Seminars in Arthritis and Rheumatism 43 (2013) 303–313

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Health economics in the field of osteoarthritis: An Expert's consensus paper from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)

Mickaël Hiligsmann, PhD[a,b,*], Cyrus Cooper, MD[c], Nigel Arden, MSc, MD[d], Maarten Boers, MSc, MD, PhD[e], Jaime C. Branco, MD[f], Maria Luisa Brandi, MD[g], Olivier Bruyère, PhD[b], Francis Guillemin, MD, PhD[h], Marc C. Hochberg, MD, MPH[i], David J. Hunter, MBBS, PhD[j], John A. Kanis, MD[k], Tore K. Kvien, MD, PhD[l], Andrea Laslop, MD[m], Jean-Pierre Pelletier, MD[o], Daniel Pinto, PT, PhD[p], Susanne Reiter-Niesert, MD[q], René Rizzoli, MD[r], Lucio C. Rovati, MD[s], Johan L. (Hans) Severens, PhD[t], Stuart Silverman, MD[u], Yannis Tsouderos, MD[n], Peter Tugwell, MD[v], Jean-Yves Reginster, MD, PhD[b]

[a] *Department of Health Services Research, School for Public Health and Primary Care (CAPHRI), Maastricht University, P.O. Box 616, 6200 MD, Maastricht, The Netherlands*
[b] *Department of Public Health, Epidemiology and Health Economics, University of Liège, Liège, Belgium*
[c] *MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK*
[d] *Department of Musculoskeletal Epidemiology and Biobank, University of Oxford and Southampton, Oxford, UK*
[e] *Department of Epidemiology and Biostatistics; and Rheumatology, VU University Medical Center, Amsterdam, Netherlands*
[f] *CEDOC, Department of Rheumatology, Faculdade de Ciências Médicas, Universidade Nova de Lisboa/CHLO, EPE—Hospital Egas Moniz, Lisbon, Portugal*
[g] *Department of Internal Medicine, University of Florence, Florence, Italy*
[h] *Université de Lorraine, Université Paris Descartes, Nancy, France*
[i] *Division of Rheumatology & Clinical Immunology, University of Maryland School of Medicine, Baltimore, MD*
[j] *Royal North Shore Hospital and Kolling Institute, University of Sydney, Sydney, Australia*
[k] *WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, UK*
[l] *Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway*
[m] *Scientific Office, Austrian Agency for Health and Food Safety (AGES), Vienna, Austria*
[n] *Institute of Research International Servier, Suresnes, France*
[o] *Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, Quebec, Canada*
[p] *Department of Physical Therapy and Human Movement Sciences/Center for Healthcare Studies, Feinberg School of Medicine, Northwestern University, Chicago, IL*
[q] *Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany*
[r] *Service of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland*
[s] *Clinical Research Unit, Rottapharm/Madaus, Monza, Italy*
[t] *Institute of Health Policy & Management, Erasmus University Rotterdam, Rotterdam, The Netherlands*
[u] *Cedars-Sinai Medical Center, UCLA School of Medicine and the OMC Clinical Research Center, Beverly Hills, CA*
[v] *Department of Medicine, University of Ottawa, Ottawa, Canada*

ARTICLE INFO

Keywords:
Review
Cost-effectiveness
Cost–utility
Osteoarthritis
Arthroplasty
Economics
Methods

ABSTRACT

Objectives: There is an important need to evaluate therapeutic approaches for osteoarthritis (OA) in terms of cost-effectiveness as well as efficacy.
Methods: The ESCEO expert working group met to discuss the epidemiological and economic evidence that justifies the increasing concern of the impact of this disease and reviewed the current state-of-the-art in health economic studies in this field.
Results: OA is a debilitating disease; it is increasing in frequency and is associated with a substantial and growing burden on society, in terms of both burden of illness and cost of illness. Economic evaluations in this field are relatively rare, and those that do exist, show considerable heterogeneity of methodological approach (such as indicated population, comparator, decision context and perspective, time horizon, modeling and outcome measures used). This heterogeneity makes comparisons between studies problematic.

* Corresponding author at: Department of Health Services Research, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands.
E-mail address: m.hiligsmann@maastrichtuniversity.nl (M. Hiligsmann).

http://dx.doi.org/10.1016/j.semarthrit.2013.07.003

Conclusions: Better adherence to guidelines for economic evaluations is needed. There was strong support for the definition of a reference case and for what might constitute "standard optimal care" in terms of best clinical practice, for the control arms of interventional studies.

Introduction

Osteoarthritis (OA) is a common chronic joint disease that most frequently affects the knee, hand, and/or hip. The disease generally develops progressively over a number of years before potentially becoming "a painful problem," potentially leading to disability and social isolation. It has high prevalence in the population older than 65 years, and the prevalence in younger age groups appears to be on the increase [1,2]. Severe cases are increasingly referred for total joint replacement [3].

As a result of this trend toward disability with all its consequences, the economic burden of OA is high [4], in terms of both direct health-related costs and indirect costs. The treatments are, as yet, ineffective in limiting the progression of the disease and most are focused on symptom modification, particularly pain control. Some non-pharmaceutical therapies try to promote lifestyle changes which may help to maintain functional performance longer [5]. It is anticipated that the future will bring disease-modifying treatments, but it is likely that these will be expensive and ineffective in some patients. It is therefore vital that the costs and the impact on the quality of life (QoL) of the disease are understood and that the cost-effectiveness of treatments can be examined and compared in a methodical fashion allowing the rational allocation of limited healthcare resources.

It was against this background that the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) held an expert working group meeting in 2012 to present the current state-of-the-art in health economics investigations in this field and to discuss what still needs to be done to reach this goal. This paper was prepared on the basis of the presentations and discussions surrounding that meeting.

Diagnosis of OA

The diagnosis of OA is usually based on a combination of clinical features and where needed radiographic confirmation (referred to as symptomatic OA) [1]. While the diagnosis may be made on radiographic features alone, it is frequently observed that about half of the persons identified in this way will have no related symptoms or disability. Thus, the clinical relevance of certain radiographic features is not entirely clear [6], but this approach has relevance in epidemiological studies to define the population. The most widely used criteria for diagnosing OA are those of the American College of Rheumatology [7,8], and for a recent review and discussion, the reader is directed to Bijlsma et al. [9] and Nelson and Jordan [10], respectively.

The natural history of the disease is variable between patients and between joints [11]. In many cases, the condition remains stable for many years, while in others, the progression to severe disability may take less than 1 year. There remains much uncertainty concerning the contributory factors to disease progression, which to some extent, appear joint specific [11] and genetic [12].

The burden of OA

The burden of musculoskeletal diseases on global health is considerable. The recently published Global Burden of Disease study [13] estimated that musculoskeletal diseases were responsible for almost 166 million years lived with disability (YLDs) in 2010 (second only to mental and behavioral disorders at 176 million YLDs). Within this grouping, osteoarthritis accounts for slightly over 17 million YLDs in 2010, an increase of 64% over the period 1990–2010 (set against a 40% growth for musculoskeletal diseases as a whole).

Total joint arthroplasty

The indication for total joint arthroplasty (TJA) may be seen as the end stage of OA (for the knee and hip) [14]. Although the rates of TJA are highly variable among different countries with, amongst OECD countries, a 36-fold difference in the rate of hip replacements and a 70-fold difference in knee replacements, there is a steadily increasing in demand in recent years [15]. In a retrospective epidemiological study over the period 2001–2005, Piscitelli et al. [16] collected data on the costs associated with joint arthroplasty in Italy. For knee replacements in the male population, the annual change in the number of joint arthroplasty was +16.6% and in the female population was +12.4%. The overall incidence in 2005 was 99.9/100,000. For hip replacements (THA), the annual change was +5.8% in the male population and +3.6% in the female population. The overall incidence in 2005 was 94.4/100,000. Approximately 30% of hip arthroplasty and 20% of knee arthroplasty were performed annually in patients older than 65 years, impacting the workforce. For 2005, it was estimated that over a million working days were lost in Italy due to joint arthroplasty.

In a recent Finnish study [2], the changes in the incidence of unicondylar knee arthroplasty (UKA) and total knee arthroplasty (TKA) were assessed between 1980 and 2006. The annual cumulative incidence of UKA and TKA has increased rapidly among 30–59-year-olds. For UKA, the incidence increased from 0.2 to 10 per 100,000 inhabitants, and for TKA, the incidence increased from 0.5 to 65 per 100,000 inhabitants. The incidence of both interventions was higher in women than in men. Most of the increase occurred among patients in the older age group (50–59 years) than in younger ones (30–39 and 40–49 years). On time–frequency plots, the growth trajectories of TKA for men and women overall and TKA for the older age group appear as exponentials. Nevertheless, an increased demand for TJA by the "baby-boom" generation seems to be sustained, and some estimates suggested that the volume in the USA could expand by 17 times from that in 2006 [17]. A number of reasons seem to underlie this change, including a more active lifestyle when younger (therefore more joint injuries), increasing longevity, increasing expectations of active life at older ages, and greater incidence of obesity. It is unlikely however that these hypothetical projections will be attained because of the increasing pressure on healthcare costs and surgical workforce issues.

