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Bioventus	Economic model	005	025 - 028	Cost-utility analysis: Oral, topical and transdermal pharmacological treatments The assessment acknowledges the high lifetime cost of oral, topical and transdermal (OTT) pharmacological treatments (20-100 per month at minimum cost of the maximum dose) and that each drug class is thought to be associated with different harms, however there is no consideration for the potential clinical and cost impact of interventions that may lead to reductions in OTT medication use, such as hyaluronic acid injections. While it is stated that these factors are outside of the scope of the assessment, given the high lifetime cost pharmacological management strategies and potential for clinically serious side effects associated with their long-term use, therapies included elsewhere in the review that have demonstrated potential to attenuate (or conversely increase) dependence on pharmacological management should be acknowledged (references 1-2) and recommendation for further research in this area should be made in order to capture the true cost-effectiveness of therapies under consideration throughout the full patient lifecycle. References: 1. McIntyre LF, Beach W, Bhattacharyya S, Yadalam S, Bisson B, Kim M. Impact of hyaluronic acid injections on utilization of pain	Thank you for your comment and the provision of study references. These studies were not included in the review as they were non-randomised studies which were excluded in the protocol. Regarding the cost of OTT medicines, the model base case considered a lifetime horizon with a treatment duration of 3 months to account for the short-term use of OTT medicines. Therefore, the modelled results have an underlying assumption that the duration of drug treatment will be limited. Reduction in OTT medication use or that additive effects of intramuscular corticosteroids on medication use after surgery were not outcomes considered in the protocol. The committee agreed the most important outcomes to analyse for intra-articular injections were quality of life, pain, physical function, psychological distress, flares and serious adverse events. The evidence suggested that hyaluronic acid did not significantly improve quality of life, pain or physical function. The committee agreed that as there were over 70 RCTs related to hyaluronic acid included in this review, and the evidence did not suggest a benefit for hyaluronic acid then there was sufficient research done for hyaluronic acid and did not think further research in this area was a priority or warranted.

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				management medications. American Journal of Pharmacy Benefits. 2017;9:195-199. 2. Wilson LA, Liu J, Fiasconaro M, Poeran J, Nwachukwu BU, Memtsoudis SG. Increased Use of Intra-Articular Steroid Injection to Treat Osteoarthritis is Associated With Chronic Opioid Dependence After Later Total Knee Arthroplasty But Not Total Hip Arthroplasty. J Arthroplasty. 2020 Aug;35(8):1979-1982.	
Bioventus	Evidence Review J	120 - 121	040 - 043	Line no: 040-043 012-013 The total number of patients reported to experience a flare following hyaluronic acid injection to the hip across all included studies is 9 (Atchia[22], Qvistgaard[383], Richette[398]), and among studies that included flares as an outcome measure, 1 did not define the meaning of flare in the study (Atchia[22]) and 2 did not clearly define the meaning of flare, simply stating "pain after treatment" or "pain flares" (Qvistgaard[383], Richette[398]). We are concerned that the conclusion that there was a clinically important harm of hyaluronic acid for hip osteoarthritis in the interpretation of evidence is based on a limited number of patients across a small number of studies which are inconsistent and unclear in their definition of the meaning of a flare and how this was measured. While this may be an effect of hyaluronic acid injections in the hip, the amount of evidence included is insufficient to draw this conclusion	Thank you for your comment. This outcome was agreed to be a clinically important harm due to the number of events being large per 1,000 people (120 people). However, the committee's confidence in this, based on the quality rating, is very low. We agree that there are a limited number of events inside of small studies showing flares, as defined by the study authors, are present in the trial arms where participants received hyaluronic acid with no events in the control arm. We agree that the study sizes are small and so adverse event data needs to be viewed with this in mind. This outcome was rated as very low quality and the committee took this into account when making their decision.

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				unequivocally and further research should be recommended in this area if it is of concern. *Reference numbers used are based on reference numbers for studies as they appear in evidence review J	
Bioventus	Evidence Review J	115 - 116	General	General: Section 1.1.12 Economic Evidence Statements The only economic evidence included as part of the assessment is for intraarticular hyaluronic acid injections, with two of three included analyses concluding the potential for cost-effectiveness over standard of care. No economic evidence included accounts for the cost implications in the potential for corticosteroids to accelerate time to joint replacement via increased cartilage degradation (references 1-2), the potential for hyaluronic acid injections to delay time to total joint replacement (references 3-4), the impact of hyaluronic acid injections on reducing pain medication consumption (reference 5), or improved quality of life associated with longer duration of action of hyaluronic acid relative to corticosteroid (references 6-8). References: 1. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients	Thank you for your comment and provision of study references. The economic evidence statements were summaries of any economic evaluations that were identified during the economic review. The references provided do not appear to be based on economic evaluations and would therefore be excluded from the economic evidence review. Regarding their suitability for the clinical review, with the exception of Askari 2016, Bisicchia 2016, Caborn 2004 and McAlindon 2017 (which were all included studies in the evidence review), studies were not included in the review as they were non-randomised trials. We agree that the design of the review did not consider the risk of joint replacement as a single outcome. However, the committee acknowledged potentially serious risks such as joint infection and need for joint replacement would have been included as a part of the serious adverse events outcome in the review if available in the included studies. This review was designed to investigate people with osteoarthritis and did not aim to

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				with knee osteoarthritis: a randomized clinical trial. JAMA. 2017;317(19):1967-75. doi:10.1001/jama.2017.5283 2. Wijn SRW, Rovers MM, Tienen TG, Hannink G. Intra-articular corticosteroid injections increase the risk of requiring knee arthroplasty. 3. Jurado RM, Fidalgo EA, Villar RV, Medina MJ, López SB. Factors Related With the Time to Surgery in Waiting-list Patients for Knee Protheses. Reumatol Clin. 2013. 9(3):148-55. 4. Altman R, Lim S, Steen RG, Dasa V. Hyaluronic Acid Injections Are Associated with Delay of Total Knee Replacement Surgery in Patients with Knee Osteoarthritis: Evidence from a Large U.S. Health Claims Database [published correction appears in PLoS One. 2016;11(1):e0148591]. PLoS One. 2015;10(12):e0145776. Published 2015 Dec 22. doi:10.1371/journal.pone.0145776 5. McIntyre LF, Beach W, Bhattacharyya S, Yadalam S, Bisson B, Kim M. Impact of hyaluronic acid injections on utilization of pain management medications. American Journal of Pharmacy Benefits. 2017;9:195-199. 6. Askari A, Gholami T, NaghiZadeh MM, Farjam M, Kouhpayeh SA, Shahabfard Z. Hyaluronic acid compared with corticosteroid injections for the treatment of osteoarthritis of the knee: a randomized control trail. Springerplus. 2016; 5:442	include people who were having or had just had joint replacement surgery. With regards to hyaluronic acid, the committee reviewed the clinical evidence presented to them and concluded that there was unlikely to be a clinically important effect and therefore recommended hyaluronic acid should not be used. This absence of effect was seen at less than 3 months and greater than 3 months (longest follow up was a length of 39 weeks). Regarding corticosteroids, based on the evidence that consistently showed clinically important benefits in reducing pain at less than 3 months and their expert opinion and consensus, the committee agreed to consider intra-articular corticosteroids.

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				7. Bisicchia S, Bernardi G, Tudisco C. HYADD 4 versus methylprednisolone acetate in symptomatic knee osteoarthritis: a single-centre single blind prospective randomised controlled clinical study with 1-year follow-up. Clinical and Experimental Rheumatology. 2016;34(5):857-863 8. Caborn D, Rush J, Lanzer W, Parenti D, Murray C, Synvisc 901 Study G. A randomized, single-blind comparison of the efficacy and tolerability of hylan G-F 20 and triamcinolone hexacetonide in patients with osteoarthritis of the knee. Journal of Rheumatology. 2004;39 31(2):333-343	
Bioventus	Evidence Review J	115	General	Section 1.1.11 Other Calculations The assessment of corticosteroid injections captures the minimal quality-adjusted life year (QALY) gain required for the therapy to be cost effective, however this calculation isbased on the assumption that a single corticosteroid injection will be performed and does not consider the potential for patients to receive more than one corticosteroid injection. Previously stated risks associated with corticosteroid injections (including risk of periprosthetic joint infection if joint replacement is performed in the months following corticosteroid injection and increased degeneration of the joint) and the cost of these complications from a resource use and quality of life perspective are not captured in the assessment. Although the committee acknowledged that the clinical review was not designed to evaluate	Thank you for your comment. A simple threshold analysis was conducted to calculate the minimum QALY gain needed a for a single corticosteroid injection at the lowest cost to be cost effective. The committee acknowledge there is a lack of evidence on the repeated use of corticosteroid injections and have made a research recommendation to assess their clinical and cost effectiveness. A cost comparison between hyaluronan and corticosteroid injections was not necessary since the committee concluded, based on the clinical evidence, that there was a lack of improvement demonstrated in quality

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				these elements in their entirety, these factors have a direct impact on the potential cost effectiveness of the intervention. While it is helpful to demonstrate the minimal QALY gain required for corticosteroids to be effective, without conducting an analysis that incorporates alternative potential intraarticular treatment options at various stages of osteoarthritis and patient age profiles, as well as their duration of effect in patients (which would be expected to contribute to the number of injection appointments required within a specified time frame, patient quality of life, ability to engage in activity and pain medication use) cost-effectiveness cannot be concluded. Failure to include these variables limits the ability to draw conclusions regarding the potential cost effectiveness of corticosteroid injections as compared to alternate intraarticular injections under consideration for patients with osteoarthritis.	of life, pain and physical function with hyaluronan injections.
Bioventus	Evidence Review J	116	012	Pages 116 & 120 Line No012-016, 030-031 013-022 We are concerned that osteoarthritis flares have been included as one of the important outcomes, despite the acknowledgement of the committee that these are "difficult to measure with no clear consensus on their definition" (p. 116 lines 12-16) and that flares are "not	Thank you for your comment. Key outcomes were agreed during the scoping process with stakeholder consultation feedback, which included osteoarthritis flares. This was agreed by the committee as an important outcome for people with osteoarthritis and so was included in the protocol. We believe that patient experience is an important factor to determining the effectiveness of interventions. As your comment rightly notes, the committee acknowledge the challenges in defining osteoarthritis flares and acknowledged the limitations in the definitions used in the studies included in the review.

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				frequently reported" in included studies with "no information being available for the majority of sites of osteoarthritis" (p.116 lines 30-31), while other potentially serious risks acknowledged by the committee, such as increased risk of periprosthetic joint infection if joint replacement is performed in the months following intra-articular corticosteroid injection and the risk of repeat corticosteroid injections leading to increased degeneration of the joint (p. 120 lines 13-22). While it is understood that the reason the latter risks are not considered in the current assessment as a result of the design of the review, omitting consideration of these risks while continuing to consider osteoarthritis flares (which are a common experience for patients living with osteoarthritis and by the committees own admission difficult to measure and variably defined) results in conclusions around clinically important harm that are based largely on patient experience in the short-term following intra-articular injection. Conversely, longer term, and arguably more clinically meaningful and costly risks such as risk of infection and impact on degradation of the joint do not factor into conclusions around clinical harms between the intra-articular injections under consideration. This creates a bias towards those intra-articular injections which can produce a short-term effect regardless of potential long-term harms, while reducing emphasis on those therapies that may be more clinically meaningful in the longer term.	These were downgraded for risk of bias accordingly and the quality of the outcomes was assessed as very low. However, due to the importance of the outcome to people with osteoarthritis, this was included, and the committee considered this in their deliberation. We agree that the design of the review did not consider the risk of joint replacement as a single outcome. However, the committee acknowledged potentially serious risks such as joint infection and need for joint replacement would have been included as a part of the serious adverse events outcome in the review if available in the included studies. This was review was designed to investigate people with osteoarthritis and did not aim to include people who were having or had just had joint replacement surgery, so evidence about periprosthetic joint infections would be outside of the scope of the review. The committee made the recommendations based on the available evidence. Without the evidence of benefit the committee agreed that it would not be a good use of NHS resources to recommend an intervention.

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Bioventus	Evidence Review J	119	045 - 046	Pages: 119 120 121 Line no: 045-046 036-039 024-026 Section 1.1.13.3 Within the section on key uncertainties (p. 119 lines 45-46), the committee notes that there was sufficient evidence to show an effect of intra-articular corticosteroid injections for people with knee osteoarthritis. In the summary of evidence on corticosteroid vs placebo (p. 121 lines 24-26) the committee summarized that 'in people with knee osteoarthritis there was very low-quality evidence of short-term benefit for pain but no clinically important difference in physical function or quality of life at less than three months'. Therefore, the standard for sufficient evidence within the review as it applies to corticosteroids is very low-quality evidence at less than three months related to one factor (here pain). We are concerned that a different standard for sufficient evidence has been applied to the interpretation of available evidence on intra-articular	Thank you for your comment. The committee based their recommendations on the evidence and used their expert opinion in interpreting the evidence and applying this to clinical practice. The committee agreed that further evidence would be required to completely understand the effect of corticosteroids, including the long-term effects, and made a research recommendation. However, based on the evidence that consistently showed clinically important benefits in reducing pain at less than 3 months and their expert opinion and consensus, the committee agreed to consider intra-articular corticosteroids. With regards to hyaluronic acid, more evidence was available including larger trials since the previous review in 2014 when the committee recommended 'Do not offer intra-articular hyaluronan injections for the management of osteoarthritis.'. The additional studies included low risk of bias outcomes with larger numbers of participants and when both a low risk of bias and larger number of participants were achieved indicated no clinically important difference in hyaluronic acid compared to placebo in outcomes to assess efficacy (Hangody 2018, Ke 221, Petterson 2019, van der Weegen 2015). The other additional studies for this comparison, though of a higher risk of bias, also indicated no clinically important difference (Brander 2019, Gomoll 2021). When interpreting the evidence, the committee agreed that most evidence, including the additional evidence since 2014, indicated no clinically important difference in efficacy outcomes, and where clinically important differences were

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				hyaluronic acid; within the summary of evidence on intra-articular hyaluronic acid compared to corticosteroids (p. 120 lines 36-39), the committee notes that for the knee a clinically important benefit of hyaluronic acid was seen on quality of life at less than 3 months and on pain and physical function at more than 3 months. In this assessment, hyaluronic acid therefore demonstrates clinically important benefit over steroid in knees on one factor at less than 3 months (quality of life) and two factors at more than 3 months (pain and physical function), which meets the threshold of sufficient evidence established in the summary and interpretation of evidence for corticosteroids. The committee states that the reported benefits on hyaluronic acid compared to steroids were based on very low-quality evidence from a small number of studies, however the evidence accepted to be sufficient in the evaluation of corticosteroids is also graded as low quality based on a small number of studies.	present other GRADE outcomes reporting the same protocol outcome often showed no clinically important difference. On examining the effect of more well-designed studies, the committee noted that the clinical effect was often smaller. Using this while examining all of the available evidence, the committee concluded in agreement with the committee in 2014, that there was less likely to be a clinically important effect of hyaluronic acid based on the evidence available. Therefore, due to this and weighing in the cost-effectiveness and potential adverse effects that may be present from the evidence included, the committee agreed to retain the recommendation from the previous version of the guideline, that hyaluronic acid should not be used.
Bioventus	Evidence Review J	120	018 - 022	When discussing current uncertainty regarding the long-term use of intra-articular injections in people with osteoarthritis, the committee comments on the risk of increased degeneration of the joint (and therefore accelerated time to joint replacement) associated with repeated corticosteroid injections. The committee does not however make comment on available evidence demonstrating the association of repeat hyaluronic acid injections delaying time to total joint replacement	Thank you for your comment and provision of study references. These studies were not included in the review as they were non-randomised trials, in vitro or animal studies, narrative reviews or systematic reviews. The reviews were checked and all of the studies identified that met our protocol were already included in our review. The committee agreed that there are potential risks for long term use of intraarticular corticosteroid injections.

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				(references 1-3). Although the committee states that the impacts of long-term use of intra-articular injections are not within the scope of the review, we are concerned that given the long-term nature of osteoarthritis disease management, the potentially significant risks associated with long-term corticosteroid use are given limited weighting and the potentially significant benefits associated with long-term hyaluronic acid use are not referenced in any capacity. While there is undoubtedly a place for intraarticular corticosteroid injections in short-term symptomatic treatment of osteoarthritis symptoms, given the long-term nature of osteoarthritis disease management, the negative effects and risks of using steroids for multiple treatments must be taken into consideration, particularly given that in the current draft guidance this is the only intraarticular injection therapy recommended. In-vitro studies have shown as little as one steroid treatment can be chondrotoxic and result in cartilage volume loss (references 4-7). These findings of chondrotoxicity and cartilage volume loss are synonymous with rapid progression of osteoarthritis associated with intra-articular corticosteroid injections which has been demonstrated in both the knee and the hip (references 8-11). A large matched pair cohort study comparing arthroplasty in patients who received IA steroids compared to no steroid found that each injection increased the absolute risk of requiring arthroplasty by 9.4% (reference 12). This evidence is a	The committee agreed that any therapy should be used to support therapeutic exercise. The committee agree that non-pharmacological therapies are important for managing the long-term nature of the condition and that intraarticular corticosteroids are used in the short-term management. The committee recommended that opioids (as with all oral, topical and transdermal pharmacological treatments) are used at the lowest effective dose for the shortest time possible. They recommended that strong opioids should not be used and provided conditions as to when weak opioids should be used. Therefore, they believe that their recommendations should lead to reduced chronic opioid utilisation.

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				stark contrast to that published for intraarticular hyaluronic acid which has been shown to delay the time to joint replacement with the main reported adverse events being mild arthralgia or pain shortly after injection (references 1, 13-14). Finally, in a large Truven Marketscan database study total knee arthroplasty (TKA) patients who received 2 or more preoperative corticosteroid injections experienced greater odds of chronic opioid utilization, whereas TKA patients with 2 or more HA injections in the year before surgery had decreased odds of chronic opioid use (reference 15). References 1. Altman R, Lim S, Steen RG, Dasa V. Hyaluronic Acid Injections Are Associated with Delay of Total Knee Replacement Surgery in Patients with Knee Osteoarthritis: Evidence from a Large U.S. Health Claims Database [published correction appears in PLoS One. 2016;11(1):e0148591]. PLoS One. 2015;10(12):e0145776. Published 2015 Dec 22. doi:10.1371/journal.pone.0145776 2. Concoff A, Niazi F, Farrokhyar F, Alyass A, Rosen J, Nicholls M. Delay to TKA and Costs Associated with Knee Osteoarthritis Care Using Intra-Articular Hyaluronic Acid: Analysis of an Administrative Database. Clin Med Insights Arthritis Musculoskelet Disord. 2021;14:1179544121994092. Published 2021 Mar 22. doi:10.1177/1179544121994092	

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				3. Delbarre A, Amor B, Bardoulat I, Tetafort A, Pelletier-Fleury N. Do intra-articular hyaluronic acid injections delay total knee replacement in patients with osteoarthritis - A Cox model analysis. PLoS One. 2017;12(11):e0187227. doi:10.1371/journal.pone.0187227 4. Nakazawa F, Matsuno H, Yudoh K, Watanabe Y, Katayama R, Kimura T (2002) Corticosteroid treatment induces chondrocyte apoptosis in an experimental arthritis model and in chondrocyte cultures. Clin Exp Rheumatol 20(6):773–781 5. Seshadri V, Coyle CH, Chu CR (2009) Lidocaine potentiates the chondrotoxicity of methylprednisolone. Arthroscopy 25(4):337–347 6. Dragoo JL, Danial CM, Braun HJ, Pouliot MA, Kim HJ. The chondrotoxity of single-dose corticosteroids. Knee Surg Sports Traumatol Arthrosc. 2012:20;1809-1814. 7. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. JAMA. 2017;317(19):1967-75. doi:10.1001/jama.2017.5283 8. Walker EA, Davis D, Mosher TJ. Rapidly progressive osteoarthritis: biomechanical considerations. Magn Reson Imaging Clin N Am 2011;19(2):283–294.	

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				9. Irwin LR, Roberts JA. Rapidly progressive osteoarthrosis of the hip. J Arthroplasty 1998;13(6):642–646. 10. Lohmander LS, Felson D. Can we identify a 'high risk' patient profile to determine who will experience rapid progression of osteoarthritis? Osteoarthritis Cartilage 2004;12(Suppl A):S49–S52. 11. Kompel AJ, Roemer FW, Murakami AM, Diaz LE, Crema MD, Guermazi A. Intra-articular Corticosteroid injections in the hip and knee: Perhaps not as safe as we thought? Radiology. 2019;00:1-8 12. Wijn SRW, Rovers MM, Tienen TG, Hannink G. Intra-articular corticosteroid injections increase the risk of requiring knee arthroplasty. 13. Jurado RM, Fidalgo EA, Villar RV, Medina MJ, López SB. Factors Related With the Time to Surgery in Waiting-list Patients for Knee Protheses. Reumatol Clin. 2013. 9(3):148-55. 14. Leighton R, Fitzpatrick J, Smith H, Crandall D, Flannery CR, Conrozier T. Systematic clinical evidence review of NASHA (Durolane hyaluronic acid) for the treatment of knee osteoarthritis. Open Access Rheumatol. 2018;10:43-54. 15. Wilson LA, Liu J, Fiasconaro M, Poeran J, Nwachukwu BU, Memtsoudis SG. Increased Use of Intra-Articular Steroid Injection to Treat Osteoarthritis is Associated With Chronic Opioid Dependence After Later Total Knee	

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				Arthroplasty But Not Total Hip Arthroplasty. J Arthroplasty. 2020 Aug;35(8):1979-1982.	
Bioventus	Evidence Review J	121	001 - 004	Based on the summary of evidence for this section, in knees (where there is most evidence) hyaluronic acid therefore demonstrates clinically important benefit over steroid in knees on one factor at less than 3 months (quality of life) and two factors at more than 3 months (pain and physical function), in toes on two factors at less than 3 months (pain and physical function) and in TMJ under image guidance on one factor at less than 3 months (pain). In hips and thumbs there was evidence of no clinically important difference in critical outcomes. This does not align with the conclusion that there is no evidence favouring either hyaluronic acid or corticosteroid. We are concerned that while the committee has issued a research recommendation for corticosteroid in cases where evidence is considered mixed or insufficient to draw conclusions, no research recommendation has been issued for hyaluronic acid injections in similar circumstances. Here, despite the fact that hyaluronic acid injections demonstrate clinically important benefit over steroid in the majority of included studies, the committee states that it is difficult to interpret these results due to the inconsistency of the results when compared to placebo-controlled trials. The committee however does not go on to recommend further research in this area.	Thank you for your comment. We agree that there are some individual studies that indicated of clinically important benefits for hyaluronic acid for some outcomes (notably Blanco 2008, Corrado 1995, Diracoglu 2009, Henderson 1994, Suskisson 1999, Sezgin 2005). However, clinically important harms were also identified in two quality of life outcomes and one physical function outcome for people with thumb osteoarthritis. Benefits for non-hip and non-knee joint sites were generally seen in a limited number of studies with the outcomes reported in the individual studies being of high or very high risk of bias. Whereas evidence for knee and hip osteoarthritis were generally larger studies and included low risk of bias studies. Therefore, the committee agreed that the limited evidence for non-hip and knee joint sites should be supplemented with the evidence for hip and knee joint sites and, as with corticosteroids, this evidence can be generalised to all joint sites. For knee and hip joint sites, the majority of outcomes from larger studies, that had greater weighting in the meta analysis of low risk of bias did not show a clinically important benefit for hyaluronic acid in efficacy outcomes when compared to other treatments. The studies previously noted that indicated benefits reported outcomes of high or very high risk of bias and had smaller weightings in the meta-analysis. Taking into account the findings from all of the available evidence identified in this review, the committee did not feel confident to recommend hyaluronic acid for non-knee

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				Additionally, the reported inconsistency of the results in placebo-controlled trials is attributable in large part to the fact that all intra-articular hyaluronic acid formulations have been grouped under a single product class for the purposes of the review, despite a substantial body of evidence demonstrating that effect sizes of hyaluronic acid (HA) injections are significantly different when formulations are classed according to how the product is sourced (avian vs. biofermentation) and more importantly according to the molecular weight of the product (low, medium or high). While the molecular weight thresholds of the products included each of these categories can vary, these are often defined in the following ranges: • Low molecular weight (LMW): 500–730 kDa, medium molecular weight (MMW): (800–2000 kDa), high molecular weight (HMW): average 6000 kDa (References 1-2) • LMW: ≤1500kDa, MMW: 1500-3000kDa, HMW >3000kDa (References 3-4) Regardless of if the threshold used to define HMW HA as a product class is set at >3000kDa or >6000kDA, meta-analyses comparing effect sizes of HMW HA in osteoarthritis (OA) symptom management against lower molecular weight HA formulations consistently show that HMW HA demonstrates a greater, more consistent treatment effect (References 4-7). Some of these analyses also include comparison against various classes of intraarticular corticosteroid injections	and hip joint sites based on this evidence and agreed that applying the evidence for the knee and hip joint sites, where there is more evidence, would be appropriate in this scenario. Given that trials have been conducted including a large number of people with long term follow up, the committee agreed that a research recommendation for hyaluronic acid was not required. Thank you for your thoughts on the inconsistency in the evidence. The committee did not include this as a subgroup for analysis because they agreed that the evidence indicating that the efficacy of hyaluronic acid products is related to molecular weight was inconsistent and that the purported mechanism of action was unclear. Therefore, they did not assess the effect of molecular weight in an analysis for this review. The effect of different products was completed in the 2014 version of this guideline, which led to a recommendation of 'Do not offer intra-articular hyaluronan injections for the management of osteoarthritis' as no consistent evidence of clinically important benefits in high quality outcomes was identified. New studies identified in this updated review indicated no clinically important difference between hyaluronic acid and placebo. Therefore, it is unlikely that an analysis of different product classes would have changed the outcome of the review. The studies you have referenced were not included in the guideline because either they reported comparisons between different hyaluronic acid products, interventions and outcomes that were not relevant to the protocol.

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				(References 5-7), intraarticular platelet rich plasma injections (Reference 5), saline / placebo (References 5-6) and various classes of nonsteroidal anti-inflammatories (topical, non-selective, cox-2) (Reference 7); in all cases HMW HA demonstrates greater effect size. Taken together, the available evidence supports the conclusion that effect sizes of intraarticular hyaluronic acid injections vary according to the molecular weight of the product formulation, with HMW HA consistently demonstrating superiority over LMW HA, and should therefore be considered as separate product classes. Evidence supporting the differentiation of HA's by molecular weight was used in 2021 as the basis for the American Academy of Orthopaedic Surgeons (AAOS) to downgrade the recommendation on the use of HA's from strongly do not recommend to not recommended for routine use (Reference 8). Amalgamation of LMW and HMW HA's in the present review may have distorted the overall observed effect of HA's leading to the inconsistency in the results when compared to placebo-controlled trials as interpreted by the committee. References: 1. Mochizuki T, Ikari K, Yano K, Okazaki K. Comparison of patient-reported outcomes of treatment with low- and intermediate molecular weight hyaluronic acid in Japanese patients with symptomatic knee osteoarthritis: A	

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				prospective, randomized, single-blind trial. Asia-Pacific Journal of Sports Medicine, Arthroscopy, Rehabilitation and Technology. 2020;21:22-26. 2. Maheu E, Rannou F, Reginster JY. Efficacy and safety of hyaluronic acid in the management of osteoarthritis: evidence from real-life setting trials and surveys. Semin Arthritis Rheum. 2016;45:S28-S33 3. Bahrami MH, Raeissadat SA, Cheraghi M, Rahimi-Dehgolan S, Ebrahimpou A. Efficacy of single high-molecular –weight versus triple low-molecular weight hyaluronic acid intra-articular injection among knee osteoarthritis patients. BMC Musculskeletal Disord. 2020;21(1):550. 4. Altman RD, Bedi A, Karlsson J, Sancheti P, Schemitsch E. Product differences in intra-articular hyaluronic acids for osteoarthritis of the knee. Am J Sports Med. 2016;44(8):2158-65. 5. Phillips M, Vannabouathong C, Devji T, Patel R, Gomes Z, Patel A, Dixon M, Bhandari M. Differentiating factors of intra-articular injectables have a meaningful impact on knee osteoarthritis outcomes: a network meta-analysis. Knee Surg Sports Traumatol Arthrosc. 2020;28(9):3031-3039. doi: 10.1007/s00167-019-05763-1. 6. Hummer CD, Angst F, Ngai W, et al. High molecular weight Intraarticular hyaluronic acid	

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				for the treatment of knee osteoarthritis: a network meta-analysis. BMC Musculoskelet Disord. 2020;21(702). https://doi.org/10.1186/s12891-020-03729-w 7. Concoff A, Rosen J, Fu F, Bhandari M, Boyer K, Karlsson J, Einhorn TA, Schemitsch E. A Comparison of Treatment Effects for Nonsurgical Therapies and the Minimum Clinically Important Difference in Knee Osteoarthritis: A Systematic Review. JBJS Rev. 2019;7(8):e5. doi: 10.2106/JBJS.RVW.18.00150. 8. American Academy of Orthopaedic Surgeons Management of Osteoarthritis of the Knee (NonArthroplasty) Evidence-Based Clinical Practice Guideline. https://www.aaos.org/oak3cpg. Published 08/31/2021	
Bioventus	Evidence Review J	121	007 - 009	Of the 35 knee studies included comparing hyaluronic acid to placebo, all 35 studies showed improvements in pain or function in both treatment groups, suggesting that procedures performed as placebo (in most cases saline, in 2 studies very low dose hyaluronic acid, in 1 study local anesthetic and in 1 study arthrocentesis with no additional injection) may produce a clinical effect and therefore represent an active control. In 21 of the included studies hyaluronic acid was found to be superior to placebo providing greater pain or function improvements, longer lasting results and	Thank you for your comment. The committee based their decision on the evidence from the studies that could be extracted and included according to the protocol. For pain and physical function, this included continuous reporting of outcomes where standard deviations or statistics that could be converted to find standard deviations. Therefore, responder analyses and data from graphs where this information could not be obtained was not included in the analysis, as is the case for some of the studies being referred to (Altman 1998, Altman 2009, Navarro-Sarabia 2011, Rolf 2005, Brandt 2001, Dixon 1988, Jubb 2003, Lohmander 1996).

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				greater responder rates[11,12,49,56,75,90,102,109,122,123,126,162,179,198,201,336,369,373,407,430,460]. Significant benefits over saline were found in 10 studies at 24-27 week follow up, and in a single study with long term 34 month benefits [11,12,49,56,75,123,179,198,201,407,336] A further 7 included studies show a benefit of both the hyaluronic acid and placebo treatment with no overall significant difference between the groups, however each of these studies demonstrates a benefit of HA over the placebo in specific cohorts of patients (in particular those patients without joint effusion or arthritis in a single joint only) or in a particular outcome[9,16,226,237,259,287,338]. The majority of the evidence for this comparison therefore demonstrates a potential benefit of hyaluronic acid as compared to placebo, rather than no benefit. The conclusion that the evidence for physical function at less than three months is mixed suggests the need for further research. *Reference numbers used are based on reference numbers for studies as they appear in evidence review J	Regarding the effects of individual studies using the data that was included in the review, we disagree that significant benefits were seen with the majority of referred to studies with most studies indicating no clinically important difference in efficacy outcomes. We agree that, in the majority of studies, pain and physical function outcomes favoured hyaluronic acid study arms. However, the majority of these were smaller than the minimally important differences used in the outcomes and therefore were not clinically important differences. The majority of studies also did not indicate statistical significance in these outcomes. Based on the large number of studies that indicated no clinically important difference, including trials with larger number of participants of low risk of bias, and the meta-analysis of these outcomes that indicated no clinically important difference and examining this against the whole body of evidence, the committee agreed that hyaluronic acid did not appear to have a clinically important effect on pain and physical function for people with knee osteoarthritis. Based on this lack of effectiveness, a cost effectiveness analysis of hyaluronic acid is not justified.
Bioventus	Evidence Review J	121	013 - 014	The comment that there is evidence of serious adverse events (AEs) in people with shoulder osteoarthritis at more than three months is based on a single study (Kwon[261]) where although a greater proportion in the	Thank you for your comment. We agree that the evidence for adverse events for people with shoulder pain received hyaluronic acid is limited. On reviewing the evidence we agree that although there were more adverse events with

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				hyaluronic acid (HA) group experienced serious adverse events, the rate of serious adverse events was not statistically significant between the HA group and phosphate-buffered saline (PBS) group. The authors conclude that there were comparable rates of AEs between the HA and the PBS group and that neither group reported serious or unanticipated treatment-related AEs. This is at odds with the statement that there is evidence of serious adverse events in people with shoulder osteoarthritis at more than three months. *Reference number used is based on reference numbers for studies as they appear in evidence review J	hyaluronic acid this was below the threshold for a clinically important harm. We have updated the evidence report. The committee still agree that the number of adverse events is higher in the hyaluronic acid arm, but agree that the quality of the outcome is very low and that further work would be required to understand the adverse events from hyaluronic acid for shoulder osteoarthritis. However, the committee agreed that the evidence overall did not show that hyaluronan injections improved quality of life or physical function, or reduced pain, in people with knee or hip osteoarthritis.
Bioventus	Evidence Review J	122	015 - 018	The committee states that there is insufficient evidence to determine the effectiveness of hyaluronic acid (HA) injections in the ankle, foot, toe, shoulder, elbow, wrist, hand, thumb, finger and TMJ. Rather than recommending further research in these joints the committee utilizes this insufficient evidence as part of the basis to continue to recommend against treatment. This appears at odds with the approach taken to address areas of uncertainty in the data on corticosteroid and stem cell injections. It is not possible to draw conclusions regarding the clinical viability of the therapy where there is an acknowledged lack of certainty due to insufficient evidence.	Thank you for your comment. We agree that there was uncertain evidence with some outcomes indicating a benefit for the ankle, and some indicating no clinically important difference. However, we disagree that all hyaluronic acid trials for the shoulder and thumb joints demonstrated a positive effect of hyaluronic acid treatment, where these appeared to indicate no clinically important difference when compared to saline. When compared to corticosteroids for people with thumb osteoarthritis, there was evidence that corticosteroids had clinically important benefits in quality of life and physical function when compared to hyaluronic acid, which suggested clinically important harms of hyaluronic acid in comparison.

