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# A reference case for economic evaluations in osteoarthritis: An expert consensus article from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)

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ABSTRACT

*Background:* General recommendations for a reference case for economic studies in rheumatic diseases were published in 2002 in an initiative to improve the comparability of cost-effectiveness studies in the field. Since then, economic evaluations in osteoarthritis (OA) continue to show considerable heterogeneity in methodological approach.
*Objectives:* To develop a reference case specific for economic studies in OA, including the standard optimal care, with which to judge new pharmacologic and non-pharmacologic interventions.
*Methods:* Four subgroups of an ESCEO expert working group on economic assessments (13 experts representing diverse aspects of clinical research and/or economic evaluations) were charged with producing lists of recommendations that would potentially improve the comparability of economic analyses in OA: outcome measures, comparators, costs and methodology. These proposals were discussed and refined during a face-to-face meeting in 2013. They are presented here in the format of the recommendations of the recently published Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement, so that an initiative on economic analysis methodology might be consolidated with an initiative on reporting standards.
*Results:* Overall, three distinct reference cases are proposed, one for each hand, knee and hip OA; with diagnostic variations in the first two, giving rise to different treatment options: interphalangeal or thumb-based disease for hand OA and the presence or absence of joint malalignment for knee OA. A set of management strategies is proposed, which should be further evaluated to help establish a consensus on the "standard optimal care" in each proposed reference case. The recommendations on outcome measures, cost itemisation and methodological approaches are also provided.
*Conclusions:* The ESCEO group proposes a set of disease-specific recommendations on the conduct and reporting of economic evaluations in OA that could help the standardisation and comparability of studies that evaluate therapeutic strategies of OA in terms of costs and effectiveness.


## Introduction

Osteoarthritis (OA) is a progressive and painful chronic disease affecting mainly the hand, knee and/or hip joints. OA has been shown to be associated with high costs, both in terms of direct health-related costs (long-term treatments for pain control, surgery and rehabilitation) and indirect costs (productivity losses) [1–5]. Since no structure-modifying treatments (excepting surgical interventions) are yet approved in the major regulatory jurisdictions, the current management strategies are intended to provide symptomatic improvement, using a combination of pharmacological and non-pharmacological approaches [6–12]. The costs of such strategies and their long-term success are uncertain and often difficult to compare between studies.

Economic evaluations of disease management options provide essential information with which to guide efficient resource allocation in health care, and many countries now have formal requirements for an economic evaluation of new pharmaceutical products at the time of market authorisation [13]. An objective economic comparison of existing therapeutic strategies in OA is essential for both the efficient management of the disease and the development of new treatments and management programmes. Economic evaluations can be complex, with important choices to be made in the definition of the clinical pathway, the selection of outcome measures, the most relevant comparator(s) and the accounting of resource utilisation. The diversity engendered by such decisions as well as a less-than-transparent reporting of methods in the literature give rise to substantial difficulties when it comes to comparing studies of different treatment modalities [14–16]. The efforts to tackle this problem have come from the following two directions: (a) the creation of methodological guidelines designed to help investigators with study/model design and the selection of standardised methods and (b) the creation of checklists for the reporting of studies, with the goal of ensuring that all the relevant information pertinent to the interpretation of a study is present at publication.

A recent article under the auspices of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) concluded that in the field of OA, there was a need to define a reference case and a consensus on what constitutes "standard optimal care" in terms of best clinical practice (according to the stage and affected joint) that could serve as a comparator for more experimental interventions, thus providing a standard between studies in the same clinical situation [15], while at the same time allowing flexibility to tailor treatments to the diversity of the disease condition. The present article presents the conclusions of discussions on this subject that were held during a subsequent expert working group meeting, in September 2013, and outlines the tasks that still need to be done to reach this goal. The discussions focussed specifically on cost-effectiveness and comparative economic evaluation; the methodology for evaluating the burden of disease was not discussed.

Definitions
Reference case: A set of methodological choices for a range of items relevant to conducting an economic evaluation that frame the boundaries of the study, such as model horizon, outcome measure(s), resource use and costing.
Base case: Generally used in the context of modelling, the base case defines the most plausible values for the relevant parameters. Departure from the base case may be sensitivity analyses (varying the values of a parameter) or a scenario analysis (variation in technology, model structure and/or clinical pathway).
Subgroups of interest: Patient subgroups that have a risk factor that may or may not invoke an adaptation of initial standard treatment, but which may alter the rate of progression, the risk of complications or response to treatment.

### *The case for a reference case*

The term "reference case" was first coined by the Panel on Cost-Effectiveness in Health and Medicine, set up by the US Public

Health Service in 1993 [17]. Their proposal to reduce inter-study heterogeneity was to define a set of minimal criteria that all economic analyses should include. The main points were that all resource consumption associated with an intervention (including non-health impacts) should be captured, that the health effects of an intervention should be incorporated into quality-adjusted life years (QALYs), that costs and health outcomes in the future should be discounted to present values, that sensitivity analyses should be used to address uncertainty and that studies should be reported in a standardised way.

The reference case idea was subsequently taken up by Gabriel et al. [18] in the OMERACT (Outcome Measures in Rheumatology) economics working group with the objective of defining a "core set" of disease-specific parameters for economic evaluations in rheumatology. Following a set of preliminary recommendations on methodological issues, which they saw as "controversial," a consensus set was developed for rheumatoid arthritis (RA) [19,20]. Further discussion for OA, however, left some issues unresolved [21]. More recently, a reference case for ankylosing spondylitis was published [22], as was a reference case for modelling in osteoporosis [23].

