. Guidelines developed for OA in other joints or for aspects of OA other than treatment were excluded, as were narrative reviews, commentaries and appraisals of implementation.

Quality and content assessment

English language guidelines were randomly assigned to three groups of four committee members for appraisal of quality and content. Three guidelines published in German and Dutch were appraised by three additional experts who were fluent in these languages. The quality of the guidelines was assessed using the AGREE instrument[22], in which 23 criteria in seven domains are evaluated. These include the scope and purpose of the guidelines, stakeholder participation, methodological rigour, clarity, applicability, editorial independence and overall quality. The content was extracted using a comprehensive reference list of treatment modalities. Each appraiser scored the guidelines independently and results were collected and analysed by the lead investigator (WZ) and the co-chairs (GN and RM), who did not take part in the assessment.

Data analyses

The appraisers' scores from each group were expressed as standardised domain scores on a percentage scale (0–100%)[22]. Guidelines were categorised according to the methods (expert opinion based, research evidence based or both), the target users to whom they were directed (primary care, rheumatology, physiotherapy or orthopaedics), the scope of the recommendations (general and specific treatments) and the joints for which the guidelines were applicable (hip, knee, or hip and knee). Quality scores were compared between groups using an analysis of variance (ANOVA). Agreement (%) between guidelines was calculated by

$$\text{Agreement}\ (\%) = \frac{N_r}{N_a} \times 100\%,$$

where N_r is the number of guidelines recommending the modality and N_a indicates number of guidelines addressing the modality. Levels of evidence were examined and for each modality, the best available evidence was selected according to the evidence hierarchy (Table I)[23].

SR OF RECENT EVIDENCE

Systematic literature search

A systematic search of the literature published between 31 January 2002 and 31 January 2006 was undertaken using MEDLINE, EMBASE, CINHAL, AMED, the Science Citation Index and the Cochrane Library databases. Research evidence prior to January 2002 was not sought systematically as this was available from the systematic literature review conducted by EULAR[17]. Separate searches for research evidence for each treatment modality were undertaken. Each search was conducted sequentially according to the evidence hierarchy (SRs/MAs, followed by RCTs/controlled trials (CTs), quasi-experimental and uncontrolled studies) (Table II)[23]. An example of how this search strategy was employed to obtain the best available research evidence for the efficacy of acetaminophen (paracetamol) is shown in Appendix 2. The same strategy was used for searching MEDLINE, EMBASE, CINHAL and AMED. For the Science Citation Index, however, a key word search was used and all possible terms and combinations of terms were tied in order to obtain relevant citations. Medical subject heading searches (MeSH) were used for all databases and key word searches were used if a MeSH search was not available. All MeSH search terms were exploded. The reference lists of SRs were examined and any additional studies meeting the inclusion/exclusion criteria were included.

The search in the Cochrane Library included MeSH searches of Cochrane reviews, abstracts of Quality Assessed Systematic Reviews, the Cochrane Controlled Trial Register, the National Health Service (NHS) Economic Evaluation Databases, the Health Technology Assessment Database and the NHS Economic Evaluation Bibliography Details Only. In addition, a comprehensive search for all articles including the term OA regardless of treatment was undertaken.

Inclusion/exclusion criteria

Only studies with clinical outcomes for hip and/or knee OA were included. The main focus was on SRs/MAs, RCTs/CTs, uncontrolled trials, cohort studies, case–control studies, cross-sectional studies and economic evaluations. Studies of OA at other sites such as the hand or spine, and other chronic joint diseases were excluded, apart from studies in which adverse effects of relevant pharmacologic treatments were being investigated as a primary outcome. Case reports, animal studies, non-clinical outcome studies, narrative review articles, commentaries and guidelines were excluded.

Table I
Evidence hierarchy[23]

Ia	MA of RCTs
Ib	RCT
IIa	Controlled study without randomisation
IIb	Quasi-experimental study
III	Non-experimental descriptive studies, such as comparative, correlation, and case–control studies
IV	Expert committee reports or opinion or clinical experience of respected authorities, or both

Table II
23 existing guidelines for the management of hip and/or knee OA

	N	Guidelines
Type of guidelines		
Opinion based	6	Royal College of Physicians, etc.
Evidence based	5	Prodigy Guidance, etc.
Both	12	EULAR, etc.
Topic		
General	13	ACR, EULAR, etc.
Specific	10	MOVE, Canadian NSAIDs, etc.
Target joint(s)		
Hip	1	EULAR
Knee	8	German, etc.
Both	14	ACR, etc.
Target users		
Primary care	5	Prodigy Guidance, etc.
Rheumatology	3	EULAR, etc.
Physiotherapy	3	Dutch physiotherapy, etc.
Orthopaedics	2	NIH consensus, etc.
Not specified	10	Ontario, ICSI, etc.
Language		
English	21	ACR, EULAR, etc.
Others	2	German, Malay, etc.

The efficacy of any modality of treatment was determined by using the best available evidence. For example, when the efficacy of an intervention could be confirmed by category Ia evidence (MA/SR of RCTs), then studies lower in the evidence hierarchy such as individual RCTs (category Ib) were not reviewed (Table I). If there was more than one study in the same evidence level (e.g., four SRs for NSAIDs), the study with the best quality score was used. Information concerning side effects was obtained from both RCTs and observational studies. While the efficacy of each therapeutic intervention was assessed separately for hip and knee OA, side effects were evaluated for each intervention regardless of the OA therapy and the target joint. For determination of cost effectiveness, only cost-utility analyses were included.

Quality assessment

The quality of SR/MAs was assessed using the Oxman and Guyatt checklist[24] and the quality of RCTs was evaluated using the Jadad method[25]. All quality scores were converted into percentages of the maximum score attainable. Quality assessments were not undertaken for other types of study designs, such as cohort or case–control studies. For cost-utility analysis, study perspective, comparator, time horizon, discounting, modelling and uncertainty were evaluated.

Outcome measures

Efficacy. Effect sizes (ESs) and 95% confidence intervals (CIs) compared with placebo or active control were calculated for continuous outcomes such as reduction of pain from baseline or improvement in function[26]. ES is the standard mean difference, i.e., the mean difference between

a treatment and a control group divided by the standard deviation of the difference. It is expressed as a number without units and can be used for comparisons across all interventions. From the clinical standpoint ESs of 0.2 are considered small and 0.5 moderate, while an ES $>$ 0.8 indicates a large clinical effect[27]. Statistical pooling was undertaken, as appropriate, when SRs were not available[28]. For dichotomous data, such as the percentage of patients with moderate to excellent (or more than 50%) pain relief or symptomatic improvement, the number needed to treat (NNT) was estimated[29]. The NNT is the estimated number of patients who need to be treated to achieve the target effect. Thus the smaller the NNT the better the treatment effect. The 95% CI for the NNT was calculated using Altman's method[30].

Side effects. The relative risk (RR) of side effects was calculated from RCTs or cohort studies for the *incident risk*, and from cross-sectional studies for *prevalent risk*. Odds ratios (ORs) were calculated from case–control studies[31]. Both RR and OR provide information on how many times more likely (or less likely) it is that a subject who is exposed to a treatment modality will have an adverse event, when compared with a subject who is not exposed. An RR/OR = 1 indicates no increased risk, whereas an RR/OR $>$ 1 or $<$1 indicates increased or decreased risk, respectively.

Cost effectiveness. Only cost-utility analysis was reviewed, where cost per quality-adjusted life years (QALYs) gained was used. Costs were converted into US dollars and values were discounted by 5% per year from the year in which the study was published until 2006.

Data were extracted by two investigators (WZ and a research assistant, Jane Robertson). A customised form was used for data extraction and quality assessment. Any discrepancies were discussed and agreed between the extractors prior to analysis. The data from the non-English language studies were extracted by assessors with good understanding of the languages concerned.

Results

QUALITY AND CONTENTS OF EXISTING GUIDELINES

The systematic literature search yielded 1462 citations (MEDLINE 276, EMBASE 413, CINAHL 81, AMED 27 and SCI 553, Google and Guidelines Websites 112). Of these, 23 met the inclusion and exclusion criteria specified[16–18,32–51]. Six guidelines were predominantly based on opinion, five primarily based on evidence and 12 based on both (Table II). Whilst the majority of the guidelines[14] did not separate hip and knee, eight were specific for knee but only one for hip OA. Thirteen guidelines had been developed for specific care settings (five for primary care, three for rheumatology, three for physiotherapy and two for orthopaedics); but 10 did not specify target users.

Scores for overall quality of guidelines were 28%, 41% and 51% for opinion-based, evidence-based and hybrid guidelines, respectively ($P < 0.001$) (Fig. 1). Scores for different quality criteria varied but apart from applicability, opinion-based guidelines tended to have lower scores (Table III).

Fifty-one treatment modalities were addressed in the 23 guidelines. Twenty of these modalities were recommended by all (100%) of the guidelines in which they were addressed (Table IV), but the strength of agreement for any modality appeared to be related to the number of guidelines that addressed that modality. For example, while regular telephone contact and knee fusion were recommended in 100% of the guidelines in which these modalities of therapy were considered, this was actually in only two guidelines for each modality. By contrast, although weight loss was not universally recommended, it was in fact recommended in 13/14 of the guidelines where this modality was considered.