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				The number of studies included in the review for the ankle/shoulder and thumb joints (see below) are greater in number for HA than they are for corticosteroid. All HA studies in these joints demonstrated a positive effect of the HA treatment. It therefore seems inconsistent for the committee to provide guidance that there is limited high quality data for steroid but recommend its use with further research, yet state there is little or no evidence for HA and not recommend further research • 6 HA vs placebo studies[48,81,110,261,330,416] • 8 HA vs corticosteroid studies[26,47,152,159,323,377,455,492] • 2 HA vs corticosteroid vs placebo studies[22,192] • There are no steroid studies in the ankle joint, but 3 for HA[81,110,416] *Reference numbers used are based on reference numbers for studies as they appear in evidence review J	For both hyaluronic acid and corticosteroids, the committee were consistent in giving greater emphasis in their decision making on higher quality evidence from trials with greater weighting in the meta analysis when investigating the efficacy of these treatments for knee and hip osteoarthritis to inform their recommendations. These trials indicated that hyaluronic acid did not have consistent clinical effects with outcomes that had greater weighting in the meta analysis, reported in individual studies of low risk of bias indicating no clinically important difference in efficacy outcomes. Whereas trials for corticosteroids, while with greater uncertainty, indicated clinically important benefits at less than and equal to 3 months consistently. Given this and their expert knowledge, the committee agreed that there was evidence that corticosteroids may be effective treatment for short term relief. Given the uncertainty in the evidence and lack of information about long term effects, the committee agreed this should be a 'consider' recommendation rather than an 'always offer' recommendation and that further research, particularly investigating the effectiveness of the intervention for non-knee and hip osteoarthritis, would be important. As the committee identified consistent evidence that hyaluronic acid led to no clinically important difference in efficacy outcomes and on examination of the evidence as a whole agreed that the evidence did not indicate clinically important changes, the committee did not agree that hyaluronic acid required additional research.

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Bioventus	Evidence Review J	122	031 – 035	In acknowledging the current widespread use of corticosteroid injections for people with persistent osteoarthritis symptoms in the NHS, the committee states that there is no increased risk associated with their use in joints outside of the hip, knee and finger and that the pathobiological mechanisms are anticipated to be the same. It does not however acknowledge that there is a potential to reduce certain risks and pathobiological mechanisms, such as the previously stated risk of periprosthetic joint infection following joint replacement and increased degeneration of joint potentially leading to the need for joint replacement, through the adoption of alternate interventions shown to protect against these factors, such as the use of hyaluronic acid injections for specified patient cohorts.	Thank you for your comment. The committee did not identify any evidence to state that there is increased risk associated with the use of corticosteroid injections in joints outside of the hip, knee and finger. The committee used their expert opinion to agree that the pathobiological mechanisms is not anticipated to be different between them for the case of this review. They acknowledged that there are potential risks to the use of corticosteroid injections and so recommend for further research into the long-term effects of corticosteroids and the effects in joint sites other than the hip and knee.
Bioventus	Evidence Review J	124	034 – 038	The committee states that the majority of included studies were in the short term (less than 3 months) despite the long-term duration of disease management required for people with osteoarthritis. Of those studies that did evaluate efficacy of intra-articular injections at greater than 3 months, 10 studies evaluating intraarticular injections of hyaluronic acid compared to placebo in the knee demonstrated significant benefits of hyaluronic acid over saline at 24-27 week follow-up, and a single study with demonstrated long-term 34 month benefits[11,12,49,56,75,123,179,198,201,407,336]. Within the review, in the assessment of the evidence on hyaluronic acid injections compared to corticosteroid injections in the knee a clinically important benefit of	Thank you for your comment. As with other comments, we disagree that the 10 studies evaluating intraarticular injections of hyaluronic acid compared to placebo in the knee demonstrated significant benefits, with the majority indicating no clinically important difference in efficacy outcomes and the committee agreeing after examining the evidence as a whole that there were likely no clinically important effects from the intervention. Thank you for the additional references. These studies would not be included in this review due to these studies being non-randomised studies which were excluded from the review.

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				hyaluronic acid on pain and physical function was seen at more than 3 months. Outside of included studies, there are a number of published studies available suggesting the long-term clinical effect of hyaluronic acid injections as well as the potential to increase time to total joint replacement and decrease pain medication use (references 1-5 below). Taken together, this evidence suggests that the true benefit of intraarticular hyaluronic acid injections for patients with osteoarthritis may only be seen in critical outcomes at greater than 3 months. The committee acknowledges the long-term duration of disease management for people with osteoarthritis, however omits evidence regarding the potential long-term benefits of the intra-articular injections under consideration. Failure to take a lifetime view also limits the applicability of conclusions around cost-effectiveness, particularly given evidence to suggest variability in duration of action between different intra-articular injection therapies (and the impact of this on number of injection appointments required within a given time frame, patient medication use and quality of life), impact on degradation of the joint and time to total joint replacement and safety profile in patients with multiple morbidities. Whereas there is certainly a place for corticosteroid injections in short-term pain management for selected patients living with osteoarthritis, for those patients that are living with early-stage mild to moderate osteoarthritis, and particularly those that are relatively	The long-term effect of hyaluronic acid was investigated in this review, with studies reporting outcomes beyond 3 months being included in the review. Studies with larger number of participants and of low risk of bias at these time periods indicated no clinically important difference in efficacy outcomes. The committee concluded that the effectiveness of hyaluronic acid does not appear to improve over time based on the identified evidence. The committee agreed that there was evidence that corticosteroids may be effective treatment for short term relief. However, they also agreed that there was insufficient evidence about the long-term effects of the intervention and so agreed that further research should be conducted to investigate the long-term effects of corticosteroids, including in joint sites other than the hip and knee.

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				young in age or do not qualify for corticosteroid injections due either to an acquired tolerance or comorbidities, hyaluronic acid injections may offer greater resilience to joint degradation and a longer overall duration of effect, enabling patients to engage to a greater degree in physical activity, reduce dependence on OTT medication use and delay time to eventual joint replacement. While it is understood that the cost of adopting hyaluronic acid injections for the treatment of all osteoarthritis patients would be significant to the NHS, and for this reason the therapy cannot be recommended for all patients, downgrading the recommendation from do not recommend to do not routinely recommend, and stipulating that hyaluronic acid should only be used where there are plans for governance and audit, would offer a safe and effective alternate treatment option for those patients that are determined to be clinically unsuitable to receive corticosteroid injections. Concurrently this approach would support the development of a larger evidence base on the topic of clinical and cost effectiveness of hyaluronic acid injections for specified patient cohorts. *Reference numbers shown in superscript are based on reference numbers for studies as they appear in evidence review J References: 1. Carney G, Harrison A, Fitzpatrick J. Long-term outcome measures of repeated non-animal stabilized hyaluronic acid (Durolane) injections	

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				in osteoarthritis: a 6-year cohort study with 623 consecutive patients. Open Access Rheumatol. 2021;13:285-92. Doi:10.2147/OARRR.S331562 2. Altman R, Lim S, Steen RG, Dasa V. Hyaluronic Acid Injections Are Associated with Delay of Total Knee Replacement Surgery in Patients with Knee Osteoarthritis: Evidence from a Large U.S. Health Claims Database [published correction appears in PloS One. 2016;11(1):e0148591]. PloS One. 2015;10(12):e0145776. Published 2015 Dec 22. Doi:10.1371/journal.pone.0145776 3. Concoff A, Niazi F, Farrokhyar F, Alyass A, Rosen J, Nicholls M. Delay to TKA and Costs Associated with Knee Osteoarthritis Care Using Intra-Articular Hyaluronic Acid: Analysis of an Administrative Database. Clin Med Insights Arthritis Musculoskelet Disord. 2021;14:1179544121994092. Published 2021 Mar 22. Doi:10.1177/1179544121994092 4. Delbarre A, Amor B, Bardoulat I, Tetafort A, Pelletier-Fleury N. Do intra-articular hyaluronic acid injections delay total knee replacement in patients with osteoarthritis – A Cox model analysis. PloS One. 2017;12(11):e0187227. Doi:10.1371/journal.pone.0187227 5. McIntyre LF, Beach W, Bhattacharyya S, Yadalam S, Bisson B, Kim M. Impact of hyaluronic acid injections on utilization of pain	

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				management medications. American Journal of Pharmacy Benefits. 2017;9:195-199.	
Bioventus	Evidence Review J	122 – 124	General	General: Section 1.1.13.4 Cost-effectiveness and resource use In the assessment of potential cost effectiveness and resource use of various intraarticular injections under consideration, the committee states that conclusions from two of the three economic analyses included, both of which suggest a potential cost-effectiveness of hyaluronic acid injections, would not be considered based on the assumption that quality of life estimates in analyses were overweighted. The rationale provided is that clinical review does not suggest a benefit of hyaluronic acid injections when compared to placebo for quality of life, pain and physical function. However, of the studies included in clinical review comparing hyaluronic acid injections in the knee to placebo, 21 of the included studies found hyaluronic acid to be superior over placebo providing greater pain or function improvements, longer lasting results and greater responder rates[11,12,49,56,75,90,102,109,122,123,126,162,179,198,201,336,369,373,407,430,460]. While the majority of studies included in the clinical review evaluated the short-term efficacy of intraarticular injections (< 3 months), of the studies included comparing hyaluronic acid to saline, significant benefits over saline were found in 10 studies at 24-27 week follow up, and in a single study with long term 34 month	Thank you for your comment. The committee based their decision on the evidence from the studies that could be extracted and included according to the protocol. For pain and physical function, this included continuous reporting of outcomes where standard deviations or statistics that could be converted to find standard deviations. Therefore, responder analyses and data from graphs where this information could not be obtained was not included in the analysis, as is the case for some of the studies being referred to (Altman 1998, Altman 2009, Navarro-Sarabia 2011, Rolf 2005, Brandt 2001, Dixon 1988, Jubb 2003, Lohmander 1996). Regarding the effects of individual studies using the data that was included in the review, we disagree that significant benefits were seen with the majority of referred to studies with most studies indicating no clinically important difference in efficacy outcomes. We agree that, in the majority of studies, outcomes favoured hyaluronic acid study arms. However, the majority of these point estimates were smaller than the minimally important differences agreed for the outcomes and therefore were not clinically important differences. The majority of studies also did not indicate statistical significance in these outcomes. Based on the large number of studies that indicated no clinically important difference, including trials with larger number of participants of low risk of bias, and the meta-analysis of these outcomes that indicated no

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				benefits[11,12,49,56,75,123,179,198,201,407,336]. A further 7 included studies show a benefit of both the hyaluronic acid and placebo treatment with no overall significant difference between the groups, however each of these studies demonstrates a benefit of HA over the placebo in specific cohorts of patients (in particular those patients without joint effusion or arthritis in a single joint only) or in a particular outcome[9,16,226,237,259,287,338]. Taken together, the evidence included in the clinical review does suggest a benefit of hyaluronic acid injections, particularly for patients without joint effusion, when compared to placebo on quality of life, pain and physical function. Therefore the decision to place limited weight on two thirds of the economic analyses included in the review, on the basis of there being a lack of evidence of efficacy of hyaluronic acid compared to placebo is not supported. Although the assessment demonstrates that the unit cost of corticosteroid injections is less than the cost of various hyaluronic acid formulations, this is not sufficient to draw conclusions on the cost effectiveness of the therapies as it does not take into account the potential differences in duration of effect (and the associated impact to quality of life and physical function), risks of complications, impact on degradation of the joint, differences in the number of injections required between different injection regimes (i.e. single vs. multiple injection course) or potential differences in efficacy and duration of effect between product formulations (i.e. low molecular weight hyaluronic acid	clinically important difference, the committee agreed that hyaluronic acid did not appear to have a clinically important effect on pain and physical function for people with knee osteoarthritis. Based on this agreement by the committee, a cost effectiveness analysis of hyaluronic acid is not justified.

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				vs. high molecular weight hyaluronic acid, long-lasting vs. short-lasting corticosteroid). Failing to consider the long-term cost consequences of the interventions under consideration limits the applicability of conclusions in the assessment around cost-effectiveness and resource use. *Reference numbers used are based on reference numbers for studies as they appear in evidence review J	
Bioventus	Guideline	009	010	We are concerned that the proposed Do Not Recommend status for intraarticular hyaluronic acid (HA) injections will limit access to a clinically viable pain management strategy for patients generally but particularly those unsuitable for other forms of pharmacological management, intraarticular corticosteroids or joint arthroplasty. This limitation has the potential to increase the overall burden of health in these patient cohorts living with chronic, unmanaged pain and unable to engage in regular activity. In consideration of the variability in the observed effect size of HA injections among the studies included in the review and the increased average cost per unit of HA formulations compared to corticosteroid injections, it is understood that there is insufficient evidence to issue a positive recommendation for the widespread use of HA for the management of patients with osteoarthritis. It is also acknowledged that there is a place for corticosteroid injections for short-term pain	Thank you for your comment. The review did not identify any evidence to suggest hyaluronic injections would provide benefit as a pain management strategy. This recommendation will maintain the existing recommendation from the 2014 update of the Osteoarthritis: care and management guideline and so is not expected to cause a change in current practice. The review included evidence from time periods beyond 3 months if reported in randomised controlled trials. Therefore, the review attempts to consider the clinical and cost consequences of long-term use. The committee does acknowledge the potential for corticosteroid adverse events from multiple injections. Time to total joint replacement was not included as an outcome in the review however if joint replacement was reported this would have been considered for the serious adverse event outcome. The time to joint replacement was not considered as the committee agreed that the treatment needed to be proven to have efficacy as a treatment for

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				management of specified patient cohorts, particularly those presenting with effusion and for whom pharmacological treatments are unsuitable. The review does not consider the clinical and cost consequences of long-term use of each therapy respectively, despite the long-term nature of osteoarthritis disease progression and management. In the review of evidence, the committee acknowledges evidence on the risks associated with multiple corticosteroid injections, including increased degradation of the joint and increased risk of periprosthetic joint infection, however does not discuss evidence suggesting that repeat HA injections may delay time to total joint replacement or have a longer duration of effect[11,12,49,56,75,123,151,179,198,201,336,407,475,485]. Both the acknowledged risks of long-term corticosteroid use and potential long-term benefits of HA injections have bearing on the long-term clinical and cost-effectiveness of each therapy class respectively. The viability of intra-articular HA injections as a long-term pain management solution particularly in patients where nonoperative options are ineffective is recognized by the majority of clinical practice guidelines currently published globally (Reference 1). Additionally, the review appears to place greater emphasis on the uncertainty and potential harms associated with the evidence presented on HA injections without delivering recommendation for	osteoarthritis regardless of whether the person gets a joint replacement. If hyaluronic acid did not show consistent improvements in quality of life, pain and physical function then the meaning of longer time before joint replacement is difficult to establish. As the committee agreed the evidence did not indicate this, then they agreed that hyaluronic acid should not be used for people with osteoarthritis. With regards to the absence of a research recommendation for hyaluronic acid, the committee agreed based on the evidence available that hyaluronic acid did not show consistent evidence of clinically important benefits. Furthermore, recent studies with a larger number of people reporting outcomes of low risk of bias consistently indicated no clinically important difference in efficacy outcomes. Based on this, the committee agreed that hyaluronic acid would not provide benefit and agreed that further research was unlikely to change this. Meanwhile, as you have stated for corticosteroids, there is uncertainty about the long term safety of the intervention while the committee agreed that there was evidence of short term efficacy. Therefore, the committee agreed that a research recommendation was required for investigating the long term use of corticosteroids. The presence of effusion was not included as a subgroup for the review and so the committee is not able to comment on whether treatment should be used for people with or without effusion.

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				further research. Conversely, the use of corticosteroid injections for specified patient cohorts was recommended alongside a recommendation for further research based on evidence which the committee states is low quality and based on a small number of studies. When summarizing the available evidence on HA injections compared to corticosteroid injections in the knee within evidence review J, the committee concluded that HA injections showed a clinically important benefit over corticosteroid on quality of life at less than 3 months and on pain and physical function at more than 3 months. Included within the data analysis 15 studies compared HA to steroid in the knee, these studies include approximately 1161 joints treated with HA compared to 1014 treated with a steroid[19,45,59,151,195,201,276,438,445,446,470,473,475,485,494]. All studies demonstrated an improvement in knee symptoms in both treatment groups. Comparable outcomes between treatment groups with both showing significant improvements in pain or function were demonstrated in four studies[195,201,438,445]. Steroid was found to be faster acting with maximum benefit and pain control in the first month[59,151,470,475], however, HA was found to provide longer lasting pain reduction and OA symptom improvement[19,45,59,151,276,473,494]. This appears incongruous with the final decisions not to recommend HA based upon insufficient available evidence, nor to recommend further research to resolve areas of variability or uncertainty.	Thank you for the reference. This review will not be included in the guideline as it investigates the difference in opinion between guidelines and so is not relevant to the protocol.

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				Based on the evidence presented in the review, we would conclude that hyaluronic acid is a viable option for those patients with no effusion and mild to moderate disease of the knee who have failed to respond to or are otherwise unsuitable for alternative therapies. We accept the conclusion that there are areas where evidence is lacking or inconsistent, and on this basis we believe a recommendation for further research would be suitable to address these gaps. *Reference numbers shown in superscript are based on reference numbers for studies as they appear in evidence review J Reference: 1. Phillips M, Bhandari M, Grant J, et al. A systematic review of current clinical practice guidelines on intra-articular hyaluronic acid, corticosteroid, and platelet-rich plasma injection for knee osteoarthritis: an international perspective. Orthop. J. Sports Med. 2021;9(8). Doi: 10.1177/23259671211030272	
Bioventus	Guideline	009	011 - 012	We are concerned that this recommendation does not consider patients for whom corticosteroid is no longer effective but who are unable or unsuitable for arthroplasty and/or for whom pharmacological treatments are ineffective or unsuitable (i.e. patients with renal complications, those that have had a previous reaction to corticosteroid etc.). While it is	Thank you for your comment. NICE guidelines aim to support healthcare professionals in making decisions about how to support people with a condition. They are not guidelines with information for every clinical scenario. Healthcare professionals will use guidelines to help inform their decision making but will make relevant decisions in how to best support people with

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				understood that the scope of the review is not intended to capture patients with multimorbidity's, and that CG56 is in place to address these patient cohorts, CG56 does not confer the ability to recommend therapies that are not currently recommended in other clinical guidelines. As such, in its' current format the draft guidance offers no alternative pharmacological management options for patients who are not suitable for topical, oral and transdermal medications that no longer respond to corticosteroid injections and are not candidates for arthroplasty - in these cases, the only options available to patients would be non-pharmacological management strategies such as exercise, manual therapy, acupuncture, electrotherapy and assistive devices, however patients experiencing chronic unmanaged pain may find exercise and manual therapy unsupportable, in some cases irrespective of assistive devices at their disposal, and therefore are further limited in the scope of options available to them. By recommending the use of intraarticular corticosteroids in patients for whom other pharmacological treatments are ineffective or unsuitable (despite stating that the evidence on the efficacy of corticosteroids is mixed), the committee is acknowledging the requirement for specified sub-groups of patients to receive access to therapies even where evidence of effectiveness is variable if there is no suitable therapeutic alternative available to this patient group. Exploration of the potential for	osteoarthritis. If their clinical presentation does not correlate with that expected from the guideline and will seek specialist support if they require more information. On evaluating the evidence that was included in the review, the committee concluded that hyaluronic acid use will not lead to clinically important improvements in quality of life, pain and physical function for people with osteoarthritis. Based on this, weighing in the potential for adverse events and the cost of hyaluronic acid products, they agreed that hyaluronic acid should not be used. Thank you for the reference. This will not be included in the guideline as this is not a randomised controlled trial investigating the effectiveness of an intra-articular injection and so is excluded in the protocol.

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				hyaluronic acid injections to support a subset of patients not suitable for other pharmacological management strategies appears by comparison limited. Bhadra et al have developed appropriate use criteria for the use of hyaluronic acid for the treatment of osteoarthritis in the knee evaluating evidence on which subgroups of patients respond best to hyaluronic acid, and for whom treatment with hyaluronic acid is therefore likely to be cost-effective (Reference 1). In the context of the significant amount of evidence included in the review demonstrating the potential long term clinical effectiveness of hyaluronic acid injections, particularly in those patients without joint effusion or underlying biomechanical instability, and the evidence suggesting potentially serious harms of long-term repeat corticosteroid injections, we have found the committees decision to recommend solely for the use of corticosteroid injections difficult to understand. Reference: 1. Bhadra AK, Altman R, Dasa V, et al. Appropriate Use Criteria for Hyaluronic Acid in the Treatment of Knee Osteoarthritis in the United States. Cartilage. 2017;8(3):234-254. doi: 10.1177/1947603516662503	
Bioventus	Guideline	029	005 - 006	Based on the evidence presented, it is not clear to us how the committee arrived at the conclusion "There was no evidence showing that hyaluronan injections improved quality of life or physical function, or reduced pain, in people with knee or hip arthritis."	Thank you for your comment. We have adjusted the wording in the rationale to better reflect the evidence. With regards to the interpretation of the evidence. The committee acknowledged that in the majority of evidence,

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				Within the interpretation of the evidence (evidence review J) on hyaluronic acid (HA) injections compared to corticosteroid injections in the knee, the committee acknowledges that HA injections demonstrated improvement over corticosteroid in quality of life at less than 3 months and pain and physical function at greater than 3 months. In the assessment of HA compared to placebo in the knee, 21 of the included studies demonstrated statistically significant benefit over placebo[11,12,49,56,75,90,102,109,122,123,126,162,179,198,201,336,369,373,407,430,460]. Within the hips, evidence was mixed with one study showing superiority of HA over corticosteroid and one showing superiority of corticosteroid over HA. The committee acknowledges elsewhere that the majority of the studies included in the review were short-term and did not measure outcomes past 3 months, however of the studies included that measured outcomes past 3 months, 10 studies in knees showed significant benefit of HA compared to saline placebo[11,12,49,56,75,123,179,198,201,407,336]. Of studies in the knee comparing steroid to HA, steroid was found to be faster acting with maximum benefit and pain control in the first month[59,151,470,475], however, HA was found to provide longer lasting pain reduction and osteoarthritis (OA) symptom improvement[19,45,59,151,276,473,494]. This finding is supported by the study included by Davalillo et al; at 6 months all patients in both the steroid and HA treatment groups met criteria for Minimal Clinically Important Improvement (MCII) however by 12 months	there was no difference between the two interventions at less than and more than 3 months as well as agreeing with the statement in your comment. We disagree with the statement that 21 of the included studies demonstrated statistically significant benefits over placebo, with the majority of studies not achieving this for the outcomes the committee agreed were important for this review. The committee did not state that 10 studies in the knee showed significant benefit of hyaluronic acid compared to saline placebo and we disagree with this assessment as the majority of studies indicated no clinically important difference in efficacy outcomes. While the committee note some inconsistency in the evidence for corticosteroids, the majority of the evidence indicates a clinically important benefit at ≤3 months and the committee, using their expert consensus, agreed that there may be benefits to using corticosteroids. No evidence of harm was identified, but the committee acknowledged the potential harms with long term corticosteroid use and, as with all pharmacological treatments, agreed that they should be used for the shortest time possible at the lowest effective dose. In addition, they should be considered when other treatments are ineffective or unsuitable. However, in contrast, inconsistency was also present for hyaluronic acid, however the majority of the evidence, including large trials reporting low risk of bias outcomes, indicated no clinically important difference. Some outcomes showed evidence of harm. The committee, using the evidence and their expert consensus, agreed that there

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				80% or more patients in the HA group still met the MCII criteria compared to only 10% in the steroid group[485]. HA was also found to reduce analgesic use for longer, and reduced OA grade and extent of cartilage damage compared to steroid[151,475]. On the topic of corticosteroids, the committee acknowledges a lack of consistent evidence on corticosteroids and risk of potentially accelerated degradation of the joint with multiple injections however continues to recommend considering the use of corticosteroid injections for patients where pharmacological treatments are ineffective or unsuitable and recommends further research to address inconsistencies in evidence on the clinical and cost effectiveness of the therapy. Applying this standard to the evidence included on hyaluronic acid injections, given the evidence demonstrating the potential long-term benefit of hyaluronic acid injections (and in particular as compared to corticosteroid injections where there are uncertainties in the available evidence), a logical conclusion would be the recommendation for further research. *Reference numbers used are based on reference numbers for studies as they appear in evidence review J	was likely no clinically important benefit for the use of hyaluronic acid for people with osteoarthritis.
Bioventus	Guideline	029	006 - 007	We find it difficult to understand the committee's interpretation of data and subsequent conclusions on the benefit / risk assessment of hyaluronic acid	Thank you for your comment. The first paragraph of your comment appropriately presents the reasoning for what the potential risks were with hyaluronic acid. The

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				injections and corticosteroid injections. Regarding the former, the committee stated that there are potential harms associated with hyaluronic acid injections in hips and other joints outside of the knee based on reported instances of osteoarthritis flares, which were considered important in the lived experience and management of osteoarthritis. However, these were also considered difficult to measure with no clear consensus on their definition and the committee's expressed uncertainty on the value of this piece of evidence. This appears contradictory when highlighted as an important harm as compared to the lack of emphasis placed on the potential harms associated with corticosteroid injections, including risk of periprosthetic joint infection and increased joint degradation which the committee comments on in evidence review J but does not include within the guidance itself. Studies included within this review demonstrate that the most frequent adverse event associated with hyaluronic acid is arthralgia and pain at the injection site, both of which are short-lived[277]. By contrast, the risks associated with corticosteroids mentioned above are significant and costly, with potentially long-term implications for patients. In order to deliver a balanced assessment, we propose these risks should be given a weighting proportionate to the potential impact on patients and on the NHS.	committee agree that flares are difficult to define and there is uncertainty in the outcome. However, as hyaluronic acid did not indicate sufficient evidence of clinical effectiveness, the potential harm for flares with this evidence that hyaluronic acid would not provide benefit was sufficient to the committee to recommend that they should not be used for people with osteoarthritis. With regards to corticosteroids, this is not seen as contradictory. Unlike hyaluronic acid, evidence for corticosteroids did indicate clinically important benefits in reducing pain at less than and equal to 3 months. There was no evidence of harms identified in the use of corticosteroids, with the potential harm of joint degeneration being highlighted but not demonstrated in the evidence. The committee agreed that due to this corticosteroids may have clinical efficacy in the short term (less than and equal to 3 months) and so could be considered. They also discussed the potential for long-term harms. Although this review did not identify evidence for these the committee agreed that further research was required to investigate this (and so made a research recommendation). Based on the consistent weighting of clinical efficacy, where this was indicated in the evidence for corticosteroids but not for hyaluronic acid, the committee consider these recommendations appropriate.

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				*Reference number used is based on reference numbers for studies as they appear in evidence review J	
Bioventus	Guideline	029	015 - 017	The committee states that corticosteroid is recommended based on the potential benefits of the treatment however acknowledges that potential benefits are limited to short-term reduction in pain based on inconsistent data from a small set of studies. There is no comment in the guideline regarding the specific potential risks associated with corticosteroids (which are stated in evidence review J). If we look specifically at the number of studies and patients treated with both hyaluronic acid (HA) and corticosteroid in the knee within the evidence review: • 35 HA/placebo studies[9,11,12,16,49,56,75,90,102,109,122,123,126,162,179,183,198,201,225,226,237,240,259,287,291,336,338,369,373,374,407,430,460,469,496] compared to 7 steroid/placebo studies[41,72,153,303,311,391,529] • 3863 joints treated with HA[9,11,12,16,49,56,75,90,102,109,122,123,126,162,179,183,198,201,225,226,237,240,259,287,291,336,338,369,373,374,407,430,460,469,496,407,460] compared to 305 treated with steroid[41,72,153,303,311,391,529] in studies vs placebo • Of the HA/placebo studies, 19 had more than 100 joints in one or both of the treatment arms[9,11,12,16,56,75,102,179,198,225,226,237,240,287,336,338,373,374,407]. 0 steroid/placebo studies had 100+ joints in either treatment arm	Thank you for your comment. For both hyaluronic acid and corticosteroids, the committee were consistent on using the higher quality evidence from larger trials investigating the efficacy of these treatments for knee and hip osteoarthritis to inform their recommendations. These trials indicated that hyaluronic acid did not have consistent clinical effects with studies reporting outcomes of low risk of bias, that had higher weighting in the meta-analysis, indicating no clinically important difference in efficacy outcomes. The committee, taking into account the whole body of evidence, agreed that there was no consistent evidence to indicate a clinically important effect from hyaluronic acid. Whereas trials for corticosteroids, while with greater uncertainty, indicated clinically important benefits at less than and equal to 3 months consistently. Given this and their expert knowledge, the committee agreed that there was evidence that corticosteroids may be effective treatment in the short term (to be treated in the same manner as oral, topical and transdermal treatments – to be given alongside non-pharmacological treatment and to support therapeutic exercise and to be used at the lowest effective dose for the shortest possible period of time). Given the uncertainty in the evidence, the committee agreed this should be a considered rather than always offered and that further research, particularly investigating

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				• 21 HA studies show clear benefit over placebo[11,12,49,56,75,90,102,109,122,123,126,162,179,198,201,336,369,373,407,430,460], and a further 7 show benefit over placebo in specific outcomes[9,16,226,237,259,287,338]. 5 steroid studies show benefit of steroid over placebo[41,72,153,311,529] • 10 HA studies demonstrate clear benefit over placebo at 24-27 weeks[11,12,49,56,75,123,179,198,201,407], compared to 5 steroid studies at 6-12 weeks[41,72,153,311,529] In the ankle, TMJ, toe, finger, shoulder, hip and thumb joints: • 8 HA vs placebo studies[48,54,81,110,261,330,398,416] compared to 0 steroid vs placebo studies • 10 HA vs corticosteroid studies[26,47,152,159,192,323,377,398,452,455] • 3 HA vs corticosteroid vs placebo studies[22,192,383] • There are no steroid studies in the ankle joint, but 3 for HA[81,110,416] • Much of the HA data included for these joints is positive, demonstrating improvements in pain and function Using this as the standard of evidence required for a recommendation for the use of corticosteroids, or at minimum to recommend further research, the evidence presented on hyaluronic acid is then logically sufficient to allow for the use of hyaluronic acid in selected	the long-term effectiveness and safety of the intervention for non-knee and hip osteoarthritis, would be important. As the committee identified consistent evidence that hyaluronic acid led to no clinically important difference in efficacy outcomes based on large trials of low risk of bias, the committee did not agree that hyaluronic acid required additional research.

