National Institute for Health and Care Excellence

Draft for consultation

Osteoarthritis: assessment and management (update)

[O] Evidence reviews for the indicators for referral for possible joint replacement surgery

NICE guideline <number>

Evidence reviews underpinning recommendations 1.6.1 to 1.6.2 and research recommendations in the NICE guideline

April 2022

Draft for Consultation

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ISBN:

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1.1 Review question

What are the indicators for possible joint replacement surgery?

1.1.1 Introduction

Knowing when to refer a person with osteoarthritis for consideration for a joint replacement is a challenge for healthcare professionals working in primary care. There are few contraindications to surgery now that it can be performed without a general anaesthetic. Joint replacement can have significant benefits to function, pain and quality of life. It is unclear which prognostic factors demonstrate that surgery would be beneficial, and surgeons do not have the resource to evaluate everyone. Decision making for referral does not usually occur on the basis of imaging, rather on clinical assessment. Musculoskeletal interface services often sit between primary care and orthopaedic services to support appropriate use of non-invasive approaches before referral onto surgery.

Current practice for people with osteoarthritis is to refer when patients have significant pain and functional limitation. This review aims to determine which risk factors presenting in primary care accurately predict the progression to joint replacement surgery being carried out.

1.1.2 Summary of the protocol

Table 1: PICO characteristics of review question

Population	Inclusion: • Adults (age ≥16 years) with osteoarthritis affecting any joint. Stratification by joint site ○ Hip ○ Knee ○ Shoulder ○ Mixed
Prognostic variables under consideration	Prognostic factors: • Presence of night pain • Non-response to analgesics/intra articular injections • Non-response to non-pharmacological interventions • Longer duration of symptoms • Instability symptoms • Presence of flares • EQ-5D/EQ VAS • KOOS/HOOS (summary score) • WOMAC (summary score) Oxford Knee Score by the following scale range categories: • 40-48 • 30-39 • 20-39 • 0-19

	Oxford Hip Score by the following scale range categories: • 40-48 • 30-39 • 20-39 • 0-19 Shoulder scores: • Oxford Shoulder Score (OSS) • Constant Score • Shoulder Pain and Disability Index (SPADI) • The Disabilities of the Arm, Shoulder and Hand Score (DASH)
Confounding factors	Key confounders: • Age • Body mass index All key confounders should be adjusted for in multivariate analysis. Other confounders: • Smoking status • Multimorbidity • Socio-economic factor These confounders will be assessed on a case-by-case basis.
Outcomes	Progression to a joint replacement [time-to-event or dichotomous outcomes, time-to-event data prioritised]
Study design	Prospective and retrospective cohort studies if all the key confounders have been accounted for in a multivariate analyses. In the absence of multivariate analysis, stepwise multivariate analysis would be included.

For full details see the review protocol in Appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Prognostic evidence

1.1.4.1 Included studies

Six prospective cohort studies were included in the review;[14, 20, 34, 35, 45, 52] these are summarised in below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3). All studies conducted a multivariate analysis for each prognostic value.

No relevant clinical studies investigating the effects of the following prognostic factors were identified:

- Presence of night pain
- Instability symptoms

- Presence of flares
- Shoulder scores (including the Oxford Shoulder Score, Constant Score, Shoulder Pain and Disability Index, The Disabilities of the Arm, Shoulder and Hand Score)
- WOMAC (summary score)
- EQ-5D/EQ VAS

The outcome measure was reported as time-to-event and dichotomous outcomes. Due to studies reporting different measures of prognostic variables and different types of outcome data, no studies were meta-analysed and results were instead reported individually.

Indirectness

The majority of outcomes were downgraded for indirectness for a range of reasons:

- Prognostic variable indirectness:
  - The combination of scores that were stated in the protocol to be investigated separately (for example: Oxford Hip and Knee score combined)[35]
  - The reporting of subscales of a score rather than the summary score (for example: KOOS/HOOS pain score)[14, 20]
  - The reporting of previous medication use as a surrogate measure for non-response to pharmacological interventions[14, 34, 52]
  - The reporting of pain at baseline or for a period of time (for example 3 months) as a surrogate measure for longer duration of symptoms[34, 45]
  - The reporting of pain (visual analogue scale) in a cohort that all underwent an exercise program as a surrogate measure for non-response to non-pharmacological intervention[14]

See also the study selection flow chart in Appendix A, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the prognostic evidence

Table 2: Summary of studies included in the evidence review

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Clausen 2021[14]	People with hip osteoarthritis N=3965 Number of events (joint replacement surgery over 2 years) = 1114	Multivariable Cox proportional hazards model	Non-response to analgesics/intra articular injections Non-response to non-pharmacological interventions KOOS/HOOS (summary score)	Factors included in the adjusted analysis: gender, BMI, smoking, employment, use of pain medication the last three months, self-reported radiographic osteoarthritis, presence of comorbidities, wait-listed for total hip replacement, joint replacement in other hip or knees, bilateral hip symptoms, number of painful areas during the last 24 hours, hip pain (VAS), HOOS QoL score, 40m walk test	Progression to joint replacement (time-to-event data)	Prognostic variable indirectness – HOOS scale quality of life is not the total summary statistic. Use of pain medication in the last three months was reported and assumed that if people progressed to joint replacement surgery then they did not respond. All participants underwent an exercise program and so VAS was used to determine non-response to non-pharmacological interventions.
Dabare 2017[20]	167 people with knee osteoarthritis, 80 people with hip osteoarthritis (considered as mixed osteoarthritis for the analysis). n=247 Number of events (joint replacement	Kaplan-Meier estimates, log rank test and Cox regression used in a multivariable analysis	KOOS/HOOS (summary score) – see limitations Longer duration of symptoms	Factors included in the adjusted analysis: joint type; age; gender; BMI; Kellgren Lawrence grading scale; symptom duration; osteoarthritis elsewhere and KOOS/HOOS pain score.	Progression to joint replacement (time-to-event data)	Prognostic variable indirectness – KOOS and HOOS scales pain score is not the total summary statistic for KOOS/HOOS and so is downgraded for indirectness.

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	surgery over 6 years) = 104					
Gossec 2005[34]	People with hip osteoarthritis n=505 Number of events (joint replacement surgery over 2 years) = 189	A survival curve according to Kaplan-Meier's method	Non-response to analgesics/intra articular injections Longer duration of symptoms	Factors included in the adjusted analysis: age, gender, BMI, pain, Lequesne index, Patient overall assessment, femoral head migration, joint space width.	Progression to joint replacement (dichotomous)	Risk of bias: High (due to study attrition) Prognostic variable indirectness – For both prognostic variables. Previous NSAID intake is included with the assumption that people did not respond to treatment if they required surgery, so has been downgraded for indirectness. Mean patient global assessment of pain over a specific value for the first 6 months is taken as an indirect measure of prolonged symptoms, so has been downgraded for this.
Gwynne-Jones 2020 [35]	186 (55%) with knee osteoarthritis. 151 (45%) with hip osteoarthritis. n=337 Number of events (joint replacement surgery over a mean of 6.1 years) = 186 (2 were waitlisted for surgery)	Kaplan-Meier curves. Cox regression analyses performed to investigate the relationship among baseline variables.	Oxford Hip/Knee score	Factors included in the adjusted analysis: joint affected, radiographic grade, age, gender, BMI, PROMs and time to surgery.	Progression to joint replacement (time-to-event data)	Risk of bias: High (due to study participation) Prognostic variable indirectness – the prognostic variable combines the Oxford Knee and Hip score, while the protocol requested them to be separate.

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Lane 2004 [45]	People with radiographic hip osteoarthritis n=936 Number of events (joint replacement surgery over a mean of 8.3 years) = 96	Logistic regression used to estimate the adjusted odds ratios for predictors of dichotomous measures of progression. Linear regression was used for continuous measures of change that included changes in the MJS and lower extremity disability scores.	Longer duration of symptoms	Factors included in the adjusted analysis: age, weight, height (the presence of weight and height is used in the place of BMI, as BMI can be calculated from this. Therefore, this study was not excluded for absence of adjustment of key confounders), estrogen use, calcaneal BMD, health status, and baseline radiographic severity using the sum total of all individual radiographic feature scores.	Progression to joint replacement (dichotomous)	Risk of bias: Very high (due to study participation and study attrition) Prognostic variable indirectness – the value is used with the assumption that pain at baseline would indicate a longer duration of symptoms. As this is an assumption, this has been downgraded due to indirectness.
Maillefert 2002[52]	People with hip osteoarthritis n=466 Number of events (joint replacement surgery between years 2 and 3) = 75	Multivariate Cox models performed with backward elimination of variables	Non-response to analgesics/intra articular injections – study reports two ways of measuring this (NSAID intake and analgesic intake both during the 3 months preceding the evaluated visit)	Factors included in the adjusted analysis: age, gender, BMI, pain, Lequesne index, Patient overall assessment, femoral head migration, joint space width.	Progression to joint replacement (dichotomous)	Risk of bias: High (due to study attrition) Prognostic variable indirectness – Previous NSAID/analgesia intake is included with the assumption that people did not respond to treatment if they required surgery, so has been downgraded for indirectness

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2 See Appendix D for full evidence tables.

1.1.6 Summary of the prognostic evidence

Table 3: Clinical evidence summary: non-response to analgesics/intra articular injections for people with hip osteoarthritis

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Progression to joint replacement (previous NSAID intake) at 2 years[a]	505 (1) 2 years	VERY LOW[b.c] Due to risk of bias, indirectness	Adjusted OR: 1.50 (1.00 to 2.25)
Progression to joint replacement (NSAID intake during the 3 months preceding the evaluated visit) at 3 years[a]	466 (1) [d] 3 years	VERY LOW[b.e] Due to risk of bias, indirectness	Adjusted RR: 2.31 (1.34 to 3.98)
Progression to joint replacement (analgesic intake during the 3 months preceding the evaluated visit) at 3 years[a]	466 (1) [d] 3 years	VERY LOW[b.e] Due to risk of bias, indirectness	Adjusted RR: 1.98 (1.16 to 3.38)
Progression to joint replacement (use of pain medication in last 3 months) at 2 years[a]	3657 (1) 2 years	MODERATE[e] Due to indirectness	Adjusted HR: 1.42 (1.23 to 1.64)

(a) Methods: multivariable analysis, including key covariates used in analysis to assess if non-response to analgesics/intra articular injections is an independent risk factor. Key covariates included: age, BMI.
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of evidence was at very high risk of bias.
(c) Downgraded by 1 or 2 increments because of prognostic variable indirectness (use of previous NSAID usage as a surrogate measure for non-response as people went on to have joint replacement surgery).
(d) One study reported both NSAID intake during the 3 months preceding the evaluated visit and analgesic intake during the same time period. These have both been included in the analysis, but it should be noted that analgesic intake during the 3 months may include NSAID intake.
(e) Downgraded by 1 increment because of prognostic variable indirectness (use of analgesics in the past three months as a surrogate measure for non-response as people went on to have joint replacement surgery)

Table 4: Clinical evidence summary: non-response to non-pharmacological interventions for people with hip osteoarthritis

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Progression to joint replacement (hip pain [VAS]) at 2 years[a]	3657 (1) 2 years	MODERATE[b] Due to indirectness	Adjusted HR: 1.00 (1.00 to 1.02)

(a) *Methods: multivariable analysis, including key covariates used in analysis to assess if non-response to analgesics/intra articular injections is an independent risk factor. Key covariates included: age, BMI.*
(b) *Downgraded by 1 or 2 increments because of prognostic variable indirectness (use of hip pain in a cohort who had completed an exercise program as a surrogate measure for non-response to a non-pharmacological intervention)*

Table 5: Clinical evidence summary: longer duration of symptoms for people with hip osteoarthritis

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Progression to joint replacement (mean patient global assessment over the first 6 months >47) at 2 years[a]	466 (1) 2 years	VERY LOW[b,c] Due to risk of bias, indirectness	Adjusted OR: 2.20 (1.40 to 3.46)
Progression to joint replacement (pain present at baseline) at 8.3 years[d]	745 (1) 8.3 years	VERY LOW[b,c] Due to risk of bias, indirectness	Adjusted OR: 9.10 (4.20 to 19.72)

(a) *Methods: multivariable analysis, including key covariates used in analysis to assess if non-response to analgesics/intra articular injections is an independent risk factor. Key covariates included: age, BMI.*
(b) *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of evidence was at very high risk of bias.*
(c) *Downgraded by 1 or 2 increments because of prognostic variable indirectness (use of a higher pain outcome score or pain being present at the start of the study as a surrogate measure for a longer duration of symptoms).*
(d) *Methods: multivariable analysis, including key covariates used in analysis to assess if non-response to analgesics/intra articular injections is an independent risk factor. Key covariates included: age, weight, height (weight and height have been considered as analogues for BMI, as they are used to calculate this, and so this study was included in the analysis)*

Table 6: Clinical evidence summary: longer duration of symptoms for people with mixed osteoarthritis (hip and knee)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Progression to joint replacement (symptom duration, years) at 6 years[a]	247 (1) 6 years	LOW[b,c] Due to risk of bias, imprecision	Adjusted HR: 0.98 (0.94 to 1.02)

(a) *Methods: multivariable analysis, including key covariates used in analysis to assess if non-response to analgesics/intra articular injections is an independent risk factor. Key covariates included: age, BMI.*
(b) *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of evidence was at very high risk of bias.*
(c) *95% CI around the effect crosses null line.*

Table 7: Clinical evidence summary: Oxford Hip/Knee Score for people with mixed osteoarthritis (hip and knee)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Progression to joint replacement (Oxford Hip/Knee Score) at 6.1 years[a]	216 (1) 6.1 years	VERY LOW[b.c] Due to risk of bias, indirectness	Adjusted HR: 0.74 (0.66 to 0.83)

(a) Methods: multivariable analysis, including key covariates used in analysis to assess if non-response to analgesics/intra articular injections is an independent risk factor. Key covariates included: age, BMI.
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of evidence was at very high risk of bias
(c) Downgraded by 1 or 2 increments because of prognostic variable indirectness (use of a combined Oxford Hip and Knee Score, rather than the singular scores specified in the protocol)

Table 8: Clinical evidence summary: KOOS/HOOS (summary score) for people with mixed osteoarthritis (hip and knee)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Progression to joint replacement (KOOS and HOOS scales pain score) at 6 years[a]	247 (1) 6 years	LOW[b.c] Due to risk of bias, indirectness	Adjusted HR: 0.97 (0.96 to 0.98)
Progression to joint replacement (HOOS quality of life score) at 2 years[a]	3657 (1) 2 years	MODERATE[e] Due to indirectness	Adjusted HR: 0.98 (0.97 to 0.99)

(a) Methods: multivariable analysis, including key covariates used in analysis to assess if non-response to analgesics/intra articular injections is an independent risk factor. Key covariates included: age, BMI.
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of evidence was at very high risk of bias
(c) Downgraded by 1 or 2 increments because of prognostic variable indirectness (use of subscales of the total KOOS/HOOS score instead of the summary score)

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in **Error! Reference source not found.**.