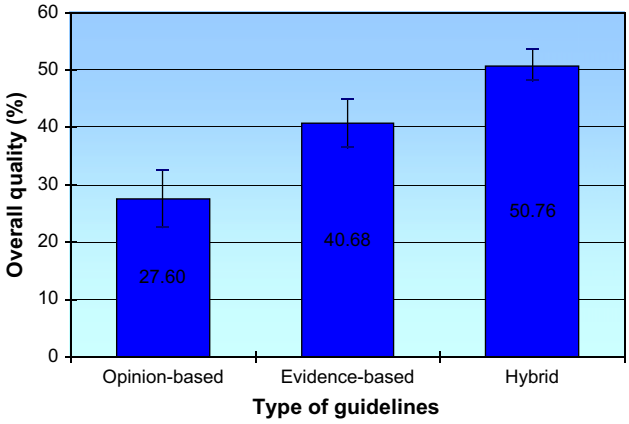

Fig. 1. Overall quality score of guidelines (mean ± S.E.M.).

Evidence to support recommendations ranged from Ia (SR of RCTs) to IV (expert opinion), and did not necessarily reflect the extent of agreement (Table IV). For example, while canes/sticks, total joint replacement and osteotomy were not supported by RCTs, they were still universally recommended in the guidelines which addressed them. In contrast, despite evidence from SRs of RCTs for the efficacy of chondroitin sulphate and ultrasound, they were recommended by $<$50% of the guidelines in which these modalities were considered (Table IV).

RECENT EVIDENCE

The results of the SR of research papers published between January 2002 and January 2006 are shown in Table V.

Efficacy

With the exception of combination therapy, the use of a cane/stick and referral, all the non-pharmacologic and pharmacologic therapies recommended universally by existing guidelines were supported by recent SRs of RCTs (Ia) or RCTs (Ib) published after 2002. By contrast, there were no placebo controlled trials of surgical modalities of treatment such as total joint replacement and osteotomy, and supporting evidence came from uncontrolled or non-experimental observational studies (Table V). Overall quality scores for evidence ranged between 40% and 100% but 24/40 studies (60%) scored 100% (Table V).

The ES for pain relief scores varied from small (e.g., education ES = 0.06, 95% CI 0.02, 0.10) to moderate (e.g., aerobic exercise ES = 0.52, 95% CI 0.34, 0.70). No modality of therapy had an ES as high as 0.80 – the accepted criterion for a large clinical effect[27] (Fig. 2). ESs for pain relief score with oral analgesics such as acetaminophen (ES = 0.21 95% CI 0.02, 0.41) and NSAIDs (ES = 0.32, 95% CI 0.24, 0.39) were small (Fig. 3 and Table V).

Table III
Quality scores (%)

	Mean ± S.E.M.			
	Opinion based	Evidence based	Hybrid	*P*
n	6	5	12	
Scope	45.90 ± 7.30	79.26 ± 8.00	74.23 ± 5.37	0.007
Stakeholder	17.36 ± 6.12	30.56 ± 8.62	37.27 ± 4.42	0.058
Rigour	14.68 ± 5.29	28.57 ± 11.39	57.80 ± 5.57	<0.001
Clarity	42.66 ± 4.60	68.19 ± 10.35	63.14 ± 10.35	0.026
Applicability	15.48 ± 6.47	12.78 ± 4.78	21.53 ± 2.14	0.313
Editorial	19.25 ± 6.30	24.72 ± 7.84	50.58 ± 7.33	0.013
Overall	26.09 ± 4.48	40.68 ± 4.24	50.76 ± 2.70	<0.001

S.E.M.: standard error of mean.

ESs for improvement in function were also generally small, and very similar to those for pain relief, for a number of modalities of non-pharmacological therapies (Table V). However, the ES for improvement in function for >10% weight reduction was 0.69 (95% CI 0.24, 1.14) compared with the ES for pain relief (0.13, 95% CI −0.12, 0.38). ESs for reduction in stiffness were also available for a few modalities of treatment (Table V).

Some studies provided data, which allowed calculation of NNTs. For example, weight reduction (>10%) was associated with an NNT of three (95% CI 2, 9), i.e., one in three patients with knee OA who achieved this loss of weight would have more than 50% reduction in the total Western Ontario and McMaster Universities (WOMAC) Osteoarthritis index[52]. The NNT for topical NSAIDs was also three (95% CI 2, 4), indicating that one in three patients with pain associated with knee OA treated with a topical NSAID would be expected to experience moderate to excellent pain relief[53].

In general, non-pharmacologic therapies had numerically smaller ES (ES = 0.25, 95% CI 0.16, 0.34) than pharmacological therapies (ES = 0.39, 95% CI 0.31, 0.47) (Figs. 2 and 3). Among surgical treatments, ES could only be calculated for arthroscopic lavage and debridement. An SR of four RCTs showed that arthroscopic joint lavage and debridement were no more effective than placebo[54]. One placebo controlled RCT (with a quality score of 100%) included in this review demonstrated that the ES for arthroscopic lavage and debridement vs placebo were 0.09 (95% CI −0.27, 0.44) and −0.01 (95% CI −0.37, 0.35), respectively[55]. Similar results were obtained for improvement in function (Table V). Although there are no placebo controlled

Table IV
*Agreement and level of evidence for modalities of therapy recommended by existing guidelines**

Level of evidence†	Agreement (number of guidelines recommending the modality/total number of guidelines addressing the modality)				
	<25%	25%–	50%–	75%–	100%
Ia	Ultrasound (1/5)	Chondroitin sulphate (2/7)	Heat/ice (7/10) Glucosamine sulphate (6/10) NSAID + H2-blockers (5/8)	NSAIDs (15/16) Insole (12/13)‡ Braces (8/9)‡ Topical capsaicin (8/9)‡ IA HA (8/9)‡ IA steroid (11/13)‡ TENS (8/10) Topical NSAIDs (7/9)‡	Aerobic exercise (21/21) Strengthening exercise (21/21) Acetaminophen (16/16) Education (15/15) COX-2 inhibitors (11/11) Opioid (9/9) Self-management (8/8) Water-based exercise (8/8) NSAID + PPI (8/8) NSAID + misoprostol (8/8) Telephone (2/2)
Ib	Laser (1/6) Electrotherapy/EMG (1/8)	Nutrients (1/3)	Acupuncture (5/8) Massage (1/2) Diacerhein (1/2)	Weight loss (13/14) Patellar tape (12/13) Avocado soybean unsaponifiables (3/4)	Combination therapy (12/12) Joint lavage (3/3) Herbs (2/2)
III					TJR (14/14) Osteotomy (10/10)
IV	Oral steroid (0/2)			Arthroscopic debridement (5/6)	Cane/stick (11/11)‡ Referral (5/5) Knee fusion (2/2)‡ Knee aspiration (2/2)‡

TENS = Transcutaneous Electrical Nerve Stimulation; EMG = Electromyography; TJR = Total Joint Replacement.

*Modalities were grouped according to strength of agreement and level of evidence. Modalities addressed by only one guideline were not included, such as radiotherapy, sauna/spa, gait aid, topical rubefacients, oestrogen, patellar resurfacing, and anti-depressants. Modalities not directly related to the treatment such as consideration of risk factors, clinical features, etc. were excluded.

†Level of evidence: Ia = SR of RCTs; Ib = RCT, IIa = CT; IIb = quasi-experiment; III = cohort/case–control study; and IV = expert opinion. Only the highest level of evidence has been selected for each modality.

‡Specific for knee OA.