A number of general guidelines and recommendations for the design and conduct of cost-effectiveness analyses have appeared in the last decade and of particular note is the series of Good Research Practices published by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [24–28]. Although these guidelines have not explicitly endorsed the reference case approach, they have retained the principles summarised above and have helped foster a degree of concordance in methodology that has helped improve inter-study comparability. In an editorial in 2006, Lyles [29] regretted that few cost-effectiveness analysis (CEA) studies could be found in a MEDLINE search using the term "reference case" and that considerable heterogeneity continued to exist. This is still true but, although not labelled as such, the reference case approach has been largely accepted by the health care economics community since it guarantees standardisation without stifling methodological development [30].

In parallel to the good research practice recommendations, numerous reporting checklists have been produced with the aim of harmonising the presentation of information and thus raising the quality standard of CEA research articles. The most recent addition is the ISPOR-backed Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [31] that proposes a checklist of 24 items, each with a corresponding recommendation. This checklist was produced using an approach consistent with that used for producing the CONSORT statement for reporting randomised controlled trials (RCTs) (www.consort-statement.org), which has achieved widespread recognition and acceptance [32,33]. The aim of this report was to enhance the interpretability of comparative effectiveness research in osteoarthritis, by proposing a reference case scenario for each of the main manifestations of the disease (the hand, knee and hip).

## Methods

Four subgroups of the ESCEO working group on economic assessments were formed, focusing on comparators, outcomes, costs and methods. These comprised 5–6 experts each for a total of 13 individuals [N. Arden, M. Boers, A. Boonen, ML. Brandi, C. Cooper, M. Drummond, F. Guillemin*, M. Hiligsmann*, M. Hochberg*, D. Hunter, D. Pinto, J.L. Severens, and P. Tugwell* (* denotes sub-group leaders)], representing diverse aspects of clinical research and/or economic evaluations. Each subgroup prepared a list of the most important topics based on their review of the literature and then made a set of preliminary recommendations. The subsequent step was a face-to-face meeting for the whole group to make amendments and discuss further recommendations. The recently published CHEERS statement [31] was taken as a platform on which the group's recommendations could be presented so as to provide the maximum coherence.

## Results

Recommendations of additional text are suggested for eight items judged most sensitive to disease-specific choices and these are provided in Table 1 alongside the CHEERS statement. All items of the CHEERS statement are reproduced, along with the additional guidance as indicated. Additionally, text is proposed for the introduction, and the creation of a new item "study design" (as in CONSORT list) is recommended. This new item is numbered as item 3, following the merging of items 1 and 2 (title and abstract), as in CONSORT, and the renumbering of the introduction as item 2. Furthermore, it was suggested that item 11 (which included certain aspects of study design) be modified to "measurement of clinical effectiveness or harms."

These additions and modifications are explained in the accompanying text (below) and, where relevant, an example of good reporting for the item is provided. Thus, the suggestions in this article should be seen as additional to the general guidance in the CHEERS explanatory article [34].

### *Introduction (item no. 2)*

*CHEERS* provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.

*Modification for economic evaluations in general:* Frame the research question using evidence-based practice methodology, e.g., the GRADE 2 guideline: Framing the question and deciding on important outcomes and using the Population, Intervention, Comparator and Outcome (PICO) process.

*Example*: "In patients (age range, sex…) with symptomatic knee OA, how does a topical NSAID compare with an oral NSAID for costs and outcomes for equivalent pain control over the short-term in out-patients in the context of the UK National Health Service?"

*Explanation*: It was considered particularly helpful, to both investigators and readers, to clearly frame the clinical research questions using evidence-based practice methodology. A useful guideline in this respect is the Grading of Recommendations Assessment, Development and Evaluation (GRADE) number 2: *Framing the question and deciding on important outcomes* [35]. As a part of this process, the guideline recommends using the PICO (or PICOTS: Population, Intervention, Comparator, Outcome, Time and Setting) methodology [36] (which is also applied, but non-explicitly, in the CHEERS explanation). The "question framing" part, although not necessarily specific to OA studies, is crucially important. Risk profiling should be used in order to identify how similar patients are within the study population and for identifying subgroups of interest. An important process for researchers performing meta-analyses and indirect (network) comparisons is the description and categorisation of the important outcome from patients' viewpoint (those that are critical, important or of limited importance). As stated in the CHEERS explanation, the decisional question (and whether the research was conducted for a decision maker) should be detailed.