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				patient cohorts for whom a corticosteroid is no longer effective but who are unsuitable for arthroplasty, in addition to warranting a research recommendation. *Reference numbers shown in superscript are based on reference numbers for studies as they appear in evidence review J	
British Acupuncture Council British Medical Acupuncture Society Acupuncture Association of Charted Physiotherapists	Evidence review F	070	028 – 029	*"Given the lack of benefit seen from acupuncture when compared to sham acupuncture, the health economic model did not include acupuncture"* We feel the rationale for this decision has not been established within the evidence review and we would like clarification. The criterion that the evidence must demonstrate MID superiority to sham prior to being included in the economic evaluation stage is not set out in the methods; therefore, it appears to be a post-hoc addition. We believe it was not the correct decision for several reasons: 1. The estimated effect size is likely to be an underestimate; therefore, setting an MID of 0.5 is inappropriate 2. It is not a comparison relevant to clinical practise 3. A rigorous network meta-analysis has demonstrated that both acupuncture and sham acupuncture outrank the recommended interventions included within the previous	Thank you for your comments. This was a complicated review due to the heterogeneity in the research available leading to challenges for the interpretation, which you have rightly noted. Unfortunately, published minimal important differences appropriate for use in this guideline were not identified. Therefore, default minimal important differences were used for the interpretation of the values (please see the methods document in the supporting information to explain this). However, in the absence of this evidence, the committee accepted the default value of 0.5 SD (SMD) for use throughout the guideline for consistency (as is established methodology used at the time of guideline work). The methods used for minimal important differences and the methods used throughout the guideline are reported in the methodology report. The committee acknowledged their limitations and considered this in their assessment of the evidence. To address concerns with the use of placebo and sham acupuncture. The committee acknowledge that the definition for sham acupuncture is highly variable across

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				guidelines and this draft guideline.[1] This makes the exclusion of acupuncture illogical 4. Influence on future design. **Underestimation of the effect size** Definitions of placebo and sham acupuncture do not to appear to have been provided within the available documentation. Definitions of placebo within the literature vary.[2] To help us understand the rationale behind its decisions we would be grateful if the committee could provide its definition of placebo. We accept that there is no clear definition within the literature of 'sham acupuncture'; however, it is important that the effect size of an active control procedure be borne in mind when interpreting the results. There should be some means of assessing this issue. For example, the sham procedures could be assessed by experts in the field and ranked according to perceived activity. This could then be used as the basis for subgroup or sensitivity analyses. The Evidence Review refers to both sham acupuncture and sham electroacupuncture as sham acupuncture. However, there appears to have been no evaluation of the sham procedures. Therefore, an RCT which used a sham electroacupuncture technique of 'needling acupoint(s) but without electrical stimulation' would be classed as sham acupuncture. If needles are inserted at the same acupuncture points without	the research. This review included any studies that defined their treatment as 'sham acupuncture' as an example of sham acupuncture. Ju 2015 did not define the comparison as sham acupuncture. However, this was comparable with other sham techniques that were included and so the study was included for this comparison. The committee acknowledged the limitations in this and considered it in their decision making (please see the committee's discussion and interpretation of the evidence). However, they noted that limitations were also present compared to no treatment, as this could exaggerate the effect of acupuncture due to the complex nature of the intervention. The committee, consistent with previous NICE approaches in the Chronic pain guideline, agreed prior to looking at the evidence that clinical effectiveness needed to be indicated when compared to sham acupuncture, while cost effectiveness needed to be shown when compared to no treatment. This has been made clear in the methodology report. The committee, while acknowledging some evidence of clinical benefit when compared to sham acupuncture and to no treatment, agreed that both were insufficient to indicate a clinically important effect from acupuncture due to heterogeneity in effects. There was no consistent explanation for this heterogeneity. Corbett did not fit the protocol for the review because it reported different definitions of no treatment and of the

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				electrodes, in another clinical trial, the procedure would be interpreted as real acupuncture. Review methods that permit an intervention, needling of a set of acupuncture points, to be simultaneously classed sham and real acupuncture has methodological flaws. From the detail provided in Table 2 of Evidence Review F it appears that at least three studies fall into this category. The 'sham' acupuncture are described as follows: Ju 2015 (p18) Same treatment [as electro-acupuncture], but the intensity of electrical stimulation was relatively weak so that people couldn't feel the electroacupuncture stimulus and then an additional 1mA was added. Sangdee 2002 (p27) Same areas [as electro-acupuncture], but electrodes were connected to a sound producing dummy mode that did not produce a current. Weiner 2007 (p35) Same needle insertion, but no stimulation of the needles in bone. Two needles were inserted into the soft tissue on the upper third of the tibial shaft and were stimulated with 100Hz for 1 minute. In Weiner 2007 (p35) electroacupuncture was "Periosteal stimulation therapy using four 30 gauge acupuncture needles being inserted into the medial femoral condyle, lateral femoral condyle, flare of tibia and head of fibula. The needles were stimulated with	outcomes, was not comparable with the rest of the guideline, and therefore was excluded. The Vickers, et al individual patient data meta-analysis was considered for inclusion in this review. However, as this study includes people with chronic pain that did not have osteoarthritis, this was not relevant to this guideline (which discusses people only with osteoarthritis). If people have chronic pain then they should be considered under the guidance in the Chronic pain guideline [NG193]. The committee cannot comment on the use of sham/placebo arm trials for all chronic pain conditions as this guideline is focussed towards people with osteoarthritis only. The committee considered sham acupuncture trials and no treatment trials considering there to be benefits and limitations to each approach. Therefore, considering the value of comparisons to both allows for a more complete understanding that has been used for this guideline.

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				100Hz for 30 minutes." Needles are not normally inserted to this depth in practice. Therefore, not only would the 'sham' be classed as acupuncture if delivered in a different RCT but the 'sham' is more reflective of usual practice. Evidence Review F also includes other RCTs where the sham procedures appear to be almost identical to real electroacupuncture, such as Suarez-Almazor 2010.[3] This study used a sham technique which: used sham points that were so close to indicated acupuncture points that it seems likely some crossover would have occurred; the needles were probably not inserted shallowly; and a current was passed through the electrodes.[4] Could the committee please comment on this potential weakness of the methods used? The Evidence Review acknowledges some difficulties of acupuncture research: *Comparing acupuncture to sham acupuncture is challenging due to the potential for sham acupuncture to have an active effect on the outcomes investigated beyond a placebo effect (p69, line 15-16).* Yet, the results appear to have been interpreted as if the sham procedures are placebos – meaning that they	

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				control for psychological elements but have no active physical components. A substantive body of work has shown the benefits of acupuncture cannot be attributed solely to placebo effects.[5] This is the key factor that provides reassurance to healthcare professionals and patients. The results of the evidence review replicate this finding. The current challenge of interpreting the effect of real over sham acupuncture is a one-sided risk. Namely, how large is the effect. Because some active components appear to have been retained within the sham procedures the effect size can only be an underestimation. Does the committee agree that the effect size is likely to be an underestimation? If not, could you please provide further explanation? If the committee agrees that the effect size is likely to be an underestimation, could you provide clarification as to why a 0.5 MID is appropriate under these circumstances? **No relevance to standard clinical practice** On page 8, line 30-33, the review states: *A network meta-analysis was not conducted for this review. This was decided as sham acupuncture would not be given as a treatment in standard clinical practice making their use for*	

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				recommendations more limited. Therefore, the committee agreed that the additional benefit of a network meta-analysis would be limited. This statement appears to be at odds with the committee's decision to emphasise sham-controlled trials. Sham acupuncture *would not be given as a treatment in standard clinical practice,* therefore, the estimated effect size is not relevant in terms of MID. As the two statements (p70 line 28 & p8, line 30) appear to be incongruous, could the committee further explain its position on the relevance of sham acupuncture to standard clinical practice? Of relevance to this discussion is a network meta-analysis (NMA) performed using the data from Vickers *et al* [5] individual patient data meta-analysis of acupuncture for chronic pain including osteoarthritis.[6] In this large and rigorous NMA a chance finding was that sham acupuncture significantly outperformed no acupuncture controls in health related quality of life (HRQoL). This included the category of osteoarthritis. Such data cannot be ignored when considering the question of measuring HRQoL of real acupuncture against sham. It suggests that the estimates in this draft must be considerably underestimating the real-world effect of acupuncture in practice on HRQoL. **Sham acupuncture out-ranks the recommended interventions**	

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				Although the committee opted not to undertake a network analysis, high-quality network analyses already existed. In these studies sham-acupuncture out ranked both muscle strengthening exercise and weight loss, both of which have been included in CG177 and this draft guideline.[1] As a consequence, it appears the committee set a criterion that acupuncture must outperform an intervention (sham acupuncture) that ranked higher than the recommended interventions. We find this decision difficult to understand and would appreciate further explanation. The section 1.1.12.3 Benefits and harms appears to touch on the rationale for setting the criterion of efficacy for acupuncture whilst not doing so for other interventions. The section groups interventions that require patient participation (exercise and weight loss) on one side and those are more passive, (pharmacological, acupuncture and manual therapy) on the other. We would like further clarification regarding how this relates to the requirement for efficacy studies. We believe a more relevant way to divide interventions are those where a high degree of certainty exists that the placebo/sham interventions do not retain any active components. The benefits of acupuncture cannot be attributed solely to placebo effects.[5] In this era of patient centred healthcare, we believe it would be perfectly possible to include acupuncture in the guidelines with a caveat	

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				similar to one provided for manual therapy (1.3.7 If discussing manual therapy, explain to people with osteoarthritis that there is not enough evidence to support its use alone for managing osteoarthritis). It could be explained to the patients that the relative proportion of the benefits are derived from the needling/placebo effect is unclear. **Influence on future design** NICE Guidelines are internationally recognised. Because of this the way NICE committees interpret evidence shapes the design of future clinical trials. The Evidence Review F comments on future research (**1.1.12.5.)** In the draft guidance the committee has placed a specific emphasis on sham/placebo controlled clinical trials. This may encourage future research to include a sham/placebo arm. The Helsinki Declaration states the following in regard to the use of placebo: *33. The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:* *Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or* *Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best*	

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				proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention. The individual patient data meta-analysis has determined that for chronic pain acupuncture has efficacy – the results cannot be explained simply in terms of placebo.[5] It is unlikely that any future RCT will change the findings of this study. Moreover, as discussed, it is not possible to evaluate the degree to which the effect is underestimated without a better understanding of the active components in sham procedures. Consequently, patients enrolled in an RCT and randomised to a sham/placebo arm will receive an inferior treatment for no scientific gain. This may be considered unethical. Could the committee please confirm whether they consider a sham/placebo arm to be scientifically important within clinical trials of acupuncture for chronic pain conditions? And elaborate on the scientific and ethical basis is for such a decision? References 1 Corbett MS, Rice SJC, Madurasinghe V, *et al.* Acupuncture and other physical treatments for the relief of pain due to osteoarthritis of the knee: network meta-analysis. *Osteoarthritis Cartilage* 2013;**21**:1290–8. doi:10.1016/j.joca.2013.05.007	

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				2 Blease C, Annoni M, Hutchinson P. Editors' Introduction to Special Section on Meaning Response and the Placebo Effect. *Perspect Biol Med* 2018;**61**:349–52. doi:10.1353/pbm.2018.0047 3 Suarez-Almazor ME, Looney C, Liu Y, *et al.* A randomized controlled trial of acupuncture for osteoarthritis of the knee: effects of patient-provider communication. *Arthritis Care Res* 2010;**62**:1229–36. doi:10.1002/acr.20225 4 Appleyard I, Lundeberg T, Robinson N. Should systematic reviews assess the risk of bias from sham–placebo acupuncture control procedures? *Eur J Integr Med* 2014;**6**:234–43. doi:10.1016/j.eujim.2014.03.004 5 Vickers AJ, Vertosick EA, Lewith G, *et al.* Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis. *J Pain* 2018;**19**:455–74. doi:10.1016/j.jpain.2017.11.005 6 Saramago P, Woods B, Weatherly H, *et al.* Methods for network meta-analysis of continuous outcomes using individual patient data: a case study in acupuncture for chronic pain. *BMC Med Res Methodol* 2016;**16**:131. doi:10.1186/s12874-016-0224-1	
British Acupuncture Council	Evidence review F	283	Appendix F	We noted a substantial number of rows where certainty was graded as high. For example, 13 of 18 rows from p283 to p286 are graded high certainty. It has been unusual to see this level of certainty in acupuncture research in the past. Generally, even sham controlled	Thank you for your comment. We assess risk of bias for outcomes from each study individually, considering that particular study's methodology. We agree that practitioner blinding is important as a component to considering risk of performance bias. However, in the assessment of this

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British Medical Acupuncture Society Acupuncture Association of Charted Physiotherapists				trials are downgraded for high risk of performance bias based on unblinded practitioners. We note that the outcomes here are all subjective, and blinding is considered to be most relevant for subjective outcomes. Can you confirm that a lack of practitioner blinding in trials with subjective outcomes is no longer considered a reason for downgrading for risk of bias in sham controlled trials of acupuncture?	trial, it was noted that the outcome assessor was a different person to that performing the acupuncture (the practitioner). We agreed that there was sufficient blinding of both the participant and the outcome assessor such as to minimise risk of performance bias in the reported outcome. On considering the information provided in this specific study we assessed that: - There was no indication of deviations from the intended intervention that arose from the experimental context (all people were offered and appeared to take up the same number of concomitant therapies, previous therapy use was reported). - It used a modified intention-to-treat analysis and so an appropriate analysis was used to estimate the effect of assignment to the intervention. - The study reports the James Blinding Index which appeared to indicate blinding between participants (value of 0.63 [0.46 to 0.79] on a 0-1 scale at 8 weeks indicating likely random guesses when asked about blinding). . Following the Cochrane Risk of Bias 2.0 checklist, if there is evidence that a study does not have deviations from the intended intervention which arose from the experimental context and uses an appropriate method of analysis, then the (risk of bias) assessor can consider whether this minimises the bias in this area. In this case, we agreed it was unlikely that the absence of blinding of the practitioner would have a large effect on the risk of bias for the outcome. This was a consistent approach used when considering similar studies for this and other reviews where relevant. However, please note this does not mean that lack of practitioner blinding in trials with

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					subjective outcomes is not considered a reason for downgrading for risk of bias in sham-controlled trials of acupuncture, as the full study methodology should always be taken into account. We have checked the GRADE rating for this particular study and can confirm that we still rate the evidence as high quality.
British Acupuncture Council British Medical Acupuncture Society Acupuncture Association of Charted Physiotherapists	Guideline	006	012 - 014	In this draft guideline the level of evidence for electroacupuncture appears to have reached the same thresholds as for acupuncture in NG193 ie an efficacy effect size exceeding MID in some relevant outcomes and within the threshold for cost effectiveness in most assessments. In NG193 we saw a recommendation to consider acupuncture with certain limitations related to cost. We suggest that the most equitable approach given the evidence would be a similar recommendation to 'consider a course of electroacupuncture' with certain limitations to control costs rather than 'do not routinely offer…'. At the Royal London Hospital for Integrated Medicine, we successfully set up a group clinic to provide electroacupuncture to patients with chronic knee pain with 5 or 6 patients being treated simultaneously.[7] This was set up in 2005 and ran successfully for over a decade until commissioning restrictions resulted in the service closing. This is the sort of model that we think would suit the NHS in providing an initial course of probably the most effective form of intervention for osteoarthritis of the knee. Subsequent long-term maintenance treatment could be provided by low-cost services in the third sector. Our	Thank you for your response. The committee agreed that the effect size reached a similar threshold to that in NG193. However, the committee noted that there was uncertainty in the evidence. Therefore, they changed the recommendation to not make a recommendation on the use of electroacupuncture and to adapt the research recommendation to investigate the effect of electroacupuncture, including comparisons that would provide additional information to help understand the complexity of the intervention. Thank you for the information relating to the set up at the Royal London Hospital. This guideline does not cover service delivery and would leave decisions on how to set up services to other organisations.

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				three organisations have discussed and collaborated to encourage such development (see statement here). Clearly the best place for provision is in the community, but it is also necessary to have centres of excellence to take a lead. References 7 Berkovitz S, Cummings M, Perrin C, *et al.* High Volume Acupuncture Clinic (Hvac) for Chronic Knee Pain – Audit of a Possible Model for Delivery of Acupuncture in the National Health Service. *Acupunct Med* 2008;**26**:46–50. doi:10.1136/aim.26.1.46	
British Association of Prosthetists & Orthotists	Evidence Review H	General	General	The committee responsible for reviewing this guideline did not include an orthotist. It is the British Association of Prosthetists and Orthotists' strong position that where NICE projects are considering orthotic intervention an HCPC registered orthotist must be on the assessment and management guideline committee to ensure an appropriate level of orthotic acumen.	Thank you for your comment. We advertised for an orthoptist and did not get a response. Therefore, we recruited a podiatrist with orthotic experience. NICE notifies all registered stakeholders about the scope consultation and recruitment for the guideline committee and welcomes stakeholder organisations encouraging individuals from their professional community applying for committee roles.
British Association of Prosthetists & Orthotists	Evidence Review H	093	033 - 038	The rationale used to determine *"the absence of strong evidence"* for the use of devices for the management of OA has also been used to determine the risk of potential harm from said devices, such as blisters. It is unclear how evidence deemed not strong enough to	Thank you for your comment. The committee used the evidence and their experience to make the recommendations. Their main concern was that there was no evidence of benefit to suggest that devices are cost-effective.

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				demonstrate device efficacy can be deemed strong enough to determine potential adverse events.	Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.'
British Association of Prosthetists & Orthotists	Evidence Review H	093	033 - 038	This recommendation will be a challenging change in practice because it does not take into consideration service users who are not appropriate or decline pharmacological or surgical interventions, leaving them with a dearth of conservative treatment options. We strongly feel that the current guideline recommendations will reduce service users' options for conservative treatment and request the committee reviews their recommendation and re-words it to allow options to be explored to enable service users to better meet their physical goals as part of holistic care.	Thank you for your comment. The committee looked for evidence of benefit for devices in all groups of people with osteoarthritis including those in whom pharmacological interventions were not appropriate or may have been declined but no evidence of benefit was identified. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and

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					• the addition of an aid or device is likely to improve movement and function.'
British Association of Prosthetists & Orthotists	Evidence Review H	093	033 - 038	The recommendation states *"based on the absence of strong evidence of benefit and some evidence of harm, that these devices should not be routinely offered".* The word routinely requires clarification as it is open to interpretation. It is the British Association of Prosthetists and Orthotists' strong opinion that the recommendation should be changed to state "do not routinely refer in the absence of biomechanical symptoms including pain or joint instability".	Thank you for your comment. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.'
British Association of Prosthetists & Orthotists	Evidence Review H	093	033 - 038	Orthotic devices are not only prescribed to reduce pain and/or control biomechanical deficits as a standalone treatment for OA. Orthoses are also prescribed as an adjunct to surgical procedures to keep the surgical site intact whilst healing and/or during rehabilitation. Similarly, orthotic devices are required following a surgical procedure which results in a change of function. E.g., arthrodesis of the ankle which may require re-creation of the foot/ankle rockers as an adjunct to the surgical procedure. The guideline does not make any recommendations on whether orthotic devices should be prescribed for the plethora of adjunct treatment requirements. The ambiguity of the current guidelines will, in our opinion, negatively impact	Thank you for your comment. We did not look at the effectiveness of devices as an adjunct to surgical treatment because we excluded joint replacement from the scope of the guideline. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and

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				practice if practitioners are not clear on when they should refer for orthotic input.	• the addition of an aid or device is likely to improve movement and function.'
British Association of Prosthetists & Orthotists	Evidence Review H	093	033 - 038	The current recommendation states "*potential harms from the devices were identified (such as blisters with braces)".* The British Association of Prosthetists and Orthotists strongly believes that the risk of potential harm would be significantly reduced if orthotic devices were fitted and reviewed by appropriately trained healthcare professionals, who are experts in the field of orthotic provision or can demonstrate appropriate competencies. "The 2014 NICE guidance on the management of OA states *"Insoles are commonly provided by podiatrists and orthotists but may also be provided by physiotherapists and occupational therapists", The* British Association of Prosthetists and Orthotists believes the recommendation for healthcare professionals to provide orthotic devices outside of their expertise based on a job title rather than competencies increases the risk of potential harm. We believe it would significantly mitigate the potential risk of harm if the committee revised their recommendation to allow orthotic provision for the management of OA by appropriately trained healthcare professionals based on competencies and area expertise.	Thank you for your comment. The committee agree that correct application of bracing may help to reduce the risk of adverse events. However, they also agreed that they would expect trials to be conducted with people who were sufficiently trained to apply braces. Despite this likelihood the evidence from this review still showed a harm from adverse events albeit very low-quality data. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.'
British Geriatrics Society	Guideline	General	General	Older people are at high risk of rapid deterioration from osteoarthritis losing independence, mobility and function. Early referral for specialist assessment and shared decision making involving a clinician with expertise in the peri-operative care of older people should be encouraged	Thank you for your comment. The recommendations for referral for joint replacement in section 1.6 were written in a way that allow this to happen. However, the committee agreed that the decision to refer should be based on the criteria in recommendation 1.6.1 regardless of a person's age. The recommendation states

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					'Consider referring people with hip, knee or shoulder osteoarthritis for joint replacement if: • their joint symptoms (such as pain, stiffness, reduced function or progressive joint deformity) are substantially impacting their quality of life and • non-surgical management (for example, therapeutic exercise, weight loss, pain relief) is ineffective or unsuitable.
British Orthopaedic Association	Guideline	013–-017	General	No major issues with research prospects, but additionally fundamental research for prevention and arrest of progression of primary osteoarthritis is vital with the ultimate aim of rare or even historical joint replacements	Thank you for your comment. Prevention and arrest of progression was not included as a review question and therefore the committee have not made a research recommendation in this area.
British Orthopaedic Association	Guideline	010 - 013	General	Acceptable, but with reiteration of the above reservation and well-merited and justified emphasis on long term successful outcomes following joint replacements (especially hip and knee) and appropriate additional consideration of joint preserving surgeries as well as partial or local and resurfacing replacements of joints selectively. Patient-initiated follow up is a good idea as an additional option, but is not a substitute for clinical evaluation and judgment especially by specialists.	Thank you for your comment. The efficacy of joint replacement surgery is not included in this guideline and is considered in NG157. The committee agree that patient-initiated follow up and clinical evaluation and special assessment are not mutually exclusive. Patient-initiated follow up may include initiated follow up leading to specialist assessment.
British Orthopaedic Association	Guideline	008 - 009	General	Proposed pharmacological management in the absence of imaging may be fraught with certain risks including potentially missed stress fractures, insufficiency fractures, infections, AVN, SPONK and neoplastic lesions including malignant lesions	Thank you for your comment. The committee did not identify any evidence investigating the use of imaging to support management of osteoarthritis. Using their expert opinion, they agreed that imaging should not be used routinely for follow-up and to guide non-surgical management of osteoarthritis. Imaging to check for other

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					conditions that are suspected by a healthcare professional may be appropriate dependent on the reason for investigating and, as in the section regarding diagnosis, imaging may be used when people present with atypical features.
British Orthopaedic Association	Guideline	001	003	We recommended considering changing 'guideline' to 'guidelines' or 'guidance'.	Thank you for your comment. This is standard wording that is used for all NICE guidelines and therefore we have left it as written in the draft guideline. As part of our 5-year strategy, NICE is currently looking at how we best present our guidance to ensure it is useful and usable. We will forward your comments on for consideration.
British Orthopaedic Association	Guideline	001	004	Consider changing the title to 'Primary Osteoarthritis: Diagnosis, Assessment and Management' as the content does not include secondary osteoarthritis.	Thank you for your comment. The guideline title was agreed during scoping. We don't specify that this is primary osteoarthritis in the scope nor refer to this in the guideline.
British Orthopaedic Association	Guideline	001	005	'Who is it for?' Consider adding 'researchers' as the fourth group.	Thank you for your comment. We have added 'Researchers with an interest in osteoarthritis' as another group.
British Orthopaedic Association	Guideline	001	005	'What does it include?' Consider replacing 'the recommendations' by 'guidance', which would be consistent with 'guidance context' later in the sub-section.	Thank you for your comment. This is standard wording that is used for all NICE guidelines and therefore we have left it as written in the draft guideline.
British Orthopaedic Association	Guideline	001	General	Consider changing 'This guideline covers…' to 'These guidelines cover'.	Thank you for your comment. This is standard wording that is used for all NICE guidelines and therefore we have left it as written in the draft guideline.
British Orthopaedic Association	Guideline	001	General	The guideline mentions it covers 'non-surgical' management, which suggests that there is no surgical management. We are questioning if the title of the	Thank you for your comment. The main focus of this guideline is non-surgical management. We also excluded joint replacement from the scope because it is covered by

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				guideline should be changed to 'surgical and non-surgical management'.	the joint replacement guideline **(**https://www.nice.org.uk/guidance/NG157). We have added 'Referral for joint replacement' to this section.
British Orthopaedic Association	Guideline	002	001	Contents Consider adding 'Joint preserving procedures' as content number 9	Thank you for your comment. The contents and wording were agreed during scoping. Joint preserving procedures was not a term used and has not been used in our recommendations therefore we haven't added it to the list of contents.
British Orthopaedic Association	Guideline	003	003 — 010	The current document states that "Diagnose osteoarthritis clinically without investigations in people who • are 45 or over **and** • have activity-related joint pain **and** • have either no morning joint-related stiffness or morning stiffness that lasts no longer than 30 minutes." And recommends • "Do not routinely use imaging to diagnose osteoarthritis unless there are atypical features or features that suggest an alternative or additional diagnosis." These imply the recommendation of general application of clinical diagnosis without imaging in the clinical framework of the stated strict criteria in patients aged 45 or over, but with certain unequivocal latitude outside the stated parameters, deemed variable and overlapping atypical features with potential for unmissable alternative diagnoses.	Thank you for your comment. The guidance recommends that for people who fulfil the criteria stated, osteoarthritis may be diagnosed without further investigation as long as atypical features are not present. If people fall outside of the criteria stated in recommendation 1.1.1 or have atypical features then they may require further investigations as appropriate for the possible differential diagnoses before a diagnosis of osteoarthritis can be made. These recommendations refer to imaging for the use of diagnosis only. Imaging for management is discussed in recommendation 1.5.4, where it is stated that imaging should not be used for the management of osteoarthritis outside of surgical management (this does not include procedures that may require image guidance, such as intra-articular injections for some joint sites). If a person has atypical features at any point after the diagnosis, then these should be investigated appropriately as would be the case for any time when healthcare professionals are concerned. The committee agreed that frequent imaging to monitor osteoarthritis is not appropriate as clinical symptoms may not correlate with imaging findings,

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				By implication, criteria of imaging under 45 years are also different. These subtle in-built exceptional implications must be clearly understood to reflect in clinical practice. The timing of imaging outside these criteria, however, is not universally and uniformly agreeable in practice not only for assessment, diagnosis, monitoring and management of primary osteoarthritis, but also pre-empt potentially disastrous misses. One such miss in clinical practice constitutes one too many.	recurrent imaging poses potential risks from recurrent exposure to x-rays and imaging will be unlikely to change management (outside of surgical management where imaging will be required). Based on the committee's expert opinion, imaging should not be used for the majority of people with osteoarthritis for diagnosis. They agreed that because it rarely shows anything that helps with diagnosis it is not a good use of NHS resources.
British Orthopaedic Association	Guideline	003	004 – 006	Osteoarthritis under 45 is not uncommon; many over 45 with severe pain, crepitus, or deformity will not get an x-ray to assess underlying joint structure, pathology, alignment. We recommend these be added to details on atypical features.	Thank you for your comment. The committee acknowledge that osteoarthritis can occur under the age of 45. Recommendation 1.1.1 specifies that osteoarthritis can be diagnosed without imaging in people of or above the age of 45. If people are below this age then further investigations may be required. Rapid worsening of deformity has been added to the list of atypical features (as deformity that is not rapidly worsening may be a feature of osteoarthritis). The committee agree that severe pain would be considered within the current definition of rapid worsening of symptoms. Crepitus may be a symptom of osteoarthritis, therefore the committee did not agree that this was an atypical feature. An extra category of atypical features for people with concerns that may suggest infection or malignancy has been added. If healthcare professionals

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					are concerned about another cause for symptoms, then they should investigate this as they see appropriate.
British Orthopaedic Association	Guideline	004	010	The term 'weight loss' is better replaced by 'weight reduction' here and throughout the document.	Thank you for your comment. We have changed the heading in the guideline to 'weight management'. The recommendations still use the words 'weight loss' as this is what they are specifically aiming to achieve.
British Orthopaedic Association	Guideline	004	016	The document notes 'managing day-to-day pain and changes in pain'. This is the first time pain is mentioned, which is not consistent with the stated criteria in page 3 above.	Thank you for your comment. We have changed this bullet point to 'managing their symptoms'.
British Orthopaedic Association	Guideline	004	019	The document notes 'benefits of treatment', but up to here it is only management, and no treatment.	Thank you for your comment. This recommendation details the points the clinicians should cover when advising patients where to find information.
British Orthopaedic Association	Guideline	005	003–-005	The document recommends to 'offer tailored therapeutic exercise to all people' and 'consider supervised therapeutic exercise for people with osteoarthritis'. We question how practical and resource-oriented are these?.	Thank you for your comment. The committee noted that current practice around exercise therapy varies, They agreed that the recommendations may lead to a change in practice by recommending tailored exercise (including supervised exercise) but they believe it is practical. Exercise, including supervised is already recommended in NICE's guideline on obesity https://www.nice.org.uk/guidance/cg189 and NICE's guideline on weight management.
British Orthopaedic Association	Guideline	005	005–-009	Terms 'discomfort' and 'pain' are interchangeably used.	Thank you for your comment. We have looked at the consistency of how we used these terms and have edited this recommendation (1.3.3) to 'pain or discomfort'. We have also changed the bullet point in patient information recommendation 1.2.3 to 'managing their symptoms' to encompass discomfort (it previously read managing their day to day pain and changes in pain).

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British Orthopaedic Association	Guideline	005	General	General for section 1.3 on Non-pharmacological management – Therapeutic exercise Therapeutic exercise should be generally comfortable but patients with severe osteoarthritis are unlikely to do well with aerobic exercise. We recommend the recommendations need to exclude severe symptoms/deformity of atypical features. Additionally, general aerobic fitness is not realistic for all osteoarthritis patients above 45 years in the NHS.	Thank you for your comment. The committee agree and with this in mind recommended that exercise tailored to the needs of the person should be offered. If people have severe symptoms/deformity then the exercises they are able to do should be considered by the healthcare professional working with them.
British Orthopaedic Association	Guideline	009	001	We question why paracetamol is the only option for those unable to take NSAIDs. We question discouraging the use of paracetamol.	Thank you for your comment. The committee do not agree that paracetamol is the only option for people unable to take NSAIDs. Non-pharmacological management and other pharmacological management is recommended in the guideline and paracetamol is not recommended for routine use. The committee agreed that paracetamol did not show sufficient evidence of clinical effectiveness to recommend for it to be used for people with osteoarthritis, with the effect sizes identified in the evidence being very similar to that of placebo comparisons. The committee acknowledge that paracetamol may be useful for some people to try under specific circumstances. The recommendation has been updated to 'Do not routinely offer paracetamol or weak opioids unless: • they are only used infrequently for short-term pain relief and not as part of an ongoing pain management plan

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					• all other pharmacological treatments are contraindicated, not tolerated or ineffective.' Explain to people with osteoarthritis that there is no strong evidence of benefit for paracetamol.'
British Orthopaedic Association	Guideline	009	009	A clear explanation is required of the potential complications acutely and longer term with intra-articular injections	Thank you for your comment. The adverse events identified in the clinical review are discussed in the rationale and the committee discussion of the evidence for the intra-articular injection review. This is not a complete safety review and so may include additional events not identified in the studies. The committee would expect clinicians to refer to other sources of information, such as the BNF, for extra information. Recommendations about communicating the risks, benefits and consequences of treatments with patients are in the NICE guideline Shared decision making which is cross referred to in recommendation 1.1.1.
British Orthopaedic Association	Guideline	010	General	General for section 1.5 Follow-up and review A clear explanation is required for patients who return with worsening symptoms or a change in symptoms - Red flag symptoms - Especially as many will not have had imaging It is important that some sinister pathologies are not missed - Insufficiency fractures even neoplastic concerns	Thank you for your comment. We agree that healthcare professionals should give a clear explanation when talking to people with osteoarthritis about reasons to initiate follow up. The reasons for follow up will be specific to the person so are not specified in detail in this recommendation. The committee anticipate that should anyone present with a worsening or change of symptoms then the healthcare professional concerned will offer the appropriate management.