Table V
Recent evidence for efficacy of treatment of hip and knee OA

Modality	Joint	QoS (%)	LoE	Recent evidence (2002–)			
				ES_{pain} (95% CI)	$ES_{function}$ (95% CI)	$ES_{stiffness}$ (95% CI)	NNT (95% CI)
General							
Risk factors							
Clinical phase							
Combination therapy							
Non-pharmacological							
Self-management	Both	100	Ia	0.06 (0.02, 0.10)[89]	0.06 (0.02, 0.10)[89]		
Telephone	Both	100	Ia	0.12 (0.00, 0.24)[90]	0.07 (0.00, 0.15)[90]		
Education	Both	100	Ia	0.06 (0.02, 0.10)[89]	0.06 (0.02, 0.10)[89]		
Strengthening	Knee	100	Ia	0.32 (0.23, 0.42)[91]	0.32 (0.23, 0.41)[91]		
Aerobic	Knee	100	Ia	0.52 (0.34, 0.70)[91]	0.46 (0.25, 0.67)[91]		
Water-based exercise	Both	60	Ib	0.25 (0.02, 0.47)[64,92]	0.23 (0.00, 0.45)[64]	0.17 (−0.05, 0.39)[64]	
Balneotherapy	Knee	75	Ia				NS[93]
Spa/sauna	Both	75	Ib	0.46 (0.17, 0.75)[94]			NS
Weight reduction	Knee	40	Ib	0.13 (−0.12, 0.38)[52,95]	0.69 (0.24, 1.14)[52]	0.36 (−0.08, 0.80)[52]	3 (2, 9)[52]
Nutrients (e.g., SAM-e)	Knee	100	Ia	0.22 (−0.25, 0.69)[96]	0.31 (0.10, 0.52)[96]		
TENS	Both	75	Ia				2 (1, 5)[97]
Laser	Both	100	Ia				4 (2, 17)[98]
Ultrasound	Both	50	Ia	0.06 (−0.39, 0.52)[99]			
Radiotherapy	Both	50	IIb	Similar effects between OA and RA from an MA of uncontrolled trial[100]			
Heat/ice	Knee	75	Ia	0.69 (−0.07, 1.45)[101]	1.03 (0.44, 1.62)[101] for quads strength; 1.13 (0.54, 1.73)[101] for flexion	0.83(−0.03, 1.69)[101] for swelling	
Massage	Knee	40	Ib	0.10 (−0.23, 0.43)[102]			
Acupuncture	Knee	40	Ib	0.51 (0.23, 0.79)[63]	0.51 (0.23, 0.79)[63]	0.41 (0.13, 0.69)[63]	4 (3, 9)[63]
Insoles	Knee	100	Ia	No different between type of insoles, no placebo/usual care comparisons[103]			
Cane/stick							
Joint protection (braces)	Knee	100	Ia	More benefits with a knee brace than a neoprene sleeve[103]			
Electrotherapy/EMG	Knee	75		0.77 (0.36, 1.17)[104]			
Referral							
Pharmacological							
Acetaminophen	Both	100	Ia	0.21 (0.02, 0.41)[105]			2 (1, 2)[106]
NSAIDs	Both	100	Ia	0.32 (0.24, 0.39)[107]			
NSAIDs + PPIs	OA/RA	100	Ia				
NSAIDs + H2 blockers	OA/RA	100	Ia				
NSAIDs + misoprostol	OA/RA	100	Ia				
COX-2 inhibitors	Both	100	Ia	0.44 (0.33, 0.55)[108] (exc Deek's for OA/RA)			
Topical NSAIDs	Knee	100	Ia	0.41 (0.22, 0.59)[53]	0.36 (0.24, 0.48)[53]	0.49 (0.17, 0.80)[53]	3 (2, 4)[53]
Topical capsaicin	Knee	75	Ia				4 (3, 5)[109]
Opioids	Both	50	Ia				
Other narcotics							
Oral steroid							
IA Corticosteroid	Knee	100	Ia	0.72 (0.42, 1.02)[110]	0.06 (−0.17, 0.30)[110]		4 (2, 11)[110]
IA Hyaluronic acid	Knee	100	Ia	0.32 (0.17, 0.47)[111]	0.00 (−0.23, 0.23)[112]		
Glucosamine sulphate	Both	100	Ia	0.61 (0.28, 0.95)[113]	0.07 (−0.08, 0.21)[113]	0.06 (−0.11, 0.23)[113]	5 (4, 7)[114]
Chondroitin sulphate	Knee	100	Ia	0.52 (0.37, 0.67)[114]			5 (4, 7)[114]
Diacerhein	Both	–	Ib	0.22 (0.01, 0.42)[81–85]			

ASU	Both	75	Ia	More beneficial for hip OA[115]		
Herbal remedy	Both	75	Ia			7 (4, 27)[116]
Oestrogen						
Bisphosphonates						
Antidepressants						
Surgical						
Arthroscopic lavage	Knee	100	Ib	0.09 (−0.27, 0.44)[55]	−0.10 (−0.45, 0.26)[55]	
Arthroscopic debridement	Knee	100		−0.01 (−0.37, 0.35)[55]	−0.09 (−0.27, 0.45)[55]	
Patellar resurfacing	Knee	100	Ib			9 (5, 25)[117]
Osteotomy	Knee	50	IIb	60% Pain relief from an SR of uncontrolled trial[57]		
Joint distraction						
TJR	Both	100	III	TJR is effective to improve QoL, more beneficial for hip OA from an SR of cohort studies[56]		
Knee aspiration						
Knee fusion						

ES = 0.2 is considered small, ES = 0.5 is moderate, and ES > 0.8 is large; NNT for symptom relief, e.g., ≥50% pain relief, unless otherwise specified; SAM-e: S-adenosylmethionine; ASU: avocado soybean unsponifiable. *LoE (level of evidence): Ia: MA 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, cross-sectional studies); IV: expert opinion. †QoS (quality of study) was assessed using validated scales, e.g., the Oxman and Guyatt scale for SR and the Jadad's scale for clinical trials. The percentage score was calculated for each study. The best available evidence was presented, i.e., SR with the highest quality, RCT with the highest quality followed by uncontrolled or quasi experiment, cohort and case−control study.

RCTs of total joint (knee or hip) replacement or osteotomy, two recent SRs of uncontrolled trials and cohort studies confirmed that they were highly effective in relieving pain and improving quality of life[56,57].

Side effects

Evidence for side effects of treatments has been mainly investigated in pharmacologic therapies. Oral NSAIDs were associated with 3–5 times the risk of gastrointestinal (GI) side effects when compared with placebo or non-exposure[58], whereas treatment with topical NSAIDs resulted in no more adverse GI events than placebo (RR = 0.81, 95% CI 0.43, 1.56)[53] or non-exposure (OR = 1.45, 95% CI 0.84, 2.50)[59] (Table VI). Whether or not long-term treatment with acetaminophen 4 g daily is associated with GI and renal side effects remains inconclusive (Table VI). Treatment with cyclooxygenase-2 (COX-2) selective drugs or conventional non-selective NSAIDs together with proton pump inhibitors (PPIs) or misoprostol has been shown to be associated with a reduction in the risk of NSAID-induced upper GI side effects. However, treatment with rofecoxib has been shown to be associated with an increased risk of cardiovascular (CV) events (RR = 2.24, 95% CI 1.24, 4.02)[60] and treatment with misoprostol with an increased risk of diarrhoea (RR = 1.81, 95% CI 1.52, 2.61)[61]. Following the withdrawal of rofecoxib, a number of RCTs and SRs of the CV safety of other coxibs and conventional non-selective NSAIDs have been undertaken. While the increased risk of CV side effects with rofecoxib was confirmed, the evidence for similar CV toxicity with celecoxib, valdecoxib and conventional non-selective NSAIDs was inconsistent (Table VI). However, 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)[62] (Table VI).

Cost effectiveness

Four cost-utility analyses have been undertaken since 2002. One in Germany, in which acupuncture was compared with sham acupuncture[63]; two in the UK, which studied treatment with water-based exercises and GI protective strategies[64,65]; and one in Canada, which looked at treatment with intra-articular injections of hyaluronic acid[66]. Two previous studies which had compared total hip and knee replacements with conventional pharmacologic and non-pharmacologic therapy were retrieved for comparison purpose[67,68]. Cost/QALY varied with modalities, countries, comparators, perspectives, time horizons and discounting rates and remained variable, even after adjustment for discounting and conversion of the original cost per QALY to the current value of the US dollar (Table VII).

Discussion

Clinical guidelines are frequently defined as 'systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances'[69]. OA is the most prevalent form of arthritis throughout the world[1–7] and OA related knee pain is the leading cause of physical disability in older adults[1].The prevalence of both symptomatic and radiographically defined hip OA[7–11] is less than that of knee OA[2–6] and varies from one country to another[7,8,70]. The treatment of

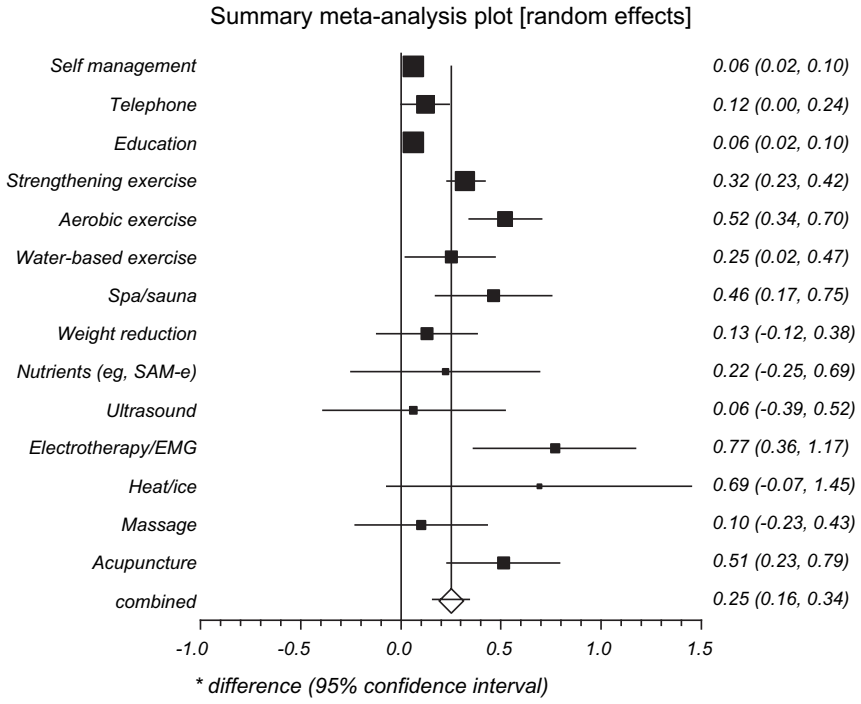

Fig. 2. ES for pain relief with non-pharmacological therapies.

symptomatic OA of the knee and hip are global problems, which present challenges to the clinical skills and judgement of health professionals everywhere. As there is no single treatment modality which will relieve pain, improve mobility and prevent structural progression of disease, effective management relies on the appropriate use of a number of available therapies, each of which has only limited efficacy. While a number of national and regional guidelines have been developed to assist physicians and other health professionals in their management of hip and/or knee OA[16–18,32–51], there are currently no universally agreed recommendations, even for a core group of safe and effective therapies, that can be recommended for the treatment of OA of the knee and hip throughout the world. As a prelude to developing updated, evidence-based, international, expert consensus recommendations for the management of hip and knee OA, the OARSI Treatment Guidelines Committee undertook a critical appraisal of existing published guidelines and an SR of more recent evidence for relevant therapies. The purpose of these preliminary appraisals was (1) to establish the extent to which different modalities of therapy are recommended in existing guidelines, and to