1.1.8 Summary of included economic evidence

There was no economic evidence found.

1.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.10 Economic evidence statements

- No relevant economic evaluations were identified.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

This study included one critical outcome, progression to a joint replacement. This was agreed to be the outcome most appropriate to answering the question. This was examined with a range of prognostic variables, including: presence of night pain, non-response to analgesics/intra articular injections, non-response to non-pharmacological interventions, longer duration of symptoms, instability symptoms, presence of flares, EQ-5D/EQ VAS, KOOS/HOOS summary score, WOMAC summary score, Oxford Knee and Hip Score, and shoulder scores (including the Oxford Shoulder Score, Constant Score, Shoulder Pain and Disability Index and the Disabilities of the Arm, Shoulder and Hand Score). These prognostic variables were decided as these would be potential reasons that people may be referred to a surgeon that may influence the decision of the surgeon as to whether the person would require joint replacement surgery.

The evidence discussed people with hip osteoarthritis or mixed osteoarthritis, including hip and knee osteoarthritis. No studies included people with shoulder osteoarthritis.

1.1.11.2 The quality of the evidence

Evidence was reported for people with hip and mixed (hip and knee) osteoarthritis. All studies included a multivariate analysis adjusting for key confounders (age and body mass index). Only a limited number of prognostic variables were studied including:

- Non-response to analgesics/intra articular injections – 3 outcomes for people with hip osteoarthritis that were of very low quality due to risk of bias and indirectness
- Non-response to non-pharmacological interventions – 1 outcome for people with hip osteoarthritis that was of moderate quality due to indirectness
- Longer duration of symptoms – 2 outcomes for people with hip osteoarthritis that were of very low quality due to risk of bias and indirectness, 1 outcome for people with mixed osteoarthritis that was of low quality due to risk of bias and imprecision
- Oxford Hip/Knee Score – 1 outcome for people with mixed osteoarthritis of very low quality due to risk of bias and indirectness
- KOOS/HOOS (summary score) – 1 outcome for people with mixed osteoarthritis of low quality due to risk of bias and indirectness

Outcomes were commonly downgraded for risk of bias and indirectness. Regarding risk of bias, outcomes were commonly downgraded due to study confounding, as while studies adjusted for the key confounders, no study adjusted for all of the other confounders listed in the protocol (including smoking status, multimorbidity and socio-economic factors). Otherwise, where further risk of bias was identified, studies were more commonly downgraded for study participation or study attrition bias.

The majority of included studies were deemed to have indirect evidence, in particular prognostic variable indirectness. The reasons for this included: using a combination of scores where the protocol requested them to be investigated separately (for example: Oxford Hip and Knee score combined); reporting subscales rather than a summary score and reporting surrogate measures for outcomes (for example: previous medication use as a surrogate measure for non-response to pharmacological interventions, pain at baseline and for a specified period of time as a measure for longer duration of symptoms). However, no outcomes were downgraded for imprecision or inconsistency.

As studies were not comparable (by not adjusting for the same confounding variables, including different definitions of outcomes and different populations) no outcomes were meta-analysed and instead the outcomes from each study were reported separately.

No evidence was identified for the following comparisons:

- Presence of night pain
- Instability symptoms
- Presence of flares
- EQ-5D/EQ VAS
- WOMAC summary score
- Any shoulder scores (including the Oxford Shoulder Score, Constant Score, Shoulder Pain and Disability Index and the Disabilities of the Arm, Shoulder and Hand Score)

1.1.11.3 Benefits and harms

Key uncertainties

The committee noted the limitations in the design of the review to answer the question. This review investigated if people with specific risk factors had joint replacement surgery. These risk factors were in part selected from expert knowledge of the factors that would be considered by surgeons when deciding if someone should have joint replacement surgery. Due to this, current practice already considers these factors important and so this may affect decision making by a GP as to whether to refer someone for joint replacement surgery, and so it is difficult to know whether the prognostic factor led to someone deciding joint replacement surgery was necessary, or if previous guidance stated that people with these prognostic factors should be considered for joint replacement surgery led to the procedure. This makes it difficult to interpret the answer from this evidence, and so the committee used their expert opinion while making the recommendations.

When examining previous use of analgesics/intra articular injections, the studies investigating this examined the use of non-steroidal anti-inflammatory drugs or analgesia, with no specification of the type. Given this, it is difficult to relate the evidence available to the use of intra articular injections. It was acknowledged that people receiving intra articular injections are likely to have worsened symptoms then people who may not need these injections, and so may introduce some confounding.

Additionally, no evidence was found for the following prognostic variables:

- Presence of night pain
- Instability symptoms
- Presence of flares
- EQ-5D/EQ VAS
- WOMAC summary score
- Any shoulder scores (including the Oxford Shoulder Score, Constant Score, Shoulder Pain and Disability Index and the Disabilities of the Arm, Shoulder and Hand Score)

Limited evidence that the committee concluded was unlikely to provide sufficient evidence was found for the non-response to non-pharmacological interventions prognostic variable.

The committee acknowledged that given the limited evidence and number of indirect outcomes, they concluded that this was an absence of evidence rather than evidence of an absence of effect. Therefore, they considered that, even though evidence may not be present for all prognostic factors, the factors not mentioned may be relevant for decision making.

Non-response to analgesics/intra articular injections

This prognostic variable was investigated in two studies (with one study reporting two surrogate outcomes that were included in the analysis: NSAID intake during the 3 months preceding the evaluation visit and analgesic intake during the previous 3 months preceding the evaluation visit). All outcomes were rated to be of low quality. It should be noted that neither study explicitly discussed the use of intra articular injections before surgery.

While noting the limitations of the evidence given the indirectness of the outcomes, the committee agreed that there was consistent evidence to show that non-response to analgesia lead to more people having a joint replacement procedure. The committee noted that the evidence did not discuss intra articular injections and focussed on oral medication, specifically non-steroidal anti-inflammatory drugs.

On further discussion, the committee agreed that non-response to analgesics may indicate that the symptoms of osteoarthritis are not manageable with other treatments. Non-response to a treatment would be specific to the individual and should be explored with the healthcare professional. In general, the committee discussed that non-response may be seen at 2 to 4 weeks of analgesic treatment. However, people may present after having a flare of disease activity, which may be present throughout this time period and so this evaluation needs to be made taking into account the entire clinical picture of the person. Due to this, using their expert opinion, they made recommendation.

Non-response to non-pharmacological interventions

This prognostic variable was investigated indirectly in one study. This study followed up participants who had been involved in an exercise programme preceding the study. Therefore, the pain at the start of trial was used in this review as a surrogate measure for whether people responded to the exercise programme. The committee agreed that the use of this evidence was limited and was unlikely to give a complete understanding of the effect of this prognostic variable. It was agreed to include this outcome for consideration, but to emphasise the indirectness of the finding.

The outcome showed no difference in people with pain at the start of the study with those who had lower amounts of pain. Based on this evidence and the limitations identified, the committee concluded that further research would be required to investigate the effect of this prognostic variable on predicting whether someone required surgery.

Longer duration of symptoms

This prognostic variable was investigated in three studies (two for people with hip osteoarthritis, and one for people with hip or knee osteoarthritis). Outcomes were rated to be of moderate to low quality evidence. For people with hip osteoarthritis, outcomes showed that a longer duration of symptoms may lead to more joint replacement procedures. For people with hip or knee osteoarthritis, outcomes showed that there was no significant difference in the number of joint replacement surgeries in people with different durations of symptoms.

The committee acknowledged that these findings were contradictory. On examining the quality of the evidence, the committee acknowledged that the outcomes for people with hip osteoarthritis only were downgraded for indirectness as the outcomes used surrogate measures for longer duration of symptoms while the outcome used in people with mixed osteoarthritis was more direct. Furthermore, the committee acknowledged that longer duration of symptoms could be confounded by other risk factors, such as response to analgesics, and so this could influence the results being seen.

Given the evidence and weighing up the benefits and the risks of surgery, the committee agreed that people should receive all appropriate recommended treatments delivered in an

appropriate manner before they should be referred to surgery whilst taking into account the duration and rate of progression of the pain and functional deterioration.

Oxford Hip/Knee Score

This prognostic variable was investigated in one study. The outcome was rated to be of low quality. The outcome showed that people with higher Oxford Hip/Knee Scores may be less likely to have joint replacement surgery then people with lower scores.

Due to the limited evidence available, the committee used their expert opinion while making recommendations. The committee discussed that scores such as the Oxford Hip and Knee scores are not designed for preoperative prediction of whether someone requires surgery, and instead clinical judgement based on the experience of the person with osteoarthritis should be the main determinant. Instead, the Oxford Hip and Knee scores are more useful for indicating change in pain and functional outcome after surgery, and so can be used to look at the success of the surgery. Current guidance would indicate that these scores should not be used to determine whether someone should have surgery or not. However, there is inconsistency in how scores are used in current practice. Weighing up the potential benefits and risks, the committee agreed it was inappropriate to use these scores to determine whether someone should have surgery and that the clinical presentation of the person should be of greater emphasis in making this decision.

KOOS/HOOS (summary score)

This prognostic variable was investigated in one study. The outcome was rated to be of low quality. Where reported, only the pain subscale of the KOOS/HOOS scale was used, which limited the interpretation of the evidence. However, the evidence present showed that there was no apparent difference in the number of joint replacement procedures for people with different KOOS/HOOS scores.

As with the Oxford Hip and Knee score, the committee agreed that numerical scales were unlikely to be useful as a main determinant as to whether someone with osteoarthritis should have joint replacement surgery. Furthermore, the evidence showed that KOOS/HOOS scores were not determinants as to whether someone had a joint replacement surgery.

Consideration for the evidence for the recommendations

Overall, the committee concluded that, using the limited available evidence combined with their expert opinion and the approaches in current practice, that people with persistent symptoms that are affected their quality of life and are non-responsive to non-surgical treatments may benefit from surgery. Therefore, they agreed recommendation 1.6.1. In recommending this, the committee extended the evidence of non-response to analgesics to non-pharmacological management, which the committee agreed would also influence decision making even though the evidence for this was not found in this review (this absence of evidence influenced the decision to recommend a research recommendation). Given the evidence and weighing up the benefits and the risks of surgery, the committee agreed that people should receive all appropriate recommended treatments delivered in an appropriate manner before they should be referred to surgery. Through this, the committee made recommendation 1.6.2.

As there was limited evidence, the committee made a research recommendation to investigate the effect of other prognostic variables states in the protocol to investigate if they influence joint replacement surgery rates.

1.1.11.4 Cost effectiveness and resource use

There were no published economic evaluations found specifically about referral for joint replacement. Cost-effectiveness modelling was not feasible since a model would require

good evidence of clinical effectiveness, which was not the focus of this review. However, the committee were aware that there is a body of evidence showing that surgery itself is highly effective at improving quality of life and is cost effective in appropriately selected patients.

The committee's decision to continue to recommend referral for joint surgery for people with osteoarthritis who experience joint symptoms that have a substantial impact on their quality of life and are refractory to medical management. This is unlikely to have an impact on resource use since it reflects current practice and ensures that patients continue to receive current standard of care.

The committee also made a research recommendation to assess whether the presence of night pain, non-response to non-pharmacological interventions, instability symptoms, presence of flares and various summary scores can be suitable indicators for joint replacement surgery. If such indicators were to be recommended as suitable for referral to surgery in future, it would be expected to cause a significant increase in resource use since the surgical procedure itself is costly. However, the additional costs may be justified if there were evidence of improved quality of life post-surgery and/or subsequent reductions in resource use.

1.1.11.5 Other factors the committee took into account

The committee considered health inequalities while making recommendations. The studies mostly included people with a mean age between 60 and 75 years. Older people may be more likely to develop osteoarthritis and so require consideration for surgery. The studies included did not report socioeconomic status. People from lower socioeconomic backgrounds may be more likely to develop osteoarthritis and could be more likely to have other factors that will influence the decision-making regarding surgery (for example: people may be of a higher or lower weight). Ethnicity was not reported in the included studies, though one included study was a sub-study of another trial where non-white women were excluded. Intersectionality may exist with other groups that experience health inequities. The committee agreed that any further research should be representative of the population, including people from different family backgrounds, and socioeconomic backgrounds, disabled people, and people of different ages and genders. Future work should be done to consider the different experiences of people from diverse communities to ensure that the approach taken can be made equitable for everyone. With this in mind the committee included these protected characteristics in the multivariate analysis for their research recommendation where appropriate while suggesting that people from each group should be included in the research to ensure that it is applicable to the entire population.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.1 to 1.6.2 and the research recommendation on referral for joint replacement. Other evidence supporting these recommendations can be found in evidence review O.