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British Orthopaedic Association	Guideline	011	001	We recommend a title such as ''Referral for specialist evaluation and/or consideration of joint replacement' is more appropriate	Thank you for your comment. The simpler title has been used so that it matches the scope.
British Orthopaedic Association	Guideline	011	002	We recommend also considering the following for indications for referral: - Referral with progressive or fixed deformity or worsening malalignment - Joint crepitus Rest pain/night pain	Thank you for your comment. The committee agreed that progressive joint deformity should be included and have added this. Pain includes rest pain/night pain, and so is already considered. The committee did not agree that joint crepitus alone would be a reason to refer someone from surgery, and this would likely be because other symptoms already listed would substantially impact the person's quality of life and so did not add this.
British Orthopaedic Association	Guideline	011	019	We recommend also reassuring patients that the following be true for joint replacement: - Excellent clinical and functional outcomes - Established longevity in the hip and knee - Low complication rates - Rapid recovery - Revision options if needed As many still have a very historical understanding of what modern joint arthroplasty surgery can and does achieve in the right hands and with the right indications	Thank you for your comment. The aim of the recommendation is to relate it to the previous recommendation and not go into the details of the benefits of joint replacement. The committee agreed the surgeon would be best placed to discuss the benefits of joint replacement with the individual.
British Orthopaedic Association	Guideline	012	006	We recommend that these atypical features be added: - Rest night pain - Deformity - Crepitus - Previous history of childhood joint conditions Previous history of joint infection	Thank you for your comment. The committee agreed that rapid worsening of deformity was an atypical feature (but deformity in itself could be a feature of osteoarthritis) therefore we added rapid worsening of deformity as an atypical feature.

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					Crepitus was considered to be a possible symptom of osteoarthritis so was not included. Rest night pain and previous history of childhood joint conditions and joint infection are all features that the committee concluded could be seen in people with osteoarthritis and so were not included. This list is not exhaustive and healthcare professionals are advised to use their clinical judgement to support their decision making.
British Orthopaedic Association	Guideline	012	007	We question if this should include walking poles	Thank you for your comment. We assume you meant page 13 line 7 and your comment related to including walking poles as part of the definition for walking aids. The committee do not think walking poles should be included as these would not be prescribed on the NHS.
British Orthopaedic Association	Guideline	019	General	There is no real mention or supportive comment about the success and benefits and longer term durability of modern surgery for end stage disease, or options for younger and more active patients.	Thank you for your comment. The guideline scope excluded joint replacement and therefore no specific statement was made in relation to this. The recommendations are intended to cover all age groups. The committee anticipated the tailored approach recommended for exercise would include advice to reflect the age and activity levels for those people.
British Orthopaedic Association	Guideline	032	General	There is no mention of the potential and established benefits of joint replacement.	Thank you for your comment. Because the guideline excluded joint replacement as an intervention, we have not discussed its benefits. The committee agreed that the surgeon would be best placed to discuss this should a person be referred for joint replacement.
British Society for Rheumatology	Guideline	General	General	We welcome the updated full guideline, which addresses several long-standing issues not addressed in most recent partial update, CG177.	Thank you for your comment. We have responded to those points in turn.

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				In particular, we welcome the withdrawn recommendation for paracetamol and caution with opioids. However, there are some issues, raised in the points below:	We have revised the recommendation related to paracetamol to: 'Do not routinely offer paracetamol or weak opioids unless: • they are only used infrequently for short-term pain relief and not as part of an ongoing pain management plan • all other pharmacological treatments are contraindicated, not tolerated or ineffective. Explain to people with osteoarthritis that there is no strong evidence of benefit for paracetamol.'
British Society for Rheumatology	Guideline	007	007	*We consider there is inappropriate emphasis in statements where strong evidence is lacking such as:* 1.3.10 Consider walking aids (such as walking sticks) for people with lower limb osteoarthritis. *Compared to devices with more compelling data* 1.3.11 Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis. A blanket 'do not offer' for devices like braces seems inappropriate, where there is both systematic review level evidence and a large ongoing NIHR HTA trial, which is likely to report in the next 12-18 months. We will not rehearse all the arguments here, as these will be expressed more eloquently by Keele University on	Thank you for your comment. The committee recommended considering the use of walking aids because they agreed that walking aids have the advantage of reducing the pressure in the leg joints, helps stability and movement to encourage physical activity and independence. This is particularly the case while waiting for joint replacement or if surgery cannot be undertaken and the stick helps aid exercise and confidence with walking. Overall, they agreed that the evidence, supported by their expert opinion, was enough to recommend walking aids for people with lower limb osteoarthritis. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to:

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				behalf of the PROP OA investigators. But we support their contention that bracing has a level of evidence which justifies targeted use, including health economic data and long-term benefits greater than harm. It seems at least some of this difference is due to an inconsistent approach to the non-specific treatment effects interventions which cannot be effectively blinded in trials. We would argue the pragmatic approach taken with sticks should prevail, which would logically lead to a cost level at which braces should be offered pending definitive trial evidence, which might lead to a planned partial review of NICE guidance if results are as expected.	'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.'
British Society for Rheumatology	Guideline	008	018	We note the recommendation for PPI has changed considerably from the 2008/2014 guidance, which was itself an update on a prior technology appraisal (therefore having more force than the clinical guideline itself): *1.5.9 When offering treatment with an oral NSAID/COX-2 inhibitor, the first choice should be either a standard NSAID or a COX-2 inhibitor (other than etoricoxib 60 mg). In either case, co-prescribe with a proton pump inhibitor (PPI), choosing the one with the lowest acquisition cost.* ***[2008]*** To: 1.4.4 Consider adding a gastroprotective treatment	Thank you for your comment. The committee agree that the change is not supported with new evidence and therefore have made the recommendation a strong recommendation. This has been changed to 'Offer a gastroprotective treatment (such as a proton pump inhibitor) for people with osteoarthritis while they are taking an NSAID. Thank you for the references. These will not be included in the guideline as they do not report specifically for people with osteoarthritis or are non-randomised studies that are excluded in the protocol.

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				(such as a proton pump inhibitor) for people with osteoarthritis while they are taking an NSAID. The reasoning is somewhat opaque, but appears to relate observational studies and is not confirmed by an updated health economic analysis, whereas alternative methodologies, including RCTs do not confirm the association of increased cardiovascular events from PPIs themselves, but rather residual confounding: Demcsák A, Lantos T, Bálint ER, Hartmann P, Vincze Á, Bajor J, Czopf L, Alizadeh H, Gyöngyi Z, Márta K, Mikó A, Szakács Z, Pécsi D, Hegyi P and Szabó IL (2018) PPIs Are Not Responsible for Elevating Cardiovascular Risk in Patients on Clopidogrel—A Systematic Review and Meta-Analysis. Front. Physiol. 9:1550. doi: 10.3389/fphys.2018.01550 Park, Ju-young, Yoo, Joonsang, Jeon, Jimin, Kim, Jinkwon, Kang, Sangwook. Proton pump inhibitors and risk of cardiovascular disease: a self-controlled case series study, The American Journal of Gastroenterology: May 04, 2022 - Volume - Issue - 10.14309/ajg.0000000000001809 doi: 10.14309/ajg.0000000000001809 We would suggest this change is likely to increase GI morbidity and mortality from NSAIDs and the evidence is not strong enough to change the existing recommendation. It is likely that a revised health	

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				economic model would strongly support naproxen + cheapest PPI.	
British Society for Rheumatology	Guideline	009	004	We would suggest this section: 1.4.8 If discussed, explain that there is no strong evidence of benefit for paracetamol or glucosamine, and the risks of strong opioids may outweigh the benefits. *Might be revised to:* 1.4.8 If discussed, explain that there is no strong evidence of benefit for paracetamol or glucosamine, the risks strong opioids may outweigh the benefits and the risks and lack of benefit of paracetamol, especially as a weak NSAID make it important not to take with other NSAIDs. *Or a clearer separate statement on this issue be included, such as* 1.4.x Given no strong evidence of benefit for paracetamol, consensus it is a weak NSAID with all attendant risks and evidence combining with ibuprofen gives no benefit and substantially increased risk, give clear advice that paracetamol must not be taken with ibuprofen or any other NSAIDs. Unlike the PPI data, the evidence of harm from paracetamol is rather compelling, shown to be an NSAID with all attendant toxicities not only in several high-profile systematic reviews and meta-analyses of observational studies, but also this RCT- Doherty et al,	Thank you for your comment. The committee have updated the paracetamol recommendation to 'Do not routinely offer paracetamol or weak opioids unless: • they are only used infrequently for short-term pain relief and not as part of an ongoing pain management plan • all other pharmacological treatments are contraindicated, not tolerated or ineffective. Explain to people with osteoarthritis that there is no strong evidence of benefit for paracetamol.' The committee agreed that the protocol for this review would not include combinations of therapies and would only compare treatments being used by themselves so they could assess the effectiveness of the individual treatments. With regards to paracetamol, clinically important harms were identified in hepatorenal adverse events based on low quality evidence. We agree that randomised control trial evidence is not typically powered to detect harms. A safety review of paracetamol was not undertaken for this version of the guideline. The committee recommended that paracetamol should not be routinely used based on the evidence showing limited effects when compared to placebo, whether in combination with other pharmacological therapies or not.

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				2011- even though RCTs are not typically powered to detect harms: See especially evidence of additive moderate blood loss (10g/l Hb) with low dose combination of paracetamol and ibuprofen (500mg tds/200mg tds) and moderate dose combination achievable with over the counter (1g tds/400mg tds), compared to paracetamol alone and ibuprofen alone (24%, 38%, 20%, 20%). This compares to synergistic toxicity for more severe blood loss (20g/l Hb): 2%, 7%, 1%, 1%, even though the doses of each are achievable with over-the-counter self-medication. Given most GPs are still recommending paracetamol and NSAID use together, there is a major opportunity to achieve a step-change in patient safety (given the combination is not effective and prescribers would never use other NSAIDs concurrently). We would therefore suggest that rather clearer guidance is included in this update, that paracetamol must not be used alone or with other NSAIDs for this or other chronic indications to reverse the current damaging prescribing and recommendation inertia for this dangerous combination. Doherty M, Hawkey C, Goulder M, Gibb I, Hill N, Aspley S, Reader S. A randomised controlled trial of ibuprofen, paracetamol or a combination tablet of ibuprofen/paracetamol in community-derived people	However, they acknowledged that paracetamol may be useful for some people to try under specific circumstances and have updated the recommendation as written at the beginning of this comment.

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				with knee pain. Ann Rheum Dis. 2011 Sep;70(9):1534-41. doi: 10.1136/ard.2011.154047.	
Chamwell Centre	Guideline	General	General	We have many members with arthritis who attend our public accessible hydro pool on a regular basis. They tell us that the warmth and exercises help them feel less pain, better sleep and allows them to practice movements they cannot do on dry land. The water allows weightless exercise so that there is no pressure on joints. They can work out in warm water which would be impossible in cold water or on land. It assists their ADL skills in transfers, balance and perception. Social interaction in water means that everybody is equal. It makes them feel they belong to a group of people who are all in the pool together for different reasons. Warm pool activities can be given in a programme by physiotherapists and supervised by physiotherapist assistants individually or in groups, or patients themselves take on their programme independently. The pool and building need to be accessible. Research is needed to demonstrate the benefits of aquatic therapy for the many people who have diagnosed or undiagnosed arthritis.	Thank you for your comment. The combination of water and exercise was not included as a specific intervention in the review protocol but was considered as part of the stratification labelled as 'other supervised exercise' in our review. Therefore, the committee have not made a recommendation or research recommendation in this area. We will flag this with the NICE surveillance team to consider as part of a future update for the guideline.
Connect Health	Guideline	006 - 024	General	Page 6, 7, 8, 24 Lines 13, 2, 7, 27, Rec 1.3.8 Rec 1.3.9 Rec 1.3.11 Rec 1.4.6	Thank you for your comment. Those recommendations have been discussed again by the committee to make them clearer. Recommendation 1.3.8 now states 'Do not offer acupuncture or dry needling to manage osteoarthritis.' and the research recommendation limited to

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				With reference to the above recommendations for which more detail has been provided, an example of where is done well, is in Rec 1.45 and Rec 1.48.	electroacupuncture only. The committee agreed this was clearer as there was no evidence of benefit for acupuncture and therefore should not be recommended. They also agreed that there was uncertainty for electroacupuncture and its potential as an intervention for osteoarthritis should be researched. Recommendation 1.3.9 has also been made a strong do not offer recommendation listing out all the types of electrotherapies that should not be offered. Extracorporeal shockwave therapy is not listed in that recommendation and is still a research recommendation as the committee agreed there was uncertainty in this area. Recommendation 1.3.11 has been updated to state 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.' Recommendation 1.4.6 has been deleted. Paracetamol has been moved into the same recommendation as weak opioids (1.4.5) to give a clearer indication on when it may be an appropriate intervention. Glucosamine has been changed to a strong 'Do not offer' recommendation and included with strong opioids recommendation (now 1.4.5).

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Connect Health	Guideline	005	003 - 012	Whilst there is empirical evidence that seems to suggest exercise may benefit those with OA, we feel pertinent critical sources of evidence have been excluded. For example, this paper by Dean et al (2021): Exercise therapy with or without other physical therapy interventions versus placebo interventions for osteoarthritis–- systematic review (whiterose.ac.uk) This paper shows that when exercise is compared to placebo there is a small significant effect size however, if the smaller trials with higher risk of bias are removed this becomes non-significant. It is important also for the recommendation to acknowledge that there are no primary trials evaluating the effectiveness of exercise for shoulder arthritis (this should be a research recommendation given the epidemiology and prevalence). Aligned to this, the secondary health benefits referred to in the rationale section are likely to be conferred at a higher dose of exercise than a lot of the included trials offer. It would be oversight to not acknowledge this.	Thank you for your response. When designing the protocol for this review, the committee agreed that placebo exercise would not be included as a comparison. This was because they believed that any additional intentional movement will potentially have an effect on the outcomes of the person and so make interpretation of placebo exercise inappropriate. Based on this they agreed that the comparison would only be to other types of exercise and no treatment (which included usual care). Therefore, Dean 2021 was not included within the evidence for the guideline. The committee acknowledged that evidence for shoulder osteoarthritis, as well as other types of osteoarthritis that were not the knee or the hip, was limited or not present. They agreed by consensus that the results from the included studies could be applied to other joint sites. This is stated in the committee discussion of evidence (please see Evidence Review C, section 1.1.12). The research recommendation for this area is designed to be a pragmatic trial including people with osteoarthritis affecting any joint site, which could include shoulder and give more information for the future.
Connect Health	Guideline	006	013	Rec 1.3.8 The rationale explains the lack of benefit and some evidence of harm, and lack of cost effectiveness. The rationale also shows conflicting evidence for electroacupuncture, but no cost effectiveness evidence. There is no clear population who might benefit. Electroacupuncture is more expensive because equipment needs to be regularly tested,	Thank you for your comment. The evidence for electroacupuncture indicated some evidence of benefit. Health economic evidence was generated from modelling which indicated that electroacupuncture may be cost effective. The committee acknowledged the limitations in the quality of the evidence and so agreed that further research was required before it would be recommended. Therefore, they did not make a recommendation to

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				serviced and calibrated. Also, this is a significant change from current practice and would require staff training and investment in appropriate equipment. There are other treatments in the guideline where there are greater clinical benefits and which are cost effective. So there are little grounds to leave this as 'do not routinely offer' unless you can give clear guidance about whom is should be offered to. Further, with regards to shared decision-making, it is not necessary to add 'do not routinely' to everything that is not being recommended. NICE are very clear that guidelines are not tramlines and do not replace shared decision-making. You may wish to refer to NICE chronic pain guideline NG193 where a person has both chronic primary pain and osteoarthritis, where it might be appropriate to consider acupuncture for chronic primary pain. (See recs 1.1.21 "When chronic primary pain and chronic secondary pain coexist…" and 1.2.5 "Acupuncture for chronic primary pain"	discuss electroacupuncture but did make a research recommendation. The recommendation for acupuncture has been changed to 'do not offer acupuncture or dry needling for people with osteoarthritis' based on the evidence of no clinically important difference in osteoarthritis symptoms. The guidance on chronic pain regarding acupuncture is for people with chronic primary pain, which would likely be a different group to people with osteoarthritis (who would have chronic secondary pain) and so guidance may not apply in this area.
Connect Health	Guideline	007	002	Rec 1.3.9 There are many types of electrotherapy: TENS, PENS, EMS, interferential, shortwave diathermy, laser, ultrasound etc. This rec is so vague that it is unhelpful! If there is limited evidence for use of a particular modality in certain identifiable patient cohorts, please specifiy. There is also a lack of cost-effectiveness evidence and most of these treatments are no longer offered in the NHS, so as drafted this might lead to increased use of electrotherapy. Also, this is a	Thank you for your comment. The recommendation has been changed to specify the different types of electrotherapies where the committee agreed, based on the evidence, that they would not be clinically effective for people with osteoarthritis. The recommendation has been changed to 'do not offer' instead of 'do not routinely offer'. The research recommendation is limited to extracorporeal shockwave therapy, Evidence indicated a benefit for this when compared to sham. However, the committee

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				significant change from current practice and would require staff training and investment in appropriate equipment. There are other treatments in the guideline where there are greater clinical benefits and which are cost effective. So there are little grounds to leave this as 'do not routinely offer' unless you can give clear guidance about which modalities and to whom it should be offered to. Further, with regards to shared decision-making, it is not necessary to add 'do not routinely' to everything that is not being recommended. NICE are very clear that guidelines are not tramlines and do not replace shared decision-making.	agreed that the sham was likely inadequate to achieve blinding and would be difficult to compare to. There was conflicting evidence when compared to no treatment based on one small trial. Therefore, they have not included this in the 'do not' recommendation but have included a research recommendation to try and gain additional evidence before making a recommendation.
Connect Health	Guideline	007	007	Rec 1.3.11 The are many types of insoles, braces, tape, splints or supports. Some of these such as AposHealth insoles and Action Reliever Knee Braces are being actively promoted to NHS providers and commissioners to assist people who are either waiting for surgery or as an alternative to surgery. These devices and assessments associated with them are expensive for the NHS and we are unaware of long-term cost effectiveness studies or cost impact. Indeed, if these devices simply delay surgery or are used as a stopgap, then the NHS is effectively paying twice – once for the device and once for surgery. This rec is so vague that it is unhelpful! If there is limited evidence for use of a particular modality in certain identifiable patient cohorts, please specifiy. There are little grounds to leave this as 'do not routinely offer' unless you can give clear guidance about which modalities and to whom should be offered to. Also, this is a significant	Thank you for your comment. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.'

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				change from current practice and would require staff training and investment in appropriate equipment. There are other treatments in the guideline where there are greater clinical benefits, and which are cost effective. Further, with regards to shared decision-making, it is not necessary to add 'do not routinely' to everything that is not being recommended. NICE are very clear that guidelines are not tramlines and do not replace shared decision-making.	
Connect Health	Guideline	008	0027	Rec 1.4.6 The wording of the rec is inconsistent with the rationale. The rationale implies that paracetamol has not been shown to be effective. However, there are significant risks, and many international guidelines now recognise the potential for adverse events: increased risk of GI bleeding, hypertension, CKD and MI. A systematic review carried out by the previous guideline committee suggests "a considerable degree of paracetamol toxicity especially at the upper end of standard analgesic doses" http://dx.doi.org/10.1136/annrheumdis-2014-206914 Therefore, it would be sensible to either recommend intermittent, 'PRN' or lower doses, particularly in older adults, or to not recommend the drug at all. Similarly, for glucosamine, there is conflicting clinical evidence and no cost-effectiveness evidence. The only reason that glucosamine is not used in current practice (as stated in the rationale) is because the last version of the guideline stated, 'do not offer'. The nutraceutical remains on prescription, and, as currently	Thank you for your comment. The recommendation regarding the use of paracetamol has now changed to 'Do not routinely offer paracetamol or weak opioids unless: • they are only used infrequently for short-term pain relief • all other pharmacological treatments are contraindicated, not tolerated or ineffective.' This is to reflect the lack of certainty that paracetamol will be effective, while acknowledging that there may be some people who would want to choose paracetamol in the absence of other effective treatments. The recommendation regarding the use of glucosamine has changed to 'Do not offer strong opioids or glucosamine to people with osteoarthritis.'

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				drafted, some people, particularly those who do not pay for prescriptions, will approach their GPs to prescribe. If this 'do not routinely' rec is to remain, please explain for whom this would be appropriate, which preparation (e.g. glucosamine sulphate 1500mg) and how long for. Please also confirm that this is a cost-effective strategy, and an analysis of cost impact has been made. There are other treatments in the guideline where there are greater clinical benefits, and which are cost effective. Further, with regards to shared decision-making, it is not necessary to add 'do not routinely' to everything that is not being recommended. NICE are very clear that guidelines are not tramlines and do not replace shared decision-making.	
Connect Health	Guideline	010	001 - 019	The principles of personalised care are clear throughout the document and are welcomed – this is clearly set out within section 1.5 and we welcome the recommendations.	Thank you for your comment.
Connect Health	Guideline	011	002	Rec 1.6.1 – The shoulder, hip, and knee, are mentioned explicitly. This is a change in approach with reference to the rest of the guideline structure. Is this warranted? The principles appear sound so could this not be applied to ankle etc.?	The review protocol was limited to the most common types of joint replacement, hip, knee and shoulder as other types of joint replacement are less common and their effectiveness as interventions is less clear.
Connect Health	Guideline	011	004 - 007	Rec 1.6.1 – Suggestion to add within the wording of the current statement: **From:**	Thank you for your comment. The committee considered this and did not add this to the recommendation as they agreed that some elements may not be optimisable for all people (for example: weight loss) and introduced additional uncertainty. They agree that treatments should

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				"non-surgical management (for example, therapeutic exercise, weight loss, pain relief) is ineffective or unsuitable." **To:** "non-surgical management (for example, therapeutic exercise, weight loss, pain relief) **has been optimised and** is ineffective or unsuitable."	be tried for a suitable length of time and so the rationale was adjusted to emphasise this.
Connect Health	Guideline	011	018 - 019	Rec 1.6.4 – Outlining the key risks to consider, as well as quantifying how BMI may increase this risk to clearly, and consistently inform shared decision making when implementing the recommendations within this guideline.	Thank you for your comment. We have broadened the recommendation out to include all the factors included in recommendation 1.6.3. This includes age, sex or gender, smoking and comorbidities. The guideline doesn't go into all the details of risks and benefits of joint replacement because the committee think this is best addressed by a surgeon should the person be referred for a joint replacement.
Connect Health	Guideline	012	015 – 016	Within the section titled "Treatment Package" – it appears strange to include treatments that are advised not to be routinely offered. As per our concern above, this could lead to loose guideline interpretation and drive unwarranted variation.	Thank you for your comment. The definition of treatment packages has been amended to remove acupuncture and electrotherapy.
Connect Health	Guideline	024	013	It is not correct to say that 'do not routinely' reflects current practice and no change in practice or resource impact. The last guideline buried acupuncture with a firm 'do not use'. As currently drafted, some providers will want to start investing in equipment and training again. So there will be an unquantifiable resource impact, which will also divert therapists from more effective treatments in the guideline. If you want to	Thank you for your comment. The recommendation for acupuncture has now changed to 'Do not offer acupuncture or dry needling to manage osteoarthritis'. The research recommendation has been updated to cover electroacupuncture only and not acupuncture and dry needling. Therefore, the recommendation now reflects current practice.

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				leave this rec as 'do not routinely', please provide a credible cost impact analysis, tested with stakeholders.	
DJO UK	Guideline	005	006–-010	Braces for osteoarthritis are a drug-free method of pain relief. They are therefore supportive of the recommendation to employ therapeutic exercise as non-pharmacological management. Drug-free relief of pain enables patients to perform therapeutic exercise)	Thank you for your comment. The committee acknowledge that devices may be helpful to support exercise. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.'
DJO UK	Guideline	008	020 - 023	Braces for osteoarthritis are a drug-free method of pain relief and are supportive of the recommendation to not routinely offer weak opioids. As a non-pharmacological intervention, they have no polypharmacy issues.	Thank you for your comment. The committee acknowledged that braces may be important for some people however, no evidence was found to show a benefit. While the committee agree that avoiding polypharmacy issues where possible is important, they would like to see evidence of benefit for alternative interventions before making a recommendation for their widespread use. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless:

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					• there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.'
DJO UK	Guideline	025	015	The committee state there is not enough evidence for braces. We have supplementary evidence for efficacy of the range of braces DJO UK Ltd sells in the UK for knee osteoarthritis (list shown below). Clinical summaries of the findings of all these can be sent on request (as attachments to this document are not permitted) • Unloader Bracing for Knee Osteoarthritis: A Pilot Study of Gait and Function (Mont 2015) – not in DB • Effects of knee orthosis adjustment on biomechanical performance and clinical outcome in patients with medial knee osteoarthritis. Brand et.al, 2017 -obs • Effects of an unloader knee brace on knee-related symptoms and function in people with post-traumatic knee osteoarthritis after anterior cruciate ligament reconstruction. Hart et.al 2015 • Orthoses versus gait retraining: Immediate response in improving physical performance measures in healthy and medial knee osteoarthritic adults. Khan, et.al	Thank you for your comment and for providing supplementary evidence. This review was limited to RCTs and systematic reviews of RCTs, as there were RCTs available and to base the recommendations on the highest quality of evidence. The first study (Unloader Bracing for Knee Osteoarthritis: A Pilot Study of Gait and Function) is an RCT. However, the comparator group is unclear and may include people receiving additional treatments that are not available to the intervention arm (such as intraarticular corticosteroids). Therefore, this has been added to the excluded studies for the review. All other studies did not appear to be randomised trials, included people who did not have osteoarthritis, investigated biomechanical outcomes only rather than the outcomes specified in the protocol or were not published at this time. Therefore, these were not included in the review.

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				• Clinical and Biomechanical Evaluation of the Unloading Brace, *Finger S, Paulos LE, J Knee Surg. 2002;15(3):155-9* • Bracing of the Reconstructed and Osteoarthritic Knee during High Dynamic Load Tasks *Hart HF, Crossley KM, Collins NJ, Ackland DC. Med Sci Sports Exerc. 2017 Jun;49(6):1086-1096* • Immediate Effects of a Brace on Gait Biomechanics for Predominant Lateral Knee Osteoarthritis and Valgus Malalignment After Anterior Cruciate Ligament Reconstruction *Hart HF, Collins NJ, Ackland DC, Cowan SM, Hunt MA, Crossley KM Am J Sports Med. 2016 Apr;44(4):865-73.* • In Vivo Three-Dimensional Determination of the Effectiveness of the Osteoarthritis Knee Brace: A Multiple Brace Analysis *Nadaud MC, Komistek RD, Mahfouz MR, Dennis DA, Anderle MR, J Bone Joint Surg Am. 2005;87 Suppl 2:114-9.* • Is valgus unloader bracing effective in normally aligned individuals: implications for post-surgical protocols following cartilage restoration procedures. *Orishimo KF, Kremenic IJ, Lee SJ, McHugh MP, Nicholas SJ, Knee Surg Sports Traumatol Arthrosc. 2013 Dec;21(12):2661-6* • Effects of a Knee Varus Brace on Nonoperative Lateral Compartment Osteoarthritis *Paula Click Fenter, PT, DHSc, GCS* • Bracing improves clinical outcomes but does not affect the medial knee joint	

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				space in osteoarthritic patients during gait *Jeffrey A. Haladik, William K. Vasileff, Cathryn D. Peltz, Terrence R. Lock, Michael J. Bey* • Realignment treatment for medial tibiofemoral osteoarthritis: randomised trial. *David Hunter, K D Gross, Paula McCree, Ling Li, Kelly Hirko, William F Harvey* • A comparison of the biomechanical effects of valgus knee braces and lateral wedged insoles in patients with knee osteoarthritis *Richard K. Jones, Christopher J. Nester, Jim D. Richards, Winston Y. Kim, David S. Johnson, Sanjiv Jari, Philip Laxton, Sarah F. Tyson* • Contributions of Muscles and External Forces to Medial Knee Load Reduction Due to Osteoarthritis Braces *Bandon, Scott CE, Brown, Marcus J, Clouthier, Allison L, Campbell, Aaron, Richards, James and Deluzio, Kevin J* • Prospective randomized comparative study to demonstrate the medical benefit and usability in practical application for: DONJOY CLIMA-FLEX OA • Prospective study with comparison group to demonstrate the medical benefit and usability in practical application for: DONJOY MATRIX OA Prospective randomized study to demonstrate the medical benefit and usability in practical application through scores and light-optical leg axis measurement. Knee orthoses for relief	

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DJO UK	Guideline	025	015 - 016	The recommendations here do not consider the breadth of product designs on the market. Just within our own range of braces for knee osteoarthritis, we offer soft to semi-rigid to rigid options, offering different levels of support and offloading for different levels of osteoarthritis severity. Eg: [Image removed]	Thank you for your comment. The committee acknowledge that there is a wide range of products provided that fall within the categories stated in the protocol for this review. They considered the individual studies and the features of the products investigated. However, they agreed that the evidence available was not sufficient to recommend for routine use of devices unless the criteria specified in the update recommendation below were met. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.' Large, well designed and conducted, randomised controlled trials would be required to further understand the effectiveness of devices, including specific products.
DJO UK	Guideline	025	015 - 023	There seems to be inconsistency over the level of evidence that is being recognised specifically for knee bracing.	Thank you for your comment. The committee agreed that the amount of evidence for all devices was insufficient to show their efficacy. While there was more evidence for braces than other devices, this evidence was limited to

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				The committee admit that most evidence exists for braces for knee osteoarthritis (line 22), yet also states an overall lack of evidence to support the use of braces (line 15). It is then notable that there is no recommendation for additional research of knee devices, yet there is such a recommendation for foot and ankle (line 23). Therefore with evidence for knee bracing, but not other forms for support, the guidelines should state this clearly, and not dismiss one form of support for lack of evidence elsewhere.	small trials with the majority of outcomes being of very low quality. The committee were aware of an ongoing randomised controlled trial on the uses of braces in knee osteoarthritis (https://www.keele.ac.uk/propoa/) and therefore they did not make a research recommendation in this area. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.'
DJO UK	Guideline	025	023	We would support the call for more research on devices for foot and ankle osteoarthritis. Additional research in the field is always welcomed.	Thank you for your comment and support for the research recommendation.
DJO UK	Guideline	026	002	We are concerned that the recommendation is being made in part to save the NHS money by not recommending bracing. This is short-sighted as, for example, braces available on the UK Drug Tariff for knee osteoarthritis cost less than courses of opioids.	Thank you for your comment. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless:

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				Additionally, the use of such braces for unicompartmental knee osteoarthritis has been shown as cost-effective in bridging to and delaying knee surgery (Lee PYF, Winfield TG, Harris SRS, et al. Unloading knee brace is a cost-effective method to bridge and delay surgery in unicompartmental knee arthritis. BMJ Open Sport Exerc Med 2017;2:e000195 doi:10.1136/bmjsem-2016- 000195). Thereby saving the NHS considerable sums overall.	• there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.' The cost effectiveness study you cite was rated as partially applicable with very serious limitations. Analysis uses non-comparative prospective cohort data for intervention treatment effects, and separate trial for control group. The populations in the two studies are very different and therefore not considered suitable for use in this way. For this reason it was excluded from the health economic review.
Fidia Pharma	Evidence Review J	079	003	[Table setting out details of potential RCTs for inclusion deleted, as not possible to embed within this comments table.]	**Response on eligibility of cited studies** Thank you for your comment. We have reviewed your report and have concluded that the studies you have identified did not meet the protocol criteria for this review and therefore were not included. They were not included for the following reasons: 1) Different population to that specified in the protocol – This NICE guidance is 'Osteoarthritis: care and management' and so only people with osteoarthritis were included in the guideline (please see the review protocol in appendix A). This concerns: Priano 2017, Zorzi 2015, Di Martino 2016, Filardo 2016, Ometti 2020.