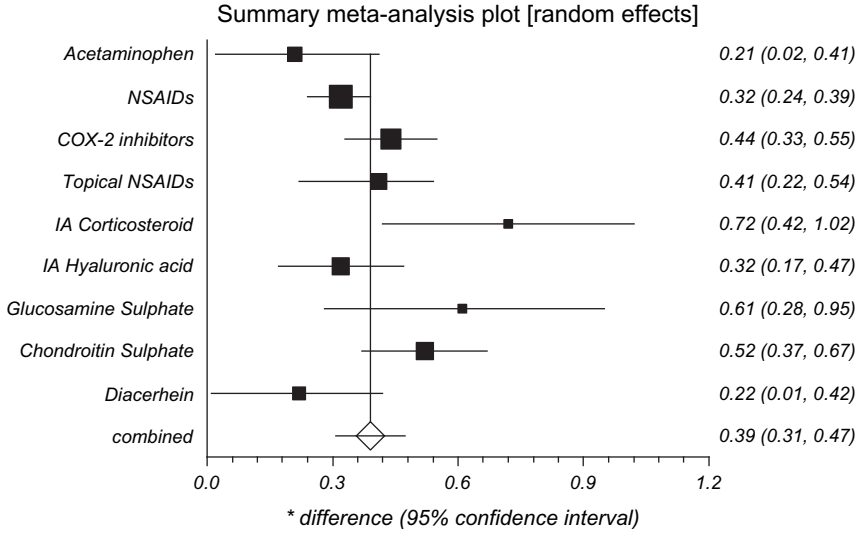

Fig. 3. ES for pain relief with pharmacological therapies.

Table VI
Safety profiles – RR or OR and 95% CI*

Intervention†	Adverse events	RR/OR (95% CI)	Evidence (references)
Acupuncture	Any	0.76 (0.13, 4.42)	RCT[63]
Acetaminophen	GI discomfort	0.80 (0.27, 2.37)	RCTs[105]
	GI perforation/bleed	3.60 (2.60, 5.10)	CC[118]
	GI bleeding	1.2 (0.8, 1.7)	CCs[119]
	Renal failure	0.83 (0.50, 1.39)	CS[120]
	Renal failure	2.5 (1.7, 3.6)	CC[121]
NSAIDs	GI perforation/ulcer/bleed	5.36 (1.79, 16.10)	RCTs[58]
	GI perforation/ulcer/bleed	2.70 (2.10, 3.50)	CSs[58]
	GI perforation/ulcer/bleed	3.00 (2.70, 3.70)	CCs[58]
	Myocardial infarction	1.09 (1.02, 1.15)	CSs[122]
Topical NSAIDs	GI events	0.81 (0.43, 1.56)	RCTs[53]
	GI bleed/perforation	1.45 (0.84, 2.50)	CC[59]
H2 blocker + NSAID vs NSAID	Serious GI complications	0.33 (0.01, 8.14)	RCTs[62]
	Symptomatic ulcers	1.46 (0.06, 35.53)	RCTs[62]
	Serious CV or renal events	0.53 (0.08, 3.46)	RCTs[62]
PPI + NSAID vs NSAID	Serious GI complications	0.46 (0.07, 2.92)	RCTs[62]
	Symptomatic ulcers	0.09 (0.02, 0.47)	RCTs[62]
	Serious CV or renal events	0.78 (0.10, 6.26)	RCTs[62]
Misoprostol + NSAID vs NSAID	Serous GI complications	0.57 (0.36, 0.91)	RCTs[62]
	Symptomatic ulcers	0.36 (0.20, 0.67)	RCTs[62]
	Serious CV or renal events	1.78 (0.26, 12.07)	RCTs[62]
	Diarrhoea	1.81 (1.52, 2.61)	RCTs[61]
COX-2 inhibitors			
Coxibs vs NSAID	Serious GI complications	0.55 (0.38, 0.80)	RCTs[62]
	Symptomatic ulcers	0.49 (0.38, 0.62)	RCTs[62]
	Serious CV or renal events	1.19 (0.80, 1.75)	RCTs[62]
Celecoxib	Myocardial infarction	2.26 (1.0, 5.1)	RCTs[123]
	Myocardial infarction	0.97 (0.86, 1.08)	CSs/CCs[122]
Rofecoxib	Myocardial infarction	2.24 (1.24, 4.02)	RCTs[60]
	Myocardial infarction	1.27 (1.12, 1.44)	CSs/CCs[122]
Valdecoxib	CV events	2.3 (1.1, 4.7)	RCTs[124]
Opioids	Any	1.4 (1.3, 1.6)	RCTs[125]
	Constipation	3.6 (2.7, 4.7)	RCTs[125]
Glucosamine sulphate	Any	0.97 (0.88, 1.08)	RCTs[113]
Diacerhein	Diarrhoea	3.98 (2.90, 5.47)	RCTs[81,85]

H2-blockers: histamine type 2 receptor antagonists.

*RR: Relative Risk; OR: Odds Ratio; CC: case–control study; CS: cohort study. Pooled RR/OR was provided if more than one study were included.

†Compared with placebo/non-exposure unless otherwise stated.

explore the possibility that there may be a core set of recommendations common to all the guidelines; (2) to investigate the extent to which these guidelines are based on available research evidence; (3) to assess the quality of the guidelines using the widely accepted AGREE criteria; and (4) to examine the extent to which more recent research evidence confirms, or fails to confirm, recommendations in existing guidelines.

Table VII
Cost per QALY

Intervention	Comparator	Perspective*	Time horizon	Discounting	Year published	Country	Cost/QUALY	
							Original	Converted ($)†
Water-based exercise	Usual care	Societal	1 Year	No	2005	UK	£5738	10483[64]
Acupuncture	Sham acupuncture	Societal	3 Months	No	2005	Germany	17845 €	22297[63]
NSAID + PPI	NSAIDs	NHS	6 Months	No	2005	UK	£33889	61915[65]
NSAID + misoprostol	NSAIDs	NHS	6 Months	No	2005	UK	£8889	16240[65]
COX-2 specifics	NSAIDs	NHS	6 Months	No	2005	UK	£36923	74298[65]
COX-2 selectives	NSAIDs	NHS	6 Months	No	2005	UK	£30000	60367[65]
Intra-articular hyaluronic acid	Standard care	Societal	1 Year	No	2002	Canada	$10000	10453[66]
Total hip replacement	Conventional therapy	Societal	Life	5%	1996	US	$4754	8131[67]
Total knee replacement	Pre-operation	Institutional	2 Years	No	1997	US	$5856	10325[68]

*Perspective = perspective for economic evaluation (Societal = costs and benefits to whole society; NHS = costs and benefits to UK National Health Service; Institutional = costs and benefits to other payers, e.g., insurance company).

†The original Cost/QALY was converted into US$ with a discount rate of 5% pa from the date of the publication to the current value on 10 March 2006.

TREATMENT MODALITIES RECOMMENDED IN EXISTING GUIDELINES, CORE RECOMMENDATIONS AND THEIR EVIDENCE BASE

The critical appraisal of the 23 existing guidelines showed that of 51 treatment modalities addressed, 20 were universally recommended in those guidelines in which they were considered (100% agreement in Table IV). These included recommendations for non-pharmacological modalities of therapy such as education, exercise, patient contact by telephone and provision of walking aids and pharmacological treatments such as acetaminophen, non-selective NSAIDs with co-prescription of gastroprotective agents or selective COX-2 inhibitors, opioids and some herbal remedies. Surgical treatments recommended in all the guidelines in which they were considered included knee aspiration and joint lavage as well as osteotomy, knee fusion and total joint replacements. Self-management and the combination of non-pharmacologic and pharmacologic treatments were also uniformly recommended core recommendations. It is apparent that this core set of recommended therapies must reflect the availability of treatments. The less than universal recommendation for some modalities of therapy may have been a consequence of them not being universally available, e.g., topical NSAIDs and avocado soybean unsaponifiables are available in Europe but not in the USA. It is also important to consider the number of guidelines, which considered any particular modality of therapy in ones interpretation of the reliability of the strength of agreement for that treatment. Clearly, the confidence one can have in the universal recommendation for exercise, where this modality of treatment was considered and endorsed in 21/21 guidelines, is likely to be greater than the confidence one has in the recommendation for knee fusion, which was only considered and endorsed in 2/2 guidelines.

It was also apparent that some of the core set of universally recommended therapies were not supported by evidence from RCTs. For example, while exercise of various types was supported by SR of RCTs (level Ia), total joint replacement was only supported by uncontrolled or cohort studies (level III) and the recommendations for knee aspiration and knee fusion were based on expert opinion (level IV). The extent to which RCTs should be the gold standard for the recommendation of all treatments has been the subject of previous discussion and controversy[71,72]. Nevertheless, the level of research evidence and clinical effectiveness have been important considerations in the development of recent guidelines for the treatment of knee and hip OA[17,18] and in the development of the OARSI recommendations. Clearly guidelines based on recommendations for treatments for which there is proven evidence of benefit should at least have the potential for improving clinical outcomes and the quality of health care for patients, although success is certainly not guaranteed and evidence-based guidelines are only one option for improving the quality of health care.