While there may be rather different criteria used for surgical intervention in different countries, there appears to be an increasing demand for joint arthroplasty in westernized populations that are living longer and perhaps having greater expectations of more active lifestyles in later age.

The impact of OA on quality of life

The burden of illness in OA at the individual level has been investigated recently by Tarride et al. [18], who compared in a cross-sectional study of Canadian health records the self-reported health status and health-related quality of life (HR-QoL) in OA patients vs. matched controls (matched by age, sex, and

rural/urban status). The results showed that OA patients reported a worse perceived health status than controls, with 34.8% reporting a status of poor or fair vs. 18.5% of controls. OA patients also had a lower HR-QoL (mean: 0.68 vs. 0.84 on Health Utility Index 3 score; $p < 0.0001$). Similar differences were found in the analyses by subgroups according to age, sex, obesity, and number of medical conditions. The study also reported that comorbidities were relatively more frequent in the OA patients, with 52.1% having 4 or more comorbid conditions vs. 26.9% in controls. Particularly prevalent among OA patients were back problems [adjusted odds ratio (adj OR) = 2.5], stomach/intestinal ulcers (adj OR = 3.7), bowel disorders (adj OR = 3.0), fibromyalgia (adj OR = 3.4), and chronic fatigue syndrome (adj OR = 3.2). It is not clear to what extent these conditions are a consequence of OA, or its treatment, or whether there is some underlying predisposition to medical conditions that may also predispose to OA.

Losina et al. [19], starting with US census and obesity data for persons aged 50–84 years, used a mathematical model to estimate the quality-adjusted life year (QALY) losses in subgroups according to obesity and knee OA. The total losses per person ranged from 1.857 years in non-obese persons with OA to 3.501 years in obese persons with OA, resulting in an overall 86.0 million quality-adjusted life years lost. Thus, OA seems to be linked to a considerable decline in overall health.

In patients with severe OA, total joint replacement can improve HR-QoL. This has been shown in short-term follow-up studies (e.g., [20]) and more recently in a long-term follow-up study [21]. In the latter, consecutive patients who had just undergone an OA-related TJA (hip or knee) were recruited and assessed for HR-QoL at various intervals up to 7 years. In the 39 subjects who completed the full follow-up period, the more marked improvements in both SF-36 and WOMAC scores were seen at 6 months and at 7 years. The authors concluded that QoL improvements are therefore maintained over the long-term. Studies that have estimated costs and outcome over the patient's projected lifetime using modeling techniques [22] (in TKA) or over 5 years in a trial-based health economic study [23] (in THA) have confirmed the long-term benefits and cost-effectiveness of TJA in a wide variety of patients.

A greater incidence of death in OA patients, which had been suggested in a review of clinical studies [24], has recently been confirmed by Nuesch et al. [25] in a retrospective epidemiological study using general practice data from the south of England. This research found that the all-cause mortality risk was greater in individuals with symptomatic OA (knee or hip) with radiological confirmation ($n = 1163$; aged ≥ 35 years) than in the general population (standardized mortality ratio = 1.55). All disease-specific causes contributed to the effect but it was mostly driven by cardiovascular- and dementia-associated mortality. Once again, it was not clear to what extent OA is related to these events or whether there is some underlying predisposition.

Costs associated with OA

The economic cost of OA is considerable [26]. Whether one examines just the direct healthcare costs (hospital admissions, medical examinations, drug therapy, etc.) or includes indirect costs (e.g., losses in productivity resulting from absence from work), the total costs relating to the treatment of OA are very high—estimated at between 1% and 2.5% of the gross domestic product (GDP) for westernized countries [27].

The direct costs of OA treatment are mostly driven by the cost of surgery for TJA. In Great Britain, this was estimated to account for 85% of the total direct costs of just over £1 billion in 2010 [28]. It was noted that while there was no national tariff for joint replacement in the UK (they vary between healthcare trusts), the final cost was mostly dependent on the length of stay in hospital. In USA, hospital prices can vary considerably and in a very recent study [29] that requested a "bundled price" (hospital plus physician fee) for THA, the researchers received fee estimates ranging from $11,100 to $125,798. This study also noted that the majority of hospitals were reluctant (unable or unwilling) to quote a bundled fee. The total direct cost attributed to joint replacement in the USA in 2009 was estimated to be $42 billion [30]. Costs that must be integrated into these analyses are those associated with post-surgical rehabilitation, costs that tend to be higher in older patients for strategies with varying effectiveness [31,32]. While the cost-effectiveness of TJA is not further discussed in this report, the reader is directed to the following references of interest [33–35].

The healthcare costs for OA sufferers are considerably higher than that for age-matched controls. In a 1997 cohort analysis of Olmsted County data, Gabriel et al. [36] estimated that the direct annual medical costs for OA patients (which included costs for concomitant conditions) were $2655 (median $664) vs. $1688 (median $232) in controls—a strongly statistically significant difference ($p < 0.0001$ following adjustment for age and sex). Other studies of the same period also found that OA patients incurred markedly higher healthcare costs than non-affected individuals [37,38]. More recently, in the pharmacoepidemiological study by Tarride et al. [18] (mentioned above), the healthcare costs to OA patients (i.e., for physician services, outpatient procedures, and hospitalizations) were also noted to be about twice, per person per year, than that of the non-OA controls (Canadian $2233 vs. $1033). This conclusion was not dependent on age group ($< 65/\geq 65$ years) but was more pronounced in men (OA patients incurred 3.2 times the cost of controls) and in obese individuals (3.1 times cost of controls). This study did not include drug costs nor the costs associated with non-physician healthcare providers or indirect costs, so the total costs to patients could be even higher. In another recent cohort of OA sufferers in active employment, the economic burden of the disease significantly correlated with self-rated disease severity [39].

The indirect costs of OA are driven mainly by the loss of productivity due to absenteeism from paid work. These costs, along with direct costs, are usually included in economic studies of disease burden (termed societal costs). In the British study discussed above, the estimated cost due to lost economic production for OA was £3.2 billion in 2002 [28]. The study also estimated that £258 million of indirect costs could be attributed to community and social services involvement. In a recent Dutch study, patients with mild to moderate OA (of at least 6 months duration, with conservative treatment and in paid employment) had mean lost productivity costs of €722 (median €217) per patient per month [40].

As joint arthroplasty has been increasing in recent years (including in younger patients), thereby pushing up direct healthcare costs, it seems reasonable to assume that total costs associated with OA to society are rising fast. Piscitelli et al. [16] estimated that the costs of TJA in Italy increased by 46% over the period 2001–2005; Chen and colleagues estimated the costs of TJA in the UK increased by 66% over the period 2000–2010. Additionally, Kurtz et al. [17] noted that there is greater demand for "premium" implant technologies that are longer lasting, but more expensive amongst the younger TJA candidates. The costs are therefore set to increase for the foreseeable future.

Therapeutic options in OA

Evidence-based guidelines for OA treatment have been published under the auspices of the European League Against Rheumatism (EULAR) [41,42], Osteoarthritis Research Society International (OARSI) [43], the National Institute for Health and

Clinical Excellence (NICE) [44], and more recently by the American College of Rheumatology (ACR) [45].

NICE groups the therapeutic options into 3 concentric rings, based on the weight of evidence and the relative safety for the patient (see Fig.). Starting in the center, the recommendations are that all persons with OA should receive advice concerning strengthening exercises, aerobic fitness training, and weight loss (where appropriate). The next ring of treatment strategies includes the relatively safe pharmaceutical options of paracetamol and topical non-steroidal anti-inflammatory drugs (NSAIDs), while the outer ring proposes oral NSAIDs and adjunctive treatments, a variety of less well-proven methods for symptom relief. The final option of joint arthroplasty is also included in the outer ring. The OARSI and ACR guidelines add acupuncture to these adjunctive treatments for pain relief.

All these therapies aim to reduce joint pain and stiffness and thereby maintain or improve functional capacity.

The existing treatment options may therefore be grouped as those which have a non-pharmacological approach and those which have a pharmacological approach. From a standpoint of health economics (HE) analysis, such a division makes intuitive sense.

The health economic evaluation

The economic evaluations of healthcare provide essential information with which to guide efficient resource allocation. In many countries now, there is also a formal requirement for economic evaluations to be included in the market authorization dossier for a new pharmaceutical product or medical device (particularly for reimbursement purposes) [46]. These economic evaluations are often considered as the "fourth hurdle" of drug/device approval, after efficacy, safety, and quality [47].

There are 4 possible types of full economic evaluation, i.e. the comparative analysis between 2 or more health technologies in terms of costs and effects [48]

- *Cost-minimization analysis*: where therapies are compared on their costs only and there is no difference in effect (outcome)—which is rather rare.
- *Cost-effectiveness analysis*: where therapies are compared on their costs and outcomes, based on natural units (WOMAC score, pain, quality of life, life years, etc.).
- *Cost–utility analysis*: where therapies are compared on their costs and outcomes, based on their utility (the quality of living adjusted by a value given by society) QALYs.
- *Cost–benefit analysis*: where therapies are compared on their costs and outcomes, based on effects in monetary terms (net benefit). The practical difficulties of measurement and valuing health benefits have limited the use of this type of analysis in healthcare.

All 4 types therefore add-up to the costs similarly, but then differ in how the patient outcomes are approached.