**Table 1**
Set of disease-specific recommendations on the conduct and reporting of economic evaluations in osteoarthritis (presented in the format of the CHEERS statement)

| Section | Item | Standard CHEERS description | Specificity for economic evaluations in OA |
|---|---|---|---|
| Title and abstract | 1 | Identify the study as an economic evaluation, or use more specific terms such as "cost-effectiveness analysis" and describe the interventions compared.<br>Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions | |
| Introduction | | | |
| Background and objectives | 2 | Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions | Frame the research question using evidence-based practice methodology, e.g., the GRADE 2 guideline: Framing the question and deciding on important outcomes and using the Population, Intervention, Comparator and Outcome (PICO) process. |
| Methods | | | |
| Study design/model structure | 3 | *[New item incorporating aspects of items 11 and 15]* | Describe the basic design of the study or model structure (see items 11 and 15) to help frame the subsequent description of methods. |
| Target population and subgroups | 4 | Describe characteristics of the base case population and subgroups analysed including why they were chosen | Three separate reference cases for OA are proposed, hand, knee or hip, in patients seeking medical advice for a painful joint affected by OA (the ACR criteria). Variants on each reference case may be considered: e.g., interphalangeal or thumb-based complaints for hand OA; the presence of clinically important malalignment for knee OA and severe disease with persistent pain and marked disability.<br>Subgroups of interest might include age, gender and BMI, also comorbidity factors (e.g., GI or CV risk). |
| Setting and location | 5 | State relevant aspects of the system(s) in which the decision(s) need (s) to be made | |
| Study perspective | 6 | Describe the perspective of the study and relate this to the costs being evaluated | If no specific official/national guideline/decision making context needs be followed, then a broad perspective ("societal"), including a wide range of costs and benefits, falling on the healthcare system, patients and broader economy, is preferred. |
| Comparators | 7 | Describe the interventions or strategies being compared and state why they were chosen | The most appropriate comparators will depend on the reference case considered (the hand, knee or hip). Ideally, one comparator would be "standard optimal care." |
| Time horizon | 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate | Since OA is a chronic disease, the application of a lifetime horizon is encouraged. For comparative studies in pain control, shorter horizons are acceptable. |
| Discount rate | 9 | Report the choice of discount rate(s) used for costs and outcomes and say why appropriate | |
| Choice of health outcomes | 10 | Describe what outcomes were used as the measure(s) of benefit in the economic evaluation and their relevance for the type of analysis performed | The QALY has been endorsed by OMERACT and ESCEO for use in musculoskeletal studies. |
| Measurement of clinical effectiveness or harm | 11a | Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data | The effect of treatment should be assessed on the core set outcomes for rheumatology studies (pain, functional ability [using a validated disease-specific QoL instrument] and patient global assessment [PGA]). Adverse events should be reported using the OMERACT common toxicity criteria. |
| | 11b | Synthesis-based estimates: Describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data | Relevant outcome measures should be selected using the GRADE system. |
| Measurement and valuation of preference-based outcomes | 12 | If applicable, describe the population and methods used to elicit preferences for outcomes | The EQ-5D is the preferred indirect (multiattribute) utility estimator (although SF-6D and HUI-2 or -3 can also be used). The score from the disease-specific QoL instrument should also be converted to a utility score for use in a sensitivity analysis. |
| Estimating resources and costs | 13a | Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs | A process-based categorisation of resources and costs into predefined domains is recommended, with use (where possible) of national standardised lists of costs for valuation. |
| | 13b | Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs | |
| Currency, price date and conversion | 14 | Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate | |
| Choice of model | 15 | Describe and give reasons for the specific type of decision-analytic model used. Providing a figure to show model structure is strongly recommended | |
| Assumptions | 16 | Describe all structural or other assumptions underpinning the decision-analytic model | |

**Table 1** (*continued*)

| Section | Item | Standard CHEERS description | Specificity for economic evaluations in OA |
|---|---|---|---|
| Analytic methods | 17 | Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (e.g., half-cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty | |
| Results | | | |
| Study parameters | 18 | Report the values, ranges, references, and if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended | |
| Incremental costs and outcomes | 19 | For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios (ICERs) | |
| Characterising uncertainty | 20a | Single study-based economic evaluation: Describe the effects of sampling uncertainty for estimated incremental cost, incremental effectiveness, and incremental cost-effectiveness, together with the impact of methodological assumptions (such as discount rate, study perspective) | |
| | 20b | Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions | |
| Characterising heterogeneity | 21 | If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information | |
| Discussion | 22 | Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge | |

ACR: American College of Rheumatology; BMI: body mass index; CV: cardiovascular; GI: gastrointestinal.

*Methods—Study design/model structure (item no. 3)*

New item incorporating aspects of items 11 and 15.

*Modification for economic evaluations in general*: Describe the basic design of the study or model structure (see items 11 and 15) to help frame the subsequent description of methods.

*Examples*: Study design in comparative clinical studies:

- "This economic evaluation was a retrospective longitudinal cohort study using data from the GPRD."
- "An economic evaluation was conducted alongside a cluster randomised controlled trial comparing behavioural graded activity and usual care according to…"

Model Structure (as outlined in item 15 of CHEERS):

- "A decision analytic model was developed comparing the decision options and reflecting the clinical events in terms of their probabilities of taking place and the consequences in terms of costs and utilities…"
- "The disease process was formulated as a transition through a series of health states, modelled using a Markov approach"

*Explanation*: It was considered particularly helpful if the main features of the study design or model structure are described in the first paragraph of the methods section. Thus, the design of the study should be outlined, e.g., whether it was an RCT or pragmatic design or if it was a data extraction from a general practice database or a mathematical model synthesising data from several sources including meta-analyses. As stated in item 11 of CHEERS, attention should be paid to fulfilling other applicable reporting requirements (CONSORT for RCTs and pragmatic designs [32,37]; STROBE for observational designs [38] and PRISMA for meta-analyses [39]). Although the use of a single RCT as a data source for economic analysis may be questionable [40], the data obtained from such studies can be instructive on an initial basis for decision making especially during early clinical drug development. If the analysis concerns modelling of economic data, then the model structure, as outlined in item 15 of CHEERS, should be detailed, taking account of existing good practice guidelines [41,42].