1.1.13 References

1. Agricola R, Heijboer MP, Bierma-Zeinstra SM, Verhaar JA, Weinans H, Waarsing JH. Cam impingement causes osteoarthritis of the hip: a nationwide prospective cohort study (CHECK). Annals of the Rheumatic Diseases. 2013; 72(6):918-923

2. Agricola R, Reijman M, Bierma-Zeinstra SM, Verhaar JA, Weinans H, Waarsing JH. Total hip replacement but not clinical osteoarthritis can be predicted by the shape of the hip: a prospective cohort study (CHECK). Osteoarthritis and Cartilage. 2013; 21(4):559-564

3. Barr RJ, Gregory JS, Reid DM, Aspden RM, Yoshida K, Hosie G et al. Predicting OA progression to total hip replacement: can we do better than risk factors alone using active shape modelling as an imaging biomarker? Rheumatology. 2012; 51(3):562-570

4. Bastick AN, Damen J, Agricola R, Brouwer RW, Bindels PJ, Bierma-Zeinstra SM. Characteristics associated with joint replacement in early symptomatic knee or hip osteoarthritis: 6-year results from a nationwide prospective cohort study (CHECK). British Journal of General Practice. 2017; 67(663):e724-e731

5. Bastick AN, Runhaar J, Belo JN, Bierma-Zeinstra SM. Prognostic factors for progression of clinical osteoarthritis of the knee: a systematic review of observational studies. Arthritis Research & Therapy. 2015; 17:152

6. Betancourt MC, Linden JC, Rivadeneira F, Rozendaal RM, Zeinstra SM, Weinans H et al. Dual energy x-ray absorptiometry analysis contributes to the prediction of hip osteoarthritis progression. Arthritis Research & Therapy. 2009; 11(6):R162

7. Bevers K, Vriezekolk JE, Bijlsma JW, van den Ende CH, den Broeder AA. Ultrasonographic predictors for clinical and radiological progression in knee osteoarthritis after 2 years of follow-up. Rheumatology. 2015; 54(11):2000-2003

8. Bihlet AR, Bjerre-Bastos JJ, Andersen JR, Byrjalsen I, Karsdal MA, Bay-Jensen AC. Clinical and biochemical factors associated with risk of total joint replacement and radiographic progression in osteoarthritis: Data from two phase III clinical trials. Seminars in Arthritis and Rheumatism. 2020; 50(6):1374-1381

9. Birch S, Stilling M, Mechlenburg I, Reinholdt MB, Hansen TB. Association between pain catastrophizing, physical function and pain at first visit in the outpatient knee clinic. Knee. 2019; 26(6):1286-1291

10. Birrell F, Afzal C, Nahit E, Lunt M, Macfarlane GJ, Cooper C et al. Predictors of hip joint replacement in new attenders in primary care with hip pain. British Journal of General Practice. 2003; 53(486):26-30

11. Bouyer B, Mazieres B, Guillemin F, Bouttier R, Fautrel B, Morvan J et al. Association between hip morphology and prevalence, clinical severity and progression of hip osteoarthritis over 3 years: The knee and hip osteoarthritis long-term assessment cohort results. Joint, Bone, Spine: Revue du Rhumatisme. 2016; 83(4):432-438

12. Bruyere O, Cooper C, Pavelka K, Rabenda V, Buckinx F, Beaudart C et al. Changes in structure and symptoms in knee osteoarthritis and prediction of future knee replacement over 8 years. Calcified Tissue International. 2013; 93(6):502-507

13. Chan WP, Hsu SM, Huang GS, Yao MS, Chang YC, Ho WP. Creation of a reflecting formula to determine a patient's indication for undergoing total knee arthroplasty. Journal of Orthopaedic Science. 2010; 15(1):44-50

14. Clausen S, Hartvigsen J, Boyle E, Roos EM, Gronne DT, Ernst MT et al. Prognostic factors of total hip replacement during a 2-year period in participants enrolled in supervised education and exercise therapy: a prognostic study of 3657 participants with hip osteoarthritis. Arthritis Research & Therapy. 2021; 23(1):235

15. Collins JE, Katz JN, Dervan EE, Losina E. Trajectories and risk profiles of pain in persons with radiographic, symptomatic knee osteoarthritis: data from the osteoarthritis initiative. Osteoarthritis and Cartilage. 2014; 22(5):622-630

16. Collins JE, Neogi T, Losina E. Trajectories of Structural Disease Progression in Knee Osteoarthritis. Arthritis Care and Research. 2021; 73(9):1354-1362

17. Conaghan PG, D'Agostino MA, Le Bars M, Baron G, Schmidely N, Wakefield R et al. Clinical and ultrasonographic predictors of joint replacement for knee osteoarthritis: results from a large, 3-year, prospective EULAR study. Annals of the Rheumatic Diseases. 2010; 69(4):644-647

18. Costa D, Rodrigues A, Cruz E, Canhao H, Branco J, Nunes C. Healthcare use among people with knee osteoarthritis is driven by social determinants - results from a cross-sectional nationwide study. Osteoarthritis and Cartilage. 2021; 29 (Suppl 1):S385-S386

19. Costello KE, Astephen Wilson JL, Hubley-Kozey CL. Association of low physical activity levels with gait patterns considered at risk for clinical knee osteoarthritis progression. ACR Open Rheumatology. 2021; 3(11):753-763

20. Dabare C, Le Marshall K, Leung A, Page CJ, Choong PF, Lim KK. Differences in presentation, progression and rates of arthroplasty between hip and knee osteoarthritis: Observations from an osteoarthritis cohort study-a clear role for conservative management. International Journal of Rheumatic Diseases. 2017; 20(10):1350-1360

21. Dakin H, Gray A, Fitzpatrick R, MacLennan G, Murray D, Group KATT. Rationing of total knee replacement: a cost-effectiveness analysis on a large trial data set. BMJ Open. 2012; 2(1):e000332

22. Davis JE, Liu SH, Lapane K, Harkey MS, Price LL, Lu B et al. Adults with incident accelerated knee osteoarthritis are more likely to receive a knee replacement: data from the Osteoarthritis Initiative. Clinical Rheumatology. 2018; 37(4):1115-1118

23. Dieppe P, Cushnaghan J, Tucker M, Browning S, Shepstone L. The Bristol 'OA500 study': progression and impact of the disease after 8 years. Osteoarthritis and Cartilage. 2000; 8(2):63-68

24. Dieppe P, Lim K, Lohmander S. Who should have knee joint replacement surgery for osteoarthritis? International Journal of Rheumatic Diseases. 2011; 14(2):175-180

25. Dougados M, Gueguen A, Nguyen M, Berdah L, Lequesne M, Mazieres B et al. Requirement for total hip arthroplasty: an outcome measure of hip osteoarthritis? Journal of Rheumatology. 1999; 26(4):855-861

26. Dreinhofer KE, Dieppe P, Sturmer T, Grober-Gratz D, Floren M, Gunther KP et al. Indications for total hip replacement: comparison of assessments of orthopaedic surgeons and referring physicians. Annals of the Rheumatic Diseases. 2006; 65(10):1346-1350

27. Driban JB, Harkey MS, Price LL, Lo GH, McAlindon TE. The Inverse OARSI-OMERACT criteria is a valid indicator of the clinical worsening of knee Osteoarthritis: data from the Osteoarthritis initiative. Journal of Rheumatology. 2021; 48(3):442-446

28. Driban JB, Price LL, Lynch J, Nevitt M, Lo GH, Eaton CB et al. Defining and evaluating a novel outcome measure representing end-stage knee osteoarthritis: data from the Osteoarthritis Initiative. Clinical Rheumatology. 2016; 35(10):2523-2530

29. Faschingbauer M, Kasparek M, Schadler P, Trubrich A, Urlaub S, Boettner F. Predictive values of WOMAC, KOOS, and SF-12 score for knee arthroplasty: data from the OAI. Knee Surgery, Sports Traumatology, Arthroscopy. 2017; 25(11):3333-3339

30. Ferguson R, Prieto-Alhambra D, Peat G, Delmestri A, Jordan KP, Strauss VY et al. Influence of pre-existing multimorbidity on receiving a hip arthroplasty: cohort study of 28 025 elderly subjects from UK primary care. BMJ Open. 2021; 11(9):e046713

31. Fox KM, Hochberg MC, Resnik CS, Kenzora JE, Hebel JR, Zimmerman SI et al. Severity of radiographic findings in hip osteoarthritis associated with total hip arthroplasty. Journal of Rheumatology. 1996; 23(4):693-697

32. Gillam MH, Lie SA, Salter A, Furnes O, Graves SE, Havelin LI et al. The progression of end-stage osteoarthritis: analysis of data from the Australian and Norwegian joint replacement registries using a multi-state model. Osteoarthritis and Cartilage. 2013; 21(3):405-412

33. Gossec L, Paternotte S, Maillefert JF, Combescure C, Conaghan PG, Davis AM et al. The role of pain and functional impairment in the decision to recommend total joint replacement in hip and knee osteoarthritis: an international cross-sectional study of 1909 patients. Report of the OARSI-OMERACT Task Force on total joint replacement. Osteoarthritis and Cartilage. 2011; 19(2):147-154

34. Gossec L, Tubach F, Baron G, Ravaud P, Logeart I, Dougados M. Predictive factors of total hip replacement due to primary osteoarthritis: a prospective 2 year study of 505 patients. Annals of the Rheumatic Diseases. 2005; 64(7):1028-1032

35. Gwynne-Jones JH, Wilson RA, Wong JMY, Abbott JH, Gwynne-Jones DP. The outcomes of nonoperative management of patients with hip and knee osteoarthritis triaged to a physiotherapy-led clinic at minimum 5-year follow-up and factors associated with progression to surgery. Journal of Arthroplasty. 2020; 35(6):1497-1503

36. Hafezi-Nejad N, Guermazi A, Roemer FW, Eng J, Zikria B, Demehri S. Long term use of analgesics and risk of osteoarthritis progressions and knee replacement: propensity score matched cohort analysis of data from the Osteoarthritis Initiative. Osteoarthritis and Cartilage. 2016; 24(4):597-604

37. Harms S, Larson R, Sahmoun AE, Beal JR. Obesity increases the likelihood of total joint replacement surgery among younger adults. International Orthopaedics. 2007; 31(1):23-26

38. Hawker GA, Badley EM, Borkhoff CM, Croxford R, Davis AM, Dunn S et al. Which patients are most likely to benefit from total joint arthroplasty? Arthritis and Rheumatism. 2013; 65(5):1243-1252

39. Hirschmann MT, Testa E, Amsler F, Friederich NF. The unhappy total knee arthroplasty (TKA) patient: higher WOMAC and lower KSS in depressed patients prior and after TKA. Knee Surgery, Sports Traumatology, Arthroscopy. 2013; 21(10):2405-2411

40. Huynh C, Puyraimond-Zemmour D, Maillefert JF, Conaghan PG, Davis AM, Gunther KP et al. Factors associated with the orthopaedic surgeon's decision to recommend total joint replacement in hip and knee osteoarthritis: an international cross-sectional study of 1905 patients. Osteoarthritis and Cartilage. 2018; 26(10):1311-1318

41. Kanthawang T, Lee A, Baal JD, Joseph GB, Vail T, Link TM et al. Predicting outcomes in patients undergoing intra-articular corticosteroid hip injections. Skeletal Radiology. 2021; 50(7):1347-1357

42. Kany J, Benkalfate T, Favard L, Teissier P, Charousset C, Flurin PH et al. Osteoarthritis of the shoulder in under-50 year-olds: A multicenter retrospective study of 273 shoulders by the French Society for Shoulder and Elbow (SOFEC). Orthopaedics & Traumatology, Surgery & Research. 2021; 107(1):102756

43. Kastelein M, Luijsterburg PA, Belo JN, Verhaar JA, Koes BW, Bierma-Zeinstra SM. Six-year course and prognosis of nontraumatic knee symptoms in adults in general

practice: a prospective cohort study. Arthritis Care and Research. 2011; 63(9):1287-1294

44. Kwoh CK, Guehring H, Aydemir A, Hannon MJ, Eckstein F, Hochberg MC. Predicting knee replacement in participants eligible for disease-modifying osteoarthritis drug treatment with structural endpoints. Osteoarthritis and Cartilage. 2020; 28(6):782-791

45. Lane NE, Nevitt MC, Hochberg MC, Hung YY, Palermo L. Progression of radiographic hip osteoarthritis over eight years in a community sample of elderly white women. Arthritis and Rheumatism. 2004; 50(5):1477-1486

46. Ledingham A, Cohn ES, Baker KR, Keysor JJ. Exercise adherence: beliefs of adults with knee osteoarthritis over 2 years. Physiotherapy Theory & Practice. 2020; 36(12):1363-1378

47. Leung YY, Allen JC, Jr., Noviani M, Ang LW, Wang R, Yuan JM et al. Association between body mass index and risk of total knee replacement, the Singapore Chinese Health Study. Osteoarthritis and Cartilage. 2015; 23(1):41-47

48. Levine ME, Nace J, Kapadia BH, Issa K, Banerjee S, Cherian JJ et al. Treatment of primary hip osteoarthritis for the primary care physician and the indications for total hip arthroplasty. Journal of Long-Term Effects of Medical Implants. 2013; 23(4):323-330

49. Leyland KM, Judge A, Javaid MK, Diez-Perez A, Carr A, Cooper C et al. Obesity and the relative risk of knee replacement surgery in patients with knee osteoarthritis: A prospective cohort study. Arthritis & Rheumatology. 2016; 68(4):817-825

50. Lievense AM, Koes BW, Verhaar JA, Bohnen AM, Bierma-Zeinstra SM. Prognosis of hip pain in general practice: a prospective followup study. Arthritis and Rheumatism. 2007; 57(8):1368-1374

51. MacIntyre NJ, Johnson J, MacDonald N, Pontarini L, Ross K, Zubic G et al. Characteristics of people with hip or knee osteoarthritis deemed not yet ready for total joint arthroplasty at triage. Physiotherapy Canada. 2015; 67(4):369-377

52. Maillefert JF, Gueguen A, Nguyen M, Berdah L, Lequesne M, Mazieres B et al. A composite index for total hip arthroplasty in patients with hip osteoarthritis. Journal of Rheumatology. 2002; 29(2):347-352

53. Maillefert JF, Roy C, Cadet C, Nizard R, Berdah L, Ravaud P. Factors influencing surgeons' decisions in the indication for total joint replacement in hip osteoarthritis in real life. Arthritis and Rheumatism. 2008; 59(2):255-262

54. Mancuso CA, Ranawat CS, Esdaile JM, Johanson NA, Charlson ME. Indications for total hip and total knee arthroplasties. Results of orthopaedic surveys. Journal of Arthroplasty. 1996; 11(1):34-46

55. Mandl LA. Determining who should be referred for total hip and knee replacements. Nature Reviews Rheumatology. 2013; 9(6):351-357

56. Mari K, Degieux P, Mistretta F, Guillemin F, Richette P. Cost utility modeling of early vs late total knee replacement in osteoarthritis patients. Osteoarthritis and Cartilage. 2016; 24(12):2069-2076

57. McHugh GA, Campbell M, Luker KA. GP referral of patients with osteoarthritis for consideration of total joint replacement: a longitudinal study. British Journal of General Practice. 2011; 61(589):e459-468

58. Medical Advisory Secretariat. Technologies for osteoarthritis of the knee: an evidence-based analysis. Toronto. 2005.