Costs

The cost items that may be included are given by the "perspective" of the analysis. Multiple perspectives exist, including the societal perspective (the broadest view), which includes all direct costs and indirect costs resulting from the condition and its treatment; this perspective is theoretically preferred. However, most local guidelines require the adoption of the decision maker or healthcare payer perspective, which includes only the direct medical costs. Other perspectives can be that of the patient, an employer, or department budget [49]. Whichever approach is adopted, it is recommended that the cost items should be individually enumerated to facilitate comparisons between studies [49].

Outcomes

The clinical outcomes of OA are pain, functional disability, and mortality; the patient's global assessment is also frequently identified as a "core" variable in clinical trials [50]. With the exception of mortality, these outcomes are most often captured in a HR-QoL questionnaire, which might be generic or disease specific, but they can be scored using stand-alone tools for each variable separately. Mortality is often not measured as an outcome parameter since most clinical studies are of relatively short duration (most being concerned with pain control), but for health economic studies, it is considered important to be able to model the lifetime costs and outcomes.

The QoL tools can be generic or specific to diseases. Generic instruments include EQ-5D, SF-36, or Health Utility Index and can be used in any intervention and disease [51]. Disease-specific

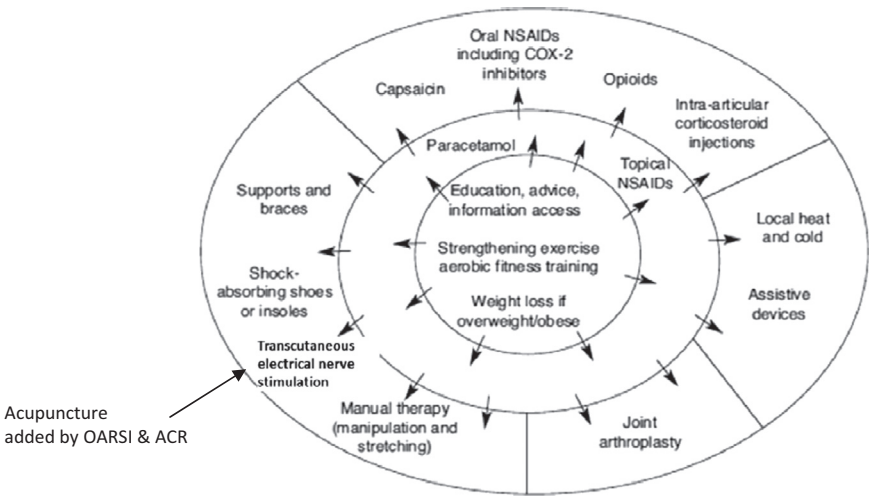

Fig. Therapeutic options in OA grouped according to weight of evidence and the relative safety for the patient, with the first options/recommendations at the center (NICE, 2008).

questionnaires (such as the WOMAC in OA) provide greater sensitivity to the clinical condition under consideration, but they do not allow comparison with other disease areas.

To demonstrate treatment effect, the results of such tools are usually summarized as means by treatment group to demonstrate treatment effect, but some experts have argued for the adoption of response thresholds, either on a composite outcome or pain alone [52,53].

A major factor for the patients who require long-term use of oral NSAIDs is the avoidance of serious gastrointestinal adverse events, such as ulcers, perforation, obstruction, or bleeding [54].

The most widely used type of health economic analysis is the cost–utility analysis since it allows comparisons of different diseases with different clinical outcomes. The outcome measure used in cost–utility analyses is the QALY, a product of life expectancy and QoL or, in other words, the remaining years of life and the utility of those years. While these factors are clearly dependent on the age of the individual, other concomitant health problems, and prevailing QoL, the average indicators by age group are possible to calculate. The QALY approach has been endorsed by the OMERACT expert group [55].

Conducting an economic evaluation

The costs of an intervention and its associated outcomes can be recorded (or estimated) by 2 different approaches: either a clinical trial-based evaluation or by decision analytic modeling. Trial-based evaluations of a type known as "explanatory trials" are particularly found in the earlier stages of drug's lifecycle. In these studies, the treated population is rigorously selected and homogeneous (and therefore a high internal validity). More frequently encountered, however, are "pragmatic trials," where patients are treated in a "real-world," clinical practice setting. Such studies have a high external validity, i.e. in tune with real clinical practice, but the internal validity (particularly randomization and treatment blinding) can be strongly compromised.

The modeling studies use initial values obtained from clinical trials, and then mathematical models to synthesize all downstream information regarding treatment process, costs, and outcomes. They therefore provide a version of reality, which may be simplified or complex but must remain credible. The preferred modeling methods include decision trees, health-state transition models (Markov), and discrete-event simulations.

The pros and cons of these economic approaches have been extensively discussed [56–58].

Incremental cost-effectiveness ratio and willingness-to-pay

Pharmaceutical treatments or therapeutic procedures can therefore be compared, against "standard care" or a therapy of established cost-effectiveness, using the observed costs and outcomes. While many HE trials compare just 2 treatments, it may be that no single comparator is appropriate and more than one should be included. Torrance has advocated that a new drug or treatment should be compared to "all feasible alternative treatments at all levels of intensity," while admitting that such an approach is usually impractical [59].

To compare 2 treatments based on their cost per QALY, the incremental cost-effectiveness (or utility) ratio (ICER) is calculated. This is defined as the difference between the costs of 2 interventions (A and B) divided by their difference in terms of effectiveness.

$$\frac{(\mathrm{Cost_A}-\mathrm{COST_B})}{(\mathrm{QALY_A}-\mathrm{QALY_B})}=\mathrm{ICER}$$

If an ICER is below an arbitrary threshold of "willingness-to-pay" (per effectiveness unit), then the new intervention (as opposed to the reference) is economically sound and should be adopted.

The willingness-to-pay (WTP) for a treatment is a theoretical value that is put on a treatment's effectiveness (i.e., per QALY). In the UK, this is usually taken to be about £30 000 per QALY, although NICE (who performs the economic analyses) has stated that it does not put a threshold as to what constitutes an unacceptable price, emphasizing that above this threshold the justification needs to be increasingly strong [60].

Most other countries have no generally accepted or recommended thresholds for cost-effectiveness, or even a formal acceptation of the QALY as an economic construct. Nevertheless, the ICER of new therapies does indeed influence the probability of which they are reimbursed [61]. Therapies with low ICERs have relatively high probabilities of being reimbursed whereas those with high ICERs do not.

The World Health Organization (WHO) has suggested a cost-effectiveness threshold based on evaluating each disability-adjusted life-year (DALY) as 3 times the gross domestic product (GDP) per capita [62], where a DALY is the sum of the expected number of years of life lost (due to the disease) plus the expected number of years lived with disability (due to the disease). On this basis, a willingness-to-pay of 2-times the GDP per capita was recommended and used to define intervention thresholds in osteoporosis [63].

Non-pharmacological treatments for osteoarthritis: Are they value for money?

While the importance of maintaining physical activity is well-recognized [64], the targets proposed in guidelines are frequently unmet [65–68]. In part, this is because the percentage of GPs who actually advise their OA patients to exercise or refer them for physical therapy can be very low, with rates varying between 6% and 63% [65]. This may be due to the inherent conflict in the recommendation: exercise is beneficial but maintaining adherence is often difficult. Specialized pain reduction techniques and lifestyle modifications may be beneficial in this respect, but they require additional resources and health expenditure to be put in place. So far, there is limited evidence that such non-pharmacologic, non-surgical interventions in OA are cost-effective. Hence, the recent study by Pinto et al. [69] that attempted to answer the question: "do these interventions represent good value for money?"

Their approach was to search electronic databases for all randomized controlled trials (RCTs) or quasi-RCTs that specified hip or knee OA and were published before October 1, 2010. Excluded were studies on chronic knee pain (modeling studies were also excluded since they are virtually non-existent in this field). The studies were assessed for the quality of economic reporting using the QHES (Quality of Health Economic Studies) instrument [70] and classified as either "high" quality (≥ 75 points) or "low" quality (< 75 points). The studies were also assessed for their "risk of bias" using an internal validity checklist developed by Cochrane Back Review Group [71] and classified as having either a high risk (< 6 items satisfied) or low risk (≥ 6 items satisfied). The costs were converted to US$ (as valued in 2008), and where multiple costs were captured, the societal costs were reported. The primary health outcome reported was the QALY, and the WTP threshold was $50,000. They assessed 11 studies that investigated the health economics of exercise, acupuncture, rehabilitation, and lifestyle change.

Table 1 presents a selection of the included studies with the summary details and outcome measures.