A pilot survey of the perceived usefulness of the treatment modalities addressed by the existing guidelines was conducted among physicians and other health care professionals attending a New York University – OARSI Rheumatology Symposium in 2006. The purpose of the survey was to collect the users' opinions on the usefulness of current treatment guidelines. The usefulness of each recommended treatment modality was assessed by the participants using a 5-point categorical scale (not useful, slightly useful, moderately useful, very useful and absolutely essential). Votes (%) on "very useful or absolutely essential" were calculated. Of 19 participants who completed the questionnaire (four general physicians, eight rheumatologists, one physiotherapist, one orthopaedic surgeon, one pharmacist and four other health professionals), 94% perceived total joint replacement to be very useful or essential therapy for both knee OA and hip OA. Combination therapy was judged to be very useful or essential by 79% for knee OA and 72% for hip OA. Weight reduction was perceived to be more useful for knee than hip OA by 68%, whereas NSAIDs, NSAID plus PPIs, COX-2 inhibitors, self-management, education and exercise were considered useful for both hip and knee OA. Although this survey was far from being truly representative of all potential guideline users and only involved a very small number of participants, most of whom were from the United States, the views expressed about the usefulness of various modalities of treatment were at least consistent with the appraisal of existing guidelines that has led to the definition of a tentative core set of recommended treatment modalities. It also points to a possible way of assessing the potential applicability of any future recommendations for other modalities of therapy being considered as additions to this core set.

QUALITY OF EXISTING GUIDELINES

The methodology involved in the development of treatment guidelines for OA has evolved considerably in the last decade. Between the publication of the first guidelines for the treatment of OA by the Royal College of Physicians in 1993[49] and the publication of the EULAR recommendations in 2005[18], the paradigm has shifted from purely opinion-based guidelines[49] to entirely evidence-based guidelines such as the Prodigy Guidance[34] and subsequently to hybrid guidelines based on both research evidence and clinical expertise such as the EULAR recommendations[17,18]. However, no attempt had been made to try and assess the quality of these guidelines. We have therefore used the AGREE instrument to evaluate the quality of all existing guidelines for scope and purpose, stakeholder participation, methodological rigour, clarity, applicability, editorial independence and overall quality[22]. Overall quality was better in evidence-based than opinion-based guidelines, and significantly better still in the hybrid guidelines that combined research evidence with expert opinion (Fig. 1). This is mainly attributable to the improved scores for scope and purpose ($P = 0.007$), rigour of development ($P < 0.001$) and editorial independence ($P = 0.013$) in the hybrid guidelines (Table III). There is a tendency for evidence-based guidelines to have lower applicability, although the differences are not statistically significant (Table III). This may, in part, reflect the gap that exists between RCTs which demonstrate that an intervention works ("efficacy") and how often and well the intervention works in clinical practise ("clinical effectiveness"). Hybrid guidelines can be expected to demonstrate improved applicability as clinical expertise can temper the rigidity of research data and close the gap between research and clinical practise.

In the development of hybrid guidelines by the EULAR OA Task Force, expert consensus on the most important propositions was followed by a systematic search for published supporting research evidence, prior to assigning a strength and confidence of recommendation for each treatment proposition. These were based on combined

consideration of the research evidence and clinical expertise after also considering risks and benefits, including potential adverse effects and the cost of each treatment modality[18]. This method is clinically driven and evidence supported. The sequence of steps has been modified slightly for the development of the OARSI Treatment Guidelines. An initial SR of research evidence was followed by the development of expert consensus based on a combined consideration of the research evidence and the clinical expertise of the members of the committee. This was then followed by assignment of strength and confidence of recommendation for each proposition as before. This current method is evidence-driven and clinically supported. Another important difference in the methodology used in the development of the OARSI recommendations has been that the committee has not arbitrarily restricted the number of treatment options that it would consider, as was the case in the development of the EULAR guidelines[17,18].

LIMITATIONS

There are a number of limitations to this study.

Firstly it was inevitably necessary to set fixed timelines for the literature search, i.e., from January 2002 to January 2006. Evidence before this time was obtained from the EULAR SR. For technical reasons it has not been possible, to date, to pool the data, so that the SRs of the relevant scientific literature before January 2002 and from January 2002 to January 2006 remain as two separate data sets. Evidence that has been published after January 2006 has yet to be systematically reviewed. There have been a number of new studies published after 31 January 2006, examples are those for glucosamine, chondroitin, diacerhein and self-management[73–77]. It has not been possible to update the SR following the Delphi exercise, which is described in detail in the second part of this report. The methods used to develop the guideline involved undertaking an SR of the research evidence to inform and assist in the development of the expert consensus. Any new evidence or proposals for changes in the consensus recommendations after completion of the Delphi exercise should properly be considered in the context of the full evidence and propositions. This would have required another systematic literature search for all evidence and a further Delphi exercise, which would not have been feasible within the timeframe. Sensitivity analysis[78] was therefore undertaken to examine whether these recently published studies would alter any of the evidence-based conclusions (Table VIII). For example, the results of two further RCTs for glucosamine hydrochloride, The National Institutes of Health Glucosamine/Chondroitin Arthritis Intervention (GAIT) Trail and sulphate (GUIDE) Trial have recently been published[74,75]. The addition of the data from these two studies to the main body of trial outcomes did not alter ESs for glucosamine sulphate or hydrochloride significantly. Treatment with glucosamine sulphate remained superior to placebo while treatment with glucosamine hydrochloride was not. However, following the addition of the new data on chondroitin sulphate from the GAIT study to the results of the earlier RCTs, treatment with chondroitin sulphate was no longer superior to placebo[74,76] (Table VIII). However, there are a number of studies that have been reported in 2007 that have not been included, two examples are trials of chondroitin sulphate and of weight reduction which were published after the analyses and discussion for this manuscript were completed[79,80]. Treatment with diacerhein was the subject of a recent Cochrane SR[77]. The calculations of ES and RR were similar to those found in this study (Table VIII). No attempt has been made to pool the data as the majority of trials included in the Cochrane review are already included in our main analysis[81–85]. A new RCT of self-management (class training package plus educational booklets) vs educational booklets alone did not show any difference for the WOMAC pain scores between groups[73]. Unfortunately, numerical data were not available and a sensitivity test could not be conducted.

As it is of course almost certain that additional studies, which may be relevant to the analyses and conclusions contained in this report, will be published in due course, we plan to review accumulating evidence annually, and to formally update the guidelines as required within 3–5 years.

Secondly, research evidence can be prone to publication bias. Although we have searched Cochrane library, unpublished/unregistered trials cannot be comprehensively assessed. We would therefore encourage investigators to register any trials that are being undertaken or planned.

Thirdly, caution must be taken when looking for cross-treatment comparisons unless the evidence has been obtained from a direct comparison. Most of the evidences summarised in this report are from placebo controlled studies. Placebo effects may vary across trials and indirect comparison can be misleading[86]. In addition, there are numerous differences between trials such as differences in study period, severity of disease, age, gender and co-morbidities, etc. For example it is not appropriate to make a direct comparison of ESs between

Table VIII
Sensitivity analyses

Modality	Outcome measure(s)	Point estimate (95% CI)		
		Data 2002–2006	Data 2006–	Pooled
Glucosamin sulphate	ES_{pain}	0.68 (0.32, 1.04)	0.26 (−0.01, 0.54)[75]	0.45 (0.04, 0.86)
Glucosamin hydrocloride	ES_{pain}	0.13 (−0.27, 0.53)	−0.03 (−0.18, 0.13)[74]	−0.01 (−0.15, 0.14)
Chondroitin sulphate	ES_{pain}	0.52 (0.37, 0.67)	−0.02 (−0.18, 0.14)[74] 0.42 (0.04, 0.79)[76]	0.30 (−0.10, 0.70)
Diacerhein	ES_{pain}	0.22 (0.01, 0.42)	0.22 (0.01, 0.42)[77]	NA
	$RR_{diarrhoea}$	3.98 (2.90, 5.47)	3.81 (2.54, 5.71)[77]	
Self-management	ES_{pain}	0.06 (0.02, 0.10)	No difference for WOMAC pain[73]	

NA: not applicable as the new study is an updated SR.

electrotherapy (ES = 0.77, 95% CI 0.36, 1.17) and NSAIDs (ES = 0.32, 95% CI 0.24, 0.39) and to draw the conclusion that electrotherapy is more effective than NSAIDs.

Finally, evidence was selected sequentially according to the evidence hierarchy (Table I) and the quality of the studies, and only the best available evidence was considered. Whether this is an adequate approach is open to discussion. An MA is not necessarily superior to a large scale well-conducted RCT[87], and RCTs are not necessarily better than observational studies[88]. Differences in the underlying populations being examined may also impact the results of a study.

In summary, a critical appraisal of existing treatment guidelines across countries and regions has identified a core set of treatments for the management of hip and knee OA. The quality and applicability of these guidelines increased when research evidence and expert opinions were combined. The study suggests that there is room for improvement in the quality and applicability of guidelines for the management of hip and knee OA in the future. Regular SR of research evidence and update of recommendations are important to ensure that guidelines remain current.

Acknowledgements

The authors would like to thank Jane Robertson for work on the literature search, data extraction and database development, Joanna Ramowski for guideline collection and digitisation, and Diann Stern and Helen Richardson for logistics support throughout the project. We also thank Professors Leo Van de Putte, Frank Wollheim and Burkhard Leeb for their participations in quality and content assessment of the non-English guidelines. Financial support came from OARSI.

Conflicts of interest: Full disclosure statements from all members of the OARSI treatment guidelines committee are shown in Appendix 3. These have been reviewed by the OARSI ethics committee. No potential conflict of interest was identified that should preclude the participation of any member of the committee in this critical appraisal.