59. Mezhov V, Laslett LL, Ahedi H, Blizzard CL, Aspden RM, Gregory JS et al. Predictors of total hip replacement in community based older adults: a cohort study. Osteoarthritis and Cartilage. 2021; 29(8):1130-1137

60. Miura T, Kijima H, Konishi N, Kubota H, Yamada S, Tazawa H et al. Preoperative medications is one of the factor affecting patient-reported outcomes after total hip arthroplasty. Journal of Orthopaedics. 2021; 23:78-82

61. Mujica-Mota RE, Watson LK, Tarricone R, Jager M. Cost-effectiveness of timely versus delayed primary total hip replacement in Germany: A social health insurance perspective. Orthopedic Reviews. 2017; 9(3):7161

62. Mujica Mota RE. Cost-effectiveness analysis of early versus late total hip replacement in Italy. Value in Health. 2013; 16(2):267-279

63. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated October 2020]. London. National Institute for Health and Care Excellence, 2014. Available from: https://www.nice.org.uk/process/pmg20

64. Neufeld ME, Masri BA. Can the oxford knee and hip score identify patients who do not require total knee or hip arthroplasty? Bone & Joint Journal. 2019; 101-B(6 Suppl B):23-30

65. Peer MA, Lane J. The Knee Injury and Osteoarthritis Outcome Score (KOOS): a review of its psychometric properties in people undergoing total knee arthroplasty. Journal of Orthopaedic and Sports Physical Therapy. 2013; 43(1):20-28

66. Pelletier JP, Cooper C, Peterfy C, Reginster JY, Brandi ML, Bruyere O et al. What is the predictive value of MRI for the occurrence of knee replacement surgery in knee osteoarthritis? Annals of the Rheumatic Diseases. 2013; 72(10):1594-1604

67. Perry TA, Wang X, Gates L, Parsons CM, Sanchez-Santos MT, Garriga C et al. Occupation and risk of knee osteoarthritis and knee replacement: A longitudinal, multiple-cohort study. Seminars in Arthritis and Rheumatism. 2020; 50(5):1006-1014

68. Ponzio DY, Rothermel SD, Chiu YF, Stavrakis AI, Lyman S, Windsor RE. Does physical activity level influence total hip arthroplasty expectations, satisfaction, and outcomes? Journal of Arthroplasty. 2021; 36(8):2850-2857

69. Pope JE, McCrea K, Stevens A, Ouimet JM. The relationship between NSAID use and osteoarthritis (OA) severity in patients with hip and knee OA: results of a case control study of NSAID use comparing those requiring hip and knee replacements to those in whom surgery was not recommended. Medical Science Monitor. 2008; 14(12):CR604-610

70. Price AJ, Kang S, Cook JA, Dakin H, Blom A, Arden N et al. The use of patient-reported outcome measures to guide referral for hip and knee arthroplasty. Bone & Joint Journal. 2020; 102-B(7):941-949

71. Quintana JM, Escobar A, Azkarate J, Goenaga JI, Bilbao A. Appropriateness of total hip joint replacement. International Journal for Quality in Health Care. 2005; 17(4):315-321

72. Rahman MM, Kopec JA, Sayre EC, Greidanus NV, Aghajanian J, Anis AH et al. Effect of sociodemographic factors on surgical consultations and hip or knee replacements among patients with osteoarthritis in British Columbia, Canada. Journal of Rheumatology. 2011; 38(3):503-509

73. Rajamaki TJ, Moilanen T, Puolakka PA, Hietaharju A, Jamsen E. Is the preoperative use of antidepressants and benzodiazepines associated with opioid and other analgesic use after hip and knee arthroplasty? Clinical Orthopaedics and Related Research. 2021; 479(10):2268-2280

74. Reijman M, Bierma-Zeinstra SM, Pols HA, Koes BW, Stricker BH, Hazes JM. Is there an association between the use of different types of nonsteroidal antiinflammatory drugs and radiologic progression of osteoarthritis? The Rotterdam Study. Arthritis and Rheumatism. 2005; 52(10):3137-3142

75. Riddle DL. Prevalence of similar or worse symptom and osteoarthritis severity of index and contralateral knees prior to knee arthroplasty: A cross-sectional multicenter cohort study. Knee. 2020; 27(2):485-492

76. Riddle DL, Dumenci L. Self-rated health and symptomatic knee osteoarthritis over three years: data from a multicenter observational cohort study. Arthritis Care and Research. 2013; 65(2):169-176

77. Riddle DL, Jiranek WA. Knee osteoarthritis radiographic progression and associations with pain and function prior to knee arthroplasty: a multicenter comparative cohort study. Osteoarthritis and Cartilage. 2015; 23(3):391-396

78. Riddle DL, Kong X, Jiranek WA. Factors associated with rapid progression to knee arthroplasty: complete analysis of three-year data from the osteoarthritis initiative. Joint, Bone, Spine: Revue du Rhumatisme. 2012; 79(3):298-303

79. Riddle DL, Perera RA, Stratford PW, Jiranek WA, Dumenci L. Progressing toward, and recovering from, knee replacement surgery: a five-year cohort study. Arthritis and Rheumatism. 2013; 65(12):3304-3313

80. Schiphof D, Runhaar J, Waarsing JH, van Spil WE, van Middelkoop M, Bierma-Zeinstra SMA. The clinical and radiographic course of early knee and hip osteoarthritis over 10 years in CHECK (Cohort Hip and Cohort Knee). Osteoarthritis and Cartilage. 2019; 27(10):1491-1500

81. Tambascia RA, Vasconcelos RA, Mello W, Teixeira PP, Grossi DB. Pre-operative functional parameters of patients undergoing total knee arthroplasty. Physiotherapy Research International. 2016; 21(2):77-83

82. Teirlinck CH, Dorleijn DMJ, Bos PK, Rijkels-Otters JBM, Bierma-Zeinstra SMA, Luijsterburg PAJ. Prognostic factors for progression of osteoarthritis of the hip: a systematic review. Arthritis Research & Therapy. 2019; 21(1):192

83. Teng GG, Leung YY, Ang LW, Yuan JM, Koh WP. Gout and risk of knee replacement for severe knee osteoarthritis in the Singapore Chinese Health Study. Osteoarthritis and Cartilage. 2017; 25(12):1962-1968

84. Tolpadi AA, Lee JJ, Pedoia V, Majumdar S. Deep learning predicts total knee replacement from magnetic resonance images. Scientific Reports. 2020; 10(1):6371

85. Turcotte JJ, Kelly ME, Aja JM, King PJ, MacDonald JH. Risk factors for progression to total knee arthroplasty within two years of presentation for knee osteoarthritis. Journal of Clinical Orthopaedics & Trauma. 2021; 16:257-263

86. van de Sande MA, Brand R, Rozing PM. Indications, complications, and results of shoulder arthroplasty. Scandinavian Journal of Rheumatology. 2006; 35(6):426-434

87. Vinciguerra C, Gueguen A, Revel M, Heuleu JN, Amor B, Dougados M. Predictors of the need for total hip replacement in patients with osteoarthritis of the hip. Revue du rhumatisme (english edition). 1995; 62(9):563-570

88. Wang Y, Simpson JA, Wluka AE, Urquhart DM, English DR, Giles GG et al. Reduced rates of primary joint replacement for osteoarthritis in Italian and Greek migrants to Australia: the Melbourne Collaborative Cohort Study. Arthritis Research & Therapy. 2009; 11(3):R86

89. Wang Y, You L, Chyr J, Lan L, Zhao W, Zhou Y et al. Causal discovery in radiographic markers of knee osteoarthritis and prediction for knee osteoarthritis severity with attention-long short-term memory. Frontiers in Public Health. 2020; 8:604654

90. Weigl M, Pietzner J, Kisch R, Paulus A, Jansson V, Grill E. Effects of a medical second opinion programme on patients' decision for or against knee arthroplasty and their satisfaction with the programme. BMC Musculoskeletal Disorders. 2021; 22(1):595

91. Wijn SRW, Rovers MM, van Tienen TG, Hannink G. Intra-articular corticosteroid injections increase the risk of requiring knee arthroplasty. Bone & Joint Journal. 2020; 102-B(5):586-592

92. Zeng C, Lane NE, Hunter DJ, Wei J, Choi HK, McAlindon TE et al. Intra-articular corticosteroids and the risk of knee osteoarthritis progression: results from the Osteoarthritis Initiative. Osteoarthritis and Cartilage. 2019; 27(6):855-862

93. Zeni JA, Jr., Axe MJ, Snyder-Mackler L. Clinical predictors of elective total joint replacement in persons with end-stage knee osteoarthritis. BMC Musculoskeletal Disorders. 2010; 11:86

Appendices

Appendix A – Review protocols

Review protocol for what are the indicators for possible joint replacement surgery?

ID	Field	Content
0.	PROSPERO registration number	CRD42021230913
1.	Review title	What are the indicators for referral for possible primary joint replacement surgery?
2.	Review question	8.1 What are the indicators for possible joint replacement surgery?
3.	Objective	To determine which risk factors presenting in primary care accurately predict the progression to joint replacement surgery being carried out.
4.	Searches	The following databases (from inception) will be searched: • Embase • MEDLINE Searches will be restricted by: • English language • Human studies • Letters and comments are excluded Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Osteoarthritis or suspected osteoarthritis (of any joint) in adults.
6.	Population	Inclusion: • Adults (age ≥16 years) with osteoarthritis affecting any joint. Stratification by joint site ○ Hip

		○ Knee ○ Shoulder If there is a mixed joint site population we would use an 80% cut-off point. Exclusion: • Children (age <16 years) • People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, diseases of childhood that may predispose to osteoarthritis, medical conditions presenting with joint inflammation and malignancy).
7.	Risk factors	Include any reasonable definition in the studies considered relevant to the factor of interest. Prognostic factors: • Presence of night pain • Non-response to analgesics/intra articular injections • Non-response to non-pharmacological interventions • Longer duration of symptoms • Instability symptoms • Presence of flares Oxford Knee Score by the following scale range categories: • 40-48 • 30-39 • 20-39 • 0-19 Oxford Hip Score by the following scale range categories: • 40-48 • 30-39 • 20-39 • 0-19 Shoulder scores: - Oxford Shoulder Score (OSS) - Constant Score - Shoulder Pain and Disability Index (SPADI) - The Disabilities of the Arm, Shoulder and Hand Score (DASH) KOOS/HOOS (summary score) WOMAC (summary score) EQ-5D/EQ VAS ○
8.	Confounding factors	Confounding factors that may be independently associated with prognostic variable:

		Key confounders: • Age • Body mass index All key confounders should be adjusted for in multivariate analysis. Other confounders: • Smoking status • Multimorbidity • Socio-economic factor These confounders will be assessed on a case-by-case basis.
9.	Types of study to be included	Prospective and retrospective cohort studies if all the key confounders have been accounted for in a multivariate analyses. In the absence of multivariate analysis, stepwise multivariate analysis would be included.
10.	Other exclusion criteria	• Non-English language studies • Case-control studies • Studies not accounting for all key confounders (prognostic factors) in a multivariable analysis • Studies using a univariate analysis or matched groups (matching for confounders alone is not sufficient as there are multiple confounders) • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Previous recommendations included patient-specific factors (e.g. age, sex, smoking, obesity and comorbidities) which should not be barriers to referral for joint replacement surgery. It was thought important that these recommendations are strengthened in this guideline so that there is not a restriction to access based on non-clinical factors. Therefore in this review we have tried to find the actual prognostic factors, presenting in primary care that will accurately predict the need to refer on for joint replacement.
12.	Primary outcomes (critical outcomes)	Progression to a joint replacement [time-to-event or dichotomous outcomes, time-to-event data prioritised]
13.	Secondary outcomes (important outcomes)	Not applicable
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.

		A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.	
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual • The QUIPs checklist will be used to assess risk of bias of each individual study.	
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. • Data from the meta-analysis will be presented and quality assessed in adapted GRADE tables taking into account individual study quality and the meta-analysis results The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each risk factor. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. Heterogeneity between studies in the effect measures will be assessed using the I^2 statistic and visual inspection. We will consider an I^2 value great than 50% as indicative of substantial heterogeneity. If significant heterogeneity is identified during meta-analysis then subgroup analysis, using subgroups predefined by the GC, will take place. If this does not explain the heterogeneity, the results will be presented using a random-effects model.	
17.	Analysis of sub-groups	None	
18.	Type and method of review	☐	Intervention
		☐	Diagnostic
		☒	Prognostic

		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	23/08/2019	
22.	Anticipated completion date	25/08/2021	
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☐ / ☐
		Piloting of the study selection process	☐ / ☐
		Formal screening of search results against eligibility criteria	☐ / ☐
		Data extraction	☐ / ☐
		Risk of bias (quality) assessment	☐ / ☐
		Data analysis	☐ / ☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail [Guideline email]@nice.org.uk [Developer to check with Guideline Coordinator for email address] 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre	

25.	Review team members	From the National Guideline Centre: Carlos Sharpin [Guideline lead] Julie Neilson [Senior systematic reviewer] George Wood [Systematic reviewer] David Wonderling [Senior health economist] Joseph Runicles [Information specialist] Amber Hernaman [Project manager]	
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10127	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Adults; Joint replacement surgery; Osteoarthritis; Prognostic; Quality of life; Referral; Secondary care	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☒	Ongoing
		☐	Completed but not published

		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

Table 9: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken for all years using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published in 2005 or later, that were included in the previous guidelines, will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[63] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies.

	Setting: • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2005 or later (including any such studies included in the previous guidelines) but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as 'Not applicable'. • Studies published before 2005 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

- What are the indicators for referral for possible primary joint replacement surgery?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[63]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed by combining an Osteoarthritis population with prognostic/risk factor terms and search filters.

Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 17 November 2021	Observational studies Prognostic studies Exclusions (animals studies, letters, comments)
Embase (OVID)	1974 – 17 November 2021	Observational studies Prognostic studies Exclusions (animals studies, letters, comments)

Medline (Ovid) search terms

1.	exp osteoarthritis/
2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3.	(degenerative adj2 arthritis).ti,ab.
4.	coxarthrosis.ti,ab.
5.	gonarthrosis.ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/

21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	predict.ti.
28.	(validat* or rule*).ti,ab.
29.	(predict* and (outcome* or risk* or model*)).ti,ab.
30.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
31.	decision*.ti,ab. and Logistic models/
32.	(decision* and (model* or clinical*)).ti,ab.
33.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
34.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
35.	ROC curve/
36.	or/27-35
37.	Epidemiologic studies/
38.	Observational study/
39.	exp Cohort studies/
40.	(cohort adj (study or studies or analys* or data)).ti,ab.
41.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
42.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
43.	Controlled Before-After Studies/
44.	Historically Controlled Study/
45.	Interrupted Time Series Analysis/
46.	(before adj2 after adj2 (study or studies or data)).ti,ab.
47.	exp case control studies/
48.	case control*.ti,ab.
49.	Cross-sectional studies/
50.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
51.	or/37-50
52.	((hip* or knee* or shoulder* or joint*) adj (replace* or arthroplast* or prosthe* or endoprosthe* or implant* or artifical)).ti,ab.
53.	exp *arthroplasty, replacement, hip/ or exp *arthroplasty, replacement, knee/ or exp *arthroplasty, replacement, shoulder/
54.	52 or 53
55.	26 and 54
56.	55 and (36 or 51)
57.	exp "referral and consultation"/
58.	(assessment* or evaluation* or decision* or criteria*).ti,ab.
59.	(refer or referr* or consult* or progress* or recommend*).ti,ab.