Most of the 11 studies in the review were identified as being pragmatic ("real-world") trials, but designed (or reported) in a way that raised concern of possible bias. In no study was the outcome

Table 1
Summary details of a selection of the studies reviewed by Pinto et al. [69]

Type and reference	Participants and indication (Payer perspective)	Intervention (duration) total study duration	Primary health outcome Result (relative to control)
Exercise programs			
Richardson et al. [72] (UK)	214 Patients; knee OA (NHS and social services)	Physiotherapist-led classes + home exercise vs. home exercise alone (8 wk) 1 yr	Locomotor function (significantly improved) Costs were 1% lower in intervention gp and mean QALY/person doubled (cost saving)
Cochrane et al. [73] (UK)	312 Patients; hip and/or knee OA; (Societal)	Instructor-led water exercises ($n \leq 84$) vs. usual care (1 yr) 1.5 yr	WOMAC pain subscore (significantly improved) Costs were 25% lower and incremental QALY gain reported (cost saving)
Acupuncture			
Reinhold et al. [74] (Germany)	489 Patients; hip and/or knee OA; (Societal)	10–15 acupuncture sessions over vs. delayed acupuncture trt (3 mo)	WOMAC index (significantly improved) Costs were almost 9-fold higher, but incremental QALY gain reported. Incremental cost per QALY gained = $25,707 (good value for money)
Rehabilitation programs			
Coupé et al. [75] (the Netherlands)	200 Patients; hip and/or knee OA; (Societal)	18 sessions of behavioral-graded activity (BGA)[a] vs. standard physiotherapy (12 wk) 1 yr	WOMAC pain subscore and pain VAS (NS difference over short and long-term) Costs were 24% lower, but at 1 yr QALYs were lost for a saving of $63,019/QALY lost (poor value for money)
Hurley et al. [76] (UK)	418 Patients; knee pain (mild-severe); 3-arm (NHS and social services)	12 sessions of ESCAPE program[b] (either individual or grp) vs. usual care (6 wk) 7.5 mo	Responders on WOMAC functional subscore (i.e. ≥15% improvement): (sig. improved for both rehab arms vs. usual care; nd not sig diff from each other Costs increased 2.5 fold for individual sessions and 1.6 fold for groups; QALY loss and ICER dominated by usual care (poor value for money)
Jessep et al. [77] (UK)	64 Patients; knee pain (mild-severe) (unspecified)	10 sessions of modified ESCAPE program[b] vs. "usual physical therapy" (5 wk) 1 yr	WOMAC function subscore (NS difference between arms at 12 mo) Costs were 45% lower and incremental QALY gain reported (good value for money)
Lifestyle			
Lord et al. [78]	170 Patients; knee OA (Societal, NHS, and individual)	Nurse-led patient education program vs. usual care (4 wk) 1 yr	WOMAC index (NS for all subscales) Cost increases to $659 ($p < 0.001$), QALY increases to 0.001 Costs increased 3.2 fold for no QALY change; ICER dominated by usual care (poor value for money)
Patel et al. [79]	812 Patients; hip and/or knee OA (health and social services and Societal)	6 sessions of self-management program plus booklet vs. education booklet alone (6 wk) 1 yr	SF-36 physical and mental health subscores (NS difference at 1 yr) Healthcare costs increased 1.6 fold at 1 yr; societal costs were 3% lower. A slight QALYs loss was reported: a saving of $4400/QALY lost (poor value for money)

OA, osteoarthritis; UK, United Kingdom; wk, week; mo, month; yr, year; NHS, National health service; vs., versus; trt, treatment; sig, significant; NS, non-significant.

[a] *BGA*: A process of encouraging increasing levels of activity via long- and short-term goal setting (operant conditioning) & integrating these activities into lifestyle; provided by trained physiotherapists.

[b] ESCAPE = Enabling Self-management and Coping with Arthritic Knee Pain through Exercise, a rehabilitation program integrating exercise, self-management, and active coping strategies.

assessor blinded to the intervention, and several studies did not reach the minimal threshold on the internal validity checklist. Only 5 studies satisfied the quality threshold of the QHES.

The review noted that in such economic evaluations, much of the interpretation depends on the comparator used and whether it has known cost-effectiveness and approval in the clinical setting (disease and population under investigation). If this is the case, then the new treatment may be tested and the overall efficiency of healthcare spending compared.

The review also criticized that only one of the studies [80] included a clinical outcome measure (% responders) that has been recommended by OMERACT-OARSI for use in evaluations of treatments for OA, although another study [76] did use the percentage of responder patients on their improvement according to physical function [52]. Also that, although most studies used the WOMAC scale as an outcome measure, this was often expressed only as one or other of the subscales and less frequently as the total score.

An interesting outcome scenario was observed for the study of behavioral-graded activity vs. a standard physiotherapy program. The BGA program had lower costs but also QALY losses, so that the ICER, with a saving of $63,000 per QALY lost, was situated in the south-west (lower left) quadrant of the cost-effectiveness plane. With a willingness-to-pay threshold estimate at $50,000, this intervention would seem to be acceptable. However, the review pointed out that the value which society is willing to pay for a QALY gain is not necessarily the same as what will be accepted for QALY loss, thus breaking the symmetry of the cost–benefit relationship [81,82]. In this case, a greater WTP threshold in the lower left quadrant is appropriate, and this intervention should be rejected. It might be noted that the authors of the original research concluded that BGA yielded "similar" results to usual care and therefore an acceptable alternative.

Previous reviews [5,83] of exercise programs for the management of osteoarthritis (OA) of the knee have concluded on their utility, and the Ottawa Panel [84] concluded that for obese/overweight OA patients, an intervention comprising physical activity with diet produced the most beneficial results. The most cost-effective method to establish an effective exercise habit over the long-term however remains elusive.

The points for future research indicated by this review are the potential cost savings of employing non-healthcare professionals for the exercise training programs; that studies of training programs should try to establish a dose effect on outcome measures (as has been recently shown for physical activity levels [64]); the need for longer and perhaps standardized time horizons (e.g., 3 years); the possible effects of exercise on structural aspects of the arthritic joint; and the interest of trying to quantify

independently the effects of exercise on weight loss and the effects of exercise on pain relief to estimate how weight may directly impact joint pain.

Pharmacological treatments for osteoarthritis: Are they value for money?

Previous systematic reviews have examined the cost-effectiveness of cyclooxygenase-2 (COX-2)-selective non-steroidal anti-inflammatory drugs (NSAIDs), including the ones by Maetzel et al. [85] and more recently Chen and colleagues. Other reviews have examined glucosamine and chondroitin supplements [86]. The Chen et al. review is particularly notable for its highly detailed approach, with discussions of modeling methods and cost items.

For the purposes of the expert group meeting, a review was made of full economic evaluations that have compared the costs and outcomes of a least 2 pharmacological interventions and published between 2003 and the end of September 2012. A search was made of PubMed/Medline-referenced English language articles using the key words (and Boolean operators): [osteoarthritis] AND [cost-effectiveness, cost–utility, economic, cost]. Two reviewers (M. Hiligsmann and J. Severens) independently applied these criteria to identify citations during title and abstract screening.

A total of 16 studies that satisfied the inclusion criteria were included in our review. These are presented in Table 2 with the summary details, outcome measures, and results.

A total of 10 studies investigated COX-2-selective NSAIDs, comparing them most frequently with a traditional NSAIDs (diclofenac, ibuprofen, and naproxen) or high-dose acetaminophen. The effects of various gastroprotective agents, such as proton pump inhibitors (PPIs), histamine H2 receptor antagonists (H2RA), and misoprostol, were also tested. One study examined the semi-synthetic opioid analgesic oxycodone in 2 formulations. Three studies examined oral doses of proteoglycan precursors, glucosamine (sulfate or hydrochloride), and chondroitin sulfate (which may help repair joint cartilage).

A variety of patient groups were studied, with in some cases a mixed population of OA and rheumatoid arthritis sufferers. Subgroups of patients included those who did not respond to acetaminophen; those who did not respond to acetaminophen and at high risk of developing an adverse gastrointestinal event; those at high risk of an upper gastrointestinal event; and elderly patients.

The investigators used different outcome measures, including intermediary clinical outcomes, such as the number of serious gastrointestinal disorders or the number patients without side effects, and generic outcome measures, such as years of life saved and QALYs.

Only one study [87] specifically examined the incidence of serious CV event (myocardial infarction, stroke, and CV death) risk.

The studies were found to constitute a very heterogeneous ensemble, making comparisons of the results between the studies problematic.

The studies were performed in several different countries with quite diverse public health systems including Canada, the UK, the USA, Taiwan, Australia, Germany, Mexico, the Netherlands, and Belgium. Various analytical models were used including decision tree analysis, Markov model, discrete-event simulation, simulation model, and trial-based economic evaluation. The time horizon of the analysis varied from 4 months to lifetime.

Because of the large heterogeneity observed in the treatment comparisons and methodologies, few firm conclusions could be reached. In common with Chen et al. [54], it was noted that drug manufacturers sponsored a majority of published analyses. Studies not supported by the drug manufacturers were considerably less favorable to COX-2-selective NSAIDs. Longer follow-up is needed to allow a clearer understanding of adverse event rates and their associated outcomes.

In some cases, it was noted that the different payer perspectives used in the studies could affect the interpretation of the results. So, by example, in the study of Marshall et al. [92], oxycodone was cost-effective compared with oxycodone–acetaminophen from the societal perspective, but probably not from the healthcare perspective. The working group therefore recommends using a 3-step approach, capturing (a) the cost of intervention, (b) all healthcare costs, and (c) societal costs, and attempt to illustrate each of these on the same cost-effectiveness plane.

Discussion and conclusions

From this short review and the expert discussion, it is apparent that OA is a growing problem in Western societies. Recent epidemiological research suggests that, for individuals of 60 years of age or older, the prevalence of symptomatic OA is about 10% for knee OA and 5–7% for hip OA, but these levels could increase in the future because of the increasing rates of obesity and longevity [1,2].