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.
Roy D. Altman, University of California at Los Angeles, Agua Dulce, CA, USA.
Nigel K. Arden, Medical Research Council, Southampton General Hospital, Southampton, UK.
Sita Bierma-Zeinstra, Erasmus Medical Center, Rotterdam, Netherlands.
Kenneth D. Brandt, Indiana University School of Medicine, Indianapolis, IN, USA.
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.
Kent Kwoh, University of Pittsburgh Department of Medicine, Pittsburgh, PA, USA.
Stefan Lohmander, Department of Orthopaedics, Lund University Hospital, Lund, Sweden.
Peter Tugwell, Institute of Population Health, University of Ottawa, Ottawa, Canada.

Appendix 1. Search strategy for guidelines – example from MEDLINE

Database: Ovid MEDLINE(R) <1966 to October Week 2 2005>

	Search strategy
1	guideline$.mp. or exp Practice Guideline/ (106190)
2	recommendation$.mp. (61755)
3	standard$ of care.mp. (5830)
4	practice standard$.mp. or exp Professional Standard/ (3195)
5	exp Algorithm/or clinical algorithm$.mp. (55742)
6	practice algorithm.mp. (15)
7	clinical guideline$.mp. (2325)
8	expert$ consensus.mp. (332)
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (218508)
10	hip osteoarthritis.mp. or exp hip Osteoarthritis/or exp hip arthrosis/(2534)
11	hip osteoarthrosis.mp. (23)
12	coxarthritis.mp. or exp coxitis/(55)
13	osteoarthritis.mp. or exp OSTEOARTHRITIS/ (30570)
14	osteoarthrosis.mp. (2401)
15	osteophyte.mp. or exp OSTEOPHYTE/(682)
16	joint space narrowing.mp. (534)
17	degenerative joint disease$.mp. (1304)
18	hip pain.mp. (837)
19	hip.mp. or exp HIP/(61176)
20	13 or 14 or 15 or 16 or 17 (32523)
21	19 and 20 (6981)
22	10 or 11 or 12 or 18 or 21 (7688)
23	knee osteoarthritis.mp. or exp knee Osteoarthritis/ (2966)
24	knee osteoarthrosis.mp. (41)
25	gonarthritis.mp. (104)
26	knee pain.mp. or exp knee pain/(1580)
27	osteoarthritis.mp. or exp OSTEOARTHRITIS/ (30570)
28	osteoarthrosis.mp. (2401)
29	osteophyte.mp. or exp OSTEOPHYTE/(682)
30	joint space narrowing.mp. (534)
31	degenerative joint disease$.mp. (1304)
32	27 or 28 or 29 or 30 or 31 (32523)
33	knee.mp. or exp KNEE/(60576)
34	32 and 33 (9001)
35	23 or 24 or 25 or 26 or 34 (10200)
36	22 or 35 (16242)
37	9 and 36 (289)
38	remove duplicates from 37 (280)
39	limit 38 to human (276)

Appendix 2. Search strategy for research evidence

Database: Ovid MEDLINE(R) <2002 to January Week 1 2006>

	Search strategy
1	hip osteoarthritis.mp. or exp hip Osteoarthritis/or exp hip arthrosis/(1716)
2	hip osteoarthrosis.mp. (11)
3	coxarthritis.mp. or exp Coxitis/(15)
4	osteoarthritis.mp. or exp OSTEOARTHRITIS/ (14265)
5	osteoarthrosis.mp. (764)
6	osteophyte.mp. or exp OSTEOPHYTE/(365)
7	joint space narrowing.mp. (365)
8	degenerative joint disease$.mp. (521)
9	hip pain.mp. (501)
10	hip.mp. or exp HIP/(27430)
11	4 or 5 or 6 or 7 or 8 (15077)
12	10 and 11 (2892)
13	1 or 2 or 3 or 9 or 12 (3290)
14	knee osteoarthritis.mp. or exp Knee Osteoarthritis/(3035)
15	knee osteoarthrosis.mp. (20)
16	gonarthritis.mp. (45)
17	knee pain.mp. or exp Knee Pain/(1096)
18	osteoarthritis.mp. or exp OSTEOARTHRITIS/(14265)
19	osteoarthrosis.mp. (764)
20	osteophyte.mp. or exp OSTEOPHYTE/(365)
21	joint space narrowing.mp. (365)
22	degenerative joint disease$.mp. (521)
23	18 or 19 or 20 or 21 or 22 (15077)
24	knee.mp. or exp KNEE/(26787)
25	23 and 24 (5157)
26	14 or 15 or 16 or 17 or 25 (5922)
27	13 or 26 (8262)
28	exp Meta-Analysis/or systematic review.mp. (10753)
29	meta-analysis.mp. (17026)
30	quantitative review$.mp. (171)
31	quantitative overview$.mp. (36)
32	statistical pool$.mp. (82)
33	28 or 29 or 30 or 31 or 32 (21462)
34	27 and 33 (103)
35	paracetamol.mp. or exp Acetaminophen/(4505)
36	34 and 35 (7)
37	limit 36 to yr = "2002 - 2006" (6)

Same strategy was used for MEDLINE, EMBASE, CINHAL and AMED. In Science Citation Index and Cochrane Lib, however, we used key word search for every possible term and combined them to obtain the relevant citations.

No further search for the lower level of evidence was needed for paracetamol as there are a number of SRs/MAs. However, for some modalities, such as weight loss and massage, the search carried on with RCT/CT, or cohort/case–control/cross-sectional studies, using the following alternative strategies.

Database: Ovid MEDLINE(R) <2002 to January Week 1 2006>

	Search strategy
1	exp Randomized Controlled Trials/or randomised controlled trial.mp. or exp Clinical Trials/or exp Random Allocation/(103055)
2	double blind.mp. or exp Double-Blind Method/(46335)
3	exp Single-Blind Method/or single blind.mp. (8025)
4	placebo.mp. or exp Placebos/(50690)
5	comparative Study/(519952)
6	1 or 2 or 3 or 4 or 5 (653644)
7	limit 6 to year = "2002 - 2006" (323312)

Database: Ovid MEDLINE(R) <2002 to January Week 1 2006>

	Search strategy
1	exp Cohort Studies/(302725)
2	cohort stud$.mp. (57984)
3	exp Prospective Studies/(123278)
4	prospective stud$.mp. (134288)
5	relative risk$.mp. (19680)
6	incidence.mp. or exp INCIDENCE/(169499)
7	1 or 2 or 3 or 4 or 5 or 6 (457813)
8	exp Case-Control Studies/(206064)
9	case control stud$.mp. (65217)
10	exp Retrospective Studies/(148360)
11	retrospective stud$.mp. (152256)
12	exp Odds Ratio/(20377)
13	odds ratio$.mp. (48727)
14	8 or 9 or 10 or 11 or 12 or 13 (245705)
15	exp Cross-Sectional Studies/(45147)
16	cross sectional stud$.mp. (48194)
17	risk.mp. or exp RISK/(467774)
18	prevalence.mp. or exp PREVALENCE/(126109)
19	15 or 16 or 17 or 18 (569453)
20	7 or 14 or 19 (963666)
21	limit 20 to yr = "2002 - 2006" (453748)

To search for economic evaluation, the following strategy was used in combination with the search terms for OA and paracetamol.

Database: Ovid MEDLINE(R) <2002 to January Week 1 2006>

	Search strategy
1	"Costs and Cost Analysis"/or Cost-Benefit Analysis/ or "Quality of Life"/(66609)
2	economic evaluation$.mp. (2102)
3	cost effectiveness anal$.mp. (2232)
4	cost utility anal$.mp. (449)
5	cost benefit anal$.mp. (22265)
6	cost minimisation analysis.mp. (48)
7	exp Health Services Research/or exp Quality-Adjusted Life Years/(46689)
8	1 or 2 or 3 or 4 or 5 or 6 or 7 (110077)
9	limit 8 to yr = "2002 - 2006" (52844)

Appendix 3. 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 Bionocare Endo Merck Novartis Pfizer Rottapharm Sanofi-Aventis	Nil	Nil	Nil	
G. Nuki	AstraZeneca Savient Gelita Co	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	
M. Dougados	Abbott AstraZeneca BMS CombinatoRx Merck Negma Novartis Ofizer Pharmasciences Proctor & Gamble Roche Wyeth	Nil	Nil	Nil	
M. Hochberg	Amgen AstraZeneca Bayer Biogen idec Bionicare Bristol Myers Squibb				