*Target population and subgroups (item no. 4)*

*CHEERS* describe characteristics of the base case population and subgroups analysed including why they were chosen.

*Extension for economic evaluations in OA*: Three separate reference cases for OA are proposed, the hand, knee or hip, in patients seeking medical advice for a painful joint affected by OA (the American College of Rheumatology criteria). Variants on each case may be considered: e.g., interphalangeal or thumb-based complaints for hand OA, and the presence of clinically important malalignment for knee OA, and severe disease with persistent pain and marked disability. Subgroups of interest might include age, gender and body mass index, including comorbidity factors (e.g., gastrointestinal or cardiovascular risk).

*Explanation*: The working group proposes the following three distinct reference cases: patients seeking medical advice for a painful joint affected by OA in the (i) hand, (ii) knee or (iii) hip. In each, the clinical diagnosis should fulfil the current American College of Rheumatology (ACR) classification criteria for OA [43,44]. Variants on the reference case could be envisaged to encompass different presentations of the disease, e.g., interphalangeal or thumb-based complaints for hand OA and the presence of any clinically important malalignment for knee OA.

In the last decade, a number of studies have added considerably to our understanding of the natural history of OA [25,45–49] and brought out the differences between these disease conditions in terms of prevalence and risk factors (both intrinsic and extrinsic) and the medical impact at a level of functional independence and all-cause mortality. Furthermore, it is now clear that biomechanical changes in the joint have a strong influence on progression, hence the need to consider varus/valgus deformity separately [50]. Other variants should be considered for patients having severe knee or hip OA, which are characterised by persistent pain and marked disability. The subsequent step for these individuals would be elective joint replacement.

Subgroups of interest might be defined along demographic criteria, such as age and gender or according to comorbidity factors, including obesity or risks relating to gastrointestinal or cardiovascular events. It might be useful to add a measure of comorbidity [51] since this as well as health-related quality of life (QoL) are powerful predictors of health care outcomes and costs [47,52,53].

*Study perspective (item no. 6)*

*CHEERS* describe the perspective of the study and relate this to the costs being evaluated.

*Extension for economic evaluations in OA*: If no specific official/national guideline/decision-making context needs be followed, then a broad perspective ("societal"), including a wide range of costs and benefits, falling on the health care system, patients and broader economy, is preferred.

*Explanation*: If the main objective of the analysis is regulatory, then the guidelines of the competent national authority (e.g., UK's National Institute for Health and Care Excellence (NICE) or the Canadian Agency for Drugs and Technologies in Health; see www.ispor.org for worldwide directory of Health Technology Assessment bodies) need to be followed (e.g., the decision maker's perspective, specific health care provider or third party payer). If this is not the case, then because of the chronic nature of OA and its impact on productivity costs, the broad perspective is preferred.

*Comparators (item no. 7)*

*CHEERS* describe the interventions or strategies being compared and state why they were chosen.

*Extension for economic evaluations in OA*: The most appropriate comparators will depend on the reference case considered (the hand, knee or hip). Ideally, one comparator would be "standard optimal care."

*Explanation*: Recommendations and guidelines on the management of OA have been published by learned bodies on several occasions over the last 15 years; notable are the recommendations by the European League Against Rheumatism (EULAR) for knee (2003), hip (2005) and hand (2007) OA [6–8], those of the Osteoarthritis Research Society International (OARSI) for hip and knee (2008) OA, updated in 2010 [9,11], and the guidelines by NICE (2008) [10] and the American College of Rheumatology (ACR; 2012) for hand, hip and knee OA [12]. These have generally used a Delphi process, or other voting systems, to find a consensus amongst invited experts for the various therapeutic strategies proposed.

The recommendation is to first select one of the three reference cases in OA and then consider the most appropriate comparators. Table 2 lists some suggested comparators for each of the proposed reference cases. Since our knowledge is still imperfect, a single "standard optimal care" proposal for each condition is not possible at this time. The table provides the most plausible options, but these should be empirically tested head-to-head before we can be more certain of the "standard" treatment. Until that time, it would be supportive if researchers used at least one of the proposed options in their study design.

**Table 2**
Proposals for intervention comparators according to OA reference case

| Reference case | Comparator possibilities according to reference case variants |
|---|---|
| Hand | Interphalangeal disease: Topical capsaicin vs. topical NSAID gel (e.g., diclofenac gel)<br>Thumb-based disease: Intra-articular (IA) glucocorticoids vs. IA hyaluronate (with or without splinting) |
| Knee | Non-pharmacologic interventions:<br>Nutritional counselling for weight loss vs. the same plus exercise (either aerobic or resistance)<br>In patients with malalignment: Bracing vs. osteotomy<br>Pharmacologic interventions:<br>Glucosamine sulphate vs. chondroitin sulphate vs. both vs. oral paracetamol vs. oral NSAIDs<br>IA glucocorticoids vs. hyaluronate in patients with an inadequate response to either paracetamol or NSAIDs |
| Hip | IA glucocorticoids vs. hyaluronate in patients with an inadequate response to either paracetamol or NSAIDs |

NSAIDs: Non-steroidal anti-inflammatory drugs.

All guidelines have underlined the diversity of the OA condition and noted that optimal management needs a combination of non-pharmacological and pharmacological treatment modalities that are individualised to the patient's requirements.