OA is associated with higher risk of QoL decline, comorbidity, and death. It is associated with productivity losses in individuals who are gainfully employed, and with the socioeconomic demands to increase the retirement age, the burden of this productivity loss will rise. The direct costs associated with OA are high and mostly driven by the cost of surgery and hospitalization. The actual costs remain challenging to measure because of the high variability of cost estimates and the different pricing structures (as illustrated by the recent US study requesting bundled prices for THA).

The inference that OA constitutes a considerable burden of illness on western societies is not new (e.g. [101,102]), but is supported by numerous recent HE studies with rigorous methodological approaches. In particular, the burden of the disease in Europe has been addressed, with more consensual diagnosis criteria and consistent methodological approaches.

In view of these epidemiologic and economic pressures, there is a growing urgency for more effective treatments for OA: both symptomatic treatments, which are safe over the long-term, and disease-modifying treatments, which could slow or halt disease progression. It is also important to promote non-pharmacological approaches, already adopted by guidelines, to help patients bring about beneficial lifestyle changes. For each of these approaches, it is necessary to find the most cost-effective options and, eventually, identify optimal combinations of these options.

The HE studies that were reviewed and discussed during this meeting showed considerable heterogeneity in terms of methodology and reporting, which seriously undermines their usefulness in meta-analyses and understanding the reasons for outcome differences. The variety of methodological approaches is a short-coming that has been recognized before. In 2002, an article published under the auspices of the Outcome Measures in Rheumatology (OMERACT) and the International League Against Rheumatism (ILAR) [103] warned against the "lack of agreement on methods" considering it to be a "threat to the validity, usability, and comparability of such [economic] research and [having] major implications on regulatory decisions." Although several guidelines on the subject are available (ISPOR, OARSI, etc.; [104,105]), it seems that their advice goes unheeded.

As recommended previously [103,106,107], the present working group was strongly supportive of the development of a reference case for HE studies in OA, i.e. a "core set" of minimum criteria that should be included to allow comparability across studies. But, in addition to this, the present working group advocated that the "standard optimal care" be more clearly defined, in terms of best clinical practice, for the control arms of interventional studies. Such an optimal care guideline would have to integrate stage of the

Table 2
Summary details of cost-effectiveness and cost–utility of pharmacological treatments in osteoarthritis

Reference and country	Model	Outcome measure(s)	Intervention	Results
Kamath et al. [88] (USA)	Decision tree	GI adverse events/patients who achieved perceptible relief pain	Rofecoxib and celecoxib vs. high-dose acetaminophen or ibuprofen with or without misoprostol	In average-risk population, acetaminophen dominates the other options in terms of cost per GI event averted In high-risk patients (for GI events) and those who do not respond to acetaminophen, rofecoxib dominates ibuprofen
Maetzel et al. [85] (Canada)	Markov	Quality-adjusted life years (QALY)	Rofecoxib vs. with naproxen and celecoxib vs. with ibuprofen and diclofenac	For patients with RA at average risk, both rofecoxib and celecoxib are not cost-effective. In high-risk patients, they are cost-effective
Spiegel et al. [89] (USA)	Decision tree	QALY	Rofexocib and celecoxib (coxibs) vs. naproxen	US$ 275,809 per QALY in average-risk patients US$ 55,803 per in patients with a history of bleeding ulcers
Moore et al. [90] (UK)	Decision tree	QALY	Etoricoxib vs. non-selective NSAIDs	Cost saving over non-selective NSAIDs used with a PPI or misoprostol £12,466 per QALY vs. non-selective NSAIDs alone £6438 per QALY vs. NSAIDs co-prescribed with H2 antagonists
Yen et al. [91] (Taiwan)	Decision tree	QALY	Celecoxib vs. naproxen Hyaluronan vs. celecoxib	US$ 21,226 per QALY US$ 42,000 per QALY
Marshall et al. [92] (Canada)	Trial-based economic evaluation	QALY	Oxycodone vs. oxycodone–acetaminophen	Dominant (societal perspective) US$ 75,810 per QALY (healthcare perspective)
Loyd et al. [87] (Canada)	Decision tree	QALY	Celecoxib vs. NSAIDs	US$ 31,097 per QALY (base model)
Ward et al. [93] (Germany)	Discrete-event simulation	QALY	OROS hydromorphone vs. oxycodone	€8343 per QALY
Al et al. [94] (Netherlands)	Decision tree	Life year gained (LYG)	NSAIDs, arthrotec and celecoxib	For arthrotec compared to NSAIDs alone, €5676 per LYG for all patients and € 526 for medium- to high-risk patients For celecoxib vs. arthrotec, from €56,667 to €15,429 according to pat risk
Contreras-Hernandez et al. [95] (Mexico)	Decision tree	Number of patient with pain control without adverse events	Celecoxib, non-selective NSAIDs, and acetaminophen	Celexocib was dominant
Bessette et al. [96] (Canada)	Markov model	QALY	Celecoxib (first-, second-, and third-line)	Second-line celecoxib was dominant
Black et al. [86] (UK)	Cohort simulation	QALY	Glucosamine sulfate/hydrochloride and chondroitin sulfate	£21,335 per QALY for adding glucosamine sulfate to current care
Latimer et al. [97] (England and Wales)	Markov model	QALY	COX-2-selective inhibitors and traditional NSAIDs alone or in combination with PPI	ICER less than £1000 for the addition of a PPI to both COX-2-selective inhibitors and traditional NSAIDs
Bruyère et al. [98] (Belgium)	Trial-based economic evaluation	QALY	Chondroitin sulfate vs. placebo	€12,984–20,866 per QALY
Scholtissen et al. [99] (Belgium)	Trial-based economic evaluation	QALY	Glucosamine sulfate vs. paracetamol Glucosamine sulfate vs. placebo	Dominant €3617 per QALY
Brereton et al. [100] (UK)	Cohort simulation	QALY	Celecoxib plus a PPI vs. diclofenac plus a PPI	£9377 per QALY

GI, gastro-intestinal; OA, osteoarthritis; PPI, proton pump inhibitor; QALY, quality-adjusted life-year; RA, rheumatoid arthritis; vs., versus.

disease (probably a combination of non-pharmacological and pharmacological approaches) and would have to be joint specific (knee, hip, and hand). It is recognized however that due to the large number of treatment options and relatively poor evidence of their efficacy in combination, the task is considerable [108]. Be that as it may, the goal of being able to define a reference treatment would facilitate the development of any new treatment and provide a robust comparator for future meta-analysis.

In order to find a consensus for this task, it was strongly encouraged that the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process [109] be followed to evaluate studies in the field and evaluate their outcomes and quality of evidence. This process differs from other assessment methods in that it "evaluates the evidence across studies for confidence in effect for each outcome and separates out judgments about the quality of the evidence from judgments about the importance of the recommendation" [110].

The evaluation of published articles was also an area of concern for the expert group. It was often noted that important information was missing from the abstracts of reviewed articles and in some cases, useful data was also missing from the body of the article. One step toward better reporting has been taken with the publication of CHEERS statement [111]. Similar to the "CONSORT" statement for randomized controlled trials, this initiative provides a checklist of items to include when reporting economic assessments of health interventions. Efforts are also needed to promote the use of guidelines used to evaluate and grade published studies [70,112].

At the present time, the treatments for OA concern essentially pain relief. If disease-modifying OA drugs (DMOADs) could be developed in the future [113,114], then it is possible they could dominate HE evaluations. But these treatments are likely to be expensive and may not work for everyone. The clinical questions will then become, in which patients do these provide the most benefit and at what stage of OA progression they should be used.

The first question will probably be answered by the mechanism of action of the DMOAD and the biomarkers associated with and radiographic characteristics of the diseased joint. The second question, the problem of staging in OA, continues to provoke debate. The lack of a hard clinical end point (and a probabilistic model of attaining that endpoint) is one of the main differentiating factors in the economic research on OA compared with osteoporosis (OP). Although the final outcome of HE is the QALY gain/loss over lifetime, it can be informative to assess differences at an intermediate endpoint. Thus, to be able to capture QALY gain/difference at the "time of treatment failure" should be investigated and included in new analytical models.

The surrogate endpoint in OA of "time to treatment failure" or "need for joint replacement surgery" based on the structural changes and symptomatic thresholds has been proposed previously [115,116], but due to regional differences as to when to perform surgery and the inconsistencies in the decision process, this proposition has still to convince the clinical opinion leaders [14].

Due to the major cost implications of TJA, delaying such a step (where possible) has a significant effect on health budgets. Furthermore, because most TJA are elective procedures and the utilization of elective surgery is likely to increase, it has been argued that the development of appropriateness criteria to determine priorities will provide a powerful tool for controlling costs [117,118]. The use of a validated surrogate endpoint could also prove critical for the development of DMOADs. Thus, economic models of OA will, in the future, have to integrate the possibilities of structural modification and intermediate endpoints. It will also be necessary to address the question of whether by prolonging the time to arthroplasty, the success of this intervention (in terms of recovery time, QOL, revision, etc.) is negatively impacted.