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					2) Different comparator to that specified in the protocol – The protocol for this review included the following comparisons: comparing to each other (referring to the interventions: intra-articular hyaluronic acid, intra-articular corticosteroids and intra-articular stem cell therapy) and comparing to placebo. Any comparison not included in this list is specified in the protocol and so will not be included in the review. This concerns: Filardop 2012, Doria 2017, Di Martino 2018, De Lucia 2019, Falcinelli 2020, Setaro 2020, Giarratana 2014. In general this concerns two different categories of studies provided in the list by yourself: a) studies comparing hyaluronic acid to platelet-rich plasma (for evidence discussing platelet-rich plasma please see IPG637), b) studies comparing hyaluronic acid to another type of hyaluronic acid (all types of hyaluronic acid were pooled together for analysis in this review as agreed with the committee). 3) Different study type to that specified in the protocol – The protocol for this review included high-quality systematic reviews of randomised controlled trials, parallel randomised controlled trials and cross-over randomised controlled trials. Non-randomised/observational studies were excluded. Given the substantial amount of randomised evidence anticipated for this review, the expert committee agreed that excluding non-randomised studies was appropriate. This concerns: Barret 2002, Neustadt 2003, Migliore 2012, Vetro 2014, Migliore 2017, Migliore 2018, Mauro 2017, Benazzo 2016, Priano 2018, Russu 2017a, Russu 2017b, Altman 2015a, Concoff 2021, Dasa 2016, Miller

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					2017. Furthermore, observational studies that were referenced often did not compare between different treatments, and so would not be relevant to the review protocol for other reasons. Finally, Bisicchia 2016 was stated to not be included in the review. This study was already correctly identified and included in the review (please see the included studies list and reference list in the evidence report). Given these factors, we have concluded that we have correctly included all relevant studies that fulfilled the protocol criteria. Therefore, the recommendation regarding the use of hyaluronic acid has not changed.
Fidia Pharma	Evidence Review J	108	003	NICE is stating that 3 health economic studies were included one was excluded. However one of the 3 following studies were even mentioned, and as described below, we believe they are significant and should have been included based on NICE's own criteria. These three economic studies, all involving Fidia IAHA products, are as follows and we present the pertinent information below which we contend refutes NICE's claim that such products do not provide a clear economic value to the NHS: ● Miglione 2014 ● Concoff 2021 ● Miller 2017	Thank you for your comment. The review protocol for this question specified that only RCT evidence should be included. Therefore, for the review of economic evaluations only RCTs or models based upon RCT evidence were also included. The studies you cite were not based on randomised trials and therefore were not considered to be relevant. Furthermore, Concoff 2021 and Miller 2017 would have been considered inapplicable for the health economic analysis due to the costs in both studies being from the US healthcare system perspective. Migliore 2014 is in Italian, and we do not include non-English studies.

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				The Concoff study concerned a retrospective cohort study based on the evaluation of claims data from a USA payer, whereas the Miller study concerned a trial in which along the collection of clinical, an evaluation was carried out of cost of treatment data. The data for the economic evaluation were collected in the last study following an 8 week intervention with IAHA. The economic studies can be discussed in detail as follows: **Migliore et al 2014** - Total hip replacement rate in a cohort of patients affected by symptomatic hip osteoarthritis following intra-articular sodium hyaluronate (MW 1,500-2,000 kDa) ORTOBRIX study. Clin Rheumatol. 2012 Aug;31(8):1187-96. doi: 10.1007/s10067-012-1994-4. Epub 2012 Jun 8. A decision tree model was the basis of this economic evaluation assessing the use of IAHA in patients considered for a THR. The economic evaluation was carried out alongside a clinical trial, the ORTOBRIX study. Using data from this study a panel of six orthopedists, not routinely performing hip intra-articular injections, each independently assessed whether 176 patients suffering from hip OA and treated with ultrasound-guided intra-articular injections of sodium	

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				hyaluronate (MW 1,500-2,000 kDa) were candidates for THR according to the clinical data (following the IAHA injections) and review long term data. The main study result of the ORTOBRIX trial as published was: "At 24 months, 159 out of 76 (90 %) patients did not undergo THR. At 48 months, 82 % (N = 144) of the study population treated with intra-articular hyaluronic acid avoided THR. In the group of 93 patients considered candidates for THR (that is, in which 4, 5, or 6 orthopaedic surgeons agreed that the patient was a suitable candidate for THR), only 17 had undergone THR, with survival results of 82 % at 24 months. At 48 months, this percentage reduced to 66 % in this group. In the other groups of patients (in which respectively 3, 2, 1 or no surgeons were in agreement that the patient was a candidate for THR) arthroplasty is not recorded. Sodium hyaluronate (MW 1,500-2,000 kDa) given by ultrasound-guided injection seems to delay THR in the real context of actual overall management of symptomatic hip OA patients". Results of the economic analysis were presented in both the Italian NHS perspective and that of the Italian society, considering indirect costs. The baseline analysis of the study revealed that the therapeutic strategy involving the use of Hyalubrix®60/HyalOne,	

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				injected using an ultrasound guide as an alternative to THR, was the most clinically and economically favourable option, both from the NHS perspective and that of the society. The results showed that, since the treatment with Hyalubrix® enabled to avoid or delay the need for Total Hip Replacement (THR) surgery, it is possible to reduce mortality, adverse events and total costs. Hyalubrix®, given in the hip by ultrasound-guided intra-articular injection as an alternative to surgery is the most favourable option, helping preserve the survival rate over a 4-year period, of approximately 1 in 100 patients considered candidates for THR, preserve work capacity for a total differential amount of 500 days, and achieve considerable savings in economic terms, of approximately 550,000 € and 600,000€ euros from the NHS and the Societal perspectives, respectively. **Concoff et al 2021** Delay to TKA and Costs Associated with Knee Osteoarthritis Care Using Intra-Articular Hyaluronic Acid: Analysis of an Administrative Database. Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders 2021 Volume 14: 1–8 The study aimed to determine if KOA patients who received IAHA demonstrated a delay in time to TKA	

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				compared to patients who did not receive IAHA. As elicited, the study also aimed to determine if there was a difference in KOA-related costs from a payer perspective between KOA patients who had received IAHA versus those who did not receive IAHA among patients who eventually had TKA, as well as those who did not eventually undergo TKA. In the study claims were analysed retrospectively of a large commercial database (Health Intelligence Company LLC, Chicago, IL), containing data of more than 100 million patients with continuous coverage from October 1st, 2010 through September 30th, 2015. The database included anonymous claims data for all OA patients seen within this timeframe. As a retrospective review of anonymous data, no ethics approval was required for this investigation. All patients with the diagnosis of KO in the database were included. Exclusion criteria were (1) patients under the age of 18, (2) patients without OA, (3) patients with OA other than knee, (4) patients with KOA who had immediate TKA after diagnosis and no treatment, and (5) patients with KOA who had no treatment and no TKA. There were two comparison groups as follows: (1) Patients who received IAHA prior to TKA, and (2) Patients who did not receive IA-HA prior to TKA. Any	

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				other treatment provided at time of an eligible ICD-9 diagnosis code was included within the "No IAHA" group. Data on IAHA treatments were analyzed separately based on the number of treatment courses each patient received for the delay to TKA analysis. The number of courses was determined based on the suggested number of injections for each product included (either 1, 3, or 5 injections per course, depending on the product). If the appropriate number of injections was given within a 3-month timeframe for a specific product, it was considered to be 1 treatment course. Outcome measures Descriptive statistics were reported for both treatment groups. The outcome of time to TKA was defined as the time from the first record of knee OA within the database to the time of the patient's TKA. The exact date of treatment was defined as the first date in which an OA treatment code was recorded within the database for that patient. A total of 744 734 patients were included in the analysis. A major outcome of the analysis was that the median time to TKA was 1.3 years (IQR 1.57) in the IAHA group and 0.38 years (IQR 0.95) in the no IA-HA group (P<.0001).	

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				At 1year, the TKA-free survival was 85.8% (95% CI: 85.6%- 86.0%) for patients who received IAHA and 74.1% (95% CI: 74.0%-74.3%) for those who did not receive IA-HA. At 2years, the TKA free survival was 70.8% (70.5%-71.1%) and 63.7% (63.5%-63.9%) in the 2 groups, respectively. The overall TKAfree survival was significantly higher in the IA-HA group with a log-rank P value of <.0001 In patients who eventually underwent TKA, the median and IQR KOA-related costs per year for those who received IA-HA before their TKA ($860.24, range $891.04-$7480.38) were lower than those who did not ($2659.49, range $446.65-$1722.20). For patients who were in the highest percentile of KOA-related costs per year, those who received IAHA had drastically lower KOA related costs than patients who did not receive IAHA. The median and IQR for KOA-related costs per year for patients who received IA-HA and did not progress to TKA was $9.66 (range $5.01-$30.89), while it was $7.58 (IQR $2.68-$45.17) in patients who did not receive IA-HA and did not require TKA. The **significance** of this study is that the results demonstrate that within a large cohort of KOA patients,	

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				individuals who received IAHA as part of their treatment regimen had a significantly greater delay until their need for TKA in comparison to patients who did not receive IA-HA treatment. This outcome is similar to Migliore 2014 as reported above. As regards the robustness of the study design, this study utilised a real-world evidence approach to evaluate all recorded health KOA-related costs rather than employing modelling methods to derive costs: the direct evaluation of KOA-related costs within a national database as in this study, provides a more representative assessment of the costs associated with KOA and how those costs may differ when IAHA is included in the disease management approach. Another strong point of this study is its large sample size and analysis of a large administrative database. An additional strength is the conservative approach to the assessment of HA's delay to TKA. All patients who received HA but never progressed to TKA were excluded from the analysis, which potentially removes the best responders to HA treatment. However, as with any study based on retrospective data analysis, there are some caveats as well. One issue is that the analysis is limited to the data that had been	

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				collected within this database, and the authorship team was unable to consider all relevant variables that were not captured within the database. Specifically, assessments of disease severity and treatment response were unavailable and would have brought significant utility in evaluating the results obtained by the analysis. We are, however, of the opinion that the strong points of this study clearly outweigh the limitations and are therefore of the opinion that NICE should consider both Migliore 2014 and this study as (1) there is clinical evidence that IAHA postpones THR and TKA and (2) this delay is associated with resource savings as evidence by various methods (Migliore 2014, interpretation of clinical data by physician panel alongside a clinical trial and Concoff 2021, real world evidence from a large claims database). **Miller et al 2017** Long-term clinical benefit and cost-effectiveness of an 8-week multimodal knee osteoarthritis management program incorporating intraarticular sodium hyaluronate (Hyalgan) injections.Journal of Pain Research 2017:10 1045–1054	

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				In this study contacted patients were contacted, who previously participated in a single 8-week multimodal treatment program for symptomatic knee OA.18,19 Eligible patients were adults with symptomatic knee OA, who met clinical criteria for medical necessity regarding HA therapies set forth by Medicare Local Coverage Determinations, which typically included a) knee pain interfering with functional activities, b) radiographic evidence of knee joint osteophytes, sclerotic changes, or joint space narrowing, c) morning stiffness <30 minutes duration, or crepitus with knee motion, and d) lack of functional improvement following >3 months conservative therapy, or inability to tolerate nonsteroidal anti-inflammatory drugs (NSAIDs). Patients in the study received five intra-articular knee injections of sodium hyaluronate, with each injection given 1 week apart. Injections were administered under fluoroscopic guidance, which allowed for confirmation of tricompartmental HA distribution and improved injection accuracy, resulting in improved patient outcomes vs. anatomical injection guidance. Follow-up data through 2 years were available to the authors. The standpoint taken for the economic analysis was from a single payer perspective. In accordance with the	

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				Centers for Medicare and Medicaid Services reimbursement fee schedules, a cost of $3,300 per knee treated in the 8-week multimodal program and $25,600 per knee that underwent TKA during follow-up, was assumed. Total costs for patients undergoing the knee OA program were calculated as $3,300 per treated knee plus $25,600 per TKA during follow-up. Costs for patients undergoing usual care were calculated as $25,600 per TKA during follow-up. Incremental cost was defined as the average cost for patients in the knee OA treatment program minus the average cost for patients treated with usual care. The incremental cost-effectiveness ratio (ICER) was calculated as incremental cost divided by incremental effectiveness. Assessment of the ICER in relation to an established willingness-to-pay value can be used to determine whether a proposed new treatment is acceptably cost-effective compared to an existing treatment. The economic analysis showed that the multimodal knee OA treatment program was highly cost-effective with an ICER of $6,000 per QALY. Results of one-way deterministic sensitivity analysis showed an ICER range of $6,000–$10,493 per QALY when utility score change varied and an ICER range of $3,996–$8,004 per QALY when TKA rate varied.	

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				Subgroup analyses showed no significant differences in ICER by gender, age, body mass index, number of treated knees, or K-L grade. ICER was significantly higher in patients with greater knee pain severity at baseline (p=0.03). Regardless, the knee OA treatment program was highly cost-effective in all subgroups with ICERs ranging from $5,200 per QALY (age <65 years) to $7,012 per QALY (baseline NPRS <4). Further, routine pain medication use during follow-up did not influence these results (ICER=$6,191 per QALY in users and $5,789 per QALY in nonusers, p=0.38). Results of a second-order probabilistic sensitivity analysis with conservative assumptions identified a median ICER of $7,634 per QALY (95% CI: $2,992–$53,876 per QALY). A novel aspect of this study was that clinical benefit and cost-effectiveness of the 8-week program administered in real-world settings were maintained over a mean 3.7-year period. To the knowledge of the authors, this is one of the longest follow-up periods of any study of a nonsurgical knee OA therapy. For this reason, the 8 week programme involving IAHA was found to be highly cost-effective over the long term and durable clinical benefit and cost-effectiveness were realised in all subgroups analysed by gender, age, body mass index,	

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				knee pain severity, K-L grade, and number of treated knees. Finally, all reported outcomes were robust to even the most conservative sensitivity analysis assumptions. The significance of this economic evaluation is that it is based on real world clinical data and thus complies with NICE study requirements (see above). Rather than focussing on a distinct clinical question with economic impact (relationship between the use of IAHA and delay of TKA and THA), the Miller study provides an approach to the general question of the effects of an 8 week course of IAHA on a range of outcome parameters, pain and QOL being the most important ones. <u>Conclusions from presentation of economic studies Hyalgan</u> The following conclusions can be drawn from the presentation of economic evaluations of Hyalgan **not previously considered** by NICE: ● Two studies present data on the basis of a clinical investigation and one is based on real evidence; ● This makes these studies in line with study designs the NICE has judged favourable for	

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				economic evaluation of medication in general and IAHA in particular; ● Two studies present strong evidence that IAHA delays a TKA or THA and is associated with significant saving of resource inputs and budget impact savings; ● A third study is showing that clinical effects of Hyalgan in pain management as administered in an 8 week programme of IAHA has important long term clinical and economic effects; ● For these reasons, it is strongly recommended that NICE includes these economic evaluations in the upcoming clinical and economic review of care and management of adults in OA. As the results from these studies reflect real world evidence practice on the budget impact of HI products, we consider the approach NICE has taken towards a review of HE studies on treatment aspects of OA as being too narrow in scope.	
Fidia Pharma	Evidence Review J	162	003	Fidia SpA has supported a wide range of clinical studies on its product line of hyaluronic acid injectables (HI), in total around 30 studies, about half RCTs, the other half cohort and real-life studies. With the exception of three studies, not one of these studies was considered to assess the effects of HI on	Thank you for your comment. We have reviewed your report and have concluded that the studies you have identified did not meet the protocol criteria for this review and therefore were not included. Please see the response on individual studies you cited in the row titled 'Response on eligibility of cited studies'.

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				osteoarthritis by NICE, neither in CG177, nor in the supplement analysis of 2017, nor in the draft guideline presented in April 2022. We are at a loss why NICE did not consider all this evidence, since all of our studies were published in peer reviewed journals and are methodologically good quality and SHOULD have come up in the searches as set out in this section of the referenced document. We have reviewed NICE's "Key principles for developing guidelines" https://www.nice.org.uk/process/pmg20/chapter/introduction and submit that the evidence we are presenting should have been taken into account originally, however, thankfully, NICE now has the opportunity to do so having been presented in our submission with this previously-omitted evidence. The findings of the clinical studies presented are at variance with your draft OA recommendations of April 2022 and it is our view that the Committee should have considered our studies. We request therefore that the Committee now considers our studies for the final recommendations to be published in October 2022 and we have submitted an accompanying analytical report of the added clinical and economic value of our HI product range, evidence presented in internationally-respected, peer-reviewed journals, for the treatment of various forms of osteoarthritis. We request that NICE please reviews this information in the current public consultation with a view to modifying its draft OA guidelines as this important and significant clinical and economic evidence regarding HI has to date	

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				been100anaed from NICE's analysis, no doubt resulting in NICE's (we allege) incorrect conclusions about the benefits 100anagemting HI use in the NHS and in direct contrariness to countries all across Europe, North America and Australia.	
Fidia Pharma	Evidence Review J	162	004	As we have mentioned, for some reason's NICE's literature review may be an important reason why most of the clinical studies sponsored by Fidia on HI were not featured in the NICE review and this is a serious omission. Also NICE should consider that the use of HI is standard orthopaedic practice in many countries as the following overview elicits: An important review of possible adoption of IH in clinical guidelines on a global scale was published by Phillips et al 2021. As Phillips et al noted, there are many clinical practice guidelines (CPGs) for the prevention, diagnosis, and treatment of knee OA. They differ by region, considering local health care systems, along with cultural and economic factors. Currently, there are conflicting CPG recommendations across the various publications, which makes it difficult for clinicians to fully understand the optimal treatment decisions for knee OA management.	Thank you for your comment. We have reviewed your report and have concluded that the studies you have identified did not meet the protocol criteria for this review and therefore were not included. Please see the response on individual studies you cited in the row titled 'Response on eligibility of cited studies'. The committee made recommendations based on the relevant evidence identified in the clinical review. On examining the evidence, they concluded that the evidence indicated that hyaluronic acid had no clinically important effect on efficacy outcomes for people with osteoarthritis. This included evidence for some outcomes from large studies with a low risk of bias. These methods are consistent with the methods used at NICE (please see 'Developing NICE guidelines: the manual'). The protocols for the evidence reviews are agreed in advance. Committees base their recommendation on the evidence from clinical reviews and their expert knowledge. The recommendations do not always match other guideline recommendations.

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				In their analysis systematic review of the literature, Phillips et al summarised all current published CPG recommendations for the role of injections in the nonoperative management of knee OA, specifically with the use of intra-articular hyaluronic acid (IAHA), intra-articular corticosteroids (IACS), and platelet-rich plasma (PRP). The study is important as it summarises all the literature on this topic until the 2020's. The methods to conduct their review was the following: a comprehensive search identified all nonoperative knee OA CPGs within the ECRI (formerly Emergency Care Research Institute) Guidelines Trust database, the Guidelines International Network database, Google Scholar, and the Trip (formerly Turning Research Into Practice) database. Guideline recommendations were categorised by Phillips et al into strong, conditional, or uncertain recommendations for or against the use of IAHA, IA-CS, or PRP. Guideline recommendations were summarised and depicted graphically to identify trends in recommendations over time.	

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				The search strategy identified 27 guidelines that provided a recommendation on the use of injectables for knee OA. The United States was the most frequent country represented within the included guidelines. Guidelines were published between 2003 and 2020. All 27 (100%) guidelines provided a statement regarding IAHA use. The research showed that with the exception of the US AAOS and the UK NICE, all CPGs recommend the use of IH, mostly as a second line treatment if first line treatment (NSAIDs) is not effective for symptom relief when other nonoperative options are ineffective, because IAHA may demonstrate a relatively delayed but prolonged effect in comparison. AAOS and NICE do not recommend IAHA because of "uncertainty in the current evidence" and in the case of the NICE this is based on CG177. Relevance of the CPG analysis With the exception of NICE and AAOS, guidelines, in general, are favourable for IAHA use for knee OA—especially when used after conservative options have failed.	

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				IAHA in most CPGs is recommended, with an equal number of recommendations for general use and secondary treatment if other conservative options fail. As noted, the unfavourable recommendations against IAHA use issued by AAOS and NICE, was typically for a lack of certainty and risk of bias within the available evidence. There are considerations and nuances within the IA-HA literature that may contribute to this lack of certainty in the evidence, despite there being a relatively large number of trials assessing this intervention. For instance, there is a growing body of literature demonstrating that product difference, particularly the HA molecular weight, may have a significant effect on the outcomes of IAHA treatment. The distinction of IAHA molecular weight differences has been acknowledged in some CPGs, particularly more recent recommendations. <u>Studies not considered by NICE supported by Fidia</u> Seemingly due to its inclusion criteria for the review of the clinical literature, NICE did not support most of the following studies on Fidia products. According to Fidia intra-articular administration of hyaluronic acid (viscosupplementation), when using the most appropriate formulation and the optimal method of	

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				administration, can provide long-lasting pain relief, reduce the chondropathy and stimulate the damaged cartilage repair, also subsequent to joint overuse, e.g. sport-related traumatic events. Fidia has developed a number of IAHA formulations as follows: • **Hyalgan:** Natural sodium hyaluronate, source extraction, molecular weight 500-730 kDA, concentration 1% (20mg/2ml), mild-moderate OA, dosage 3-5 ia injections • **Hyalubrix:** Natural sodium hyaluronate, source biofermentation, molecular weight 1,500-2,000 kDA, concentration 1.5% (30mg/2ml), moderate-severe OA, dosage 3 ia injections • **Hyalone:** Natural sodium hyaluronate, source biofermentation, molecular weight 1,500-2,000 kDA, concentration 1.5% (60mg/4ml), moderate-severe OA, dosage 1 injection • **Hymovis:** Natural sodium hyaluronate 3% chemical modification, source biofermentation, molecular weight 500-730 kDA, concentration 0.8% (24mg/3ml), mild-moderate-severe OA, dosage 2 injections RCTs	

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				• Priano 2007 • Migliore 2009 • Filardo 2012 • Battaglia 2013 • Giarratana 2014 • Filardo 2015 • Dallari 2016 • Doria 2017 • Di Martino 2018 • De Lucia 2019 Cohort studies • Migliore 2012 • Migliore 2017 • Mauro 2017 **Hymovis** RCTs • Zorzi 2015 • Bisicchia 2016 • Di Martino 2016 • Filardo 2016 • Falcinelli 2020 • Setaro 2020 Cohort studies	

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				• Benazzo 2016 • Ometti 2020 • Priano 2018 • Russu 2017a • Russu 2017b **Hyalgan** Cohort studies • Barrett 2002 • Neustadt 2003 • Miller 2017 **Hyalone** Cohort studies • Migliore 2010 • Vetro 2014 • Migliore 2018 **Various IAHA** Cohort studies and economic evaluations • Migliore 2011 • Altman 2015a • Concoff 2021 • Dasa 2016	

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				And the following systematic reviews: ● Altman 2015b ● Bannuru 2015 All cited studies have been published in peer reviewed journals.	
Fidia Pharma	Evidence Review J	164	027	It appears that NICE has not included observational studies in the review. We consider this to be a shortcoming as in studies in OS long term aspects of pain management are very important to analyse and observational studies provide a good design for long term assessments. Also observational studies are often of a real world evidence nature and reflect actual treatment practice in an appropriate way. For HI the evidence from observational studies (see under point 6 for an enumeration of the studies) is as follows: <u>Importance of cohort studies in OA</u> Cohort studies are a powerful tool for their longitudinal study design. Longitudinal studies follow participants over a period of time. Patients in cohort studies typically share some characteristics, such as their location or their age. For assessing, the effect of medication in OA and pain management, cohort studies are particularly	Thank you for your comment. The protocol stipulated that we would not look at observational studies. This is because there are a lot of published randomised controlled trials. Therefore, the committee agreed that the review would focus on the highest quality evidence available.

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				well suited as they allow to evaluate the effects of treatment over prolonged periods of time. To study the effect of Hyalgan two types of cohort studies have been utilised in the Fidia studies: HI has long term effects, confirmed in many studies up to 7 years following its application ● Prospective cohort studies, suited as they involve recruiting a group of participants and following them over time to gather new data; ● Retrospective cohort studies, in which patients, who already have certain characteristics, are analysed. <u>Evidence from prospective cohort studies</u> The prospective studies involving Fidia's HI products, have all been published in peer reviewed journals and have been designed appropriately with statistically significant outcomes. The studies have resulted in the following set of conclusions: ● Intra-articular sodium hyaluronate was an effective and safe treatment for pain in difficult-to-treat patients with moderate to severe OA of the knee; ● A single IA injection of linear high MW HA in patients suffering from knee OA is well tolerated and provides relief from pain. A patients' overall	

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				health status can be improved demonstrated by the high scores registered at the post treatment KOOS Function in daily Living, Quality of Life and Function in Sport and Recreation subscales; ● The clinical efficacy and safety of HyalOne®/Hyalubrix®60 in patients affected by osteoarthritis in a study, reporting on a large cohort of patients in different categories with a long follow-up of seven years, was confirmed; ● Significant improvements in OA-related pain, hip disability, and patient's daily functioning as well as a reduction in NSAIDs intake; ● Results from various studies indicate that IAHA alleviates knee pain since the first treatment cycle and this effect may be reinforced with two cycles of intra-articular injections; ● Hymovis may be effective and safe in patients with FAI, showing significant results in terms of pain control as well as hip functionality and quality of life up to 1 year; ● No significant modification in joint space width at the final follow-up secondarily proved that two injections of Hymovis® may slow down narrowing in the knee joint space over a one-year period, resulting in a delay of TKA; <u>Evidence from retrospective cohort studies</u> The retrospective studies involving Fidia HI products, have all been published in peer reviewed journals and	

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				have been designed appropriately with statistically significant outcomes. The studies have resulted in the following set of conclusions: ● Hyalgan was effective in patients with moderate to severe OA, and may have delayed TKR in 80% of patients. Taller patients, patients with less severe OA, and patients with patellofemoral compartment involvement showed the greatest pain relief and improvements in QOL; ● Hip viscosupplementation should be considered as conservative treatment to perform before proposing patients for THR; ● Confirmation of the clinical effectiveness and safety of HI for up to 12 months for pain relief and function improvement in patients with knee osteoarthritis, confirming previous data on intra-articular administration of hyaluronic acid as chronic therapy in the management of knee osteoarthritis; ● Patients treated with two cycles of intra-articular injections of Hymovis® have a progressive pain reduction that is maintained up to one year after the treatment starts. Hymovis® is effective and safe in symptomatic treatment of painful knee; ● HA is not associated with allergic reactions or systemic effects; ● Real-world evidence showing that meaningful differences exist among some HA products in disease-specific cost and time to knee	

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				replacement surgery; ● Participation in a single 8-week knee OA treatment programme, which included one cycle of five intra-articular knee injections of sodium HA given at weekly intervals, is highly cost-effective and provides clinically meaningful reductions in patient symptoms that are maintained over 3.7 years of mean follow-up. Conclusions from evidence from cohort studies From the prospective and retrospective clinical studies involving HI, the following conclusions can be drawn: ● IAHA is effective in symptomatic pain management in moderate to severe OA and generally results in a better QoL of patients; ● IAHA has long term effects, confirmed in many studies up to 7 years following its application; ● IAHA results in a reduction of pain medication such as NSAIDS and analgesics; ● One injection of HA already shows clinical effectiveness, although in most cohort studies reported two or more injections were applied; ● IAHA has disease modifying capabilities and has shown to postpone TKA; ● As to disease modifying capabilities, there is convincing evidence of clinical as well as	

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				resource saving effects of using IAHA to delay TKA.	
Fidia Pharma	Evidence Review J	165	003	It is not clear what the intervention duration was relating to NICE's literature review, i.e. for patients in clinical studies. We assume that most patients were in trials for short periods of time, a maximum three months which appears to be indicated here. However, many of the HI Fidia studies, more scientifically relevant, take a much longer perspective and review the effects of HO over extended periods of time of 6-12 months and even longer (see some of the observational studies on which we report on other sections of this comment form) The effects of use of HI products over extended time periods in OA are summarised below (and in detail in the accompanying Evidence review we have provided).	Thank you for your comment. The information about the amount of time people were followed up for and, where available, the number of injections and time they were delivered over, is reported in the effectiveness evidence tables in Appendix D. This information is also summarised within the Summary of studies included in the effectiveness evidence (1.1.5) in the report. The GRADE tables provide the mean amount of time until follow up for the outcomes (see section 1.1.6 Summary of the effectiveness evidence). We agree that the majority of studies followed up the results of the treatment at less than and equal to 3 months. However, some randomised trials reported outcomes at greater than 3 months, which provided information on the efficacy of hyaluronic acid at later time periods. We have reviewed your report and have concluded that the studies you have identified did not meet the protocol criteria for this review and therefore were not included. Please see the response on individual studies you cited in the row titled 'Response on eligibility of cited studies'.
Fidia Pharma	Evidence Review J	165	004 - 006	The focus of the review by NICE is limited to HRQOL, pain and physical function measurements. However, the effects of HI have been clarified in clinical research in other important areas such as reduction of NSAID medication and delay of TKA. These extremely	Thank you for your comment. The committee agreed that health-related quality of life, pain and physical function were critical outcomes of importance for determining the efficacy of treatments for osteoarthritis. Reduction of NSAID medication was not used as this could be

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				important and relevant "other outcomes" often have significant patient utility and budget impact implications. The evidence from the Fidia sponsored studies in HI on these "other outcomes" is as follows: ● IAHA results in a reduction of pain medication such as NSAIDS and analgesics; ● One injection of HA already shows clinical effectiveness, although in most cohort studies reported two or more injections were applied; ● IAHA has disease modifying capabilities and has shown to postpone TKA; ● As to disease modifying capabilities, there is convincing evidence of clinical as well as resource saving effects of using IAHA to delay TKA.	confounded by multiple factors making the interpretation less clear. Delay of total knee replacement was not included, but total knee replacement rate was considered as a part of serious adverse events if reported. The committee wanted to assess the clinical effectiveness of the intervention, of which they found that hyaluronic acid was not clinically effective at reducing symptoms for people with osteoarthritis. Therefore, they agreed the evidence did not justify its use. The committee do not agree that one injection of hyaluronic acid shows clinical effectiveness based on the evidence identified in this review.
Fidia Pharma	Guideline	009	010	Fidia Pharma Ltd is featuring an extensive product range of hyaluronan injections (HI) products and has carried out a comprehensive clinical trial programme in OS pain management and other indications. Please refer to the accompanying extensive report which describes approximately 30 RCTs and other clinical studies in HI published in peer reviewed journals and which have not been accepted or reviewed at all so far by NICE.	Thank you for your comment. For information about why the studies referenced in your report were or were not included in the guideline, please see the response on individual studies you cited in the row titled 'Response on eligibility of cited studies'. On evaluating the evidence that was included in the review, the committee disagree that there is sufficient evidence to conclude that hyaluronic acid use will lead to clinically important improvements in quality of life, pain

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				The conclusion of all these studies is that Fidia's HI products (and HI products in general) are generally effective in symptomatic pain management in moderate to severe OA and generally result in better patient values and patient QoL. Moreover, the irrefutable evidence is that HI products have long term clinical and patient value effects, confirmed in a number of the presented clinical studies with a longitudinal stretch of up to 7 years following their application. At the same time, there is clear, clinical evidence that the (Fidia) HI product range is associated with a reduction of pain medication such as NSAIDs and analgesics and has equal effectiveness to, for instance, PRP (Platelet Rich Plasma). One injection of HA already shows clinical effectiveness, although in most clinical studies of (Fidia) HI products two or more injections were applied. Finally, and we also think very importantly, a number of studies indicate that (Fidia) HI products have disease-modifying capabilities and have shown to postpone TKA. Disease modifying capabilities are associated with substantial resource savings as documented by a number of cohort studies based on RWE data involving HI products (presented in the annex report to this form), so would save the NHS considerable expense.	and physical function for people with osteoarthritis. Based on this, weighing in the potential for adverse events and the cost of hyaluronic acid products, they agreed that hyaluronic acid should not be used.
Fidia Pharma	Guideline	029	005	Your statement that *"There was no evidence showing that hyaluronan injections improved quality of life or physical function, or reduced pain, in people with knee or hip osteoarthritis"*	Thank you for your comment. None of the studies you mentioned in your report and included in an earlier comment met the inclusion criteria for this review. Please see the response on individual studies you cited in the row titled 'Response on eligibility of cited studies'.