*Hand OA*

For the management of symptomatic interphalangeal OA, the preferred pharmacological approach is a local treatment; either topical NSAID (such as diclofenac gel) or topical capsaicin cream. Both have shown superior pain relief in placebo-controlled studies (see recommendations for references), but there are relatively few high-quality RCTs of interventions for hand OA published in the peer-reviewed literature. It has been shown that topical NSAIDs are associated with fewer GI adverse events than oral NSAIDs [54]. An economic model should be constructed to reflect the use of treatments based on the existing data of efficacy and the side-effects.

For the management of symptomatic thumb-based OA (i.e., OA of the trapeziometacarpal joint) the usual initial therapeutic approach is splinting [8,12], although the evidence for this is based mainly on expert opinion. Pain relief for these patients is oral paracetamol first line (up to 3 g/day), then oral NSAIDs second line (at the lowest dose and for the shortest duration possible) [8]. For patients who do not respond to this, the next course of action is usually intra-articular glucocorticoids or hyaluronates (although the latter is not licensed for hand OA in all countries) [12]. A factorial study design, including/excluding splinting, with pharmaceutical therapy might add considerably to our clinical knowledge.

*Knee OA*

In the management of patients with symptomatic knee OA, the first step is an attempt to correct any tendency towards overweight by prescribing a weight loss programme, usually with a physical exercise programme [55]. The recently published results of the IDEA trial [56] showed that weight loss, in obese/overweight patients, in combination with a physical exercise programme produced the best results in terms of reduction of knee joint compressive force, inflammatory biomarkers and pain vs. either the weight loss alone or the physical exercise alone. There is also strong agreement that, irrespective of bodyweight, the management of OA should include weight-bearing physical activity [57].

Cost-effectiveness studies have been carried out for a variety of weight loss and exercise programmes, but the differences in design and outcome measures so far preclude any straightforward comparisons [14]. Non-adherence to these programmes is also a big problem and these dropout rates vary widely according to the programme. This issue needs to be addressed by well-designed observational studies having suitable accepted end point(s) and long-term follow-up. Subsequently, modelling studies need to be done to test the impact of realistic, and potentially different, dropout rates.

In patients with varus (or valgus) malalignment, an important therapeutic choice is correction by bracing or osteotomy. In open-label cohort studies, bracing has shown some efficacy in reducing pain and function, but the design of these economic evaluations suffer in the absence of a comparison group (generally they receive physical therapy or static bracing). Valgus osteotomy improves knee function and reduces pain, but there is no evidence whether osteotomy is more effective than conservative treatment [58]. Short-term data also exists from case series, and some long-term data suggest that bracing may delay the need for total joint arthroplasty [59].

*Hip OA*

For the management of symptomatic hip OA, the clinical evidence supports the use of intra-articular injections of corticosteroids or hyaluronates (although the latter is not licensed for hip OA in all countries). The cost-effectiveness of these two pharmacological treatments needs to be compared. There is very limited evidence of any effective non-pharmacological modalities (e.g., exercise programmes). Curiously, while high body mass index (BMI) was found to be significantly associated with knee OA and hand OA, it did not seem to be correlated with the incidence of hip OA [60].

*Further considerations for each reference case.* It is important to distinguish between a single management strategy and a combination of pharmaceutical and non-pharmacological strategies, especially since it is recognised that optimal management often requires a combination of these two strategies. In the absence of direct (head-to-head) comparisons, estimates of effectiveness can be obtained from indirect methods based on a systematic review or network meta-analysis, as recently demonstrated for exercise interventions in patients with lower limb arthritis [61].

*Total joint replacement.* The option of major surgery as a comparator could theoretically be envisaged to evaluate surgery-sparing treatments, but consensus will be required to define a surrogate end point of "time to treatment failure" or "need for joint replacement surgery." Previous attempts to define such an end point [62,63] have not been conclusive. This clinical end point would also be a useful starting point for economic evaluations of treatment and rehabilitation strategies. The comparative effectiveness of joint replacement has been modelled for various scenarios, for example, different prostheses types in total hip replacement [64] and simultaneous vs. staged bilateral total knee arthroplasty [65].

*Time horizon (item no. 8)*

State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.

*Extension for economic evaluations in OA*: Since OA is a chronic disease, a lifetime horizon is most often appropriate. However, for comparative studies in pain control, shorter horizons are acceptable.

*Explanation*: Ideally, the time horizon for economic modelling in OA should be lifetime, as for other chronic diseases such as osteoporosis. If the data limitations make this difficult, then analyses should cover the longest time span possible. For the cost-effectiveness of NSAIDs, de Groot et al. [66] modelled over a 5-year horizon, which seems reasonable in their model that encompassed various gastrointestinal-related health states but no progression of the OA.

A common complaint of both clinical systematic reviewers and economic modellers is that the treatment durations of clinical studies in OA are frequently too short to fully assess all relevant outcomes that might be useful in a thorough economic evaluation; but such are the limitations in the face of the budgetary constraints. Modelling beyond the trial duration therefore demands a number of assumptions of continued treatment benefits, risks and adherence. These uncertainties multiply when the horizon of the model is widely different from that of the source data, and the use of long-term observational data may help to position intermediate to long-term outcomes. It is accepted, however, that models are by nature exploratory and, if well-constructed, provide valuable predictive information [67] or inform as to what essential data are lacking in a decision-making context [68].