60.	or/57-59
61.	56 and 60

Embase (Ovid) search terms

1.	exp osteoarthritis/
2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3.	(degenerative adj2 arthritis).ti,ab.
4.	coxarthrosis.ti,ab.
5.	gonarthrosis.ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	(conference abstract or conference paper).pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	or/7-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animal/ not human/
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	6 not 23
25.	limit 24 to English language
26.	predict.ti.
27.	(validat* or rule*).ti,ab.
28.	(predict* and (outcome* or risk* or model*)).ti,ab.
29.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
30.	decision*.ti,ab. and Statistical model/
31.	(decision* and (model* or clinical*)).ti,ab.
32.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
33.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
34.	Receiver operating characteristic/
35.	or/26-34
36.	Clinical study/
37.	Observational study/
38.	family study/

39.	longitudinal study/
40.	retrospective study/
41.	prospective study/
42.	cohort analysis/
43.	follow-up/
44.	cohort*.ti,ab.
45.	43 and 44
46.	(cohort adj (study or studies or analys* or data)).ti,ab.
47.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
48.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
49.	(before adj2 after adj2 (study or studies or data)).ti,ab.
50.	exp case control study/
51.	case control*.ti,ab.
52.	cross-sectional study/
53.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
54.	or/36-42,45-53
55.	((hip* or knee* or shoulder* or joint*) adj (replace* or arthroplast* or prosthe* or endoprosthe* or implant* or artifical)).ti,ab.
56.	exp *hip arthroplasty/ or exp *knee arthroplasty/ or exp *shoulder arthroplasty/
57.	55 or 56
58.	25 and 57
59.	58 and (35 or 54)
60.	exp patient referral/
61.	(assessment* or evaluation* or decision* or criteria*).ti,ab.
62.	(refer or referr* or consult* or progress* or recommend*).ti,ab.
63.	or/60-62
64.	59 and 63

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to a Gout population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updates after March 2018). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies and quality of life studies. Searches for quality of life studies were run for general information.

Table 11: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	1 January 2014 – 17 November 2021	Health economics studies Quality of life studies Exclusions (animals studies, letters, comments)

Database	Dates searched	Search filter used
Embase	1 January 2014 – 17 November 2021	Health economics studies Quality of life studies Exclusions (animals studies, letters, comments)
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp osteoarthritis/
2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3.	(degenerative adj2 arthritis).ti,ab.
4.	coxarthrosis.ti,ab.
5.	gonarthrosis.ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/

31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	quality-adjusted life years/
45.	sickness impact profile/
46.	(quality adj2 (wellbeing or well being)).ti,ab.
47.	sickness impact profile.ti,ab.
48.	disability adjusted life.ti,ab.
49.	(qal* or qtime* or qwb* or daly*).ti,ab.
50.	(euroqol* or eq5d* or eq 5*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/44-61
63.	26 and (43 or 62)

Embase (Ovid) search terms

1.	exp osteoarthritis/
2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3.	(degenerative adj2 arthritis).ti,ab.
4.	coxarthrosis.ti,ab.

5.	gonarthrosis.ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice or rodent*).ti.
22.	or/14-21
23.	6 not 22
24.	Limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	quality adjusted life year/
40.	"quality of life index"/
41.	short form 12/ or short form 20/ or short form 36/ or short form 8/
42.	sickness impact profile/
43.	(quality adj2 (wellbeing or well being)).ti,ab.

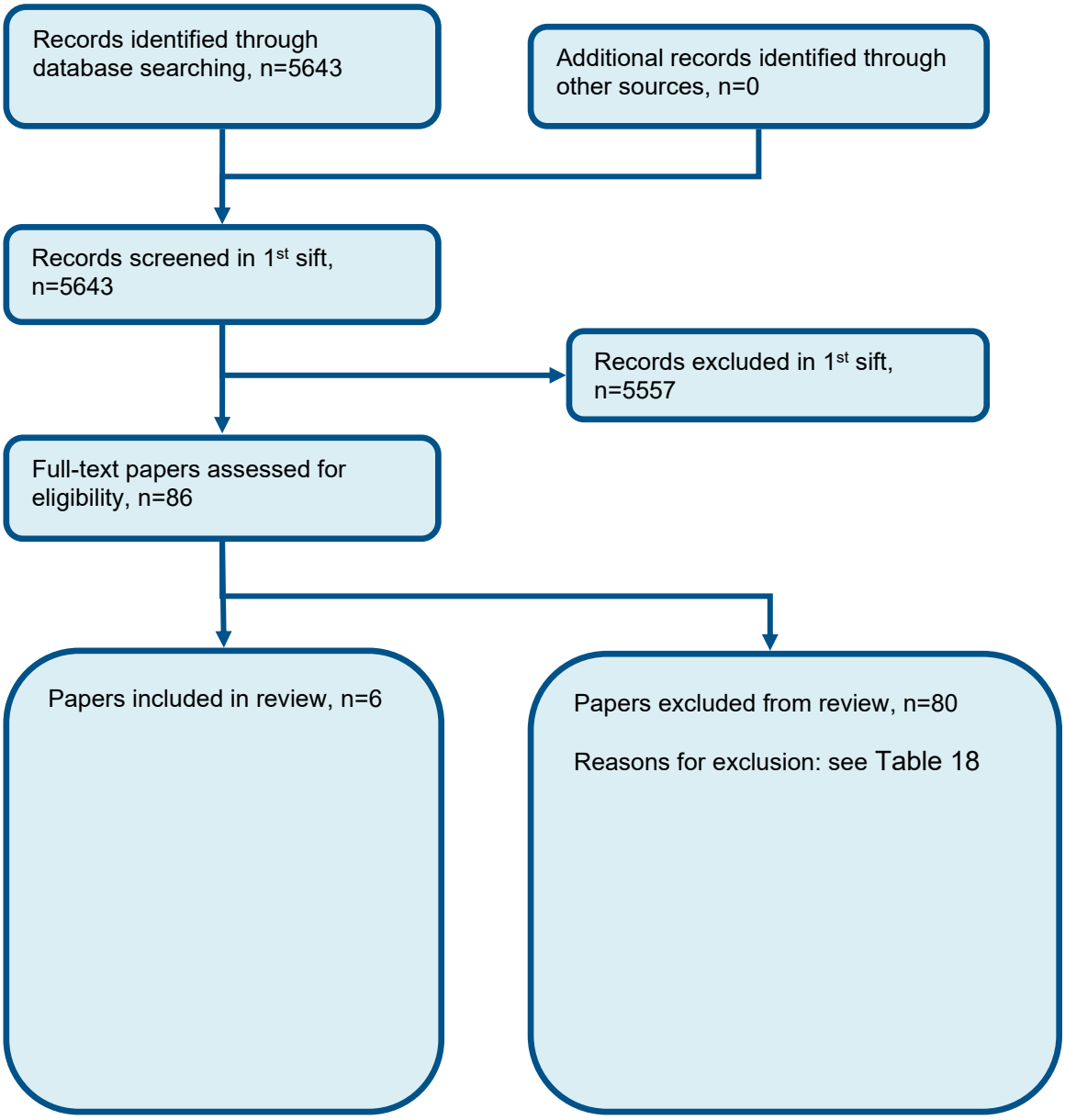
44.	sickness impact profile.ti,ab.
45.	disability adjusted life.ti,ab.
46.	(qal* or qtime* or qwb* or daly*).ti,ab.
47.	(euroqol* or eq5d* or eq 5*).ti,ab.
48.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
49.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
50.	(hui or hui1 or hui2 or hui3).ti,ab.
51.	(health* year* equivalent* or hye or hyes).ti,ab.
52.	discrete choice*.ti,ab.
53.	rosser.ti,ab.
54.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
55.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
56.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
57.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
58.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
59.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
60.	or/39-59
61.	24 and (38 or 60)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Osteoarthritis EXPLODE ALL TREES
#2.	((osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*))
#3.	((degenerative adj2 arthritis))
#4.	(coxarthrosis)
#5.	(gonarthrosis)
#6.	#1 OR #2 OR #3 OR #4 OR #5
#7.	(#6) IN NHSEED
#8.	(#6) IN HTA

Appendix C – Prognostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of the indicators for referral for possible joint replacement surgery



Appendix D – Prognostic evidence

Reference	Clausen 2021[14]
Study type and analysis	Prospective cohort study Time to joint replacement surgery within 2 years estimated using a multivariable Cox proportional hazards model. Multivariable analysis including: gender, BMI, smoking, employment, use of pain medication the last three months, self-reported radiographic osteoarthritis, presence of comorbidities, wait-listed for total hip replacement, joint replacement in other hip or knees, bilateral hip symptoms, number of painful areas during the last 24 hours, hip pain (VAS), HOOS QoL score, 40m walk test Denmark, primary care setting (using registry data).
Number of participants and characteristics	N=3965 enrolled, 308 excluded due to previous total hip replacement in the index hip (n=72) or missing data in a candidate predictor variable (n=236). No participants emigrated. 32 participants died during the study before any total hip replacement. People who received joint replacement surgery over 2 years: 1114 (30%) People who did not received joint replacement surgery over 2 years: 2543 (70%) People enrolled into the GLA:D study (Good Life with osteoarthritis in Denmark) from July 1st 2014 to March 1st 2017 including people with knee or hip osteoarthritis who attended two education sessions and twelve sessions of supervised neuromuscular exercises delivered in primary care settings by trained physiotherapists. **Inclusion criteria:** 45 years or older; had a primary complaint of hip pain. **Exclusion criteria:** Reported total hip replacement in the index hip at baseline; incomplete data for any candidate prognostic factors. **Values listed below are presented as mean (SD) or number (%) unless stated otherwise** • Age: 66.5 (8.6) years • Female: 2687 (73%) • Body mass index: 26.9 (4.7) kg/m^2

Reference	Clausen 2021[14]

	• Current smoking: 353 (9.7%)
	• Living alone: 1006 (28%)
	• Sick leave due to hip problems for more than one month during the past 12 months: 93 (2.5%).
	• Educational level:
	  ○ Primary and lower secondary school (9-10 years): 620 (17%)
	  ○ Higher general examination program (12-13 years): 372 (10%)
	  ○ Short-cycle higher education (less than three years more): 665 (18%)
	  ○ Medium-cycle higher education (three to four years more): 1550 (42%)
	  ○ Long-cycle higher education (minimum five years more): 450 (12%)
	• Employment
	  ○ Employed/student: 1026 (28%)
	  ○ Unemployed: 49 (1.3%)
	  ○ Retired: 2131 (58%)
	  ○ Self-imposed early retirement: 222 (6.1%)
	  ○ Early retirement due to low ability to work: 119 (3.3%)
	  ○ On sick leave full time or part time: 110 (3.0%)
	• Self-reported radiographic osteoarthritis
	  ○ Had x-ray with radiographic osteoarthritis: 3007 (82%)
	  ○ Had x-ray without radiographic osteoarthritis: 131 (3.6%)
	  ○ Had no x-ray or do not know: 519 (14%)
	• Wait-listed for total hip replacement of the index hip: 100 (2.7%)
	• Joint replacement in the other hip or knees: 362 (9.9%)
	• Comorbidities
	  ○ None = 1425 (39%)
	  ○ One = 1321 (36%)
	  ○ Two = 616 (17%)
	  ○ Three or more: 295 (8%)
	• Pain medication in the last 3 months
	  ○ No use of pain medication: 1308 (36%)
	  ○ Had used only paracetamol/acetaminophen and/or NSAID: 2033 (56%)
	  ○ Has used opioids (Everyone using opioids also used paracetamol/acetaminophen and/or NSAID): 316 (8.6%)

Reference	Clausen 2021[14]
	• Fear of joint damage from physical activity: 365 (10%) • Bilateral hip symptoms: 946 (26%) • Number of painful areas during the last 24 hours (median [IQR]): 3 (3) • Average hip pain for the last month (VAS) (median [IQR): 48 (21) • Duration of symptoms in the index joint (median [IQR]): 24 (40) months • UCL activity score (1-10) (median [IQR]): 6 (3) • HOOS quality of life (0-100) (median [IQR]): 68 (26) • Self-Efficacy (ASES) (10-100) (median [IQR]): 68 (26) • Health-related quality of life (EQ-5D-5L) (-0.624-1) (median [IQR]): 0.723 (0.110) • 40 m walk test (m/s) (median [IQR]): 1.49 (0.43) m/s • 30s chair stand test (number of rises) (median [IQR]): 12 (5) **Population source:** People from an exercise and education study conducted over July 1st 2014 to March 1st 2017.
Prognostic variables	Non-response to analgesics/intra articular injections – Use of pain medication in the last three months (vs. no pain medication) (note: this include paracetamol, NSAIDs and opioids only) Non-response to non-pharmacological interventions – Hip pain (VAS, 0-100) KOOS/HOOS (summary score) – HOOS quality of life score
Confounders	Multivariable analysis Factors included in the adjusted analysis: gender, BMI, smoking, employment, use of pain medication the last three months, self-reported radiographic osteoarthritis, presence of comorbidities, wait-listed for total hip replacement, joint replacement in other hip or knees, bilateral hip symptoms, number of painful areas during the last 24 hours, hip pain (VAS), HOOS QoL score, 40m walk test
Outcomes and effect sizes	Time to joint replacement **Time to joint replacement – Non-response to analgesics/intra articular injections** • **HR 1.42 (1.23, 1.63)** **Time to joint replacement – Non-response to non-pharmacological interventions** • **HR 1.01 (1.00-1.01)** **Time to joint replacement – KOOS/HOOS summary score** • **HR 0.98 (0.97-0.98)**

Reference	Clausen 2021[14]
	Follow up: 2 years
Comments	**Non-response to analgesics/intra articular injections – use of pain medication in the last three months (vs. no pain medication)** Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS LOW **Non-response to non-pharmacological intervention – Hip pain (VAS, 0-100)** Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS LOW **KOOS/HOOS summary score – HOOS quality of life score** Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding LOW

Reference	Clausen 2021[14]	
	6. Statistical analysis	LOW
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	LOW
	Indirectness: Prognostic variable indirectness – HOOS quality of life score is not the total summary statistic for HOOS and so is downgraded for indirectness. Non-response to analgesics is including people using pain medication in the last three months, using the assumption that if they have a joint replacement surgery after this then they did not respond to analgesics, and so is downgraded for indirectness. Non-response to non-pharmacological intervention assumes that hip pain would measure response to the exercise therapy received by all participants, and so is downgraded for indirectness.	

Reference	Dabare 2017[20]
Study type and analysis	Prospective cohort study Time to joint replacement surgery estimated using Kaplan-Meier estimates, log rank test and Cox regression. Multivariable analysis including: joint type; age; gender; BMI; Kellgren Lawrence grading scale; symptom duration; osteoarthritis elsewhere and KOOS/HOOS pain score. Australia, secondary care setting.

