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)

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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.

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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
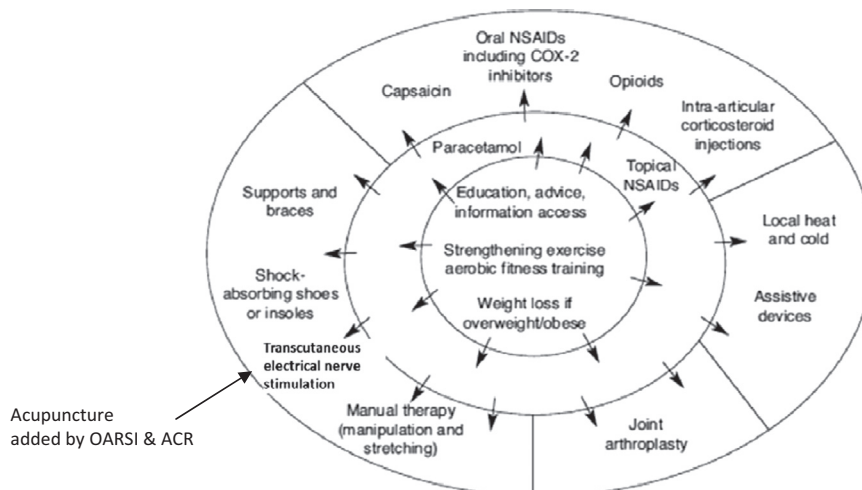

Fig. Therapeutic options in OA grouped according to weight of evidence and the relative safety for the patient, with the first options/recommendations at the center (NICE, 2008).

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.

$$\frac{(\text{Cost}_A - \text{COST}_B)}{(\text{QALY}_A - \text{QALY}_B)} = \text{ICER}$$

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. $\geq 15\%$ 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 (diclo-fenac, 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, glucos-amine (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. Sub-groups of patients included those who did not respond to acet-aminophen; 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 gastro-intestinal 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–acetami-nophen 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 epide-miological 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 meth-odological 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 Inter-national 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 sev-eral 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.

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