*Choice of health outcomes (item no. 10)*

*CHEERS* describe what outcomes were used as the measure(s) of benefit in the economic evaluation and their relevance for the type of analysis performed.

*Extension for economic evaluations in OA*: The QALY has been endorsed by OMERACT and ESCEO for use in musculoskeletal studies.

*Explanation*: The application of cost–utility analysis is recommended in OA and the use of the QALY was endorsed by the 2011 OMERACT economics working group for economic studies in musculoskeletal diseases [69]. The QALY is the common metric used by most national review agencies and its use in OA was endorsed by the ESCEO group.

*Measurement of clinical effectiveness or harms (item no. 11)*

*Item no. 11a*

*Single study-based estimates*: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.

*Extension for economic evaluations in OA*: The effect of treatment should be assessed on the OMERACT core domains of outcomes in rheumatology {pain, functional ability [using a validated disease-specific Quality of Life (QoL) instrument] and patient global assessment [PGA]}. Adverse events should be reported using the OMERACT common toxicity criteria.

*Explanation*: The core set of outcome domains and measures for phase III clinical trials in hip, knee or hand OA was established by the OMERACT III conference [70] as being pain reduction, improvement/preservation of functional ability, PGA and, for studies of 1 year or longer, structural damage as evidenced by joint imaging. To this list should be added the reporting of the incidence and seriousness of adverse events. The perimeter of the core outcome set has been extended slightly by the OMERACT 2.0 filter [71] and further consensus is required.

*Pain.* Pain intensity in the target joint should be measured using a validated self-assessment method, such as a generic visual analogue scale (VAS) or a numeric rating scale (NRS or Likert scale) using verbal pain intensity descriptors (preferably 7 or 11 points) [72]. There is a growing trend towards the use of NRS, since

this can be incorporated easily into electronic hand-held devices. Apart from these simple scales, a wide variety of outcome measures have been employed to assess pain [73] and there appears to be little consensus as to the best method. The following two distinct pain types have been identified in patients with OA: an intermittent intense pain (often with an unpredictable onset) and a dull, aching pain [74], and these are probably in some way related to the multifactorial aetiology of the disease [75]. In the past, the pain experience has also been captured by the various disease-specific QoL tools such as the Michigan Hand Outcomes Questionnaire (MHQ; [76]), the Oxford Hip and Knee Scores (OHS and OKS [77]), the Hip and Knee Osteoarthritis Outcome Scores (HOOS and KOOS [78,79]) or the Western Ontario and McMaster Universities score (WOMAC; for knee or hip [80]). It is likely, however, that these instruments distort the reporting of pain since the questions are embedded in a framework of physical functioning [74]. The Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire was developed more recently to try to capture the distinct pain types in OA [81].

*Functional ability.* This is usually assessed by one of the well-known disease-specific tools cited above, as well as others such as the Arthritis Impact Measurement Scale 2 (AIMS2 and AIMS2-SF [82]), the Functional Index for Hand OA (FIHOA [83]) or the Lequesne Algofunctional Index [84] or the generic, Health Assessment Questionnaire-Disability Index (HAQ-DI [85]). At least 158 different self-reported measures of OA burden have been published and amongst these, the representation of various aspects of OA burden is quite heterogeneous [86]. It is now accepted that emphasis of end point assessment should be preferably on patient-reported outcomes (thus diminishing the role of some of the scales above). While previous OARSI recommendations have highlighted the need to evaluate changes in OA-related fatigue, poor sleep, depressed and anxious mood and participation in valued activities, [50] there appears to be no consensus as to the most suitable instrument. The need for a different outcome assessment process following joint replacement is unlikely [87].

With the development of computerised adaptive testing, using item response theory, it is expected that new outcome instruments will appear that will alleviate the burden of questions and yet retain high degrees of accuracy and statistical power [88]. The FDA's PROMIS initiative (Patient-Reported Outcomes Measurement Information System) is of interest in this respect, since plans are to build a modular set of validated and standardised item banks ready for use in adaptive conditions [89]. It also embraces the language and concepts of the International Classification of Functioning, Disability and Health (ICF) framework of the World Health Organization (WHO), which was recently recognised by OMERACT in their 2.0 filter for core outcome measurement sets [71,90].

*The patient global assessment.* PGA asks a patient to rate on a scale how they feel overall by indicating the result on a VAS or using descriptors such as “well” or “poor.” This simple assessment has relative high retest validity.

*Adverse events.* Standardised reporting using common toxicity criteria (as proposed by the OMERACT toxicity working group) is advocated [91] and the decision should be made if any specific adverse events need to be considered in detail. It is important that any adverse effects are accurately captured by the QoL measure. Not often measured as an outcome parameter, given the relatively short duration of most clinical studies, mortality data should be obtained in retrospective observational studies and, separated where possible into OA-related death and non-related, used to populate models having lifetime horizons.

There are no validated surrogate end points in OA. Proposed definitions of “time to treatment failure” or “need for joint replacement surgery” based on the structural changes and symptomatic thresholds have been made; however, a convincing algorithm that combines the various components has yet to be found [63]. A validated surrogate end point could prove critical for the development of DMOADs, since their economic attractiveness will be in delaying this end point. A related and important question will be to test if delaying the time to arthroplasty compromises the success of this intervention.