Number of participants and characteristics	N=247 enrolled, 7 with missing data for BMI at initial presentation were excluded from the analysis, 167 people with knee osteoarthritis, 80 people with hip osteoarthritis (considered as mixed osteoarthritis for the analysis).
	People who received joint replacement surgery over 6 years: 104 (42%)
	People who did not received joint replacement surgery over 6 years: 143 (58%)
	
	People with osteoarthritis of the hip and knee at the OAHKS clinic followed up prospectively as part of a larger longitudinal study started in 2007. Consecutive patients who attended the clinic between May 2008 and August 2009 were included.
	
	Inclusion criteria:
	Patients referred to the clinic with a diagnosis of knee or hip osteoarthritis; patients had current symptoms in knee or hip joint due to osteoarthritis fulfilling the American College of Rheumatology criteria.
	
	Exclusion criteria:
	Inability to complete the questionnaire because of language barriers; patients who did not fulfil the criteria for osteoarthritis.
	
	Values listed below are presented as mean (SD) or number (%) unless stated otherwise
	
	Knee osteoarthritis
	• Age (median [IQR]): 68.00 (60.00, 76.00) years
	• Male/female: 67/100 (40.1%/59.9%)
	• Body mass index (median [IQR]): 31.32 (27.40, 36.00) kg/m^2
	• Kellgren Lawrence grading scale
	  ○ Stage 1: 5 (3.0%)
	  ○ Stage 2: 19 (11.4%)
	  ○ Stage 3: 59 (35.3%)

Reference	Dabare 2017[20]
	○ Stage 4: 68 (40.7%) • Symptom duration (years) (median [IQR]): 3.90 (2.00, 8.00) • Number of comorbid conditions (median [IQR]): 2.00 (1.00, 3.00) ○ Hypertension: 96 (56.5%) ○ Osteoarthritis elsewhere: 93 (55.7%) ○ Diabetes: 39 (23.4%) ○ Ischaemic heart disease: 27 (16.2%) ○ Back pain: 15 (9.0%) • Baseline KOOS and HOOS scales (median [IQR]) ○ Quality of Life: 25.00 (12.50, 43.75) ○ Sport/Recreation: 0.00 (0.00, 10.00) ○ Activities of daily living: 42.65 (27.94, 58.82) ○ Symptom: 44.64 (32.14, 64.29) ○ Pain: 44.44 (30.56, 58.33) • Baseline MAPT: 22.78 (4.45, 52.53) **Hip osteoarthritis** • Age (median [IQR]): 67.00 (59.00, 75.00) years • Male/female: 49/31 (61.3%/38.8%) • Body mass index (median [IQR]): 27.54 (23.36, 31.97) kg/m^2 • Kellgren Lawrence grading scale ○ Stage 1: 2 (2.5%) ○ Stage 2: 9 (11.3%) ○ Stage 3: 22 (27.5%) ○ Stage 4: 45 (56.3%) • Symptom duration (years) (median [IQR]): 2.70 (1.60, 5.60) • Number of comorbid conditions (median [IQR]): 2.00 (1.00, 3.00) ○ Hypertension: 42 (52.5%) ○ Osteoarthritis elsewhere: 41 (51.2%) ○ Diabetes: 7 (8.7%) ○ Ischaemic heart disease: 7 (8.7%)

Reference	Dabare 2017[20]
	○ Back pain: 10 (12.5%) • Baseline KOOS and HOOS scales (median [IQR]) ○ Quality of Life: 31.25 (12.50, 43.75) ○ Sport/Recreation: 12.50 (3.13, 25.00) ○ Activities of daily living: 38.24 (22.06, 57.35) ○ Symptom: 45.00 (31.25, 65.00) ○ Pain: 37.50 (25.00, 52.50) • Baseline MAPT: 39.91 (16.28, 83.57) **Population source:** Consecutive patients from a longitudinal study started in 2007.
Prognostic variables	KOOS/HOOS (summary score) – KOOS and HOOS scales pain score Longer duration of symptoms – Symptom duration (years)
Confounders	Multivariable analysis Factors included in the adjusted analysis: joint type; age; gender; BMI; Kellgren Lawrence grading scale; symptom duration; osteoarthritis elsewhere and KOOS/HOOS pain score.
Outcomes and effect sizes	Time to joint replacement **Time to joint replacement – KOOS and HOOS scales pain score** • **HR 0.97 (0.96, 0.99)** **Time to joint replacement – Symptom duration (years)** • **HR 0.98 (0.94, 1.02)** Follow up: 6 years
Comments	**KOOS/HOOS (summary score) – KOOS and HOOS scales pain score** Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH

Reference	Dabare 2017[20]	
	6. Statistical analysis	LOW
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	HIGH
	Longer duration of symptoms – Symptom duration (years)	
	Risk of bias:	
	1. Study participation	LOW
	2. Study attrition	LOW
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	LOW
	5. Study confounding	HIGH
	6. Statistical analysis	LOW
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	HIGH
	Indirectness:	
	Prognostic variable indirectness – KOOS and HOOS scales pain score is not the total summary statistic for KOOS/HOOS and so is downgraded for indirectness.	

Reference	Gossec 2005[34]
Study type and analysis	Prospective cohort study A survival curve according to Kaplan-Meier's method. Multivariate analysis including the following variables: age, sex, body mass index, duration of symptoms, location of hip osteoarthritis, osteoarthritis in contralateral hip, radiological grade, previous treatment (NSAIDs or hip intra-articular injections), baseline pain, baseline WOMAC function score, baseline patient global assessment, mean pain over the first 6 months >42, mean WOMAC function score over the first 6 months >26, mean patient global assessment over the first 6 months >47. France, secondary care setting.
Number of participants and characteristics	N=741 enrolled, 115 lost to follow up at 2 years (3 died, 63 refused further follow up by their rheumatologist or moved out of the area, 49 no specified reason), 121 data was missing at the 2 year evaluation owing to the absence of an answer from the rheumatologist, 505 included. People who received total hip replacement over 2 years: 189 (37.4%) People who did not receive total hip replacement over 2 years: 316 (62.6%) People with hip osteoarthritis in a community based setting recruited by French rheumatologists who were initially entered into a therapeutic trial (investigating the effect of an unsupervised exercise program and/or patient-administered assessment tools). **Inclusion criteria:** Ambulatory outpatients aged 40 years or more; hip osteoarthritis according to the American College of Rheumatology definition; history of hip pain of >6 months; pain scored by the patient on a 100mm visual analogue scale (VAS) at least 30; pain for at least 14 days during the previous month. **Exclusion criteria:** Secondary arthritis as defined by the Osteoarthritis Research Society International (OARSI); an operation scheduled within the 12 months after inclusion; any type of surgery, including arthroscopy, of the study hip in the previous 2 years; serious concomitant illnesses (neoplasia, infectious diseases, unstable metabolic or cardiovascular diseases, systemic diseases); any intra-articular injection (hyaluronic acid or corticosteroids) during the 2 months before inclusion, joint lavage in the 3 months before inclusion, or recent introduction of slow acting anti-osteoarthritic drugs (in the 2 months before the study); contraindication of rofecoxib; participation in another research study. **Values listed below are presented as mean (SD) or number (%)**

Reference	Gossec 2005[34]

	• Age: 64.0 (10.1) years
	• Male/female: 196/309 (38.8%/61.2%)
	• Body mass index: 26.3 (4.6) kg/m^2
	• Pain (0-100 mm VAS): 55.0 (15.8) mm
	• WOMAC function score (0-100): 44.4 (16.2)
	• Patient global assessment (0-100 mm VAS): 57.8 (18.4) mm
	• Radiological grade (Kellgren-Lawrence)
	  ○ III: 273 (54.1%)
	  ○ IV: 142 (28.1%)
	• Previous treatment:
	  ○ NSAIDs: 331
	  ○ Intra-articular injections: 20
	
	Population source: Participants recruited from a therapeutic trial.

Prognostic variables	Non-response to analgesics/intra articular injections – Previous NSAID intake Longer duration of symptoms – Mean patient global assessment over the first 6 months >47 (0-100 mm VAS)
Confounders	Multivariable analysis Factors included in the adjusted analysis: age, gender, BMI, pain, Lequesne index, Patient overall assessment, femoral head migration, joint space width.
Outcomes and effect sizes	Previous NSAID intake Mean patient global assessment over the first 6 months >47 (0-100 mm VAS) **Joint replacement – Previous NSAID intake** • **OR 1.5 (1.0 to 2.4)** **Joint replacement – Mean patient global assessment over the first 6 months >47 (0-100 mm VAS)** • **OR 2.2 (1.4 to 3.2)** Follow up: 2 years
Comments	**Non-response to analgesics/intra articular injections – Previous NSAID intake** Risk of bias:

Reference	Gossec 2005[34]	
	1. Study participation	LOW
	2. Study attrition	HIGH
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	LOW
	5. Study confounding	HIGH
	6. Statistical analysis	LOW
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Longer duration of symptoms – Mean patient global assessment over the first 6 months >47 (0-100 mm VAS)	
	Risk of bias:	
	1. Study participation	LOW
	2. Study attrition	HIGH
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	LOW
	5. Study confounding	HIGH
	6. Statistical analysis	LOW
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Indirectness:	
	Prognostic variable indirectness – For both prognostic variables. Previous NSAID intake is included with the assumption that people did not respond to treatment if they required surgery, so has been downgraded for indirectness. Mean patient global assessment of pain over a specific value for the first 6 months is taken as an indirect measure of prolonged symptoms, so has been downgraded for this.	

Reference	Gwynne-Jones 2020 [35]
Study type and analysis	Prospective cohort study Kaplan-Meier curves calculated to determine survivorship of the affected joint with the end point of joint replacement. Univariate and multivariate Cox regression analyses performed to investigate the relationship among baseline variables including joint affected, radiographic grade, age, gender, BMI, PROMs and time to surgery. New Zealand, secondary care setting.
Number of participants and characteristics	N=339 enrolled, 2 excluded as referred with painful joint replacements 186 (55%) with knee osteoarthritis. 151 (45%) with hip osteoarthritis. People who received joint replacement surgery over a mean of 6.1 years: 188 (56%) – 186 had surgery, while 2 were waitlisted for surgery People who died without having surgery or were waitlisted by died before surgery over a mean of 6.1 years: 22 (7%) People were still being managed nonoperatively over a mean of 6.1 years: 127 (38%) People with hip or knee osteoarthritis referred by their GP to the orthopaedic department who were triaged to JC for evaluation. An individualised management program was developed which included advice on their condition, optimization of analgesia, and referral for an outpatient physiotherapy osteoarthritis program, occupational therapy, dietitian advice, or orthotic management where indicated. People could be referred for FSA if their presentation was severe enough. People were reviewed every 6 months until they were discharged back to GP if their symptoms were stable, or they had deteriorated to the extent that they needed referral for surgical assessment. **Inclusion criteria:** People with hip or knee osteoarthritis referred by their GP to the orthopaedic department (treated as mixed osteoarthritis for the analysis). **Exclusion criteria:** Not explicitly stated. **Values listed below are presented as mean (SD) or number (%)** **Knee osteoarthritis** • Age: 68.1 (9.2) years • Male/female: 84/102 (45.2%/54.8%)

Reference	Gwynne-Jones 2020 [35]

	• Body mass index
	  ○ Healthy weight: 11 (10.4%)
	  ○ Overweight: 40 (37.7%)
	  ○ Obese: 55 (51.9%)
	• Kellgren Lawrence grading scale
	  ○ Stage 1: 18 (9.7%)
	  ○ Stage 2: 50 (26.9%)
	  ○ Stage 3: 88 (47.3%)
	  ○ Stage 4: 30 (16.1%)
	• Oxford Hip/Knee score: 19.5 (7.8)
	• SF-12 physical component summary: 31.9 (8.0)
	• SF-12 mental component summary: 48.4 (11.9)
	• Time to final follow-up (years): 6.1 (0.6)
	• Death prior to surgery: 11 (5.9%)
	
	Hip osteoarthritis
	• Age: 66.4 (11.6) years
	• Male/female: 66/85 (43.7%/56.3%)
	• Body mass index
	  ○ Healthy weight: 28 (25.5%)
	  ○ Overweight: 44 (40.0%)
	  ○ Obese: 38 (34.5%)
	• Kellgren Lawrence grading scale
	  ○ Stage 1: 7 (4.6%)
	  ○ Stage 2: 35 (23.2%)
	  ○ Stage 3: 80 (53.0%)
	  ○ Stage 4: 29 (19.2%)
	• Oxford Hip/Knee score: 20.3 (8.7)
	• SF-12 physical component summary: 33.2 (9.2)
	• SF-12 mental component summary: 48.8 (11.9)
	• Time to final follow-up (years): 6.1 (0.6)

Reference	Gwynne-Jones 2020 [35]
	• Death prior to surgery: 11 (7.3%) **Population source:** People referred to the orthopaedic department by their GP between June 2012 and May 2014.
Prognostic variables	Oxford Hip/Knee Score
Confounders	Multivariable analysis Factors included in the adjusted analysis: joint affected, radiographic grade, age, gender, BMI, PROMs and time to surgery.
Outcomes and effect sizes	Oxford Hip/Knee Score **Time to joint replacement – Oxford Hip/Knee Score** • **HR 0.74 (0.66, 0.85)** Follow up (mean): 6.1 years
Comments	**<u>Oxford Hip/Knee Score</u>** Risk of bias: 1. Study participation — HIGH 2. Study attrition — LOW 3. Prognostic factor measurement — LOW 4. Outcome Measurement — LOW 5. Study confounding — HIGH 6. Statistical analysis — LOW 7. Other risk of bias — LOW OVERALL RISK OF BIAS — VERY HIGH Indirectness: Prognostic variable indirectness – the prognostic variable combines the Oxford Knee and Hip score, while the protocol requested them to be separate.

Reference	Lane 2004 [45]
Study type and analysis	Prospective cohort study Logistic regression used to estimate the adjusted odds ratios for predictors of dichotomous measures of progression. Linear regression was used for continuous measures of change that included changes in the MJS and lower extremity disability scores. Analyses of the association of baseline hip pain with progression were adjusted for age, weight, height, estrogen use, calcaneal BMD, health status, and baseline radiographic severity using the sum total of all individual radiographic feature scores. United States of America, metropolitan areas setting.
Number of participants and characteristics	N=5928 enrolled with baseline and follow up hip radiographs, 936 hips in 745 women (12.6% of women) had radiographic osteoarthritis at baseline and were included in the study. People who received joint replacement surgery over a mean of 8.3 years: 96 (12.9%) People who did not receive joint replacement surgery over a mean of 8.3 years: 649 (87.1%) Participants in the Study of Osteoporotic Fractures (SOF), a multicenter cohort study initiated in 1986, with osteoarthritis who were recruited between September 1986 and October 1988 from population-based listings in 4 metropolitan areas in the United States of America. **Inclusion criteria:** People age at least 65 years **Exclusion criteria:** “Nonwhite women were excluded from the original cohort because of their low incidence of hip fractures, as were women who were nonambulatory or who had undergone bilateral hip replacement”; people with a diagnosis of rheumatoid arthritis, Paget’s disease, or prior hip fracture or hip surgery. **Values listed below are presented as mean (SD) or number (%)** • Age: 71.8 (5.2) years • Weight: 68.4 (11.8) kg • Height: 159.4 (5.9) cm • Current ERT use: 12.6% • Walk >1 block daily: 49.0%

Reference	Lane 2004 [45]

	• Disability score (range 0-15):
	  ○ % with score at least 1: 34.8%
	  ○ % with score at least 4: 9.7%
	• Radiographic findings
	  ○ In 1 hip: 552 (74.1)
	  ○ In both hips: 191 (25.6)
	
	Population source: Participants in a multicenter cohort study initiated in 1986.