In conclusion, OA is a common disease with high prevalence in later life. Although the prevalence rates vary widely across studies, due to differences in diagnostic criteria and populations, some clear patterns are beginning to emerge. One is the increasing risk in overweight individuals, whereas others are the relatively greater risk in older women than men and the increasing prevalence in younger age groups of both sexes (particularly the 50–59 years of age). The growing demand for elective surgery for joint replacement, particularly from relatively younger age groups, drives the need for more long-lasting prostheses and increases the risk of surgical revision. Even within the traditional population base, the costs of treatment (driven mainly by joint replacement) are rising steadily and pose a considerable cost burden on welfare states. Current treatments, which comprise pharmacological and non-pharmacological therapies, aim to reduce pain and maintain functional performance, but they are not always good value for money. But HE studies conducted in the field fail to allow ready comparison, and few hard conclusions can be drawn. Previously issued guidelines and reference case analysis for HE studies appear to go largely unheeded. The working group concluded that the development of a consensus on standard optimal care of OA patients (according to stage and affected joint) would greatly help in assuring comparability between studies and support the reference case. This and the fine-tuning of the concepts of "time to treatment failure" or "time to arthroplasty" will assist the regulatory pathway for future disease-modifying drugs. Thus, there remains much to be done in terms of providing clinical guidelines for treating OA as well as promoting the use of existing methodological guidelines for the conduct of HE studies before we can be certain of the real incremental cost-effectiveness between existing treatment options.

Conflicts of interest

M.H. (Mickael Hiligsmann) has received research grant, lecture fees, and/or consulting fees from Amgen, Pfizer, Novartis, Servier, and SMB. C.C. has received honoraria and consulting fees from AMGEN, GSK, Alliance for Better Bone Health, MSD, Eli Lilly, Pfizer, Novartis, Servier, Medtronic, and Roche. M.-L.B. was consultant and grant recipient from Amgen, Eli Lilly, MSD, Novartis, NPS, Roche, and Servier. O.B. has received grant research from IBSA, Merck Sharp & Dohme, Nutraveris, Novartis, Pfizer, Rottapharm, Servier, and Theramex; consulting or lecture fees from IBSA, Rottapharm, Servier, and SMB; and reimbursement for attending meetings from IBSA, Merck Sharp & Dohme, Novartis, Pfizer, Rottapharm, Servier, and Theramex. M.H. (Marc Hochberg) was a member of the Scientific Advisory Board of TREAT-OA Consortium; has served as a consultant to Abbott Laboratories, Allergan, Bioiberica S.A., Covidien, Iroko Pharmaceuticals, Merck & Co., and Pfizer Inc; and received speaker fees from Bioiberica S.A. and IBSA. D.H. receives royalties from DJO. T.K. has received fees for speaking from Abbott, AstraZeneka, Hospira, MSD/Schering-Plough, Nicox, Pfizer/Wyeth, Roche, and UCB; funds for research from Diakonhjemmet Hospital from Abbott, BMS, MSD/Schering-Plough, Pfizer/Wyeth, Roche, and UCB; and fees for consulting from Abbott, BMS, MSD/Schering-Plough, Nicox, Pfizer/Wyeth, Roche, and UCB. S.S. has served as an advisor for Lilly, Novartis, and Pfizer/Wyeth; has served as a consultant for Genentech, Lilly, Novartis, and Pfizer/Wyeth; and has received research support from Lilly and Pfizer/Wyeth. R.R. has received consulting and lecture fees for Merck Sharp and Dohme, Eli Lilly, Amgen, Novartis, Servier, Nycomed, Nestlé, and Danone. L.R. is an employee of Rottapharm. Y.T. is an employee of Servier. P.T. has received from UCB, Chelsea, and BMS. J.-Y.R. has received consulting fees, paid advisory boards, lecture fees, and/or grant support from Servier, Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed, NPS, Theramex, UCB, Merck Sharp and Dohme, Rottapharm, IBSA, Genevrier, Teijin, Teva, Ebewee Pharma, Zodiac, Analis, Novo-Nordisk, and Bristol Myers Squibb.

N.A., M.B., J.B., F.G., J.K., A.L., J.-P.L., D.P., S.R-N, and H.S. have no conflicts of interest.

Acknowledgments

The authors would like to thank Jeremy Grierson, PhD, for his assistance in preparing the draft of the manuscript from the presentations and discussions of the working group participants.

References

[1] Committee For Medicinal Products for Human use (CHMP). Guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis. CPMP/EWP/784/97 Rev. 1. 2010. European Medicines Agency, 20-1-2010.
[2] Leskinen J, Eskelinen A, Huhtala H, Paavolainen P, Remes V. The incidence of knee arthroplasty for primary osteoarthritis grows rapidly among baby boomers: a population-based study in Finland. Arthritis Rheum 2012; 64(2):423–8.
[3] Katz JN. Total joint replacement in osteoarthritis. Best Pract Res Clin Rheumatol 2006;20(1):145–53.
[4] Hiligsmann M, Reginster JY. The economic weight of osteoarthritis in Europe. Medicographia 2013;35:197–202.
[5] Roddy E, Doherty M. Changing life-styles and osteoarthritis: what is the evidence? Best Pract Res Clin Rheumatol 2006;20(1):81–97.
[6] Pereira D, Peleteiro B, Araujo J, Branco J, Santos RA, Ramos E. The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. Osteoarthritis Cartilage 2011;19(11):1270–85.
[7] Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum 1990;33(11):1601–10.
[8] Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991;34(5):505–14.
[9] Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet 2011;377(9783):2115–26.
[10] Nelson AE, Jordan JM. Defining osteoarthritis: a moving target. Osteoarthritis Cartilage 2012;20(1):1–3.