*Item no. 11b*

*Synthesis-based estimates*: Describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data.

*Extension for economic evaluations in OA*: Relevant outcome measures should be selected using the GRADE system.

*Explanation*: In the situation where the studies in the field have used a wide variety of outcome measures, it is suggested that the GRADE guideline 2 (mentioned previously) approach might be used to classify them and select the relevant one according to the perspective of the analysis. Clearly, the priority would go to the outcome measures listed in the previous section, but in the necessity to maximise the collection of information, other measures might be considered.

*Measurement of and valuation of preference-based outcomes (item no. 12)*

*CHEERS* if applicable, describe the population and methods used to elicit preferences for outcomes.

*Extension for economic evaluations in OA*: The EQ-5D is the preferred indirect (multiattribute) utility estimator (although SF-6D and HUI-2 or -3 can also be used). The score from a relevant disease-specific QoL instrument could also be converted to a utility score for use in a sensitivity analysis.

*Explanation*: The use of indirect utility measures, such as the EuroQoL-5D (EQ-5D), is preferred rather than more challenging and time-consuming methods that centre on risk and choice (e.g., chance of improvement and willingness to pay) [69,92]. Other indirect utility estimators may also be suitable, such as the Medical Outcomes Study Short-Form 6D (SF-6D) and the Health Utility Index (HUI, version 2 or 3); however, concern has been raised that systematic differences can be seen between EQ-5D and SF-6D scores [93,94]. Direct measures of patient preference can provide a valuable addition to the knowledge base, but it is cautioned that willingness-to-pay values appear to reflect the socioeconomic status of patients more than the clinical status [95].

Using mapping algorithms, the scores from a disease-specific QoL instrument can be converted to utility scores and therefore provide valuable data for sensitivity analyses. Attention should be paid, however, to the most valid mapping method and the choice of algorithm should be justified [69,96]. This method of obtaining utility values should not be preferred over the generic instrument [97,98].

*Estimating resources and costs (item no. 13)*

*Item no. 13a*

*Single study-based economic evaluation*: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.

*Extension for economic evaluations in OA*: A process-based categorisation of resources and costs into predefined domains is recommended, with use (where possible) of national standardised lists of costs for valuation.

*Explanation*: It is recommended that the costing process should be considered in stages. Mittendorf et al. [99] provide a flow diagram with a proposed process. The ESCEO group felt the need to highlight just two stages:

- Identifying the resources incurred for delivering the strategies compared (which should be the same across different countries for any given strategy). Resource use should be collected for all relevant domains including not only those associated with the intervention but also related primary and secondary care resources, as well as treatments that may not necessarily be "disease-specific." Resource use should be considered with regard to the perspective of the analysis.
- Attributing costs to these resources according to the perspective defined in the objectives of the research (which is likely to vary between different countries due to the specificities of the health care systems). Where possible, national standardised lists of costs should be used for medical procedures and treatments (available for instance in the Netherlands and currently being developed for several other countries). Treatment tariffs, on the other hand, can be misleading, in that they may not account for the resources actually used. For studies that are conducted internationally, difficulties can arise where certain cost items might be considered as direct in some countries, but indirect in others (i.e., another reason to canvas for a societal perspective).

It is justified to focus on the more frequent and significant resource utilisation rather than on rare items (unless the costs of these rare items are very high). Particular care should be paid to the collection of outpatient costs, since these are frequently long-term and borne by diverse payers. A comparison of "disease-specific" resource use may be considered in a form of sensitivity analysis with all costs as the base case scenario.

If a broad perspective is used for the analysis, then indirect costs should be attributed. In this domain, one of the more "difficult" costs to estimate is that of lost productivity. Most often, this is valued using the human capital approach (i.e., a method of lifelong salary conversion) or the friction-cost method (taking into account replacement by unemployed) [100]. Difficulty arises not only in the choice of method but also in the use of the patients' estimations of their own absenteeism. Compensation mechanisms for sick employees vary significantly between countries and, where present, they may lead to an overestimation of costs [101]. An alternative and perhaps more suitable approach to lost productivity is the introspective or "firm-level" method (i.e., what is the cost to the company to replace the incapacitated employee) [102]. Also difficult is attributing cost to "presenteeism" (i.e., the person is present at work but unable to fulfil his/her job description due to arthritis pain) since there is insufficient evidence if there is real lost productivity or if there is compensatory assistance from other workers [103]. Still, methods are being developed and in the process of being validated.

## Discussion

This proposition for a reference case (or reference cases) in OA for the conduct of economic studies follows the path started by OMERACT a number of years ago in its efforts to standardise clinical research in rheumatic diseases. The objective then, as now, was to improve the consistency of methodological approach so as to allow more meaningful comparisons between studies, with a goal of elaborating a limited number of OA models that are suitably flexible to adapt to the clinical situation and easy to use for economic evaluations. Available with open access, these models would be regularly updated with new information and available to perform for new strategies or technologies. As a platform on which to present the current recommendations in OA, the ESCEO working group chose to use the recently published CHEERS statement (a list of items to be included in the reporting of economic evaluations); thus, combining recommendations for study conduct with those for study reporting.