Appendix 3 (*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
	Chugai CombinatoRx Ferring Genzyme GlaxoSmithKline Merck NicOx Novartis Proctor & Gamble Proprius Roche Sanofi-Aventis Wyeth	Nil	Dainippon Sumitomo	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 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 [see comment] [Review] [45 refs]. Ann Rheum Dis 2001 Feb;60(2): 91–7.
2. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum 1987 Aug;30(8):914–8.
3. Lawrence JS, Bremner JM, Bier F. Osteo-arthrosis. Prevalence in the population and relationship between symptoms and X-ray changes. Ann Rheum Dis 1966 Jan 1;25(1):1–24.
4. McAlindon TE, Snow S, Cooper C, Dieppe PA. Radiographic patterns of osteoarthritis of the knee joint in the community: the importance of the patellofemoral joint. Ann Rheum Dis 1992 Jul;51(7):844–9.
5. O'Reilly SC, Muir KR, Doherty M. Screening for pain in knee osteoarthritis: which question? Ann Rheum Dis 1996 Dec 1;55(12):931–3.
6. van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis 1989 Apr 1;48(4):271–80.
7. Felson DT. Epidemiology of hip and knee osteoarthritis [Review] [183 refs]. Epidemiol Rev 1988;10:1–28.
8. Ingvarsson T, Hagglund G, Lohmander LS. Prevalence of hip osteoarthritis in Iceland. Ann Rheum Dis 1999 Apr;58(4):201–7.
9. Lanyon P, Muir K, Doherty S, Doherty M. Assessment of a genetic contribution to osteoarthritis of the hip: sibling study [see comment]. BMJ 2000 Nov 11; 321(7270):1179–83.
10. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, *et al*. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States [see comment]. Arthritis Rheum 1998 May;41(5):778–99.
11. Tepper S, Hochberg MC. Factors associated with hip osteoarthritis: data from the First National Health and Nutrition Examination Survey (NHANES-I). Am J Epidemiol 1993 May 15;137(10):1081–8.
12. 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(4):497–504.
13. Mannoni A, Briganti MP, Di Bari M, Ferrucci L, Costanzo S, Serni U, *et al*. Epidemiological profile of symptomatic osteoarthritis in older adults: a population based study in Dicomano, Italy. Ann Rheum Dis 2003; 62(6):576–8.
14. Walker-Bone K, Javaid K, Arden N, Cooper C. Regular review: medical management of osteoarthritis. BMJ 2000 Oct 14;321(7266):936–40.
15. Hunter DJ, Felson DT. Osteoarthritis. BMJ 2006 Mar 18;332(7542):639–42.
16. 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(9):1905–15.
17. 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) [Review] [82 refs]. Ann Rheum Dis 2003 Dec;62(12): 1145–55.
18. 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 May 1;64(5):669–81.
19. Pencharz JN, Grigoriadis E, Jansz GF, Bombardier C. A critical appraisal of clinical practice guidelines for the treatment of lower-limb osteoarthritis [Review] [33 refs]. Arthritis Res 2002;4(1):36–44.
20. 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(4):717–31.
21. 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 Feb;31(2):344–54.
22. The AGREE Collaboration. Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument. Available from: <www.agreecollaboration.org>; 2006.
23. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines [Review] [17 refs]. BMJ 1999 Feb 27;318(7183):593–6.
24. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. J Clin Epidemiol 1991; 44(11):1271–8.
25. 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 Feb;17(1): 1–12.
26. Hedges LV. Fitting continues models to effect size data. J Educ Stat 1982;7:245–70.
27. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edn. Hillsdale, NJ: Lawrence Erlbaum Associates 1988.
28. Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. Stat Med 1991 Nov;10(11):1665–77.
29. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. BMJ 1995;310(6977):452–4.
30. Altman DG. Confidence intervals for the number needed to treat. BMJ 1998 Nov 7;317(7168):1309–12.
31. Kleinbaum DG, Kuppler LL, Morgenstern H. Epidemiologic Research – Principles and Quantitative Methods. John Willey & Sons, Inc. 1982.
32. Algorithms for the diagnosis and management of musculoskeletal complaints. Am J Med 1997 Dec 29; 103(6 Suppl 1):S49–80.
33. Universe of Adult Patients with Osteoarthritis of the Knee – Phase I and Phase II. American Academy of Orthopaedic Surgons. Available from: <http://www.aaos.org/>; 2003 [accessed on 17 Oct 2005].
34. Prodigy guidance – osteoarthritis. Prodigy, The UK NHS, 2005. Available from: <http://www.prodigy.nhs.

uk/guidance.asp?gt=Osteoarthritis> [accessed on 18 Oct 2005].
35. Medical management of adults with osteoarthritis. Michigan Quality Improvement Consortium, 2005. Available from: <www.mgic.org> [accessed on 17 Oct 2005].
36. Albright J, Allman R, Bonfiglio RP, Conill A, Dobkin B, Guccione AA, *et al*. Philadelphia panel evidence-based clinical practice guidelines on selected rehabilitation interventions for knee pain. Phys Ther 2001; 81(10):1675–700.
37. Bennell K, Hinman R, Crossley K. APA knee joint osteoarthritis poisition statement. Australian Physiotherapy Association. Available from: <https://apa.advsol.com.au/staticcontent/staticpages/position_statements/-mpa/kneeOAsummary.pdf>; 2001 [accessed on 17 Oct 2005].
38. Bijl D, Diirven-Meijer PC, Opstelten W. General practice guidelines for non-traumatic knee complaints in adults. Huisarts Wet 1998;41(7):344–50.
39. Brosseau L, Wells GA, Tugwell P, Egan M, Dubouloz CJ, Casimiro L, *et al*. Ottawa panel evidence-based clinical practice guidelines for therapeutic exercises and manual therapy in the management of osteoarthritis. Phys Ther 2005;85(9):907–71.
40. Eccles M, Freemantle N, Mason J. North of England evidence based guideline development project: summary guideline for non-steroidal anti-inflammatory drugs versus basic analgesia in treating the pain of degenerative arthritis. BMJ 1998 Aug 22;317(7157): 526–30.
41. Enloe LJ, Shields RK, Smith K, Leo K, Miller B. Total hip and knee replacement programs: a report using consensus. J Orthop Sports Phys Ther 1996 Jan; 23(1):3–11.
42. Holbrook AM. Ontario treatment guidelines for osteoarthritis, rheumatoid arthritis and acute musculoskeletal injury. Ontario Program for Optimal Therapy. Available from: <http://www.thecem.net/Downloads/msk.pdf>; 2000 [accessed on 1 Sept 2005].
43. Lee J, Thorson D, Jurrison M, Hunt A, Harckom T, Akerman S, *et al*. Health care guideline: diagnosis and treatment of adult degenerative joint disease (DJD) of the knee. Institute for Clinical System Improvement. Available from: <www.icsi.org>; Nov 2004.
44. Lundebjerg N. Exercise prescription for older adults with osteoarthritis pain: consensus practice recommendations. J Am Geriatr Soc 2001;49(6):808–23.
45. Puhl W, Bernau A, Bohle E, Brune K, Gerhardt P, Greitemann B, *et al*. Diagnosis and treatment of knee osteoarthritis in outpatients [German]. Z Orthop Ihre Grenzgeb 2000;138(1):85–93.
46. Rankin EA, Alarcon GS, Chang RW, Cooney LM Jr, Costley LS, Delitto A, *et al*. NIH consensus statement on total knee replacement December 8–10, 2003. J Bone Joint Surg Am 2004;86(6):1328–35.
47. 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 Jan;44(1):67–73.
48. Rosman HA, Tat KLK, Veerapen K, Suk Chyn G, Gek-Liew DDRC, Hussein H, *et al*. Clinical practice guidelines on the management of osteoarthritis. Academy of Medicine of Malaysia. Available from: <http://www.acadmed.org.my/cpg/Bookleta.pdf>; 2002 [accessed on 17 Oct 2005].
49. Scott DL, Billingham M, Bourke BE, Bywaters EGL, Dieppe PA, Doherty M, *et al*. Guidelines for the diagnosis, investigation and management of osteoarthritis of the hip and knee – report of a joint working group of the British-Society-For-Rheumatology and the Research Unit of the Royal-College-of-Physicians. J R Coll Physicians Lond 1993;27(4):391–6.
50. Tannenbaum H, Peloso PM, Russell AS, Marlow B. An evidence-based approach to prescribing NSAIDs in the treatment of osteoarthritis and rheumatoid arthritis: the second Canadian consensus conference [Review] [111 refs]. Can J Clin Pharmacol 2000;7(Suppl A): 4A–16A.
51. Vogels EMHM, Hendriks HJM, van Barr ME, Dekker J, Hopman-Rock M, Oostendorp RAB, *et al*. Clinical practice guidelines for physical therapy in patients with osteoarthritis of the hip and knee. Available from: <http://www.cebp.nl/media/m11.pdf>; 2003 [accessed on 20 Oct 2005].
52. Christensen R, Astrup A, Bliddal H. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. Osteoarthritis Cartilage 2005;13(1):20–7.
53. Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. Br Med J 2004 Aug 7;329(7461):324–6.
54. Bazian L. Arthroscopic lavage for osteoarthritis of the knee. Evidence-based Healthcare & Public Health 2005;9(3):192–6.
55. Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, *et al*. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002;347(2):81–8. Date of publication: 11 Jul 2002.
56. 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(5):963–74.
57. 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(4):258–61.
58. 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(4): 804–12.
59. 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 Jul 1; 311(6996):22–6.
60. Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta- analysis. Lancet 2004;364(9450):2021–9.
61. Capurso L, Koch M. Prevention of NSAID-induced gastric lesions: H2 antagonists or misoprostol? A meta-analysis of controlled clinical studies [Italian]. Clin Ter 1991 Dec 15;139(5–6):179–89.
62. 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 Oct 23;329(7472):948–52.