Prognostic variables	Longer duration of symptoms – Pain present at baseline
Confounders	Multivariable analysis Factors included in the adjusted analysis: age, weight, height (the presence of weight and height is used in the place of BMI, as BMI can be calculated from this. Therefore, this study was not excluded for absence of adjustment of key confounders), estrogen use, calcaneal BMD, health status, and baseline radiographic severity using the sum total of all individual radiographic feature scores.
Outcomes and effect sizes	Total hip replacement for osteoarthritis **Total hip replacement –** Pain present at baseline • **OR 9.1 (4.2, 15.4)** Follow up (mean): 8.3 years
Comments	**<u>Longer duration of symptoms – Pain present at baseline</u>** Risk of bias: 1. Study participation HIGH 2. Study attrition VERY HIGH 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH

Reference	Lane 2004 [45]
	Indirectness: Prognostic variable indirectness – the value is used with the assumption that pain at baseline would indicate a longer duration of symptoms. As this is an assumption, this has been downgraded due to indirectness.

Reference	Maillefert 2002[52]
Study type and analysis	Prospective cohort study Multivariate Cox models performed with backward elimination of variables (variables measured includes age and body mass index) France

Number of participants and characteristics	N=508 recruited, 42 excluded because total hip arthroplasty was performed during the first year, 3 excluded due to missing data, 466 included in the analysis
	Total hip replacement performed between Years 2 and 3 – 75 patients
	Did not have surgery – 391 patients
	
	People in a multicentre, prospective, longitudinal, 3 year follow up study. At entry and evaluation, data was collected for various variables including: pain during physical activities, functional disability, patient's overall assessment of disease activity during the previous 2 days, nonsteroidal anti-inflammatory and analgesic intake.
	
	Inclusion criteria:
	Outpatients visiting a rheumatologist and fulfilling the American College of Rheumatology criteria for the diagnosis of hip osteoarthritis. Age between 50 and 75 years and hip pain on a daily basis for at least one month during the last 3 months.
	
	Exclusion criteria:
	Radiological joint space width <1 mm at the narrowest point; radiographic medial or axial femoral head migration; secondary hip osteoarthritis.
	
	Values listed below are presented as mean (SD) or number (%)
	
	• Age: 63 (6.8) years
	• Male/female: 194/272 (41.6%/58.4%)
	• Body mass index: 25.8 (3.5) kg/m^2
	• Pain: 43.6 (19.9) mm
	• Lequesne index: 7.6 (2.5)
	• Patient overall assessment, no. of patients
	  ○ 0 (none): 9
	  ○ 1 (mild): 105

Reference	Maillefert 2002[52]
	○ 2 (moderate): 248 ○ 3 (severe): 99 ○ 4 (very severe): 5 • Femoral head migration: ○ Superolateral: 268 ○ Superomedial: 154 ○ Concentric: 44 • Joint space width: 2.31 (0.83) mm **Population source:** Outpatients visiting a rheumatologist and fulfilling the eligibility criteria
Prognostic variables	Non-response to analgesics/intra articular injections – NSAID intake during the 3 months preceding the evaluated visit Non-response to analgesics/intra articular injections – Analgesic intake during the 3 months preceding the evaluated visit
Confounders	Multivariable analysis Factors included in the adjusted analysis: age, gender, BMI, pain, Lequesne index, Patient overall assessment, femoral head migration, joint space width.
Outcomes and effect sizes	NSAID intake during the 3 months preceding the evaluated visit Analgesic intake during the 3 months preceding the evaluated visit **Joint replacement – NSAID intake during the 3 months preceding the evaluated visit** • **≤1 day/2 – RR = 1** • **>1 day/2 – RR = 2.31 (1.34-3.94) (Coefficient = 12.4)** **Joint replacement – Analgesic intake during the 3 months preceding the evaluated visit** • **≤1 day/2 – RR = 1** • **>1 day/2 – RR = 1.98 (1.16-3.4) (Coefficient = 10.1)** Follow up: 3 years
Comments	**Non-response to analgesics/intra articular injections – NSAID intake during the 3 months preceding the evaluated visit** Risk of bias: 1. Study participation LOW 2. Study attrition HIGH

Reference	Maillefert 2002[52]	
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	LOW
	5. Study confounding	HIGH
	6. Statistical analysis	LOW
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Non-response to analgesics/intra articular injections – Analgesic intake during the 3 months preceding the evaluated visit	
	Risk of bias:	
	1. Study participation	LOW
	2. Study attrition	HIGH
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	LOW
	5. Study confounding	HIGH
	6. Statistical analysis	LOW
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Indirectness:	
	Prognostic variable indirectness – Previous NSAID/analgesia intake is included with the assumption that people did not respond to treatment if they required surgery, so has been downgraded for indirectness	

Appendix E – Forest plots

E.1 Non-response to analgesics/intra articular injections for people with hip osteoarthritis

Figure 2: Progression to joint replacement (previous NSAID intake) at 2 years

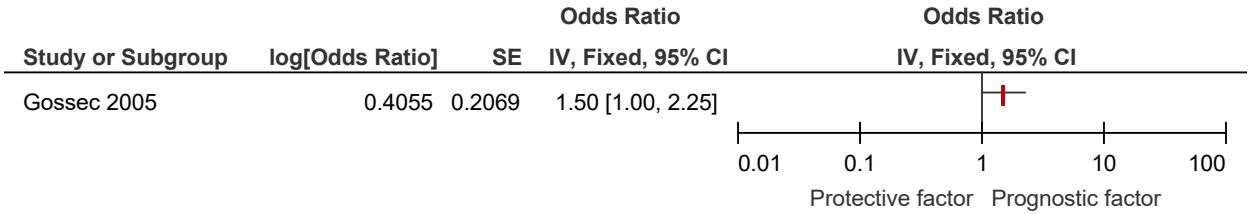


Figure 3: Progression to joint replacement (NSAID intake during the 3 months preceding the evaluated visit) at 3 years

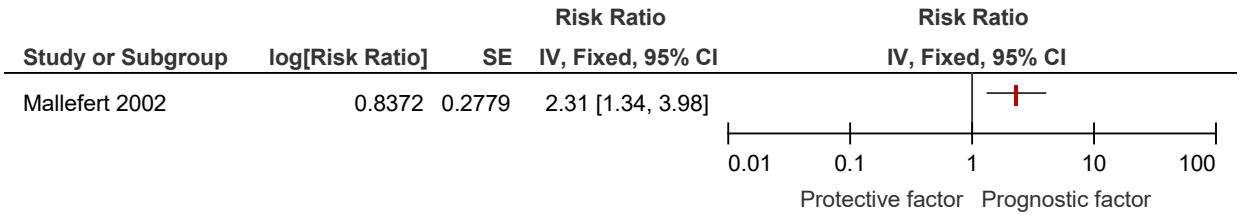


Figure 4: Progression to joint replacement (analgesic intake during the 3 months preceding the evaluated visit) at 3 years

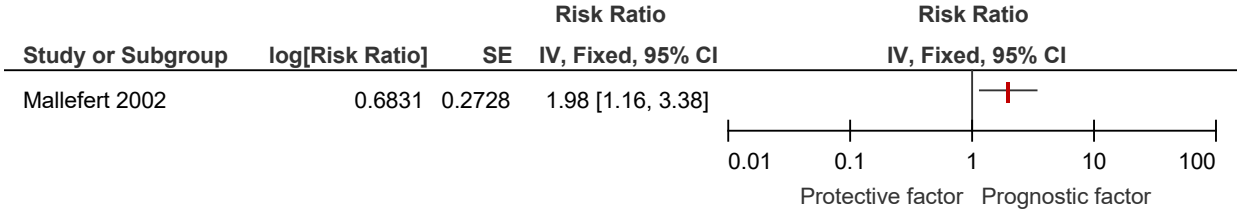
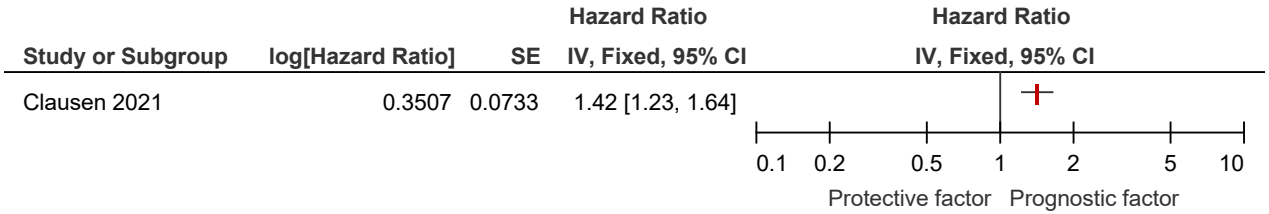
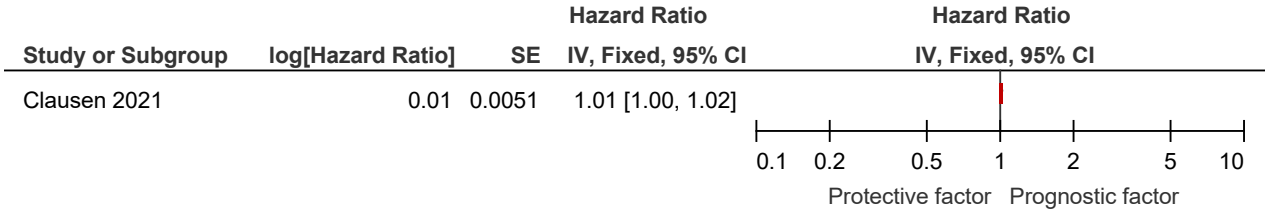


Figure 5: Progression to joint replacement (use of pain medication in last 3 months) at 2 years



E.2 Non-response to non-pharmacological interventions for people with hip osteoarthritis

Figure 6: Progression to joint replacement (VAS) at 2 years



E.3 Longer duration of symptoms for people with hip osteoarthritis

Figure 7: Progression to joint replacement (mean patient global assessment over the first 6 months >47) at 2 years

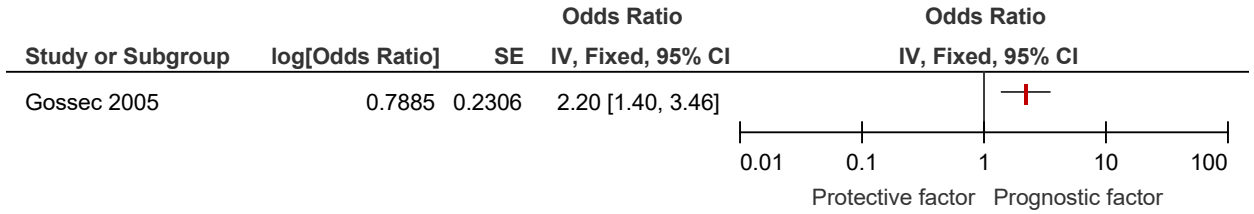
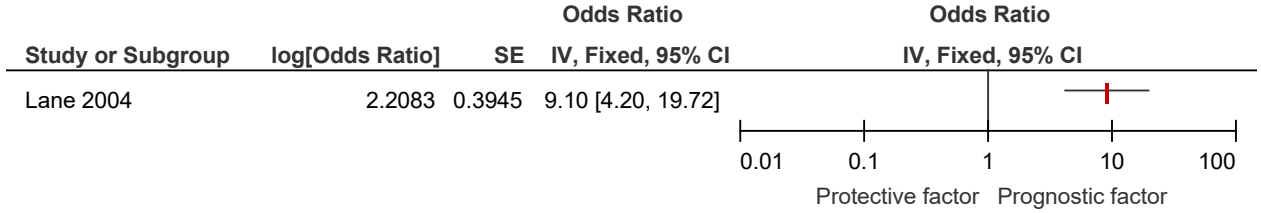
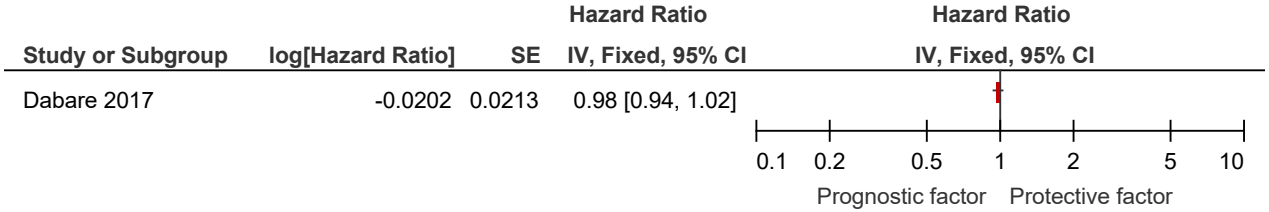


Figure 8: Progression to joint replacement (pain present at baseline) at 8.3 years



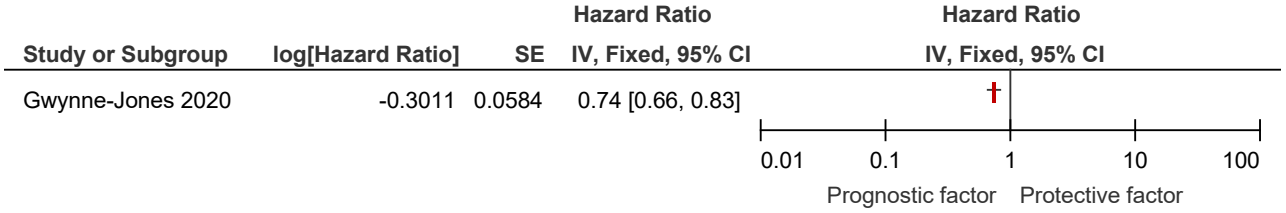
E.4 Longer duration of symptoms for people with mixed osteoarthritis (hip and knee)

Figure 9: Progression to joint replacement (symptom duration, years) at 6 years



E.5 Oxford Hip/Knee score for people with mixed osteoarthritis (hip and knee)

Figure 10: Progression to joint replacement (Oxford Hip/Knee Score) at 6.1 years



E.6 KOOS/HOOS (summary score) for people with mixed osteoarthritis (hip and knee)