Eight of the items in CHEERS, judged to be most sensitive to disease-specific choices, were given additional text to explain the situation in OA. The main additions were to the items "target populations and subgroups" and "comparators," for which the working group recommends the distinction of three reference cases in OA, the hand, knee or hip (and/or a variant according to presentation or severity), and an associated choice of treatment strategy. Another important disease-specific item was that of outcome measures that should be used to evaluate and/or model health over time, and for which the working group made recommendations based on the OMERACT core set (pain intensity, functional ability, PGA and adverse events). Utility scores should be obtained using an indirect estimator (preferably EQ-5D) and, secondarily, by mapping from a disease-specific tool. Finally, the costing of treatment in OA should follow as closely as possible, a process-based categorisation with use (where possible) of national standardised lists of costs.

For each of these main disease-specific items, it remains clear that significant gaps in our knowledge exist and that some of our recommendations rest more on expert opinion than on evidence-based medicine. The research agenda therefore remains long:

- *Therapeutic strategies*: the strategies outlined in the recommendation could be used as acceptable comparators but, ideally, further research is needed on head-to-head comparisons and on the combinations or sequences of pharmacological and non-pharmacological approaches. A key advance would be to find a consensus for each reference case on the "standard optimal care," so that this treatment strategy might be used as one of the comparator arms in any interventional study.
- *Outcome measures*: The best way to measure pain intensity and functional ability in OA remains widely debated and a key advance would be to find a consensus on their measurement scale in OA. Questions persist as to the degree of acceptable overlap in pain measurement with the assessment of functional ability and whether there should be more investigation of pain avoidance behaviours [104]. Similarly, for the assessment of functional limitations, there are questions concerning the overlap of conceptual domains in the questions asked [105]. With the two international initiatives that aim to improve the quantification of the perceived impact of a health condition on the individual, PROMIS and ICF framework, researchers have begun to re-examine older instruments, and improved assessment tools are to be expected [106,107]. Other questions arise as to how to integrate the notion of responders into the outcome measure [108,109] and responders with disease severity. Recent OMERACT conferences have discussed the usefulness of two new complementary metrics for treatment response: the Minimally Clinically Important Improvement (MCII) and the Patient Acceptable Symptom State (PASS)—both of which appear relevant in daily clinical practice [110]. The PASS, with its binary response to a simple question, correlates pain intensity measures (NRS or VAS) well [110] and has also been used to determine satisfaction after total joint replacement [111].

- *Utility scoring*: The reasons that underlie the reported differences in utility scores between EQ-5D and SF-6D and perhaps other measures [93,94] should be further investigated. It would also be instructive to evaluate the differences between mapping techniques to converting disease-specific QoL tools to utilities.
- A key advance would be to find a consensus on a default base case lifetime model including, for each reference case, an accommodation of the expected decline in QoL with increasing age [112]. Comorbidity is a major factor in these patients, and with the OA-related decrease in mobility, other chronic medical conditions then tend to accumulate. OA and depression are associated with the strongest depression of EQ-5D index scores [113]. Although the rates of chronic disability in the USA seem to have declined in recent years, it remains to be seen if this will be counteracted by increases in obesity prevalence [114]. In general, the valuing of health states for cost-effectiveness analysis remains a major concern [115].
- *Resource utilisation*: The allocation of costs in OA poses numerous challenges, especially in the situation of international comparisons or clinical trials. The provision of health care in terms of access to treatment and reimbursement varies widely in different countries even amongst those of the European Union [116]. Between-country differences also exist in mechanisms of compensation for absenteeism with the result that data on productivity loss may be more or less comparable according to the context [101]. Other questions to be resolved include whether social security benefits should be included in the analysis as transfer costs or omitted from costing and should health benefits be discounted at the same rate as costs [117].

The recently developed OMERACT filter 2.0 proposes a framework to define (and obtain consensus on) core outcome measurement sets for different health conditions [71]. It proposes a broad notion of outcome, that of the *impact of the disease*: death (either all-cause death or due to the intervention under study), life impact (health-related QoL including pain and functional indices) and resource use (i.e., economic impact), and a fourth area (outside of "impact") called the "*pathophysiological manifestations of health conditions,*" which concerns other aspects of the target organ biology (such as biomarkers and surrogate outcomes, but also including psychosocial manifestations). Thus, if one were to develop, for OA, a core set based upon this framework, one should add the following to the research agenda presented above: a consensus on the definition of OA-related deaths (and it is known that patients with OA are at a higher risk of death compared with the general population [47]), what pathophysiological manifestations of OA should be included in the outcome measure among the promising biomarker candidates [118,119] and can a consensus be obtained on a definition of relevant radiological progression in OA [120]. With regard to economic evaluations, it should be explored to what extent these variables help define relevant subgroups for OA management (perhaps also helping to better understand the pain experience and effects of innovative treatments).

## Conclusion

A number of specific recommendations are proposed concerning the conduct of economic evaluations in OA that we believe could help the standardisation and comparability of research in this area. Further refinement is still required, and it is anticipated that some of the remaining questions might be settled by launching a consultation with a Delphi-type voting process. While reference case recommendations should describe basic good practice in cost-effectiveness research, these do not necessarily imply consensus [17,18], since the idea is to create a tool to facilitate comparisons. However, it is clear that adherence to any proposition would be more likely if the consensus view were taken. It would be a considerable advance if a consensus could be found on the "standard optimal care" for each reference case, so that this treatment strategy might be used as one of the comparator arms in any interventional study. Also helpful would be a consensus on the core outcome measures, since just this step alone has the potential to improve the health care evidence base [121].

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