[11] Arden N, Nevitt MC. Osteoarthritis: epidemiology. Best Pract Res Clin Rheumatol 2006;20(1):3–25.
[12] Valdes AM, Doherty S, Muir KR, Zhang W, Maciewicz RA, Wheeler M, et al. Genetic contribution to radiographic severity in osteoarthritis of the knee. Ann Rheum Dis 2012;71(9):1537–40.
[13] Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2013;380(9859):2163–96.
[14] Altman RD, Abadie E, Avouac B, Bouvenot G, Branco J, Bruyere O, et al. Total joint replacement of hip or knee as an outcome measure for structure modifying trials in osteoarthritis. Osteoarthritis Cartilage 2005;13(1):13–9.
[15] OECD. Health at a glance 2011. OECD indicators. OECD Publishing 2011. ⟨http://dx.doi.org/10.1787/health_glance-2011-en⟩.
[16] Piscitelli P, Iolascon G, Di TG, Bizzi E, Chitano G, Argentiero A, et al. Socioeconomic burden of total joint arthroplasty for symptomatic hip and knee osteoarthritis in the Italian population: a 5-year analysis based on hospitalization records. Arthritis Care Res (Hoboken) 2012;64(9):1320–7.
[17] Kurtz SM, Lau E, Ong K, Zhao K, Kelly M, Bozic KJ. Future young patient demand for primary and revision joint replacement: national projections from 2010 to 2030. Clin Orthop Relat Res 2009;467(10):2606–12.
[18] Tarride JE, Haq M, O'Reilly DJ, Bowen JM, Xie F, Dolovich L, et al. The excess burden of osteoarthritis in the province of Ontario, Canada. Arthritis Rheum 2012;64(4):1153–61.
[19] Losina E, Walensky RP, Reichmann WM, Holt HL, Gerlovin H, Solomon DH, et al. Impact of obesity and knee osteoarthritis on morbidity and mortality in older Americans. Ann Intern Med 2011;154(4):217–26.
[20] Ethgen O, Bruyere O, Richy F, Dardennes C, Reginster JY. 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-A(5):963–74.
[21] Bruyere O, Ethgen O, Neuprez A, Zegels B, Gillet P, Huskin JP, et al. Health-related quality of life after total knee or hip replacement for osteoarthritis: a 7-year prospective study. Arch Orthop Trauma Surg 2012;132(11):1583–7.
[22] Losina E, Walensky RP, Kessler CL, Emrani PS, Reichmann WM, Wright EA, et al. Cost-effectiveness of total knee arthroplasty in the United States: patient risk and hospital volume. Arch Intern Med 2009;169(12):1113–21.
[23] Fordham R, Skinner J, Wang X, Nolan J. The economic benefit of hip replacement: a 5-year follow-up of costs and outcomes in the Exeter Primary Outcomes Study. BMJ Open 2012;2(3):e000752.
[24] Hochberg MC. Mortality in osteoarthritis. Clin Exp Rheumatol 2008;26(5 Suppl. 51):S120–4.
[25] Nuesch E, Dieppe P, Reichenbach S, Williams S, Iff S, Juni P. All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. Br Med J 2011;342:d1165, http://dx.doi.org/10.1136/bmj.d1165.:d1165.
[26] Woolf AD, Erwin J, March L. The need to address the burden of musculoskeletal conditions. Best Pract Res Clin Rheumatol 2012;26(2):183–224.
[27] March LM, Bachmeier CJ. Economics of osteoarthritis: a global perspective. Baillieres Clin Rheumatol 1997;11(4):817–34.
[28] Chen A, Gupte C, Akhtar K, Smith P, Cobb J. The global economic cost of osteoarthritis: how the UK Compares. Arthritis 2012;2012:698709, http://dx.doi.org/10.1155/2012/698709 [Epub@2012 Oct 2.:698709].
[29] Rosenthal JA, Lu X, Cram P. Availability of Consumer Prices From US Hospitals for a Common Surgical Procedure. J Am Med Assoc Intern Med 2013;11:1–6.
[30] Murphy L, Helmick CG. The impact of osteoarthritis in the United States: a population-health perspective. Am J Nurs 2012;112(3 Suppl. 1):S13–9.
[31] Herbold JA, Bonistall K, Walsh MB. Rehabilitation following total knee replacement, total hip replacement, and hip fracture: a case-controlled comparison. J Geriatr Phys Ther 2011;34(4):155–60.
[32] Westby MD. Rehabilitation and total joint arthroplasty. Clin Geriatr Med 2012;28(3):489–508.
[33] Dong H, Buxton M. Early assessment of the likely cost-effectiveness of a new technology: a Markov model with probabilistic sensitivity analysis of computer-assisted total knee replacement. Int J Technol Assess Health Care 2006;22(2):191–202.
[34] Daigle ME, Weinstein AM, Katz JN, Losina E. The cost-effectiveness of total joint arthroplasty: a systematic review of published literature. Best Pract Res Clin Rheumatol 2012;26(5):649–58.
[35] Jenkins PJ, Clement ND, Hamilton DF, Gaston P, Patton JT, Howie CR. Predicting the cost-effectiveness of total hip and knee replacement: a health economic analysis. Bone Joint J 2013;95-B(1):115–21.
[36] Gabriel SE, Crowson CS, Campion ME, O'Fallon WM. Direct medical costs unique to people with arthritis. J Rheumatol 1997;24(4):719–25.
[37] MacLean CH, Knight K, Paulus H, Brook RH, Shekelle PG. Costs attributable to osteoarthritis. J Rheumatol 1998;25(11):2213–8.
[38] Mapel DW, Shainline M, Paez K, Gunter M. Hospital, pharmacy, and outpatient costs for osteoarthritis and chronic back pain. J Rheumatol 2004;31(3):573–83.
[39] Dibonaventura MD, Gupta S, McDonald M, Sadosky A, Pettitt D, Silverman S. Impact of self-rated osteoarthritis severity in an employed population: cross-sectional analysis of data from the national health and wellness survey. Health Qual Life Outcomes 2012;10:30, http://dx.doi.org/10.1186/1477-7525-10-30.:30-10.
[40] Hermans J, Koopmanschap MA, Bierma-Zeinstra SM, van Linge JH, Verhaar JA, Reijman M, et al. Productivity costs and medical costs among working patients with knee osteoarthritis. Arthritis Care Res (Hoboken) 2012;64(6):853–61.
[41] Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007;66(3):377–88.
[42] 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(5):669–81.
[43] 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 II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008;16(2):137–62.
[44] NICE: National Institute for Health and Clinical Excellence. Osteoarthritis: The care and management of oeteoarthritis in adults. ⟨http://guidance.nice.org.uk/CG59/NICEGuidance/pdf/English⟩; 2008.
[45] Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 2012;64(4):465–74.
[46] Eichler HG, Kong SX, Gerth WC, Mavros P, Jonsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health 2004;7(5):518–28.
[47] Taylor RS, Drummond MF, Salkeld G, Sullivan SD. Inclusion of cost effectiveness in licensing requirements of new drugs: the fourth hurdle. Br Med J 2004;329(7472):972–5.
[48] Rascati KL. Essentials of Pharmacoeconomics. Philadelphia: Wolters Kluwer/Lippincott, Williams & Wilkins; 2009.
[49] Drummond MF, Sculpher MJ, Torrance GW, O'Brien B, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes. 3rd ed. Oxford, UK: Oxford University Press; 2005.
[50] Bellamy N, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol 1997;24(4):799–802.
[51] Ruchlin HS, Insinga RP. A review of health-utility data for osteoarthritis: implications for clinical trial-based evaluation. Pharmacoeconomics 2008;26(11):925–35.
[52] Dougados M, Leclaire P, van der Heijde D, Bloch DA, Bellamy N, Altman RD. Response criteria for clinical trials on osteoarthritis of the knee and hip: a report of the Osteoarthritis Research Society International Standing Committee for Clinical Trials response criteria initiative. Osteoarthritis Cartilage 2000;8(6):395–403.
[53] Bellamy N, Bell MJ, Goldsmith CH, Pericak D, Walker V, Raynauld JP, et al. Evaluation of WOMAC 20, 50, 70 response criteria in patients treated with hylan G-F 20 for knee osteoarthritis. Ann Rheum Dis 2005;64(6):881–5.
[54] Chen YF, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, et al. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess 2008;12(11):1–278 (iii).
[55] Harrison MJ, Bansback NJ, Marra CA, Drummond M, Tugwell PS, Boonen A. Valuing health for clinical and economic decisions: directions relevant for rheumatologists. J Rheumatol 2011;38(8):1770–5.
[56] Brennan A, Akehurst R. Modelling in health economic evaluation. What is its place? What is its value? Pharmacoeconomics 2000;17(5):445–59.
[57] Buxton MJ, Drummond MF, Van Hout BA, Prince RL, Sheldon TA, Szucs T, et al. Modelling in economic evaluation: an unavoidable fact of life. Health Econ 1997;6(3):217–27.
[58] Sculpher MJ, Claxton K, Drummond M, McCabe C. Whither trial-based economic evaluation for health care decision making? Health Econ 2006;15(7):677–87.
[59] Torrance GW. Designing and conduction cost-utility analyses. In: Spilker B, editor. Quality of Life and Pharmacoeconomics in Clinical Trials. 2nd ed. Philadelphia: Lippincott-Raven; 1996. p. 1105–11.
[60] Raftery J. Review of NICE's recommendations, 1999-2005. Br Med J 2006;332(7552):1266–8.
[61] Cleemput I, Neyt M, Thiry N, De LC, Leys M. Using threshold values for cost per quality-adjusted life-year gained in healthcare decisions. Int J Technol Assess Health Care 2011;27(1):71–6.
[62] World Health Organization. Macroeconomics and Health: Investing in Health for Economic Development. WHO 2011 [cited 2013 Mar 25].
[63] Strom O, Borgstrom F, Kanis JA, Compston J, Cooper C, McCloskey EV, et al. Osteoporosis: burden, health care provision and opportunities in the EU: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 2011;6(1-2):59–155.
[64] Dunlop DD, Song J, Semanik PA, Sharma L, Chang RW. Physical activity levels and functional performance in the osteoarthritis initiative: a graded relationship. Arthritis Rheum 2011;63(1):127–36.