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				is clearly incorrect when the published, peer-reviewed evidence which we have presented is taken into account. Our analysis shows that the Fidia HI product range has a positive treatment effect in terms of reduction of pain in patients with moderate to severe OA both in the knee and the hip with associated improvements in QoL and that treatment effects of these products have a long term perspective with clinical studies showing effectiveness of these products up to 7 years following application. For evidence generation, NICE disappointingly, and for reasons unknown, did not consider a large number of clinical studies which were carried out with HI products. These studies were well-designed (RCTs) and published in peer reviewed journals and should have been reviewed by NICE.	Given the absence of evidence of effect of hyaluronan acid the committee agreed that intra-articular hyaluronan injections should not be offered to manage osteoarthritis.
Fidia Pharma	Guideline	029	007	Your comment: "*Evidence 7 showed a potential harm for hip osteoarthritis. Limited evidence for other osteoarthritis-affected joints showed inconsistent benefits and some potential harms"* appears incorrect for the same reason as the previous one, i.e. that admissible, proper and very relevant evidence has been ignored. NICE did not review all the	Thank you for your comment. We have reviewed your report and have concluded that the studies you have identified did not meet the protocol criteria for this review and therefore were not included. Please see the response on individual studies you cited in the row titled 'Response on eligibility of cited studies'. Any studies relevant to the review protocol from any time before the final search were included in the review.

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				clinical evidence for HI in these indications, only looked at some older studies and did not consider the wealth of evidence generated by well-designed studies with Fidia HI products. Our accompanying evidence review report describes all these relevant studies that NICE has been ignoring.	
Fidia Pharma	Guideline	029	009	Your comment*: "Based on their expert opinion, the committee agreed that these results were generalisable to other forms of osteoarthritis and that hyaluronan injections should not be offered".* Our analysis shows that HI is recommended in medical guidelines by professional orthopaedic and other medical societies all across Europe, North America and Australia. NICE is the only exception in Europe taking a different view on the added value of HI in treating OS and pain. Of course, NICE is entitled to have its own opinion, and it would be acceptable if this was based on all available, relevant and admissible clinical evidence on HI, which it clearly has not. We have demonstrated in our submission (see accompanying evidence report) that this has not been the case and that the draft guidelines have ignored the published, peer-reviewed evidence which undermines the conclusion	Thank you for your comment. We have reviewed your report and have concluded that the studies you have identified did not meet the protocol criteria for this review and therefore were not included. Please see the response on individual studies you cited in the row titled 'Response on eligibility of cited studies'. The committee made recommendations based on the relevant evidence identified in the clinical review. On examining the evidence, they concluded that the evidence indicated that hyaluronic acid had no clinically important effect on efficacy outcomes for people with osteoarthritis. These methods are consistent with the methods used at NICE (please see 'Developing NICE guidelines: the manual'). Committees base their recommendation on the evidence from clinical reviews and their expert knowledge.

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				that HI should not be offered in the UK.	
G.R Lane Health Products Ltd	Guideline	05	General	With arthritic care expected to cost the NHS an estimated £118.6 billion in the next decade1, providing adequate self-management options to the 20 million people in the UK living with a musculoskeletal condition has never been more important. Analgesics and supplements that are available over-the-counter are not funded by the NHS and are especially cost-effective, therefore saving the healthcare system money whilst also being easily accessible for patients – particularly crucial for the estimated 100,000 arthritis patients currently overdue joint replacement surgeries due to long NHS waiting times2. The draft guideline fails to acknowledge supplements that support joint health and in doing so, is excluding clinically backed treatment options such as the galactolipid compound found in GOPO. GOPO has been clinically assessed in both randomised clinical trials and laboratory-based trials, the latter allowing determination of pharmacological effects3-6. Clinical trials confirm that GOPO has a favourable safety and tolerability profile with no reported side-effects, no known contraindications, and no interactions with other commonly used arthritis medications3-6. As well as this, GOPO is available over-the-counter and may be more effective than paracetamol and glucosamine3 whilst reducing the need for rescue medications4, therefore avoiding the risk of gastric irritation, a harmful side effect of NSAIDs and COX-IIs.	Thank you for your comment. Nutritional supplements including GOPO derived from Rosa canina, were excluded in the scope of the guideline.

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				GOPO (glycoside of mono and diglycerol) is the active compound isolated from the rose-hip Rosa canina, which has been shown to inhibit the production of nitric oxide7 and prevent the migration of white blood cells into chronically inflamed tissues8, targeting the source of the problem and breaking the vicious cycle of joint pain. GOPO has been clinically proven to help reduce joint pain9, reduce the need for rescue medicines (such as paracetamol and opioids)10, and improve flexibility and mobility11,12,13. In addition, studies have shown that due to its anti-inflammatory properties, GOPO is more effective at reducing pain and improving mobility than other supplements for osteoarthritis, such as glucosamine14. As well as this, a Cochrane Review published in 2018 which explored the effects of rose-hip on pain and joint stiffness in osteoarthritis sufferers found that taking a regular oral dose of rose-hip did in fact improve both pain and joint stiffness15. This is further supported by a breadth of clinical data on the effectiveness of the compound GOPO for the treatment of osteoarthritis, including the impact on pain16, inflammation17, movement18 and its cartilage regenerating properties19,20. In addition to the clinical studies, the 2019 Joint Health of the Nation Report which is supported by key patient organisations including ARMA (Arthritis and	

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				Musculoskeletal Alliance), Arthritis Action and PCRMM (Primary Care Rheumatology and Musculoskeletal Medicine Society), highlighted the importance of self-management options for sufferers of osteoarthritis, including considering clinically proven joint health supplements such as rose-hip extract prepared as the galactolipid GOPO. Consultant Rheumatologist Dr Rod Hughes comments: "As a nation we tend to ignore the health of our joints until they cause us problems. We do not keep our muscles in shape, our weight under control and often ignore minor injuries to our joints and don't get them treated in an effective and timely manner, resulting in an increasing number of people taking long-term analgesics to control joint pain or needing surgery to repair or replace knees or hips. We can also help to protect our joints and effectively treat joint pains by using a clinically proven joint and soft tissue supplement such as rose-hip extract prepared as the galactolipid GOPO to our daily diet. This has been shown to help protect and repair joints and should certainly be considered at the early onset of even mild joint pain or after joint injury. Not only do people report great benefit from these supplements but good quality clinical research has also proved GOPO is effective."	

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				Although NICE reviewed the evidence of rose-hip in 2017, we could not see any reference in the surveillance to rose-hip as a treatment option for osteoarthritis, nor could we see a lack of evidence in any form. With the NHS Long Term Plan focusing on supported self-management, the NHS evidenced-based review exploring health checks for the prevention of musculoskeletal problems, current global concerns regarding opioid use/addiction and the adverse effects associated with long term analgesic use, it is vital that alternative treatments are considered. Tackling the elephant in the room, NHS, 2018, https://www.england.nhs.uk/blog/tackling-the-elephant-in-the-room/ Too long to wait: the impact of COVID-19 on elective surgery, The Lancet Rheumatology, Volume 3, Issue 2, e83. February 2021 https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00001-1/fulltext Christensen R, Bartels EM, Altman RD et al. Does the hip powder of Rosa canina (rose-hip) reduce pain in osteoarthritis patients? – a meta-analysis of randomized controlled trials. Osteoarthritis Cartilage 2008; 16: 965–972. Winther K, Apel K, Thamsborg G. A powder made from seeds and shells of a rose-hip subspecies (Rosa canina) reduces symptoms of knee and hip osteoarthritis: a randomized, double-blind, placebo-	

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				controlled clinical trial. Scand J Rheumatol 2005; 34: 302–308. Willich SN, Rossnagel K, Roll S et al. Rose-hip herbal remedy in patients with rheumatoid arthritis – a randomised controlled trial. Phytomedicine 2010; 17: 87–93. Rein E, Kharazmi A, Winther K. A herbal remedy, Hyben Vital (stand. powder of a subspecies of Rosa canina fruits), reduces pain and improves general wellbeing in patients with osteoarthritis – a doubleblind, placebo-controlled, randomised trial. Phytomedicine 2004; 11: 383–391. Larsen E, Kharazmi A, Christensen LP, Christensen SB. An anti-inflammatory galactolipid from rose-hip (Rosa canina) that inhibits chemotaxis of human peripheral bloodneutrophils in vitro. J Nat Prod 2003; 66: 994–995 SchwagerJ, Richard N, Wolfram S. Anti-inflammatory and chondro-protective effects of rose hip powder and its constituent galactolipids GOPO. Poster presentation at the World Congress of Osteoarthritis (OARSI), Rome, 18–21 September 2008 Winther K et al. Scand J Rheumatol 2005; 34: 302-308 Willich SN et al. Phytomedicine 2010; 17: 87–93 Willich SN et al. Phytomedicine 2010; 17: 87–93 Rein E et al. Phytomedicine 2004; 11: 383–391 Warholm O, Skaar S, Hedman E et al. The effects of a standardized herbal remedy made from a subtype of Rosa caninain patients with osteoarthritis: a double-blind, randomized, placebo-controlled clinical trial. Curr Ther Res Clin Exp 2003; 64: 21–31	

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				SchwagerJ, Richard N, Wolfram S. Anti-inflammatory and chondro-protective effects of rose hip powder and its constituent galactolipids GOPO. Poster presentation at the World Congress of Osteoarthritis (OARSI), Rome, 18–21 September 2008 Hu, X., Corp, N., Quicke, J., Lai, L., Blondel, C., Stuart, B., Abdelmotelb, A., Leweth, G., Mallen, C. and Moore, M., 2018. Rosa canina fruit (rosehip) for osteoarthritis: a cochrane review. Osteoarthritis and Cartilage, 26, p.S344. Winther K et al. Scand J Rheumatol 2005; 34: 302-308 Schwager J, Richard N, Wolfram S. Anti-inflammatory and chondro-protective effects of rose-hip powder and its constituent galactolipids GOPO. Poster presentation at the World Congress of Osteoarthritis (OARSI), Rome, 18–21 September 2008 Warholm O, Skaar S, Hedman E et al. The effects of a standardized herbal remedy made from a subtype of Rosa caninain patients with osteoarthritis: a double-blind, randomized, placebo-controlled clinical trial. Curr Ther Res Clin Exp 2003; 64: 21–31 Schwager J, Richard N, Wolfram S. Anti-inflammatory and chondro-protective effects of rose-hip powder and its constituent galactolipids GOPO. Poster presentation at the World Congress of Osteoarthritis (OARSI), Rome, 18–21 September 2008 Scaife R, The effect of GOPO® supplementation on passive joint forces and subjective assessment of pain in a non-arthritis population. The Centre for Sport & Exercise Science, Sheffield Hallam University. 2013	

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G.R Lane Health Products Ltd	Guideline	05	02	Whilst the benefit of exercise for symptom management of osteoarthritis is clear, incorporating a clinically backed supplement can not only support an active lifestyle long-term but also encourage osteoarthritis sufferers to take up exercise in the first place by easing pain and supporting overall joint health. Founder of Move it or lose it, a network of instructors delivering exercise classes to thousands of older people every week, many of whom suffer from osteoarthritis, Julie Robinson says: "Joint pain and stiffness, such as arthritic conditions that increase with prevalence as we age, can make exercising hard, creating a vicious cycle of inactivity and reduced mobility, further exacerbating symptoms. Joint health supplements that are backed by strong scientific research are one of the ways that we can support an active lifestyle and get joint-pain sufferers back on their feet and exercising with confidence. One such example is an anti-inflammatory extract derived from rose-hip, containing an active compound called GOPO, that is shown in clinical research to reduce joint pain by as much as 80% in as little as 3 weeks1, whilst safeguarding protective joint cartilage for years to come2." In addition to the clinical data, persons with osteoarthritis have reported significant clinical	Thank you for your comment. The combination of exercise with nutritional supplements (other than glucosamine) were not considered as these (including GOPO derived from Rosa canina) were excluded from the scope of the guideline.

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				improvement and improved quality of life after three months supplementation with GOPO. One patient had a rare acute onset of osteoarthritis, with one consultant describing it as one of the worst onsets of hip destruction that they had seen. Due to their age, they were unfortunately unable to get a hip replacement, but the prescribed painkillers made them violently ill and anti-inflammatories didn't seem to help. Refusing to accept their doctor's diagnosis, they started to explore other ways to treat their condition and experienced significant changes when taking GOPO. "After just 5 weeks I was finding it easier to get dressed, and after 8 weeks I could walk unaided and was able to start driving again. I was staggered by the results and couldn't believe the degree to which it relieved my pain. Fourteen years have since passed and I still rely on GOPO to keep my joints in good working order. In fact, an MRI scan recently showed absolutely no trace of arthritis in my hip." It is clear from the draft guidance that a more holistic approach is needed in the management of osteoarthritis with the inclusion of exercise and weight loss and the withdrawal of paracetamol as a suitable pharmacological treatment. The galactolipid GOPO is an anti-inflammatory compound with good quality evidence for safety and efficacy in osteoarthritis and has been shown to reduce the consumption of analgesics. We urge NICE to review the specific	

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				evidence to support GOPO and to amend the draft guidance accordingly. 1. Schwager J, Richard N, Wolfram S. Anti-inflammatory and chondro-protective effects of rose hip powder and its constituent galactolipids GOPO. Poster presentation at the World Congress of Osteoarthritis (OARSI), Rome, 8–21 September 2008 2. Willich SN, Rossnagel K, Roll S, et al. Rose hip herbal remedy in patients with rheumatoid arthritis - a randomised controlled trial. Phytomedicine. 2010;17(2):87-93. doi:10.1016/j.phymed.2009.09.003	
Keele University	Evidence Review K & H	General	General	Treatment package joint protection principles [K] Evidence review for the clinical and cost-effectiveness of treatment packages for the management of osteoarthritis) [H] Evidence reviews for the clinical and cost-effectiveness of devices for the management of osteoarthritis The description of joint protection principles is one element that needs clarification. The use of terms such as devices (part of joint protection principles and practice) and joint protection principles needs refining. Contemporary language now describes this is as joint	Thank you for your comment. The definition of joint protection principles used are what the studies provided with no specific definition used for the guideline. The term 'joint protection principles' that was in the guideline section on terms used in this guideline has now been changed to state 'ways to reduce pain and straining when using joints'. We agree that the Dziedzic study was a 2x2 factorial trial as explained. The exercises are described in the Dziedzic 2015 trial paper as 'stretching and strengthening hand exercises' and so were reported as such. We acknowledged that there were additional components to the exercise and reported each of these in the evidence table for the study. Tap turners were outside of the scope of the question where the committee agreed the review was to study the

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				health education (joint protection is outdated in therapy circles) Dziedzic 2015(94) SMOotH trial Subsidiary papers: Dziedzic 2011(95) Oppong 2014(210) (Osteoarthritis: assessment and management (update) [K] Evidence review for the clinical and cost-effectiveness of treatment packages for the management of osteoarthritis) The SMOotH trial is the evidence for the treatment package for hand OA. This was a 2x2 factorial trial where the combined package was not examined in isolation rather hand exercises versus no hand exercises; joint protection principles versus no joint protection principles. Hand exercises are described in the draft as strengthening but in SMOotH they also included mobilising and stretching exercises. Under Devices there's the comment that the search didn't look for tap turners, but splinting for hand OA. The guideline will have missed the opportunity to show that people receiving a three-four group course of Occupational Therapy training on joint protection principles were twice as likely to be a responder to treatment than those who did not (pain/function/global improvement OMERACT/OARSI responder criteria) Devices also includes the practical application of gadgets/devices. The SMOotH study therefore hasn't	effect of devices applied to the joint rather than adaptations for daily function. We will forward your comment to the NICE surveillance team to consider for the next update of this guideline. While the SMOotH study may include device use as a component of joint protection principles, it would not be possible to separate this from other interventions (as this was combined with other joint health education components) and so there would not be a valid comparison that could be used in the devices review. It is also unclear which device was used, and so would be difficult to categorise it in reference to the devices review protocol (appearing to be more likely to refer to adaptations for daily life such as 'labour-saving gadgets' from what is written in the study). With these elements in mind, this was not included in the devices review.

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				featured here but perhaps it should: [H] Evidence reviews for the clinical and cost-effectiveness of devices for the management of osteoarthritis	
Keele University	General	General	General	*We welcome the NICE OA guidelines and congratulate the guideline development group on their excellent work in preparing this, thank you. We particularly enjoyed the emphasis on clinical diagnosis of OA and the emphasis on assessment and core treatments although there were some strong feelings in our patient group about this.* *We consulted our patient and public involvement and engagement group and their comments are highlighted in light blue and identified by a *. We did not influence their views and have reported what they shared. They wanted to convey that true to purpose, guidelines need to say what they can do to help, not what they cannot offer.* *The overall feeling of our patient and public members was disappointment and upset with the guidelines. They felt the guideline did not seem to give any thought to the quality of life for the person with OA with no say on how clinicians can help patients get on with their lives. Our patient and public members felt strongly that they needed xrays and questioned how a clinician can diagnose the problem just by looking at the joint.* *We appreciate that the consultation process has requested additional comments and we have also consulted a range of academics and health*	Thank you for your comments. We have responded to each in turn.

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				professionals therefore there are several points raised as requested for consideration.	
Keele University	General	General	General	The guideline was comprehensive, highly informative, easy to read, clear and structured in a way to easily work through it.	Thank you for your comment.
Keele University	General	General	General	The most prevalent symptomatic OA is hand OA. Wording could reflect specific joint sites rather than OA as a whole.	Thank you for your comment. The committee looked for evidence by specific joint sites with the aim of making recommendations for each where possible. However, the evidence related to predominantly hip and knee osteoarthritis, and very little evidence relating to hand osteoarthritis. Therefore, it was not possible to make recommendations specific to each joint site in most circumstances. Therefore, the committee made generic broader recommendations.
Keele University	General	General	General	**Presentation:** There is a long list of 'do not use' interventions – is there a better way of listing them? A list of effective interventions recommended would give a more positive message and then add the 'others' at the end? There's a danger that the OA guidelines come across as very negative (see our patient and public responses).	Thank you for your comment. The recommendations ordered by the review question then linked to the evidence report so that readers could find the supporting data. There is also a visual summary. This lists all the positive recommendations first then the negative at the bottom. The committee thought very carefully about the 'do not' recommendations before making them. They agreed that it was important to only recommend treatments that are shown to be effective. Some of these 'do not routinely use' recommendations have been edited to provide more clarity and give more detail on the circumstances when the interventions might be offered.

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					As part of our 5-year strategy, NICE is currently looking at how we best present our guidance to ensure it is useful and usable. We will forward your comments on for consideration. We will liaise with the NICE communications team with the aim to put more public focus on the effective interventions.
Keele University	General	General	General	We have concern over the 'wear and tear' headline featured on associated news stories, and have seen discussion on Twitter about it. If possible consider how to shape the key messages e.g. appropriate lay terms to use, when the press release goes out from NICE about the guideline.	Thank you for your comment. We will liaise with the NICE communications team with the aim to put more public focus on the effective interventions.
Keele University	Guideline	General	General	Treatment package Would the MOSAICS study looking at the cost effectiveness and clinical effectiveness of a treatment package for people with OA (hand hip knee and foot all analysed separately) versus usual care be a key study to include? The package of care included core NICE interventions, first line pharmacological treatments, advice on exercise and weight management; patient information of OA and support for self-management. It improved quality indicators of OA care. MOSAICS main papers: Dziedzic KS, Healey EL, Porcheret M, Afolabi EK, Lewis M, Morden A, Jinks C, McHugh GA, Ryan S, Finney A, Main C, Edwards JJ, Paskins Z, Pushpa-	Thank you for your comment. This study has now been added to evidence review K and discussed by the committee. They agreed it supported the recommendations already written.

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				Rajah A, Hay EM. Implementing core NICE guidelines for osteoarthritis in primary care with a model consultation (MOSAICS): a cluster randomised controlled trial. Osteoarthritis Cartilage. 2018 Jan;26(1):43-53. doi: 10.1016/j.joca.2017.09.010. Epub 2017 Oct 14. PMID: 29037845; PMCID: PMC5759997. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5759997/ Jordan KP, Edwards JJ, Porcheret M, Healey EL, Jinks C, Bedson J, Clarkson K, Hay EM, Dziedzic KS. Effect of a model consultation informed by guidelines on recorded quality of care of osteoarthritis (MOSAICS): a cluster randomised controlled trial in primary care. Osteoarthritis Cartilage. 2017 Oct;25(10):1588-1597. doi: 10.1016/j.joca.2017.05.017. Epub 2017 Jun 4. PMID: 28591564; PMCID: PMC5613776. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5613776/ Oppong R, Jowett S, Lewis M, Clarkson K, Paskins Z, Croft P, Edwards JJ, Healey E, Jordan KP, Morden A, Ong BN, Porcheret M, Finney A, Hay E, Dziedzic K. Cost-effectiveness of a model consultation to support self-management in patients with osteoarthritis. Rheumatology (Oxford). 2018 Jun 1;57(6):1056-1063. doi: 10.1093/rheumatology/key037. PMID: 29554338; PMCID: PMC5965099. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5965099/	

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Keele University	Guideline	003	012	**1.2.1 – Information and Support** *There needs to be emphasis on a range of information in Plain English, different languages, for different cultures. The health literacy readability is not good for general population. We suggest reordering for importance – 1/ Enabling patients 2/Shared decision making 3/ Delivering personalised care needs to be added	Thank you for your comment. We have recommended that information is given according to the persons' needs and have given language and culture as examples. We also mention that it should be in an accessible format. More detailed recommendations related to communication are in NICE's patient experience guideline (https://www.nice.org.uk/guidance/cg138) linked to in recommendation 1.1.1 The recommendations have been put in the order you suggest.
Keele University	Guideline	003	012	Great. Thank you, it would be great to have more resources available centrally for our seldom heard communities	Thank you for your comment.
Keele University	Guideline	004	007	**1.2.2 – Explain to people with osteoarthritis** *We have concerns that you can be diagnosed without imaging. This is scary for patients. There needs to be more information e.g. evidence why this is the case. No mention of the impact from foods in relation to inflammation. What OA actually is, is missing? A definition is needed. Weight loss should read weight management if appropriate. There needs to be more sensitivity and more information regarding explaining the benefits of this to patients. More education for patients as there is a fear when diagnosed.	Thank you for your comment. We carried out a thorough search for the evidence for imaging, but none was identified. The committee discussed the potential recommendations in detail. They agreed that without any published evidence of benefit and no evidence of benefit in their experience it is not a good use of NHS resource to recommend imaging. It would also be misleading to individuals to let them think imaging will help with their diagnosis. We have added to the recommendation so that it now states 'Explain to people with osteoarthritis that: it is diagnosed clinically and does not need imaging and management should be guided by symptoms and function.

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				Wording of guidelines in general is not aimed at patients and carers, even though it says they are part of the intended audience.	We have amended the patient information recommendation and section title for the weight management recommendations to 'Weight management'. The recommendations still use the words 'weight loss' as this is what they are specifically aiming to achieve. NICE guidelines are primarily aimed at health care professionals but written in a way that lay members can understand where possible. It is not intended to be a patient information leaflet. Other patient organisations are good at producing these and NICE does not seek to duplicate their work. A select few of these organisation's websites will be linked to from NICE's osteoarthritis guideline web page.
Keele University	Guideline	004	017	Sadly, support groups are increasingly difficult to find in times of limited resources	Thank you for your comment. There will be a link to patient information web pages and support groups from NICE's osteoarthritis guideline web page when it is published.
Keele University	Guideline	004	11	**1.2.3 – Advise them where they can find written and verbal information** *Jargonistic, need for more information for each bullet point. How would clinicians use this, is the clinician to explain regarding written information? The patient group feel disheartened, are NICE just ticking boxes? Inclusivity–- how will clinicians know if the patient has understood, does not feel inclusive at the moment.	Thank you for your comment. NICE guidelines are primarily aimed at health care professionals but written in a way that lay members can understand where possible. It is not intended to be a patient information leaflet. Other patient organisations are good at producing these and NICE does not seek to duplicate their work. A select few of these organisation's websites will be linked to from NICE's osteoarthritis guideline web page when it is published.

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				Feels like the guidelines represent the costs of treatments, also need to be for patient benefit. Pain diary would capture all the points. Missing – patients who are vulnerable. Simpler phrasing needed. Specific exercises – does this relate to physio or general? Exercise is hard to do day to day with pain. Where does the verbal information come from? What is the written information? Need specifics?	Recommendation 1.2.3 is to ensure health care professionals point patients to where they can find more information on key points. More detailed recommendations are provided in NICE's guideline on Patient experience in adult NHS services (https://www.nice.org.uk/guidance/cg138) which is linked to in recommendation 1.1.1. This covers recommendations on Knowing the patient as an individual, Essential requirements of care, Tailoring healthcare services for each patient, Continuity of care and relationships and Enabling patients to actively participate in their care, Pain diaries were not included as part of the scope so are not covered in this guideline. The exercises would need to be tailored to the individual's needs. They would differ depending on the site of osteoarthritis would likely taking into account the individual's symptoms. We removed the words 'verbal and written' from the recommendation as it seems to cause confusion. There will be a link to select organisations web site where patient information will be available. This will help provide clinicians with links to information to give patients.

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Keele University	Guideline	005	003	**1.3.1 Tailored exercise** *Is this for secondary care as well, where would onward referral come in? Sometimes patients are referred to a gym instead of a physiotherapist and this feels wrong. Repetition basically regarding exercise.	Thank you for your comment. The recommendations would apply to whoever is managing the individual whether it is a GP or from musculoskeletal services. The committee hasn't specified how exercise can be delivered as there could be a large number of ways and it needs to be tailored to the individual. It may be that the gym is suitable and an option that some people would like to try.
Keele University	Guideline	005	005	**1.3.2 Consider supervised therapeutic exercise for people with osteoarthritis** We agree it's important to consider supervised exercise but it seems odd to specifically pull out this mode of delivery when different kinds of mode of delivery have also proven to be effective. For example, particularly in light of COVID-19, remote delivery of exercise using tele-health options have also been proven effective, why not also refer to that too if remote options are required?	Thank you for your comment. The committee agreed that supervised exercise is not synonymous to in person delivery, as exercise can be supervised using tele-health and other remote solutions. Therefore, they agree that supervised exercise may include other modes of delivery that may be appropriate dependent on the person's needs and the healthcare practice in their area. However, this was not considered as part of the review protocol and therefore it has not been mentioned in the recommendations. We have noted this in the committee discussion of the evidence report.
Keele University	Guideline	005	011	**1.3.4 Consider combining therapeutic exercise with an education programme or behaviour change approaches in a structured treatment package.** A treatment package is defined as any treatment for osteoarthritis (including: exercise, manual therapy, electrotherapy, acupuncture, devices and pharmacological treatments) combined with 1 of the following: • behaviour change approaches, including joint protection principles, pain coping, skills training	Thank you for your comment. 'Joint protection principles' was referenced in studies included in the review and no specific definition was used when including in this guideline. The words 'joint protection principles' in the first bullet point of the definition for treatment packages is has been changed to 'ways to reduce pain and straining when using joints'.

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				(including spouse-assisted coping skills training), goal setting; motivational coaching; weight management counselling and workplace risk counselling • an education programme given by or more healthcare professionals over multiple sessions, including those based on behavioural theory. 'Joint protection principles' is a wide-ranging term – does this need to be more specific in terms of these principles? For example grading and pacing of activities, task modification, including use of assistive devices.	
Keele University	Guideline	005	011	We agree with this recommendation, but wonder if there is any further information about implementing a structured treatment package into clinical practice? Eg – no. of sessions, HCPs involved, community vs. hospital setting, balance of time spent on exercise vs. education/behaviour change? Anecdotally from working clinically, there are still some challenges around delivering group exercise/education programmes in physio, mainly due to covid. Examples are restrictions on the number of patients in the gym, extra time needed to maintain infection prevention and control guidelines and staff being redeployed to other areas of the hospital due to high patient demand. Some departments are offering the option of F2F vs. virtual delivery for individual and group physio appointments – is there any evidence/guidance about F2F vs. virtual delivery?	Thank you for your comment. There was evidence of benefit for treatment packages but not enough to suggest how to implement them. The committee discussed how the components of each package can vary and therefore did not think it possible to predetermine how many sessions to offer or the setting. The recommendations are written for a post covid world although the committee acknowledge that adaptations may be needed to during covid to deliver treatments. We didn't consider virtual vs face to face sessions and therefore have not made recommendations in this area. The literature included treatment packages delivered face-to-face and virtually.
Keele University	Guideline	005	014	**1.3.5 – weight loss**	Thank you for your comment. We have changed the wording in the patient information recommendation and

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				*Weight loss needs more sensitivity addressing and clinicians need to acknowledge with the patients their mitigating factors and challenges. The cost of healthy food is rising – some people can't afford to lose weight. Patients feel like they are being blamed for their weight.	the title of the section you have mentioned to 'weight management'. 'Weight loss' is still referred to in the recommendation because the committee agreed it needs to be clear to what is needed to help a person's osteoarthritis.
Keele University	Guideline	006	005	**1.3.6 – manual therapy** *The patient group discussed a concern that therapies would not be offered due to cost and the importance of giving patients autonomy	Thank you for your comment. The evidence showed a mixture of different manual therapy techniques. Therefore, the committee agreed that they could not specify a type of manual therapy that could be recommended based on this. The committee recommend that manual therapy should take place in conjunction with exercise and did not recommend that it should be used alone, and therefore it will be a part of an active treatment. This recommendation was based on evidence that showed that manual therapy was clinically effective when combined with exercise for people with osteoarthritis. Recognising the uncertainty in the literature the committee also made a research recommendation comparing manual therapy alone to manual therapy and exercise.
Keele University	Guideline	006	005	Manual Therapy is often a passive intervention: The emphasis here didn't seem to be in line with active management of OA. Does it need to more specific on exactly the technique there is evidence for as in previous guidance?	Thank you for your comment. The evidence showed a mixture of different manual therapy techniques. Therefore, the committee agreed that they could not specify a type of manual therapy that could be recommended based on this.

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				There is concern about raising expectations of patients if this is not available. Our clinical partners were surprised to see manual therapies advocated when other passive treatments, e.g. acupuncture and braces, were not. Mixed messages.	The committee recommend that manual therapy should take place in conjunction with exercise and did not recommend that it should be used alone, and therefore it will be a part of an active treatment. This recommendation was based on evidence that showed that manual therapy was clinically effective when combined with exercise for people with osteoarthritis. In contrast, evidence for acupuncture and braces did not show a clinically important effect for people with osteoarthritis and so these were not recommended. Therefore, the committee believe that this recommendation is evidence led and were not intending to make a message about passive or active therapy, but more to follow the evidence base and recommend treatments that were effective (which does include that active therapy is a significant part of the management of osteoarthritis).
Keele University	Guideline	006	005	We understand why this recommendation has been made but it does not acknowledge the lack of evidence for manual therapy for other joints and as such a recommendation cannot be made for the role of manual therapy for other joints (subtly different to only consider it for knee and hip OA).	Thank you for your comment. We have updated the rationale for the recommendation in light of your comment to state that there was no evidence identified for other joint sites.
Keele University	Guideline	007	002	**1.3.9 Electrotherapy** It's a very negative way of wording this given that there is not enough evidence. We suggest stating there is not enough evidence to support or refute the use of electrotherapy? The research recommendation on Extracorporeal shockwave therapy particularly feels like it does not fit. Why this modality and not the	Thank you for your comment. The committee, on evaluating the evidence, agreed that the evidence present was sufficient to indicate that electrotherapy would be unlikely to lead to clinically important benefits in efficacy for people with osteoarthritis.