63. 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. In: 12th Annual Symposium on Complementary Health Care – Abstracts, 19th–21st September 2005, Exeter, UK. Focus on Alternative and Complementary Therapies 2005, 10 (Suppl 1: 57–58).
64. 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–v.
65. Elliott RA, Hooper L, Payne K, Brown TJ, Roberts C, Symmons D. Preventing non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: are older strategies more cost-effective in the general population? Rheumatology 2005 Dec 20;10.1093/rheumatology/kei241
66. Torrance GW, Raynauld JP, Walker V, Goldsmith CH, Bellamy N, Band PA, *et al*. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (part 2 of 2): economic results. Osteoarthritis Cartilage 2002;10(7):518–27.
67. Chang RW, Pellissier JM, Hazen G-B. A cost-effectiveness analysis of total hip arthroplasty for osteoarthritis of the hip (Structured abstract). JAMA 1996; 275:858–65.
68. Lavernia CJ, Guzman JF, Gachupin GA. Cost effectiveness and quality of life in knee arthroplasty. Clin Orthop Relat Res 1997;134–9.
69. Lohr KN, Field MJ. A provisional instrument for assessing clinical practice guidelines. In: Field MJ, Lohr KN, Eds. Guidelines for Clinical Practice. From Development to Use. Washington DC: National Academy Press 1992.
70. Nevitt MC, Xu L, Zhang Y, Lui L-Y, Yu W, Lane NE, *et al*. Very low prevalence of hip osteoarthritis among Chinese elderly in Beijing, China, compared with Whites in the United States: The Beijing osteoarthritis study. Arthritis Rheum 2002;46(7):1773–9.
71. Black N. Evidence-based surgery: a passing fad? World J Surg 1999;23(8):789–93.
72. Black N. Why we need observational studies to evaluate the effectiveness of health care. BMJ 1996 May 11;312(7040):1215–8.
73. Buszewicz M, Rait G, Griffin M, Nazareth I, Patel A, Atkinson A, *et al*. Self-management of arthritis in primary care: randomised controlled trial. BMJ 2006 Oct 28;333(7574):879.
74. Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, *et al*. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 2006;354(8):795–808.
75. Herrero-Beaumont G, Ivorra JA, Del Carmen Trebado M, Blanco FJ, Benito P, Martin-Mola E, *et al*. Glucosamine sulfate in knee osteoarthritis symptoms: a randomised, double-blind, placebo-controlled study using acetaminophen as a side comparator. Arthritis Rheum 2007;56(2):555–67.
76. Uebelhart D, Malaise M, Marcolongo R, DeVathairell F, Piperno M, Mailleux E, *et al*. Intermittent treatment of knee osteoarthritis with oral chondroitin sulfate: a one-year, randomized, double-blind, multicenter study versus placebo. Osteoarthritis Cartilage 2004;12(4):269–76.
77. Fidelix TSA, Soares BGDO, Trevisani VM. Diacerein for osteoarthritis. In: Fidelix TSA, Soares BGDO, Trevisani VFM, Eds. Diacerein for osteoarthritis. Cochrane Database Syst Rev 2006;(1)10.1002/14651858.CD005117.pub2.2006.
78. Lau J, Ioannidis JPA, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997 Nov 1; 127(9):820–6.
79. Christensen R, Bartels EM, Astrup A, Bliddal H. The effect of weight reduction in obese patients diagnosed with knee osteoarthritis (OA): a systematic review and meta-analysis. Ann Rheum Dis 2007; 66(4):433–9.
80. Mazieres B, Hucher M, Zaim M, Garnero P. Effect of chondroitin sulfate in symptomatic knee osteoarthritis: a multicenter, randomized, double blind, placebo-controlled study. Ann Rheum Dis 2007; 66(5):639–45.
81. 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. Arthritis Rheum 2001;44(11):2539–47.
82. Lequesne M, Berdah L, Gerentes I. Efficacy and tolerance of diacerhein in the treatment of gonarthrosis and coxarthrosis. Rev Prat 1998;48(17 Suppl). Suppl 5.
83. Nguyen M, Dougados M, Berdah L, Amor B. Diacerhein in the treatment of osteoarthritis of the hip. Arthritis Rheum 1994;37(4):529–36.
84. 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(10): 2339–48.
85. Pham T, Le Henanff A, Ravoud P, Dieppe P, Paolozzi L, Dougados M. Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD101, in comparison with diacerein and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis. Ann Rheum Dis 2004;63(12):1611–7.
86. Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ 2003 Mar 1; 326(7387):472.
87. DerSimonian R, Levine RJ. Resolving discrepancies between a meta-analysis and a subsequent large controlled trial. JAMA 1999;282(7):664–70.
88. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000;342(25): 1887–92.
89. 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(6):427–38.
90. 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 Aug;48(8): 2207–13.
91. Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. Ann Rheum Dis 2005 Apr 1; 64(4):544–8.

92. 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(3): 179–85.
93. Brosseau L. Efficacy of balneotherapy for osteoarthritis of the knee: a systematic review. Phys Ther Rev 2002 Dec;7(4):209–22.
94. Nguyen M, Revel M, Dougados M. Prolonged effects of 3 week therapy in a spa resort on lumbar spine, knee and hip osteoarthritis: follow-up after 6 months. A randomized controlled trial. Br J Rheumatol 1997;36(1):77–81.
95. 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(5):1501–10.
96. Soeken KL, Lee WL, Bausell RB, Agelli M, Berman BM. Safety and efficacy of S-adenosylmethionine (SAMe) for osteoarthritis – a meta-analysis. J Fam Pract 2002;51(5):425–30.
97. Brosseau L. Efficacy of transcutaneous electrical nerve stimulation for osteoarthritis of the lower extremities: a meta-analysis. Phys Ther Rev 2004 Dec;9(4): 213–33.
98. Bjordal JM, Couppe C, Chow RT, Tuner J, Ljunggren EA. A systematic review of low level laser therapy with location-specific doses for pain from chronic joint disorders. Aust J Physiother 2003;49(2):107–16.
99. Welch V, Brosseau L, Peterson J, Shea BJ, Tugwell P, Wells G. Therapeutic ultrasound for osteoarthritis of the knee. Cochrane Database Syst Rev 2001;(3). CD003132.
100. Kresnik E, Mikosch P, Gallowitsch HJ, Jesenko R, Just H, Kogler D, *et al*. Clinical outcome of radiosynoviorthesis: a meta-analysis including 2190 treated joints. Nucl Med Commun 2002;23(7):683–8.
101. Brosseau L, Judd MG, Marchand S, Robinson VA, Tugwell P, Wells G, *et al*. Thermotherapy for treatment of osteoarthritis. The Cochrane Library (Oxford) 2003; 4 (ID #CD004522).
102. Bennell KL, Hinman RS, Metcalf BR, Buchbinder R, McConnell J, McColl G, *et al*. Efficacy of physiotherapy management of knee joint osteoarthritis: a randomised, double blind, placebo controlled trial. Ann Rheum Dis 2005;64(6):906–12.
103. Brouwer RW, Jakma TSC, Verhagen AP, Verhaar JAN, Bierma-Zeinstra SMA. Braces and orthoses for treating osteoarthritis of the knee. Cochrane Database Syst Rev 2005;(1)10.1002/14.2005.
104. Hulme JM, Judd MG, Robinson VA, Tugwell P, Wells G, de Bie RA. Electromagnetic fields for the treatment of osteoarthritis. Cochrane Database Syst Rev 2002;(1)10.1002/14651858.2002.
105. 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(8):901–7.
106. Towheed TE, Hochberg MC, Judd MG, Wells G. Acetaminophen for osteoarthritis. The Cochrane Library (Oxford) 2002;4 (ID #CD004257).
107. 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. Br Med J 2004;329(7478):1317–20.
108. Lee C, Hunsche E, Balshaw R, Kong SX, Schnitzer TJ. Need for common internal controls when assessing the relative efficacy of pharmacologic agents using a meta-analytic approach: case study of cyclooxygenase 2-selective inhibitors for the treatment of osteoarthritis. Arthritis Care Res 2005;53(4): 510–8.
109. Zhang WY, Li Wan PA. The effectiveness of topically applied capsaicin. A meta-analysis. Eur J Clin Pharmacol 1994;46(6):517–22.
110. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the Knee. The Cochrane Library (Oxford) 2005;4 (ID #CD005328).
111. Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. J Am Med Assoc 2003; 290(23):3115–21.
112. 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. Can Med Assoc J 2005;172(8): 1039–43.
113. Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, *et al*. Glucosamine therapy for treating osteoarthritis. The Cochrane Library (Oxford) 2005;4 (ID #CD002946).
114. Richy F, Bruyere O, Ethgen O, Cucherat M, Henrotin Y, Reginster J-Y. Structural and symptomatic efficacy oS100f glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. Arch Intern Med 2003;163(13):1514–22.
115. Ernst E. Avocado-soybean unsaponifiables (ASU) for osteoarthritis – a systematic review. Clin Rheumatol 2003;22(4–5):285–8.
116. Gagnier JJ, Chrubasik S, Manheimer E. Harpgophytum procumbens for osteoarthritis and low back pain: a systematic review. BMC Altern Med 2004; 4:10.
117. Nizard RS, Biau D, Porcher R, Ravaud P, Bizot P, Hannouche D, *et al*. A meta-analysis of patellar replacement in total knee arthroplasty. Clin Orthop 2005;196–203.
118. Garcia Rodriguez LA, Hernandez-Diaz S. Relative risk of upper gastrointestinal complications among users of acetaminophen and nonsteroidal anti-inflammatory drugs. Epidemiology 2001 Sep;12(5): 570–6.
119. 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.
120. Rexrode KM, Buring JE, Glynn RJ, Stampfer MJ, Youngman LD, Gaziano JM. Analgesic use and renal function in men. JAMA 2001 Jul 18;286(3): 315–21.
121. 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 Dec 20;345(25):1801–8.
122. 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(3):266–74.

123. 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(3):132–40.
124. 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(1226):10.
125. Kalso E, Edwards JE, Moore RA, Mcquay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain 2004;112(3):372–80.