[65] Cottrell E, Roddy E, Foster NE. The attitudes, beliefs and behaviours of GPs regarding exercise for chronic knee pain: a systematic review. BMC Fam Pract 2010;11:4, http://dx.doi.org/10.1186/1471-2296-11-4.:4-11.
[66] Dunlop DD, Song J, Semanik PA, Chang RW, Sharma L, Bathon JM, et al. Objective physical activity measurement in the osteoarthritis initiative: are guidelines being met? Arthritis Rheum 2011;63(11):3372–82.
[67] Manning VL, Hurley MV, Scott DL, Bearne LM. Are patients meeting the updated physical activity guidelines? Physical activity participation, recommendation, and preferences among inner-city adults with rheumatic diseases J Clin Rheumatol 2012;18(8):399–404.
[68] Song J, Hochberg MC, Chang RW, Hootman JM, Manheim LM, Lee J, et al. Racial/ethnic differences in physical activity guideline attainment among participants in the osteoarthritis initiative. Arthritis Care Res (Hoboken) 2012;17:10.
[69] Pinto D, Robertson MC, Hansen P, Abbott JH. Cost-effectiveness of non-pharmacologic, nonsurgical interventions for hip and/or knee osteoarthritis: systematic review. Value Health 2012;15(1):1–12.
[70] Ofman JJ, Sullivan SD, Neumann PJ, Chiou CF, Henning JM, Wade SW, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. J Manag Care Pharm 2003;9(1):53–61.
[71] van Tulder M, Furlan A, Bombardier C, Bouter L. Updated method guidelines for systematic reviews in the cochrane collaboration back review group. Spine (Phila Pa 1976;28(12):1290–9.
[72] Richardson G, Hawkins N, McCarthy CJ, Mills PM, Pullen R, Roberts C, et al. Cost-effectiveness of a supplementary class-based exercise program in the treatment of knee osteoarthritis. Int J Technol Assess Health Care 2006;22(1):84–9.
[73] 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–xi (1).
[74] Reinhold T, Witt CM, Jena S, Brinkhaus B, Willich SN. Quality of life and cost-effectiveness of acupuncture treatment in patients with osteoarthritis pain. Eur J Health Econ 2008;9(3):209–19.
[75] Coupe VM, Veenhof C, van Tulder MW, Dekker J, Bijlsma JW, Van den Ende CH. The cost effectiveness of behavioural graded activity in patients with osteoarthritis of hip and/or knee. Ann Rheum Dis 2007;66(2):215–21.
[76] Hurley MV, Walsh NE, Mitchell HL, Pimm TJ, Williamson E, Jones RH, et al. Economic evaluation of a rehabilitation program integrating exercise, self-management, and active coping strategies for chronic knee pain. Arthritis Rheum 2007;57(7):1220–9.
[77] Jessep SA, Walsh NE, Ratcliffe J, Hurley MV. Long-term clinical benefits and costs of an integrated rehabilitation programme compared with outpatient physiotherapy for chronic knee pain. Physiotherapy 2009;95(2):94–102.
[78] Lord J, Victor C, Littlejohns P, Ross FM, Axford JS. Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee. Health Technol Assess 1999;3(23):1–55.
[79] Patel A, Buszewicz M, Beecham J, Griffin M, Rait G, Nazareth I, et al. Economic evaluation of arthritis self management in primary care. Br Med J 2009;339:b3532, http://dx.doi.org/10.1136/bmj.b3532.:b3532.
[80] Coupé VM, Veenhof C, van Tulder MW, Dekker J, Bijlsma JW, Van den Ende CH. The cost effectiveness of behavioural graded activity in patients with osteoarthritis of hip and/or knee. Ann Rheum Dis 2007;66(2):215–21.
[81] O'Brien BJ, Gertsen K, Willan AR, Faulkner LA. Is there a kink in consumers' threshold value for cost-effectiveness in health care? Health Econ 2002;11(2):175–80.
[82] Severens JL, Brunenberg DE, Fenwick EA, O'Brien B, Joore MA. Cost-effectiveness acceptability curves and a reluctance to lose. Pharmacoeconomics 2005;23(12):1207–14.
[83] Loew L, Brosseau L, Wells GA, Tugwell P, Kenny GP, Reid R, et al. Ottawa panel evidence-based clinical practice guidelines for aerobic walking programs in the management of osteoarthritis. Arch Phys Med Rehabil 2012;93(7):1269–85.
[84] Brosseau L, Wells GA, Tugwell P, Egan M, Dubouloz CJ, Casimiro L, et al. Ottawa Panel evidence-based clinical practice guidelines for the management of osteoarthritis in adults who are obese or overweight. Phys Ther 2011;91(6):843–61.
[85] Maetzel A, Krahn M, Naglie G. The cost effectiveness of rofecoxib and celecoxib in patients with osteoarthritis or rheumatoid arthritis. Arthritis Rheum 2003;49(3):283–92.
[86] Black C, Clar C, Henderson R, MacEachern C, McNamee P, Quayyum Z, et al. The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation. Health Technol Assess 2009;13(52):1–148.
[87] Loyd M, Rublee D, Jacobs P. An economic model of long-term use of celecoxib in patients with osteoarthritis. BMC Gastroenterol 2007;7(25):25.
[88] Kamath CC, Kremers HM, Vanness DJ, O'Fallon WM, Cabanela RL, Gabriel SE. The cost-effectiveness of acetaminophen, NSAIDs, and selective COX-2 inhibitors in the treatment of symptomatic knee osteoarthritis. Value Health 2003;6(2):144–57.
[89] Spiegel BM, Targownik L, Dulai GS, Gralnek IM. The cost-effectiveness of cyclooxygenase-2 selective inhibitors in the management of chronic arthritis. Ann Intern Med 2003;138(10):795–806.
[90] Moore A, Phillips C, Hunsche E, Pellissier J, Crespi S. Economic evaluation of etoricoxib versus non-selective NSAIDs in the treatment of osteoarthritis and rheumatoid arthritis patients in the UK. Pharmacoeconomics 2004;22(10):643–60.
[91] Yen ZS, Lai MS, Wang CT, Chen LS, Chen SC, Chen WJ, et al. Cost-effectiveness of treatment strategies for osteoarthritis of the knee in Taiwan. J Rheumatol 2004;31(9):1797–803.
[92] Marshall DA, Strauss ME, Pericak D, Buitendyk M, Codding C, Torrance GW. Economic evaluation of controlled-release oxycodone vs oxycodone-acetaminophen for osteoarthritis pain of the hip or knee. Am J Manag Care 2006;12(4):205–14.
[93] Ward A, Bozkaya D, Fleischmann J, Dubois D, Sabatowski R, Caro JJ. Modeling the economic and health consequences of managing chronic osteoarthritis pain with opioids in Germany: comparison of extended-release oxycodone and OROS hydromorphone. Curr Med Res Opin 2007;23(10):2333–45.
[94] Al MJ, Maniadakis N, Grijseels EW, Janssen M. Costs and effects of various analgesic treatments for patients with rheumatoid arthritis and osteoarthritis in the Netherlands. Value Health 2008;11(4):589–99.
[95] Contreras-Hernandez I, Mould-Quevedo JF, Torres-Gonzalez R, Goycochea-Robles MV, Pacheco-Dominguez RL, Sanchez-Garcia S, et al. Cost-effectiveness analysis for joint pain treatment in patients with osteoarthritis treated at the Instituto Mexicano del Seguro Social (IMSS): Comparison of nonsteroidal anti-inflammatory drugs (NSAIDs) vs. cyclooxygenase-2 selective inhibitors. Cost Effectiveness Resour Allocation 2008;6:21, http://dx.doi.org/10.1186/1478-7547-6-21.:21-6.
[96] Bessette L, Risebrough N, Mittmann N, Roussy JP, Ho J, Zlateva G. Cost-utility of celecoxib use in different treatment strategies for osteoarthritis and rheumatoid arthritis from the Quebec healthcare system perspective. J Med Econ 2009;12(3):246–58.
[97] Latimer N, Lord J, Grant RL, O'Mahony R, Dickson J, Conaghan PG. Cost effectiveness of COX 2 selective inhibitors and traditional NSAIDs alone or in combination with a proton pump inhibitor for people with osteoarthritis. Br Med J 2009;339:b2538, http://dx.doi.org/10.1136/bmj.b2538.:b2538.
[98] Bruyere O, Scholtissen S, Neuprez A, Hiligsmann M, Toukouki A, Reginster JY. Impact of chondroitin sulphate on health utility in patients with knee osteoarthritis: towards economic analysis. J Med Econ 2009;12(4):356–60.
[99] Scholtissen S, Bruyere O, Neuprez A, Severens JL, Herrero-Beaumont G, Rovati L, et al. Glucosamine sulphate in the treatment of knee osteoarthritis: cost-effectiveness comparison with paracetamol. Int J Clin Pract 2010;64(6):756–62.
[100] Brereton N, Winn B, Akehurst R. The cost-effectiveness of celecoxib vs diclofenac in the treatment of osteoarthritis in the UK; an update to the NICE model using data from the CONDOR trial. J Med Econ 2012;15(3):465–72.
[101] Elders MJ. The increasing impact of arthritis on public health. J Rheumatol Suppl 2000;60:6–8.
[102] Hunsche E, Chancellor JV, Bruce N. The burden of arthritis and nonsteroidal anti-inflammatory treatment. A European literature review. Pharmacoeconomics 2001;19(Suppl. 1):1–15.
[103] Gabriel SE, Tugwell P, Drummond M. Progress towards an OMERACT-ILAR guideline for economic evaluations in rheumatology. Ann Rheum Dis 2002;61(4):370–3.
[104] Ramsey S, Willke R, Briggs A, Brown R, Buxton M, Chawla A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. Value Health 2005;8(5):521–33.
[105] Berger ML, Dreyer N, Anderson F, Towse A, Sedrakyan A, Normand SL. Prospective observational studies to assess comparative effectiveness: the ISPOR good research practices task force report. Value Health 2012;15(2):217–30.
[106] Drummond M, Maetzel A, Gabriel S, March L. Towards a reference case for use in future economic evaluations of interventions in osteoarthritis. J Rheumatol Suppl 2003;68:26–30.
[107] Gabriel S, Drummond M, Maetzel A, Boers M, Coyle D, Welch V, et al. OMERACT 6 Economics Working Group report: a proposal for a reference case for economic evaluation in rheumatoid arthritis. J Rheumatol 2003;30(4):886–90.
[108] 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(12):1145–55.
[109] Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 2011;64(4):380–2.
[110] Thornton J, Alderson P, Tan T, Turner C, Latchem S, Shaw E, et al. Introducing GRADE across the NICE clinical guideline program. J Clin Epidemiol 2013;66(2):124–31.
[111] Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Br Med J 2013;346:1.
[112] Brunetti M, Shemilt I, Pregno S, Vale L, Oxman AD, Lord J, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. J Clin Epidemiol 2013;66(2):140–50.
[113] Matthews GL, Hunter DJ. Emerging drugs for osteoarthritis. Expert Opin Emerg Drugs 2011;16(3):479–91.
[114] Smelter E, Hochberg MC. New treatments for osteoarthritis. Curr Opin Rheumatol 2013;25(3):310–6.
[115] Maillefert JF, Dougados M. Is time to joint replacement a valid outcome measure in clinical trials of drugs for osteoarthritis? Rheum Dis Clin North Am 2003;29(4):831–45.
[116] Gossec L, Hawker G, Davis AM, Maillefert JF, Lohmander LS, Altman R, et al. OMERACT/OARSI initiative to define states of severity and indication for joint replacement in hip and knee osteoarthritis. J Rheumatol 2007;34(6):1432–5.
[117] Ghomrawi HM, Schackman BR, Mushlin AI. Appropriateness criteria and elective procedures—total joint arthroplasty. N Engl J Med 2012;367(26):2467–9.
[118] Carr AJ, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, et al. Knee replacement. Lancet 2012;379(9823):1331–40.