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				others? Is it used often in clinical practice – we don't think it is?	With regards to extracorporeal shockwave therapy, evidence indicated a benefit when compared to sham. However, the committee agreed that the sham was likely inadequate to achieve blinding and would be difficult to compare to. There was conflicting evidence when compared to no treatment based on one small trial. Therefore, they have not included this in the 'do not' recommendation but have included a research recommendation to try and gain additional evidence before making a recommendation.
Keele University	Guideline	007	005	**1.3.10 Devices** *The patient group felt that the reasons for not recommending devices is to save on money and this is why it is being recommended to stop people using braces/splints. However this could have a negative effect on their quality of life, for some patients these work. Patients feel that they need more support than just written information and a diet and many would be put off going to see their doctor for OA if they saw these guidelines for fear of not being able to get any treatment.	Thank you for your comment. The committee were keen to only recommend treatments that were shown to be effective. They did not think it beneficial to people with osteoarthritis to be recommending treatments that do not appear to work. A key part of NICE guidelines is that they assess the cost effectiveness of an intervention, service or programme in order to help decision-makers ensure that maximum gain is achieved from limited resources. Without evidence to demonstrate the effectiveness of devices the committee agreed it is difficult to conclude they would be cost effective. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and

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					• therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.'
Keele University	Guideline	007	005	**1.3.11** The draft updated guidance signals a change in tone against the use of braces (and other devices) as a management option in osteoarthritis care having previously recommended that "people with osteoarthritis who have biomechanical joint pain or instability should be considered for assessment for bracing/joint supports/insoles as an adjunct to their core treatments." In recommending against the "routine offer" of braces to people with osteoarthritis, the wording of the new recommendation sets up a straw man (we are unaware of any evidence that braces are being routinely offered – to do so would undoubtedly be wasteful and risk potential harms) and does not achieve the committee's aim of "highlighting the uncertainty in the evidence with the possibility of harm". We realise that to some extent this may be standard wording for NICE but we encourage the committee to: • Reconsider their judgement and recommendation on braces to better represent the findings of their evidence review – that there is still insufficient evidence on clinical	Thank you for your comment. We did not split by type of braces as it was agreed when the protocol was set to keep them together. The protocol only stratified by site and all studies had knee OA therefore all studies with braces were put together except for those with different comparators. The committee were keen to ensure they were recommending interventions that were demonstrated to be effective. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.' We did not include research into the use of devices for knee osteoarthritis because the committee were aware of

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				(and cost) effectiveness and adverse events of braces • Recognise in their rationale, as recent US guidelines have, that different types of brace for knee OA (e.g. unloader-type, sleeve, neutral/hinged) have distinctive clinical indications, cost, and evidence We congratulate NICE on achieving the most inclusive review of published trial evidence for bracing of any recent international guidelines. Nevertheless, the evidence review serves principally to underline the continued lack of sufficient high-quality, independent evidence on the effectiveness and cost-effectiveness of braces. Contrary to the impression given in the draft guidance, this situation also applies to braces for knee osteoarthritis. Of 19 outcome/endpoint/control comparisons examined in the draft guidance and where there was some eligible evidence available, all bar two were based on 'low' or 'very low' quality evidence from 1-3 trials. The combined sample was less than 100 patients in 15 of these comparisons. A new health economic analysis in this area was not prioritised, so evidence on cost-effectiveness relied on health economic modelling from a previously published network meta-analysis in which only one n=24 trial of bracing vs insole featured. Evidence of adverse events are rightly noted but we believe are given undue weight in the committee's judgements. Serious adverse events are rare and unlikely to compare in significance with those associated with some	an ongoing randomised controlled trial on the uses of knee braces (https://www.keele.ac.uk/propoa/). We will let the NICE surveillance team know of this study. We have checked all the included studies from the cited systematic reviews. All but one of the studies were already in the guideline review. Horlick 1993 has been added but does not affect the results.

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				pharmacological and surgical interventions. Careful patient selection, skilled fitting, and appropriate monitoring and support are all likely to contribute to mitigating these risks (a very different model of practice from the indiscriminate use implied by the phrase 'routinely offered'). In that context, and with narrowing pharmacological options and public interest in effective non-drug management, our concern is that this recommendation will be interpreted as evidence of a lack of benefit of braces (and all other devices) and a need to turn attention to other treatment avenues. Instead, the evidence review has clearly demonstrated insufficient evidence to make a clear recommendation and this should encourage further well-designed, practice-relevant studies in this area, and not just for foot or ankle OA. There is a subtle double-standard at work here. 'Braces' are lumped together in a way that encourages people to think of these as a homogeneous and finite group of interventions. The possibility of drug discovery (rightly) remains alive in the face of evidence against several existing pharmacological options, whereas for any or all kinds of 'braces' this possibility is implicitly denied. It is of note that both ACR and AAOS guidelines have sought to consider separately unloader-type braces for tibiofemoral OA from re-alignment or sleeve-type braces for patellofemoral/undifferentiated knee OA. Emphasising the need for sham controls for high quality evidence of	

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				effectiveness further exacerbates this double-standard. Efficacy and mechanisms of valgus braces have been the subject of several high-quality reviews (Moyer et al., 2015a, 2015b). Rather than efficacy, the major evidence gap for health services is on clinical and cost-effectiveness, adherence and adverse events (Bennell & Hinman, 2015). Moyer RF, Birmingham TB, Bryant DM, Giffin JR, Marriott KA, Leitch KM. Biomechanical effects of valgus knee bracing: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2015 Feb;23(2):178-88. doi: 10.1016/j.joca.2014.11.018. Epub 2014 Nov 29. PMID: 25447975. Moyer RF, Birmingham TB, Bryant DM, Giffin JR, Marriott KA, Leitch KM. Valgus bracing for knee osteoarthritis: a meta-analysis of randomized trials. Arthritis Care Res (Hoboken). 2015 Apr;67(4):493-501. doi: 10.1002/acr.22472. PMID: 25201520. Bennell KL, Hinman RS. Osteoarthritis: What is the evidence for valgus bracing effects in knee OA? Nat Rev Rheumatol. 2015 Mar;11(3):132-4. doi: 10.1038/nrrheum.2015.2. Epub 2015 Jan 27. PMID: 25624009.	
Keele University	Guideline	007	007	'Do not routinely offer insoles, braces, tape, splints or supports' (this is very negative wording that is really just reflecting lack of evidence base). Evidence for walking aids is just as poor as for insoles etc so why recommend one and not the other? Reason given is because braces etc can have serious adverse events, but blistering etc is not serious. Consideration of the	Thank you for your comment. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless:

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				evidence seems to have been applied a little inconsistently in this instance. We understand the challenges of recommending some devices rather than others, however please see the SMOOTH trial. *Dziedzic 2015(94) SMOotH trial Subsidiary papers: Dziedzic 2011(95) Oppong 2014(210) (Osteoarthritis: assessment and management (update) [K] Evidence review for the clinical and cost-effectiveness of treatment packages for the management of osteoarthritis)* 'Devices' is a broad, non-specific term that potentially covers a wide range of products with varying aims of use. Does this term incorporate both bodily worn devices (splints) and assistive devices? *The committee concluded that there was not enough evidence to support the use of insoles, braces, tape, splints or supports. They also noted that there is a potential risk that some of these devices could cause significant adverse events, such as blistering and other pressure damage* Agree with non – routine issuing of splints – in light of OTTER II trial view as stepped care option (Adams et al cited in [H] Evidence reviews for the clinical and cost-effectiveness of devices for the management of osteoarthritis). Risk can be mitigated through discussion, advice, correct training of clinician and fitting of splint-very	• there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.' We agree that the term devices is broad and has included the derivations of devices specified in the protocol, which includes bodily worn devices but not assistive devices apart from walking aids. The committee acknowledged that risks may be reduced by involvement of a professional with expertise in the area and reflected this in the committee discussion of evidence.

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				unusual to get blistering/pressure sores especially with off the shelf splints	
Keele University	Guideline	007	007	*What are they offering patients, how would it benefit patients? They are not rationalizing resources. 'Not routinely' needs to be explained – what are the exceptions to the routine? Quality of life needs to be considered more in the guidelines	Thank you for your comment. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.'
Keele University	Guideline	008	010	**1.4.2 – Pharmacological management** Any further guidance for the use of topical NSAIDs in patients with asthma? We would start with a robust, self-management, non-pharma approach.	Thank you for your comment. Guidance for use of topical NSAIDs for people with specific comorbidities such as asthma is not within the scope of this guideline.
Keele University	Guideline	009	009	Any further evidence for Platelet Rich Plasma injections for OA?	Thank you for your comment. Platelet Rich Plasma injections were not investigated in this guideline. For information on these please see IPG637.
Keele University	Guideline	009	011	**1.4.11 Intra-articular corticosteroid injections** The recently published hip injection trial (Clinical effectiveness of one ultrasound guided intra-articular	Thank you for your comment. Unfortunately, this study was published after the date of the final searches. Searches for all reviews were rerun in November 2021 to identify studies published between since each review's

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				corticosteroid and local anaesthetic injection in addition to advice and education for hip osteoarthritis (HIT trial): single blind, parallel group, three arm, randomised controlled trial | The BMJ) provides important clinical evidence that ultrasound guided corticosteroid and local anaesthetic injections are effective at improving pain and function over a 6 month period. This was the largest trial (n=199) undertaken to date in people with hip osteoarthritis. We therefore consider - That this joint agnostic statement is a potential barrier to equitable access to joint injections. The wording has not changed substantially from the previous guideline. There is currently a 'postcode' lottery relating to availability of hip injections, and in view of the findings from our recent trial, the study team and our patient advisory group strongly believe hip injections should be available as an option to all. - that text relating to 'short term relief' should be qualified. 'Short term' could be interpreted very variably	initial search . In this case we have assessed the study and identified that this would be unlikely to change the recommendation. Therefore, we have not included the study in this version of the guideline. We will notify the NICE surveillance team so they can consider it for inclusion in future updates of the guideline review question. The committee acknowledge that there are challenges in accessing joint injections. This guideline does not provide recommendations on service utilisation but recommends that corticosteroid injections should be considered for people with osteoarthritis when other treatments are ineffective or unsuitable. As with all pharmacological interventions recommended in this guideline, these should be used alongside non-pharmacological management and with therapeutic exercise, and at the lowest effective dose for the shortest time possible. The committee based this on the potential harm that repeated corticosteroid injections may lead to joint degeneration. Short term relief is clarified in the evidence report for this review and is for up to 3 months as the outcomes for pain at less than and equal to 3 months consistently showed improvements for hip and knee osteoarthritis at this time period. Based on the studies we have added between 2 and 10 weeks recommendation and rationale to provide further clarity.
Keele University	Guideline	010	003	**1.5.1 Consider patient-initiated follow-up for most people with osteoarthritis**	Thank you for your comment. The expectation is that patient initiated follow up would continue until it is not appropriate, and the person needs planned follow up. The

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				Is there any length of time for appropriate patient-initiated follow up? It recommends patient-initiated follow-up for most people with osteoarthritis – when would patient-initiated follow up be inappropriate?	recommendation to consider planned follow up defines the likely scenarios when planned follow up would be more appropriate but it is not always the case that patient initiated follow up is inappropriate in these circumstances.
Keele University	Guideline	010	003	*Patients considered the patient initiated follow-ups to be risky – putting the responsibility on the patients to follow up is challenging, potentially time consuming and costly for clinicians and the NHS with repeat appointments for people who are worried. Could be a challenging arena where the needy expect more, or on the other hand, a lot of older people will not go back even if they are in agony, for fear of wasting the clinician's time or being a 'nuisance'. Why don't all patients have a planned follow-up? Ongoing support is important	Thank you for your comment. The committee agreed that for most people patient initiated follow up would be appropriate. This is because they may be able to self-manage their condition effectively after getting information and guidance on treatment strategies. There was not the evidence to suggest planned follow up was required for all people with osteoarthritis. It would be quite costly to the clinicians and NHS to follow up everyone it is not needed, and these recommendations are largely in line with current practice. For planned follow-up, as well as it being considered for people with osteoarthritis when their individual needs and preferences suggest that this is necessary, the committee also highlighted that people with multiple long-term conditions are likely to benefit from a tailored approach in line with NICE's guideline on multimorbidity (https://www.nice.org.uk/guidance/ng56) . This provides more detailed follow up recommendations.
Keele University	Guideline	011	002	**1.6.1 Referral for joint replacement** *Very contradictory e.g. quality of life, mention over 45 years of age so not inclusive. Many people also	Thank you for your comment. The recommendation applies to anyone with osteoarthritis who meet the criteria in recommendation 1.6.1. The criteria are those that the committee agreed were most likely to indicate a need for joint replacement.

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				diagnosed under age 45. What help do they get? Lack of practicality and pragmatism.	Should someone under the age of 45 have been diagnosed with osteoarthritis then and they meet the criteria then it is anticipated they would also be referred.
Keele University	Guideline	011	002	Too specific to hip/knee/shoulder – may refer on for other joints, and in the hand, procedures not always involving joint replacement	Thank you for your comment. The scope only included referral for joint replacement and not referral other types of surgery. Therefore, recommendations have not been made in the other areas. The review protocol was limited to the most common types of joint replacement, hip, knee and shoulder as other types of joint replacement are less common and their effectiveness as interventions is less clear. They are also not widely available on the NHS.
Keele University	Guideline	011	017	Do current BMI restrictions for joint replacement motivate patients to try to lose weight? Is there any evidence which establishes any long term effects of BMI/overweight/obesity on life of the prosthesis?	Thank you for your comment. We did not look for evidence to note whether the current BMI restrictions motivate people to lose weight. We only looked for evidence for the impact of BMI on revisions or reoperations rather than the longevity of the prosthesis. Reoperation rates for knee replacement were higher in all groups when compared to people of a healthy weight at 11 years. They were also generally higher for hip replacement in all weight categories when compared to the healthy weight group at 3 years.

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Keele University	Guideline	012	001	https://www.nice.org.uk/guidance/ta477 Can the guideline comment on the use of arthroscopy for Autologous Cartilage Implantation?	Thank you for your comment. This technology appraisal does not relate to people with osteoarthritis and therefore it has not been included.
Keele University	Guideline	012	002	Is there a caveat for patients with locking joints secondary to OA/degenerative meniscal lesions?	Thank you for your comment. The committee agreed that presence of true locking joints would be due to a condition other than osteoarthritis. As this guideline discusses people with osteoarthritis (rather than people with degenerative meniscal lesions), they agreed that this was not relevant to this recommendation. Arthroscopic procedures may be relevant for other conditions.
Keele University	Guideline	012	006	Should locking joint be included here as an atypical feature?	Thank you for your comment. The committee did not include this as an additional atypical feature as they considered this would be a part of the wider feature of trauma, which was included in the features. This list is not exhaustive and healthcare professionals are advised to use their clinical judgement to support their decision making.
Keele University	Guideline	012	012	'Psychological wellbeing' – this is the only time we can see this mentioned – does it need to be more specific in detailing the two-way nature e.g. in education about how BPS factors can impact symptoms?	Thank you for your comment. The committee think 'psychological wellbeing' would be understood and fits well with the definition.
Keele University	Recommendations for research	014	007	Should we have a separate section which addresses seldom heard communities, or ensure recommended research is inclusive for all?	Thank you for your comment. The committee did not identify specific needs for vulnerable groups. They did make a research recommendation to investigate the information needs of different ethnic and socioeconomic groups and those with learning disabilities, issues with

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					health literacy and severe mental illness. The committee believe these groups to be the key ones in which to focus research to establish their needs.
Keele University	Recommendations for research	017	001	Should PRP injections also be further researched or evidence included in this guideline?	Thank you for your comment. Plasma rich injections were not included as part of the review and therefore we have not made a research recommendation in this area.
Keele University	Recommendations for research	017	006	Have patients been asked what were the most important factors for them to decide to seek help for a joint replacement?	Thank you for your comment. All research recommendations are based on their original review question protocol contents. These are chosen by the committee which includes lay members at the beginning of the guideline development using their experience and expertise. Furthermore, stakeholders can comment on the suggestions for the research recommendations.
National Council for Osteopathic Research	Evidence Review E	038	049 – 051	What are "allied professionals"? This is confusing in relation to the term Allied Health Professionals which includes osteopaths but not chiropractors (https://www.england.nhs.uk/ahp/role/). It would be better just to say "Manual therapy would be delivered by healthcare professionals including physiotherapists, chiropractors and osteopaths".	Thank you for your comment. This has now been changed to what you have suggested ("Manual therapy would be delivered by healthcare professionals including physiotherapists, chiropractors and osteopaths") in the report.
National Council for Osteopathic Research	Guideline	003	003 — 007	These criteria are easy to use in practice and easy for patients to refer to. One may wonder how specific they are, and how much the risk of false positive is when using them. A patient with tendinitis would meet these criteria, and under the current definition would be diagnosed with osteoarthritis (OA). An alternative system could be, e.g. based on European League Against Rheumatism (EULAR)'s recommendations for knee OA diagnosis (Zhang et al. 2010), to add to the	Thank you for your comment. We acknowledge that the criteria may overlap with other conditions. The points given are guidance for people where osteoarthritis can be diagnosed without imaging to investigate other potential causes of symptoms and is not a comprehensive set of diagnostic criteria. Healthcare professionals will be expected to use this alongside history taking and examination findings to help determine the likelihood of differential diagnoses, and if another diagnosis is more

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				proposed list of criteria (please note only the first listed criterion below is based on EULAR): • one or more typical examination findings (e.g. crepitus, restricted movement, swelling or bony enlargement) • have no other diagnoses that could fully explain their symptoms. Zhang, W., Doherty, M., Peat, G., Bierma-Zeinstra, M.A., Arden, N.K., Bresnihan, B., Herrero-Beaumont, G., Kirschner, S., Leeb, B.F., Lohmander, L.S. and Mazières, B., 2010. EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. *Annals of the rheumatic diseases*, *69*(3), pp.483-489.	likely then healthcare professionals would be expected to consider this. The committee were aware of a comparison of the different diagnostic criteria conducted in a study by Skou, et al. In this study it indicated that, in a group of 13,459 people with knee symptoms or functional limitations associated with osteoarthritis, that the NICE criteria identified 89.2% of people as having osteoarthritis, while the EULAR criteria identified 47.6% of people and the ACR criteria identified 51.6% of people. Therefore, the criteria used in the previous version of the NICE guideline and again in this version, will likely detect more people who have osteoarthritis as having osteoarthritis. As far as we are aware, no studies have compared the diagnostic accuracy of these criteria to each other and so it is not possible to comment on the sensitivity and specificity of the criteria. Given the limited evidence available and their expert opinion, the committee agreed to maintain the current recommendation. Reference: Skou ST, Koes BW, Grønne DT, Young J, Roos EM. Comparison of three sets of clinical classification criteria for knee osteoarthritis: a cross-sectional study of 13,459 patients treated in primary care. Osteoarthritis Cartilage. 2020 Feb;28(2):167-172.
National Council for Osteopathic Research	Guideline	011	008 - 010	It would be preferable to say that clinical assessment should be combined with the use of a Patient Reported Outcome Measure". This allows the patient to express their view on their condition, and provides a level of	Thank you for your comment. We looked but did not find evidence to support the use of patient reported outcome measures to help decide whether to refer someone for a joint replacement. Therefore, the committee

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				monitoring to evaluate the progression of symptoms in a way that clinical assessment alone cannot deliver.	recommended that the clinical assessment should be used instead.
National Council for Osteopathic Research	Guideline	012	014 – 017	It is unclear why electrotherapy and acupuncture are included in this list when they are not recommended in the OA guideline – shouldn't treatment packagea align with the guidance recommended content?	Thank you for your comment. The definition of treatment packages has been amended to remove acupuncture and electrotherapy.
National Council for Osteopathic Research	Guideline	013	001 – 006	It would be preferable to include patient education in a less formalised manner also. Any manual therapy clinician (osteopath, physiotherapist or chiropractor) provides education to patients with OA as part of their package of care to enhance self-management. This is distinct from "an education programme" as you have described.	Thank you for your comment. This is meant to mean a more formal manner of education. The anticipation is that this would be on top of the patient information given to people with osteoarthritis when they first present.
NHS County Durham CCG	Guideline	General	General	The patient representative felt that the document was written "back to front". They felt that it needs an introduction of the condition and its impact on people's lives as well as explanations to concepts.	Thank you for your comment. The document is produced in a standard style used for all NICE guidelines. NICE guidelines are primarily aimed at health care professionals but written in a way that lay members can understand where possible. It is not intended to be a patient information leaflet. Other patient organisations are good at producing these and NICE does not seek to duplicate their work. A select few of these organisation's websites will be linked to from NICE's osteoarthritis guideline web page.
NHS County Durham CCG	Guideline	General	General	The patient representative felt that there was too much emphasis on treatments being cost effective and the guideline aiming to be cost saving, rather than being patient-focused.	Thank you for your comment. A key part of NICE guidelines is that they assess the cost effectiveness of an intervention, service or programme in order to help decision-makers ensure that maximum gain is achieved from limited resources. If resources are used for interventions or services that are not cost effective, the population as a whole gains fewer benefits.

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NHS County Durham CCG	Guideline	General	General	The patient representative felt that more information was needed on the management of flare-ups.	Thank you for your comment. Flares were considered in each review question included in the guideline. Unfortunately, there was limited evidence available to investigate the effect of treatments on managing flares and therefore the committee were not able to make specific recommendations on the management of flares. All the research recommendations include flares as an outcome in the hope that new evidence may help provide further information.
NHS County Durham CCG	Guideline	003	004	The patient representative requested clarification of the age of 45 which appeared arbitrary and above which it seems to be generally accepted that patients will suffer from osteoarthritis and that they therefore do not require further investigation.	Thank you for your comment. The criteria provided are for when osteoarthritis can be diagnosed clinically without further investigations. The committee agree that osteoarthritis can be diagnosed below this age. However, a healthcare professional may want to do more investigations before diagnosing in case there is another cause that may explain the symptoms. Other evidence (referenced below) indicates that osteoarthritis is more common above the age of 45 years, and less common below this age and therefore this value was used. The committee acknowledge that each person should be treated as an individual and this guidance may not be relevant to everyone. Healthcare professionals should use this information as guidance rather than absolute rules and if there are atypical features present then further investigation may be required. References: Spitaels D, Mamouris P, Vaes B, Smeets M, Luyten F, Hermens R, Vankrunkelsven P. Epidemiology of knee

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					osteoarthritis in general practice: a registry-based study. BMJ Open. 2020 Jan 20;10(1):e031734. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med. 2010 Aug;26(3):355-69.
NHS County Durham CCG	Guideline	010	General	Because the patient representative felt that pain and its significant social impact often goes unrecognised, they requested a clearer patient support system and a framework of holistic patient reviews.	Thank you for your comment. There was not the evidence to go into more detail in these recommendations. More detailed recommendations are in the NICE guidelines on Patient experience in adult NHS services (https://www.nice.org.uk/guidance/cg138), Shared decision making (https://www.nice.org.uk/guidance/ng197/) and the NICE guideline on Multimorbidity (https://www.nice.org.uk/guidance/ng56/) all of which are linked to from this guideline.
NHSEI	Guideline	003	003	1.1.1 Diagnose clinically without investigations – this will be problematic in primary care owing to a perception that patients "need" a radiograph of the affected joint. Without a clear public education campaign this has the potential to cause either challenging consultations or repeat consultations. Also potential to miss sinister pathology – Pancoast's tumour may be missed if radiographs are not used to exclude apical lung tumour – this is not explicitly included in red flags in the guidance.	Thank you for your comment. The definition for atypical features has been adapted to include 'concerns that may suggest infection or malignancy', to help highlight the potential for other causes of pain that may be considered if atypical features are present. We agree that this can be a challenging area. This recommendation is consistent with the 2014 version of this guideline, and so should not be a change in practice if the previous version of the guideline's recommendations were followed
NHSEI	Guideline	008	027	1.4.6 – Do not routinely offer paracetamol. This will require significant patient education through awareness raising as there is high expectation for the doctor to prescribe something.	Thank you for your comment. The committee agreed that this will require additional education and awareness and have recommended that it is explained to people with osteoarthritis that there is no strong evidence of benefit for paracetamol.

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					The recommendation has updated to 'Do not routinely offer paracetamol or weak opioids unless: • they are only used infrequently for short-term pain relief and not as part of an ongoing pain management plan • all other pharmacological treatments are contraindicated, not tolerated or ineffective.' Explain to people with osteoarthritis that there is no strong evidence of benefit for paracetamol.'
NHSEI	Guideline	009	003	1.4.7 – Do not offer strong opioids to patients with osteoarthritic – Again this may produce challenging consultations – in the absence of a good education campaign patients may request repeat consultations around this. Also where services are stretched the offer of alternatives (exercise therapy, corticosteroid injections) may not be available and this may cause inequity – areas with most need not able to provide care – this may then cause increase demand on primary care and urgent treatment centres.	Thank you for your comment. The committee agree that this is a challenge and will require additional information. The committee acknowledge the problems with services but believe that they should not recommend treatments that are potentially harmful for use and that this will potentiate inequity as people who cannot access other treatments will use harmful treatments instead. The committee were also aware of the MHRA safety warning on opioids and recommendations in NICE's guideline on medicines associated with dependence or withdrawal symptoms, which advises against the use of modified-release opioids. Therefore, the committee recommended against the use of strong opioids.
North West London CCG	Guideline & Evidence Review D	004	009	Recommendations 1.2.2 and 1.3.5 I appreciate the committee's aspirational intentions regarding the inclusion of weight loss in patient education and management for osteoarthritis. Weight	Thank you for your comment. The committee agreed that it would be useful to be able to know a goal for how much weight loss should be aimed for to provide differences in symptoms. They appreciated the complexities of weight management and that no one management strategy will

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				loss certainly stands to achieve many other pleiotropic benefits for patients beyond their osteoarthritis. However, having reviewed Evidence Review D, it appears such recommendations are veering away from NICE's standard on evidence-based interventions. Observational data very clearly links increased BMI as a risk factor for lower limb osteoarthritis. It is, however, much more unclear in the literature how effective treating this risk factor is in managing the symptoms of osteoarthritis. Regarding the improvement in knee pain/function following weight loss, it is also not clear in the literature whether this is directly due to biomechanics of weight loss, or the associated increased physical activity. Indeed, looking at randomised controlled trials rather than observational data, a combination of diet and exercise appears to potentially achieve a moderate effect size, but diet-only interventions do not seem to achieve improvements in pain (Hall 2019: https://pubmed.ncbi.nlm.nih.gov/30072112/). There also appears to be a lack of recognition around the complexity of weight-loss interventions. Studies show people who try to lose weight themselves, achieve around 2.5% in the short-term. Diet-induced weight loss programmes can achieve on average an additional 5% (up to a total average of just under 8% weight loss) in the short-term only. Contrasting with surgical weight loss which typically	work for every person, and that there is a person-specific nature to supporting people to lose weight if that is considered appropriate by them. When setting the protocol the committee were aware that NICE guidance already existed for weight loss interventions and this could be cross referred to in the osteoarthritis guideline. With that in mind their approach was to identify evidence that would help provide an incentive for people who need to lose weight. It is meant to supplement other guidelines in which weight loss interventions are already recommended and avoid duplication. Therefore, they agreed that a prognostic review investigating the amount of weight loss required to lead to clinically important changes in symptoms was important. To achieve this, they agreed that observational trial data was required. Randomised controlled trials, including the ones referenced in the Chu 2018 and Hall 2019 systematic reviews, investigate the effect of different interventions on weight loss. Therefore, for the nature of this review, this will introduce confounding where it would be less possible to distinguish between the effects of the intervention (that may have effects beyond weight loss) and the weight loss itself. Due to this, unless the trial could stratify participants by the amount of weight loss including people in both study arms in each group, which may still be affected by this confounding but to a lesser extent, then this data would likely be of insufficient quality to answer this question satisfactorily. Instead, observational data, where all participants received the same intervention and were stratified by the amount of

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				achieves 15-25% (where most people do experience some benefit in knee pain; again, unclear mechanisms). Looking at the highest quality RCTs of weight-loss interventions, meta-analysis (Chu 2018: https://pubmed.ncbi.nlm.nih.gov/30051952/) shows the effect size is small, around 0.33, which translates to around 5 points on a 100-point scale; whereas the minimum clinically important difference (MCID), *broadly speaking*, is typically around 10-points on a 100 point scale for MSK conditions. The study quoted in the committee's evidence review (Riddle 2013) suggests at least 10% weight loss is necessary for a ***statistical*** between-group difference to be demonstrated but that this is not the same as achieving an identifiable minimum important clinical difference for individual patients (for this paper, in WOMAC scores). The average WOMAC change in those achieving at least 10% weight loss was only around half of the change required to achieve an MCID. The committee's comments in 1.1.12.3 of Evidence Review D that *"losing any weight was likely to provide benefits for people with osteoarthritis who are overweight or obese"* does not appear to be a robust translation of the available evidence on the individual benefit on OA for patients. The included Atukorala study identifies between 7.7-10% of weight loss needs to be achieved to reach an MCID in function (note also the limitations around identifying MCIDs and also that an MCID may not equal a	weight loss, was seen as the more ideal study design to answer this question. The committee acknowledge the risk of bias in the studies included in this review and considered this when making recommendations. It is acknowledged that statistical significance and clinical importance are not necessarily the same. In this review, the committee used an MID of 0.5 SD using a standardised mean difference to examine the evidence. They acknowledged that smaller benefits were seen for less weight loss, but acknowledged that a clinically important benefit in physical function would have been seen for people with >10% weight loss compared to people who lost <5% of their baseline weight. They also acknowledged that a trend in benefits were seen with greater weight loss, with the results of both studies showing that benefits were of a higher magnitude as greater weight loss took place. The committee took these factors into account when making their recommendations. The recommendations are to provide advice and information that would hopefully be of benefit to people with osteoarthritis who need to lose weight. Based on the evidence available, the committee agreed that this recommendation was an appropriate interpretation. The committee acknowledge that the evidence was limited to people with knee osteoarthritis. However, in their expert consensus, they agreed that the evidence could be applied for people with osteoarthritis affecting other joints due to the potential mechanisms of actions that could

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				patient's designed change, which may well be much higher). It wasn't entirely transparent in Evidence Review D why only the two cohort studies were included in the review and the seven available RCTs (covered by Chu's 2018 review) were all excluded. As noted by the committee in Evidence Review D, the two included prospective cohort studies are at high risk of bias for several reasons and so it is surprising to see such strong recommendations based upon the methodological quality of these two studies alone. It should be important to be transparent with patients that the benefits reported in both the Atukorala 2016 study and the Riddle 2013 largely focus on improvements in function (more so than pain, where the proportion achieving and MCID are limited). We should be clear on this as many patients will be consulting to seek support around pain (varying between patients and their individual goals). Many of the positive studies included in the evidence review and these comments are in populations for ***knee*** osteoarthritis; whereas this draft guideline is for all osteoarthritis presentations; such findings cannot be generalisable to this wider population and it has not been made transparent in the draft guideline that this limited data only applies to patients with knee OA. It would be inappropriate to suggest that such benefits can be seen across the entire range of osteoarthritis	have benefits in reducing pain and function (including systemic and local inflammatory activity).

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				joints which are managed in clinical practice. For example, evidence shows at least 7.5% of weight loss may have a benefit in reducing total knee replacement incidence, with no effect on hip replacement incidence (Jin 2021 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8310800/). Whilst there may be more drugs being licensed for weight loss in the near future, at present, we do not have routine access to interventions to enable patients to readily achieve the required weight loss levels to potentially realise the clinically important benefits (which only some patients may experience from such weight loss). Furthermore, whilst it would be entirely appropriate to support patient in their own goals for weight loss, it seems antithetical to a patient-centred approach of care, for clinicians to set specific weight loss targets, particularly when the evidence base behind them is limited. The ideal weight target for the patient should be an individual patient-centred decision based on their individual values. There should be caution in parentally setting doctor-centred goals when evidence shows that the overwhelming majority of patients will fail to achieve such targets, certainly in the long-term (this would not be aligned to the basic principles of 'SMART', achievable goal setting).	

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				There is a potential resource implication with regards to this recommendation in the time spent for clinicians to attempt a challenging behaviour change intervention. There can also be an opportunity cost in the time spent by clinicians in discussing weight loss, which could be purposed to more thoroughly provide information on other treatment options (eg exercise, oral medications, injections or surgery) in order for patients to make shared decision making in these areas. It may also have implications for commissioning intentions around weight loss programmes (which themselves have undergone considerable scrutiny and decommissioning in recent years due to inadequate supporting evidence). Within Evidence Review D, the committee comments around a lack of resource impact in section 1.1.12.4 appear to lack any supporting data. This draft guideline potentially fails to recognise the complexity of weight management in practice, as well as the complexity of weight management strategies (clinician level vs public health policy level). Whilst weight loss is clearly an aspirational goal, the strength of recommendation behind this intervention appears incongruous with the available evidence. **In view of the limited, as well as, high-risk-of-bias evidence supporting routine weight loss interventions in achieving a *clinically significant* benefit for individual patients in lower limb arthritis (let alone, levels of pain/function improvement which align to patient expectations), the inability in**	

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				clinical practice to routinely achieve the weight loss required to realise this for most patients, as well as the lack of generalisability of the evidence beyond knee joints, I would suggest that the wording needs to be revised for such a key guideline document. This would be important in order maintain transparency in the advice we provide patients to enable them to make informed decisions, as well for informing local commissioning policies.	
Ossur UK	Guideline	General	General	Recent data presented at the British Association for Surgery of the Knee annual meeting showed a high percentage of patients on the waiting list for a knee replacement are presenting to A&E with GI bleeds resulting from extended use of NSAIDs, or with fractures due to decreased stability. These patients deserve a wider range of options to help them during this waiting period. Indeed a 2016 observational study of NHS patients by Lee et al* suggests that 25% of waiting list patients treated with a brace may avoid the operation all together. * Lee, P. et al, "Unloading Knee Brace Is a Cost-Effective Method to Bridge and Delay Surgery in Unicompartmental Knee Arthritis." BMJ Open Sport & Exercise Medicine 2, no. 1 (February 1, 2017): e000195. https://doi.org/10.1136/bmjsem-2016-000195.	Thank you for your comment. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.' The cost effectiveness study you cite was rated as partially applicable with very serious limitations. Analysis uses non-comparative prospective cohort data for intervention treatment effects, and separate trial for control group. The populations in the two studies are very different and therefore not considered suitable for use in

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					this way. For this reason it was excluded from the health economic review.
Ossur UK	Guideline	025	017	There appears to be an undue emphasis on the adverse events associated with bracing. By far the most common adverse event due to bracing is skin irritation. In many patients this can be avoided with correct usage instructions. If it occurs, it can be treated with brace adjustments and undersleeves enabling brace use to continue. In comparison to the life-threatening adverse effects associated with commonly prescribed medications these are negligible. Given the high incidence of comorbidities among the OA population it is important to have options that have no adverse effects on the cardiovascular, gastric and renal systems. A brace is one such option which, if ineffective, does not close doors to other options.	Thank you for your comment. The committee weighed up the quality of the evidence, inconsistency in efficacy evidence and potential safety concerns when making their recommendations. The committee acknowledge the limitations in the evidence available, which makes it difficult to conclude on the safety of devices. Further research with larger, well conducted trials would provide more information regarding this. The committee have recommended that a range of pharmacological treatments should not be used regularly and where they are to be used for a shortest-time possible at the lowest effective dose. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.'
Primary Care Rheumatology & Musculoskel	Guideline	General	General	We felt that the guideline didn't hold any surprises for us. I think that primary care might find the limitation on pain relief prescribing quite hard and hope that commissioners will be encouraged to support us by	Thank you for your comment. The definition of treatment packages has been amended to remove acupuncture and electrotherapy.

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etal Medicine Society				ensuring that we have supervised exercise and adequate access to joint replacements as referrals may increase. One area that we thought was contradictory was that acupuncture and electrotherapy is not recommended but that they're both included in a reference to a treatment package on page 12/34.	
Royal College of General Practitioners	Guideline	General	General	This appears to be sensible and appropriate advice for management of primary care. There were no alarming comments / recommendations linked to management for clinicians involved. The key research recommendations would be valuable contributions to management. We would like to see increased resource to inform the general population and clinicians of the recommendations – and help to manage traditional expectations from patients and many clinicians involved in musculoskeletal care.	Thank you for your comment and support for the guideline. The guideline will be circulated to all stakeholders when it is published.
Royal College of Nursing	Guideline	011	011 - 017	1.6.3 Refreshing to see as practice is different concerning referral to joint replacement	Thank you for your comment.
Royal College of Physicians	General	General	General	The RCP is grateful for the opportunity to respond to the above consultation. We would like to endorse the response submitted by the British Society for Rheumatology (BSR)	Thank you for your comment.
Royal College of Physicians	Guideline	General	General	The Royal College of Physicians and Surgeons of Glasgow although based in Glasgow represents Fellows and Members throughout the UK. While NICE	Thank you for your support.

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and Surgeons of Glasgow				has a remit for England (where 50% of our UK membership is based), many of the recommendations are applicable to all devolved nations including Scotland. They should be considered by the relevant Ministers of the devolved governments. The College welcomes this update on guidance on osteoarthritis, assessment and management and generally supports the document.	
Royal College of Physicians and Surgeons of Glasgow	Guideline	003	007	While morning stiffness of 30 minutes is often quoted as the discriminator between inflammatory arthritis and osteoarthritis, we are unsure of the evidence base for this. Is there data to support this?	Thank you for your comment. This is based on evidence for inflammatory arthritis rather than osteoarthritis. The reference provided below provides evidence as to why morning stiffness beyond 30 minutes was associated with the presence of rheumatoid arthritis. Therefore, the criteria states that osteoarthritis can be diagnosed clinically when, among other factors, morning stiffness is not present beyond 30 minutes. If this is present beyond this time period then a healthcare professional may wish to use other investigations before diagnosing osteoarthritis. Reference: van Nies JA, Alves C, Radix-Bloemen AL, Gaujoux-Viala C, Huizinga TW, Hazes JM, Brouwer E, Fautrel B, van der Helm-van Mil AH. Reappraisal of the diagnostic and prognostic value of morning stiffness in arthralgia and early arthritis: results from the Groningen EARC, Leiden EARC, ESPOIR, Leiden EAC and REACH. Arthritis Res Ther. 2015 Apr 23;17(1):108.
Royal College of	Guideline	003	008	While we are in general agreement that patients should not be routinely imaged, there are indications	Thank you for your comment. The committee agreed they could not produce a definitive list for atypical features.

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Physicians and Surgeons of Glasgow				(in addition to those in the section on atypical features) which would require imaging early. This includes the severity of symptoms and features in the history which would warrant immediate surgical assessment. While this is stated later, it is unclear and needs also to be stated here.	Therefore, they stated in the definition what it could include, and listed the main points. Clinicians would be expected to assess and make a judgement on whether an individual's symptom or feature is atypical or not. Severity of symptoms is included in the definition. This guideline is not about the surgical assessment of individuals. While we didn't cover referral for surgery other than joint replacement the committee would expect clinicians to refer individuals to surgeons if they suspect they need a surgical assessment.
Royal College of Physicians and Surgeons of Glasgow	Guideline	003	010	We note that early osteoarthritis may have normal radiographs. Indeed, Heberden's nodes are clinically apparent before there is radiological change (Kellgren and Lawrence).	Thank you for your comment. The committee agree that imaging findings may not correlate with symptoms experienced by the person with osteoarthritis which is why they recommend against routine imaging for the diagnosis of osteoarthritis.
Royal College of Physicians and Surgeons of Glasgow	Guideline	5	013	The obesity section is reasonably, and we concur with the advice to lose weight. Many of these programmes occur and should occur in primary care. The text could signpost this.	Thank you for your comment. The aim of these recommendations to provide an incentive to people with osteoarthritis to lose weight if they are overweight or have obesity. Therefore, we have not mentioned specific weight management programmes other than to cross refer to the NICE guidance referred to on NICE's web page on obesity (https://www.nice.org.uk/guidance/conditions-and-diseases/diabetes-and-other-endocrinal--nutritional-and-metabolic-conditions/obesity).
Royal College of Physicians and	Guideline	008	001	We agree that paracetamol alone is generally ineffective although may be of benefit as an addition to a NSAID. There is no evidence also that Chondroitin Sulphate is effective which should be stated.	Thank you for your comment. The committee agreed that combinations of therapies would not be investigated in this review as they wanted to understand the standalone effects of the medication to assess their benefit.

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Surgeons of Glasgow					Chondroitin sulphate was not included in the scope for this guideline update and so we cannot comment on the efficacy of this.
Royal College of Physicians and Surgeons of Glasgow	Guideline	008	011	One of our reviewers recommended that a minimum duration should be described for the use of topical NSAIDs. Almost all patients do not use topical NSAIDs for long enough to provide benefit.	Thank you for your comment. We didn't find evidence to indicate a minimum length of time they should be used for. In addition, as medications should be used for the shortest time period possible (as per recommendation 1.4.1) the committee did not agree that specifying a time period would be appropriate. The committee agree that healthcare professionals should ensure that medication has been trialled appropriately (ensuring technique used is effective and that treatments have been trialled for a sufficient length of time) before deciding that they are ineffective.
Royal College of Physicians and Surgeons of Glasgow	Guideline	009	11	Short term relief of pain can be helpful in maintaining mobility. This should not be underestimated. There is often a bias in reporting studies on the use of intra-articular steroids to long term effect only.	Thank you for your comment. The committee agreed that short term relief of pain can be helpful and therefore recommended that corticosteroids should be considered for people with osteoarthritis where other treatment are unsuitable or ineffective.
Royal College of Physicians and Surgeons of Glasgow	Guideline	010	014	While this is reasonable advice, many commissioners of services put patients in care management systems which does not allow this or only allow access to individuals eg Musculo skeletal services which do not have access to prescription. Some systems push patients through a pipeline where there are delays (for instance they have no access to a surgeon when surgery was indicated in the first place). A full assessment of these systems needs to be made by the	Thank you for your comment. The guideline has not looked at service delivery and makes recommendations for the best approach to care however it is delivered. The committee hope that commissioners would look at the guideline and implement care management systems that facilitate these recommendations.

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				commissioners particularly looking those blocked from receiving a service or having unnecessary delays.	
Royal College of Physicians and Surgeons of Glasgow	Guideline	011	001	Some systems have a built-in delay for referring patients for joint replacement surgery. Outcome is better if referral is early. If surgery is indicated (for instance by the Oxford knee score) referral should not be delayed. Obesity is an important consideration. Assessment needs care. Patients with a significant fixed flexion deformity of the hip or knee (as one would see in severe disease) or age-related Kyphosis may have a falsely low height giving a falsely high BMI. However, the need for joint replacement must also be balanced by the higher risk of post operative complications in those who are obese or morbidly obese. Many surgeons would not do or are barred by their commissioners from doing a TKR with a BMI of around 35 or over (not-withstanding the comment above). Sharif B, Smith C, Marshall D, Osteoarthritis and cartilage, 2017, 25, S348- | added to CENTRAL: 30 April 2018 | 2018 Issue 4	Thank you for your comment. The committee acknowledge the complexity with referral of people for joint replacement surgery. They agree that BMI may not be the correct assessment for all people and acknowledge this in the committee discussion of evidence in the evidence report for this review. They also recommend that people should not be excluded from referral for joint replacement because of overweight or obesity. The committee acknowledge that the evidence showed that higher risks of post operative complications were generally seen for people who were at the extremities of high and low weight, but not for lesser degrees (for example: people with obesity III had worse adverse events than people with obesity I and II). However, while these risks may be present the benefits are also present for all groups and, from the evidence, may be larger for people at the extremes of weight than other groups. Sharif et al looks at the outcome for those who have had a joint replacement, it does not compare this with the outcomes for those who did not have a joint replacement. This type of comparison would be better placed to demonstrate whether those who have obesity have a better quality of life with or without joint replacement. The committee agreed that the benefits and risks should be discussed with the person with osteoarthritis, and that

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					weight should not be a barrier for referral for surgical opinion.
Royal College of Physicians and Surgeons of Glasgow	Guideline	013	014	Key to the management of osteoarthritis is how patients move though care programmes. For example, those who need early surgical assessment should be able to access it without costly "hoops" to go through. Those who need review should be able to access this. Many programmes do not allow for this and push patients back to initial referral.	Thank you for your comment. We have made recommendations related to who should be referred for joint replacement and that their access should not be restricted because of age, sex or gender, smoking, comorbidities or overweight or obesity. The committee agree that those who need a review should be able to access it and hope these will mean it Is easier for this to happen.
Thuasne	Guideline	General	General	These draft NICE guidelines are removing options of conservative management for those patients who would choose a non-pharmacological route or that are not suitable for surgery. For patients that present with biomechanical knee pain or instability bracing should be a offered bracing as a management consideration.	Thank you for your comment. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.'
Thuasne	Guideline	007	007	The category of bracing and the associated evidence is too broad. Unloading/offloading bracing is widely used across secondary care in the NHS and has been for over 10 years.	Thank you for your comment. The committee acknowledged the variety of different devices used by people with osteoarthritis and considered the types used in each trial included in the analysis. The majority of outcomes were of very low quality. They agreed that the evidence for all trials was insufficient to indicate consistent evidence of benefit and agreed that larger, well designed and conducted trials would be required to

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					provide more certainty in the outcomes. The committee were aware of an ongoing randomised controlled trial on the uses of braces in knee osteoarthritis (https://www.keele.ac.uk/propoa/) and therefore they did not make a research recommendation in this area. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.'
Thuasne	Guideline	007	General	The old guidelines allowed for clinical choice. Patients with biomechanical joint pain could be assessed for suitability.	Thank you for your comment. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and

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					• the addition of an aid or device is likely to improve movement and function.'
Thuasne	Guideline	025	016 - 018	Properly applied offloading bracing for the right patient would not cause blistering and pressure damage. The evidence is deemed not strong enough to support bracing but strong enough to imply that blistering and discomfort can be caused and that this would not be the case when a patient is supported by someone who has appropriate training.	Thank you for your comment. The committee agree that correct application of bracing may help to reduce the risk of adverse events. However, they also agreed that they would expect trials to be conducted with people who were sufficiently trained to apply braces. Despite this likelihood the evidence from this review still showed a harm from adverse events albeit very low quality data. The committee took into account the quality of the evidence, inconsistency in efficacy evidence and potential safety concerns when making their recommendations. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.'
Thuasne	Guideline	025	027	We would challenge the assertion that the use of devices is inconsistent. Has any survey been undertaken with orthotists and orthopaedic consultants?	Thank you for your comment. This has been updated to 'varied'. It is based on the expert opinion of the committee members rather than on survey information.

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Thuasne	Guideline	025	General	The absence of high quality evidence should not outweigh the experience of patients and clinicians over decades of successful use.	Thank you for your comment. Based on the absence of evidence of effectiveness while acknowledging that some people may benefit from devices, the recommendation has been updated to: 'Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis unless: • there is joint instability or abnormal biomechanical loading, and • therapeutic exercise is ineffective or unsuitable without the addition of an aid or device, and • the addition of an aid or device is likely to improve movement and function.'
Total Diet and Meal Replacements Europe	Guideline	General	General	Total Diet & Meal Replacements (TDMR) Europe is the European trade body for manufacturers and distributors of total diet replacements (TDRs) and meal replacements (MRPs), which provide weight loss and weight management programmes for the overweight and obese. TDRs, which include very low-calorie diets (VLCDs) and low calorie diets (LCDs), are specifically formulated programmes that are based around formula foods that replace the whole of the daily diet. These formula foods are nutritionally balanced with key vitamins, minerals, high quality protein, essential fats, and fibre, and are designed to replace conventional foods for a period to facilitate optimal weight loss. MRPs are products presented as a replacement for one or more meals of the daily diet. They are used	Thank you for your comment and support for our weight management recommendations. We have not covered weight loss interventions in this guideline because recommendations related to this and interventions to support this are found in other NICE guidance. We have cross referred to this from the weight management recommendations. Please see Diet, nutrition and obesity guidance at https://www.nice.org.uk/guidance/lifestyle-and-wellbeing/diet--nutrition-and-obesity

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				alongside conventional food, as part of an energy restricted diet, to facilitate and maintain weight loss. High quality clinical trials and feasibility studies in primary care and community settings (with health economic analyses of these) have demonstrated that such effective weight loss interventions are feasible, clinically effective and cost-effective. TDMR Europe welcomes the review of NICE's guidelines Osteoarthritis: care and management. We are particularly pleased to see that weight loss is recognised as a core treatment for the condition and that a 10% weight loss is encouraged to manage it. We however believe that the lack of specific advice on how to achieve this weight loss is a missed opportunity. Please see our comment below.	
Total Diet and Meal Replacements Europe	Guideline	General	General	TDMR Europe urges NICE to reconsider its decision not to include weight management advice within this guideline, and then to consider the evidence for inclusion of TDRs and MRPs in the weight management recommendations for the management of osteoarthritis. Failure to do so will result in unnecessary suffering among hundreds of thousands of older people with obesity and knee osteoarthritis in the United Kingdom.	Thank you for your comment. We have not covered weight loss interventions in this guideline because recommendations related to this and interventions to support this are found in other NICE guidance. We have cross referred to this from the weight management recommendations. Please see Diet, nutrition and obesity guidance at https://www.nice.org.uk/guidance/lifestyle-and-wellbeing/diet--nutrition-and-obesity

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Total Diet and Meal Replacements Europe	Guideline	005 - 006	015 - 020	In the guideline's section on weight loss, a recommendation is made again to give people advice on how weight loss will improve their quality of life, and explain that any amount of weight loss is likely to be beneficial, but losing 10% of their body weight is likely to be better than 5%. The guideline then refers to NICE's webpage on obesity, which includes links to NICE's different guidelines on obesity prevention, identification and management. It is important to note that these guidelines, and specifically *[CG189] Obesity: identification, assessment and management* were last updated in 2014, eight years ago, and a vast amount of research on weight management has been published since. The guideline is therefore currently outdated. TDMR Europe would like to point out that a number of studies have shown the effectiveness of TDRs in tackling overweight and obesity and osteoarthritis. The exclusion of specific weight loss advice, and particularly dietary advice, is a missed opportunity to consider this scientific evidence. • Over the past decade, the Copenhagen model for weight loss in the obese with knee osteoarthritis has been tested thoroughly. This model delivers a weight reduction with 8 weeks of TDR, 4 meals a day, in total 810	Thank you for your comment. Weight management interventions such as TDRs were not included within the scope of this guideline, We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date. The current obesity guideline 'Obesity: identification and classification of overweight and obesity (update)' has recently been updated. New evidence for management of obesity was not included in the current update of the obesity guideline, however may be in future updates.

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				kCal/day reinforced by group therapy lead by a dietitian. Ordinary food is reintroduced over 4-8 weeks, though with a strict diet of 1200 kCal/day [Riecke BF, Christensen R, Christensen P, Leeds AR, Boesen M, Lohmander LS, Astrup A, Bliddal H. Comparing two low-energy diets for the treatment of knee osteoarthritis symptoms in obese patients: a pragmatic randomized clinical trial. Osteoarthritis Cartilage. 2010 Jun;18(6):746-54. doi: 10.1016/j.joca.2010.02.012. Epub 2010 Feb 17. PMID: 20206314.]. • This RCT study showed that a 10% weight loss was possible in elderly people with obesity and knee osteoarthritis. No conventional diet study has ever shown that. • In a later follow-up study, a lasting weight loss maintenance was shown over up to 4 years [Christensen P, Henriksen M, Bartels EM, Leeds AR, Meinert Larsen T, Gudbergsen H, Riecke BF, Astrup A, Heitmann BL, Boesen M, Christensen R, Bliddal H. Long-term weight-loss maintenance in obese patients with knee osteoarthritis: a randomized trial. Am J Clin Nutr. 2017 Sep;106(3):755-763. doi: 10.3945/ajcn.117.158543. Epub 2017 Jul 26. PMID: 28747328.].	

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				• This RCT over three years showed that an average weight loss of 10kg could be maintained for 3 years. No concentional diet study has ever shown this. • In a substudy of the Copenhagen CAROT/LIGHT study, a total of 175 patients, 91%, completed the 16-week program and had a body weight loss of 14.0 kg (95% confidence interval: 13.3 — 14.7; P<0.0001), consisting of 1.8 kg (1.3 — 2.3; P<0.0001) lean body mass (LBM) and 11.0 kg (10.4 — 11.6; P<0.0001) fat mass. Bone mineral content (BMC) did not change (-13.5 g; P=0.18), whereas bone mineral density (BMD) increased by 0.004 g/cm2 (0.001 –0.008 g/cm2; P=0.025). Plasma vitamin D and B12 increased by 15.3 nmol/l (13.2 — 17.3; P<0.0001) and 43.7 pmol/l (32.1 — 55.4; P<0.0001), respectively. [Christensen P, Bartels EM, Riecke BF, Bliddal H, Leeds AR, Astrup A, Winther K, Christensen R. Improved nutritional status and bone health after diet-induced weight loss in sedentary osteoarthritis patients: a prospective cohort study. Eur J Clin Nutr. 2012 Apr;66(4):504-9. doi: 10.1038/ejcn.2011.201. Epub 2011 Dec 21. PMID: 22190136; PMCID: PMC3321436.] • Vitamin D insufficiency has a high prevalence in older people in the UK and it could be said that public health measures do not adequately	

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				address this. Weight loss of any type results in some loss of bone mass and reduction of bone density. Weight loss with TDR counters this physiological effect on bone and reduces the proportion of people with vitamin D insufficiency (see figure below). [image removed] These studies prove that, with proper guidance, weight loss obtained with TDRs may lead to a significant and clinically important effect on both symptoms and nutritional status of people with osteoarthritis. Determining the effectiveness of TDR in weight loss for knee osteoarthritis should also consider the evidence for effectiveness in other obesity comorbidities and the extent to which this method of weight loss has been translated into clinical practice and 'roll-out' into real world usage. Other recent studies showing the effectiveness of TDR on weight loss are described below: • The results of DROPLET showed that GP referrals to a commercial provider offering a weight loss and maintenance programme, based on TDR with individual behavioural support, led to an average weight loss of 10.7 kg after 1 year (7.2kg more than usual weight-loss programmes offered in primary care). This	

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				was associated with significant reductions in CVD risk. [Astbury NM, Aveyard P, Nickless A, Hood K, Corfield K, Lowe R, Jebb SA. Doctor Referral of Overweight People to Low Energy total diet replacement Treatment (DROPLET): pragmatic randomised controlled trial. Nuffield Department of Primary Care Health Sciences, University of Oxford, UK. August 2018. http://dx.doi.org/10.1136/bmj.k3760] • The DiRECT trial showed that a high proportion of people with type 2 diabetes would engage with a total diet replacement weight loss programme for up to 20 weeks and that a good proportion maintained their weight loss. [Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster randomised trial. The Lancet. December 2017. https://doi.org/10.1016/S0140-6736(17)33102-1] [Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Durability of primary care-led weight-management intervention for remission of type 2 diabetes: 2 year results of the DiRECT open-label, cluster-randomised trial. The Lancet Diabetes & Endocrinology. March 2019. https://doi.org/10.1016/S2213-8587(19)30068-3][Rehackova, L, Rodrigues, AM, Thom, G, et	

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				al. Participant experiences in the Diabetes REmission Clinical Trial (DiRECT). *Diabet Med*. 2021; 00:e14689. https://doi.org/10.1111/dme.14689] • Both NHS Scotland and NHS England have rolled out diabetes remission programmes based on the DiRECT model. The DiRECT trial design was informed by the experience with the Copenhagen CAROT/LIGHT study in elderly people with obesity and knee osteoarthritis. • A recent review by Churuangsuk C etal examined 19 meta-analyses and concluded that programmes including a formula hypocaloric total diet replacement phase were the most effective for type 2 diabetes remission. Churuangsuk C etal Diets for weight management in adults with type 2 diabetes: an umbrella review of published meta-analyses and systematic review of trials of diets for diabetes remission. Diabetologia 2021 https://doi.org/10.1007/s00125-021-05577-2 • The Prevention of diabetes through lifestyle Intervention and population studies in Europe and around the World (PREVIEW) research team presented results on weight maintenance over three years in over two thousand	

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				overweight people with pre-diabetes who begin their risk-reduction with an 800kcal/d TDR diet given with a behaviour change intervention. The overall mean weight loss after 8 weeks was 10.7 + 0.4kg (10.8% of body weight). After the initial weight loss period those who achieved 8% weight loss were entered into a randomised trial of higher and lower dietary protein intake, higher and lower dietary glycaemic index levels and higher and lower physical exercise activity intensity levels for three years. The results of the three year maintenance outcomes showed that both diets and both exercise strategies were equally effective for weight-loss maintenance. [Christensen P, Larsen TM, Westerterp-Plantenga M, Macdonald I, Alfredo Martinez J, Handjiev S, Poppitt S, et al. Men and women respond differently to rapid weight loss: Metabolic outcomes of multi-centre intervention study after a low-energy diet in 2500 overweight, individuals with pre-diabetes (PREVIEW). Diabetes, Obesity and Metabolism, A Journal of Pharmacology and Therapeutics. August 2018. https://doi.org/10.1111/dom/13466] • MRPs should also be included under the guideline's weight loss advice as a useful method to lose and manage weight. A systematic review and meta-analysis of the	

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				effectiveness MRPs shows that programmes incorporating MRPs as part of their dietary intervention resulted in greater weight loss at one year than those not incorporating MRPs. Specifically, those participants who had included MRPs in their diet had lost an additional 1.49 kg at one year compared with those participants whose diet did not include MRPs. The review also showed that this greater weight loss was maintained over the longer term with data being reported after four years showing a more significant degree of weight loss maintenance in participants who had undertaken programmes incorporating MRPs. [Astbury, NM, Piernas, C, Hartmann-Boyce, J, Lapworth, S, Aveyard, P, Jebb, SA. A systematic review and meta-analysis of the effectiveness of meal replacements for weight loss. *Obesity Reviews*. 2019; 20: 569– 587. https://doi.org/10.1111/obr.12816]	
Total Diet and Meal Replacements Europe	Guideline	004	007 – 010	The guideline recommends explaining to people with osteoarthritis that the core treatments for the condition are therapeutic exercise and weight loss, along with information and support. We think this is indeed important but people with the condition should also be offered advice on how to achieve such weight loss.	Thank you for your comment. We have not covered how to lose weight in this guideline because recommendations related to this and interventions to support this are found in other NICE guidance. We have cross referred to this from the weight management recommendations. Please see Diet, nutrition and obesity guidance at https://www.nice.org.uk/guidance/lifestyle-and-wellbeing/diet—nutrition-and-obesity

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				It should also be noted that this wording might led patients to believe that the weight loss can be achieved through therapeutic exercise. Patients with osteoarthritis however are likely to have mobility difficulties and the levels of exercise they can achieve will likely not result in any significant weight loss. Weight management advice, and specifically dietary advice, is therefore particularly crucial for people with this condition. Any health care professional with experience of managing people with obesity and osteoarthritis will tell you that such people struggle to lose and maintain weight using conventional diet because a) their lean body mass (LBM) is relatively low as a result of prolonged inactivity; (b) their energy requirement is low because their LBM; and (c) they sleep badly because they are In pain thus spending longer awake with more opportunity to eat. TDR is proven to deliver weight loss in this group despite these factors.	The recommendation—s primarily aimed at health care professionals. They anticipate that healthcare professionals will tailor the information to the person in front of them and take into account other NICE guidance on weight management mentioned in the preceding paragraph. Dietary interventions were not included in the scope for this guideline and therefore no recommendations have been made for them.
Total Diet and Meal Replacements Europe	Guideline	022	003–-009	In its explanation of recommendation 1.3.5. on weight loss, NICE acknowledges that for people with knee osteoarthritis, evidence generally showed that as the amount of weight loss increased, the benefit for quality of life, pain and physical function increased. NICE also acknowledges however the challenges people can have with losing weight and maintaining this weight loss and recommends that they are supported. Therefore, it is crucial to include specific weight loss advice on this guideline especially as the evidence for this type of weight loss and maintenance is good	Thank you for your comment. This guideline only aimed to provide evidence to give an incentive to people who are overweight or have obesity to lose weight. We did not look at specific weight management interventions. Rather we refer to the NICE web pages on obesity (https://www.nice.org.uk/guidance/conditions-and-diseases/diabetes-and-other-endocrinal--nutritional-and-metabolic-conditions/obesity) which cover guidelines that include interventions related to weight management.

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				enough for the diabetes remission programme to be 'rolled out' by NHS Scotland and NHS England.	
Versus Arthritis	Guideline	008	020 - 026	**Pharmacological management - Topical, oral and transdermal medicines** This guideline makes recommendations on the use of weak opioids The guideline recommends the use of weak opioids only for "short-term pain relief" and if "all other pharmacological treatments are contraindicated, not tolerated or ineffective." This differs from previous guidelines which recommended that "If paracetamol or topical NSAIDs are insufficient for pain relief for people with osteoarthritis, then the addition of opioid analgesics should be considered". Versus Arthritis has a number of concerns with this apparent shift in approach. We recognise that (a) there was only one small study showing benefit of weak opioids, and (b) the potential harms from opioids. We believe the intention here was to reduce the scenario of continuous, full-dose weak opioid prescriptions (two co-codamol four times a day, every day). We are nevertheless concerned that the new wording will result in harm to many people with osteoarthritis. Osteoarthritis is a long-term, fluctuating condition. Many people will effectively, safely and appropriately use weak opioids **intermittently in the long-term**. This can help them manage flares, and also enable	Thank you for your comment. The committee agreed that there is generally more awareness of the harmful effects of weak opioids than there was when the 2014 update of the guideline was published. Therefore, based on the available evidence and there consensus the recommendation was changed to a 'Do not routinely offer' recommendation. We agree that there is uncertainty based on the limited evidence available. No evidence was identified investigating the long-term use of weak opioids. However, the Medicines and Healthcare products Regulatory Agency has warned that long-term use of opioid medicines for non-cancer pain (longer than 3 months) carried an increased risk of dependence and addiction. Therefore, taking this and their expert knowledge into account, the committee recommended that weak opioids should only be used for short term relief of symptoms. This does not mean that weak opioids can only be used once in a person's life, and it is acknowledged that use, in conjunction with core treatments, to relieve intermittent short-term increases in symptoms may be required. However, as with all medicines recommended for osteoarthritis in this guideline, medicines should be used for the shortest duration at the lowest effective dose.

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				them to carry out important, meaningful and healthy activities such as social participation and physical activity. By focusing on the duration of weak opioid use, rather than the dose and intensity, the phrase 'short-term pain relief' will suggest to many prescribers that such **intermittent, long-term** use is inappropriate. Secondly, previously weak opioids could be considered if pain relief from other approaches was 'insufficient', but the new wording requires other treatments to now be 'ineffective'. This is a higher bar that does not emerge from the evidence cited, and fails to take into account that many people with osteoarthritis will need to combine approaches from time to time to manage their symptoms. We ask the committee to consider revising the wording to make the intentions clearer, and enable people with this long-term condition to receive medication in the long-term, where appropriate and safe. Given the lack of evidence, one option could be to simply state that there was *insufficient evidence to make a recommendation about weak opioids, either entirely or in the long-term*. This would then be consistent with the research recommendation on weak opioids, and the research recommendation should be updated to specifically look at short- and long-term regular and intermittent use of opioids in osteoarthritis. Some suggested wording could therefore include:	

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				Offer weak opioids for pain relief for short-term pain relief, when all other pharmacological treatments are contraindicated, not tolerated or insufficiently effective. The committee were unable to make a recommendation about long-term continuous or intermittent opioid use. Another option would be to modify the wording, to distinguish between 'long-term continuous use' which should be avoided, and 'long-term intermittent use' which may be helpful. For example, the committee could add a rider such as 'where weak opioids are required for long-term symptom management, they should only be used intermittently'. Some suggested wording could therefore include: *Offer weak opioids for pain relief for intermittent use only, when all other pharmacological treatments are contraindicated, not tolerated or insufficiently effective.*	
Versus Arthritis	Guideline	010	002 - 026	**Follow-up and review** This guideline makes recommendations on the use of patient-initiated follow-up for most people with osteoarthritis and a consideration of planned follow up.	Thank you for your comment. We did not find evidence investigating the effectiveness of follow up. We have checked your report and could not see any evidence with this that matched the protocol. In the absence of evidence the committee made consensus recommendations.

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				Versus Arthritis 'Not just a touch of arthritis' report found that personalised management of osteoarthritis requires regular reviews between patients and healthcare professionals however **all too often reviews do not happen**. In addition, that as part of these reviews it should be the case that everyone with moderate or severe osteoarthritis is offered a co-produced care and support plan. And that care plans should be reviewed when there is a significant change in a person's osteoarthritis health status Currently the choice of either of *patient initiated follow-up* or "consideration of planned follow up" does not sufficiently ensure that plans being developed by healthcare providers are able to meet the needs of people with moderate and severe osteoarthritis. It leaves a gap in provision whereby people who require regular reviews and care and support planning have the potential to not be offered it. The Committee should consider further clarification of the wording to ensure that people with moderate and severe osteoarthritis are offered a co-produced care and support plan.	These are weaker 'consider' recommendations to reflect this lack of evidence. The committee agreed that while it is more likely that people with severe symptoms may need planned follow up compared to those with mild symptoms the noted that it is not always the case. Therefore, they defined the criteria when planned follow up should be considered, emphasing the person's needs and preferences. This is also followed by a recommendation advising people with osteoarthritis to seek help if their planned management is not working within an agreed follow-up time or they are having difficulties with the agreed approaches.

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*