Figure 11: Progression to joint replacement (KOOS and HOOS scales pain score) at 6 years

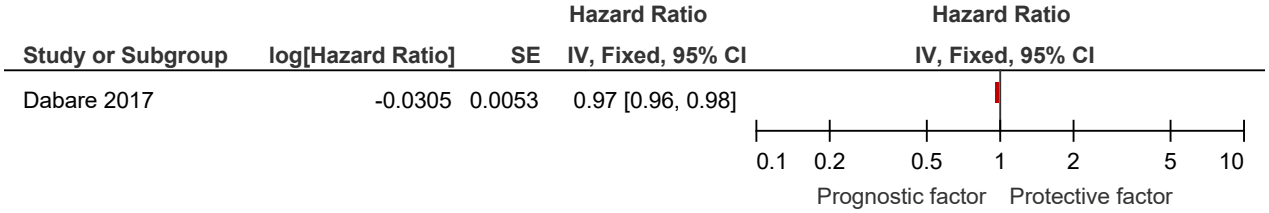
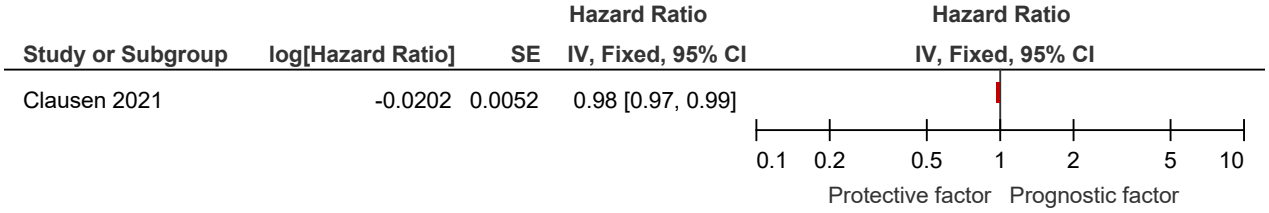


Figure 12: Progression to joint replacement (HOOS quality of life score) at 2 years



Appendix F – GRADE tables

Table 12: Clinical evidence profile: non-response to analgesics/intra articular injections for people with hip osteoarthritis

Certainty assessment							№ of patients	Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)		
Progression to joint replacement (previous NSAID intake) at 2 years										
1	prospective cohort	serious[a]	not serious	serious[b]	not serious	none	505	**OR 1.50** (1.00 to 2.25)	⨁⨁◯◯ LOW	CRITICAL
Progression to joint replacement (NSAID intake during the 3 months preceding the evaluated visit) at 3 years										
1	prospective cohort	serious[a]	not serious	serious[b]	not serious	none	466	**RR 2.31** (1.34 to 3.98)	⨁⨁◯◯ LOW	CRITICAL
Progression to joint replacement (analgesic intake during the 3 months preceding the evaluated visit) at 3 years										
1	prospective cohort	serious[a]	not serious	serious[b]	not serious	none	466	**RR 1.98** (1.16 to 3.38)	⨁⨁◯◯ LOW	CRITICAL
Progression to joint replacement (use of pain medication in last 3 months) at 2 years										
1	prospective cohort	not serious	not serious	serious[b]	not serious	none	3657	**HR 1.42** (1.23 to 1.64)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: confidence interval; **HR:** hazard Ratio; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because of prognostic variable indirectness

Table 13: Clinical evidence profile: non-response to non-pharmacological interventions for people with hip osteoarthritis

Certainty assessment							№ of patients	Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)		
Progression to joint replacement (VAS) at 2 years										
1	prospective cohort	not serious	not serious	serious[a]	not serious	none	3657	**HR 1.00** (1.00 to 1.02)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: confidence interval; **HR:** hazard Ratio

Explanations

a. Downgraded by 1 or 2 increments because of prognostic variable indirectness

Table 14: Clinical evidence profile: longer duration of symptoms for people with hip osteoarthritis

Certainty assessment							№ of patients	Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)		
Progression to joint replacement (mean patient global assessment over the first 6 months >47) at 2 years										
1	prospective cohort	very serious [a]	not serious	serious [b]	not serious	none	466	**OR 2.20** (1.40 to 3.46)	⨁◯◯◯ VERY LOW	CRITICAL
Progression to joint replacement (pain present at baseline) at 8.3 years										

Certainty assessment							№ of patients	Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)		
1	prospective cohort	very serious [a]	not serious	serious [b]	not serious	none	745	**OR 9.10** (4.20 to 19.72)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because of prognostic variable indirectness

Table 15: Clinical evidence profile: longer duration of symptoms for people with mixed osteoarthritis (hip and knee)

Certainty assessment							№ of patients	Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)		
Progression to joint replacement (symptom duration, years) at 6 years										
1	prospective cohort	serious [a]	not serious	not serious	serious [a]	none	247	**HR 0.98** (0.94 to 1.02)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 16: Clinical evidence profile: Oxford Hip/Knee score for people with mixed osteoarthritis (hip and knee)

Certainty assessment							№ of patients	Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)		
Progression to joint replacement (Oxford Hip/Knee Score) at 6.1 years										
1	prospective cohort	very serious [a]	not serious	serious [b]	not serious	none	216	**HR 0.74** (0.66 to 0.83)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because of prognostic variable indirectness

Table 17: Clinical evidence profile: KOOS/HOOS (summary score) for people with mixed osteoarthritis (hip and knee)

Certainty assessment							№ of patients	Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)		
Progression to joint replacement (KOOS and HOOS scales pain score) at 6 years										
1	prospective cohort	serious[a]	not serious	serious[b]	not serious	none	247	**HR 0.97** (0.96 to 0.98)	⨁⨁◯◯ LOW	CRITICAL
Progression to joint replacement (HOOS quality of life score) at 2 years										
1	prospective cohort	not serious	not serious	serious[b]	not serious	none	3657	**HR 0.98** (0.97 to 0.99)	⨁⨁⨁◯ MODERATE	CRITICAL

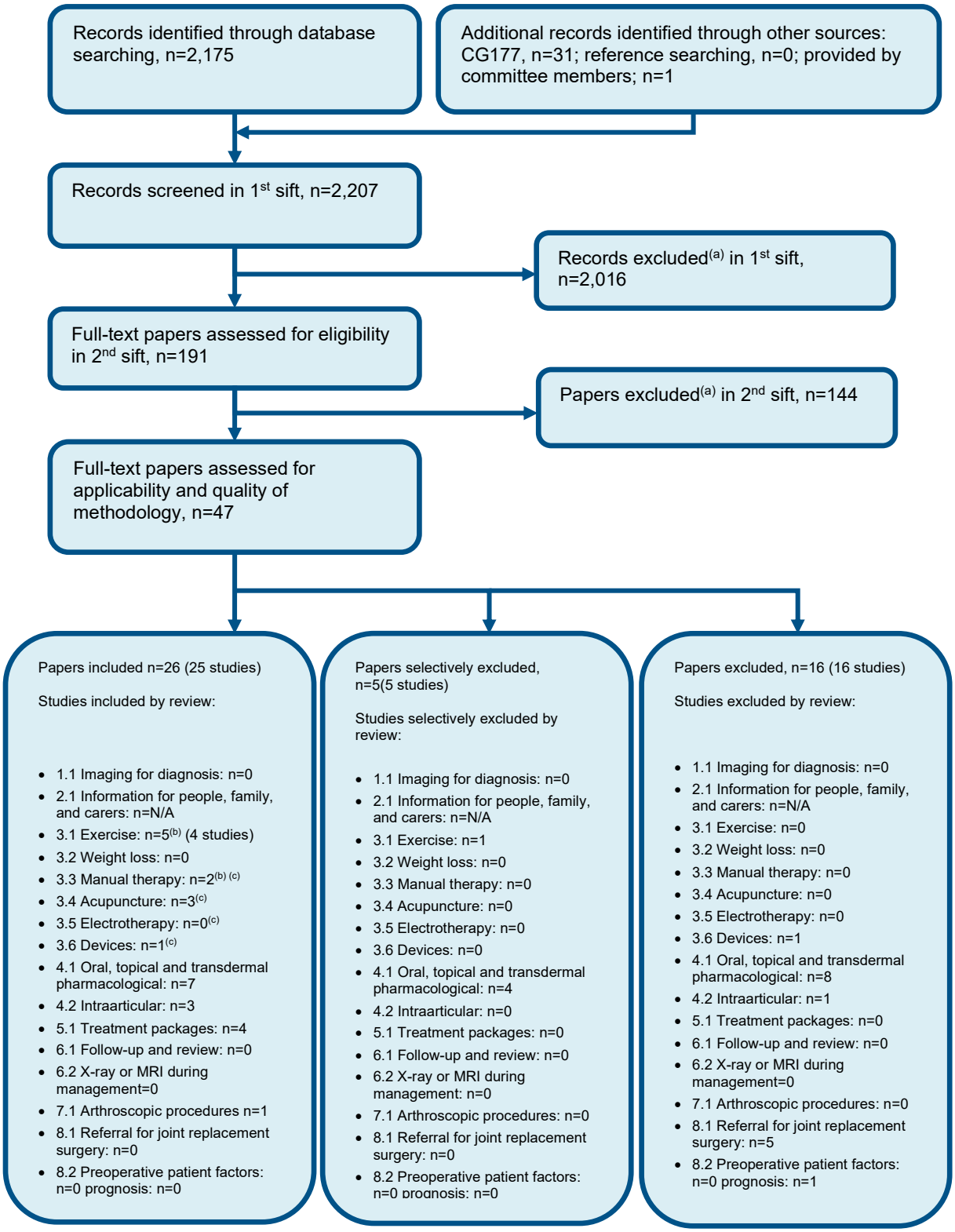
CI: confidence interval; **HR:** hazard Ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because of prognostic variable indirectness

Appendix G – Economic evidence study selection



(a) Non-relevant population, intervention, comparison, design or setting; non-English language.
(b) Two articles identified were applicable to Q3.1 and Q3.3, for the purposes of this diagram they have been included under Q3.1 only.
(c) One article identified was applicable to Q3.3, Q3.4, Q3.5 and Q3.6, for the purposes of this diagram it has been included under Q3.3 only.

Appendix H – Economic evidence tables

There were no health economic studies found in the review.

Appendix I – Health economic model

No original economic modelling was undertaken.

Appendix J – Excluded studies

Clinical studies

Table 18: Studies excluded from the clinical review

Study	Exclusion reason
Agricola 2013[1]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Agricola 2013[2]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Barr 2012[3]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Bastick 2015[5]	Systematic review; references checked
Bastick 2017[4]	Does not adjust for BMI in multivariate analysis
Betancourt 2009[6]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Bevers 2015[7]	Wrong prognostic factor (radiographic or clinical factors that were not included in the protocol), Wrong comparator (comparing to something other than whether the person goes on to need joint replacement surgery)
Bihlet 2020[8]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Birch 2019[9]	Wrong study type (cross-sectional study)
Birrell 2003[10]	Does not adjust for variable in a multivariate analysis
Bouyer 2016[11]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Bruyere 2013[12]	Outcomes not adjusted for in a multivariate analysis
Chan 2010[13]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Collins 2014[15]	Wrong comparator (comparing to something other than whether the person goes on to need joint replacement surgery)
Collins 2021[16]	Wrong comparator (comparing to something other than whether the person goes on to need joint replacement surgery)
Conaghan 2010[17]	Multivariate analysis does not adjust for age and BMI
Costa 2021[18]	Conference abstract
Costello 2021[19]	Does not adjust for age and BMI in a multivariate analysis
Davis 2018[22]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Dieppe 2000[23]	Wrong comparator (comparing to something other than whether the person goes on to need joint replacement surgery)
Dieppe 2011[24]	Narrative review
Dougados 1999[25]	Does not adjust for age and BMI in a multivariate analysis
Dreinhofer 2006[26]	Wrong study type (survey)
Driban 2016[28]	People with osteoarthritis or at risk of osteoarthritis
Driban 2020[27]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Faschingbauer 2017[29]	Does not adjust for age and BMI in a multivariate analysis
Fox 1996[31]	Does not adjust for age and BMI in a multivariate analysis
Ferguson 2021[30]	Wrong prognostic variable (comorbidity scores)

Study	Exclusion reason
Gillam 2013[32]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Gossec 2011[33]	Wrong study type (cross-sectional study)
Hafezi-Nejad 2016[36]	Does not adjust for age and BMI in a multivariate analysis
Harms 2007[37]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Hawker 2013[38]	Wrong population (people with rheumatoid arthritis and osteoarthritis, all people had surgery), Wrong comparator (comparing to something other than whether the person goes on to need joint replacement surgery)
Hirschmann 2013[39]	Wrong comparator (comparing to something other than whether the person goes on to need joint replacement surgery)
Huynh 2018[40]	Wrong study type (cross-sectional study)
Kanthawang 2021[41]	Wrong comparator (comparing to something other than whether the person goes on to need joint replacement surgery)
Kany 2021[42]	Wrong comparator (comparing to something other than whether the person goes on to need joint replacement surgery)
Kastelein 2011[43]	Wrong population (only 50% of the population had osteoarthritis)
Kwoh 2020[44]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Ledingham 2020[46]	Does not adjust for risk factors in a multivariable analysis
Leung 2015[47]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Levine 2013[48]	Systematic review not relevant to our review (looks at interventions)
Leyland 2016[49]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Lievense 2007[50]	Does not adjust for risk factors in a multivariable analysis
MacIntyre 2015[51]	Does not adjust for BMI in multivariate analysis
Maillefert 2008[53]	Factors not investigated in a multivariate analysis (examined other factors, such as comorbidity, joint space narrowing and SF-12)
Mancuso 1996[54]	Wrong study type (surveys)
Mandl 2013[55]	Wrong study type (narrative review)
McHugh 2011[57]	Does not adjust for weight and BMI in a multivariate analysis for the outcomes of interest
Mezhov 2021[59]	Does not adjust for age and BMI in a multivariate analysis
Miura 2021[60]	Wrong study type (cross-sectional study), wrong population (mixture of osteoarthritis and degenerative dysplasia of the hip)
Neufeld 2019[64]	Does not adjust for age and BMI in a multivariate analysis
Peer 2013[65]	Systematic review not relevant to our review (validity and reliability review)
Pelletier 2013[66]	Narrative review
Perry 2020[67]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Ponzio 2021[68]	Wrong population (all people had surgery)
Pope 2008[69]	Wrong study type (case control study)
Price 2020[70]	Wrong comparator (comparing to something other than whether the person goes on to need joint replacement surgery)
Quintana 2005[71]	Wrong study type (cross-sectional study)

Study	Exclusion reason
Rahman 2011[72]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Rajamaki 2021[73]	Wrong population (all people had surgery)
Reijman 2005[74]	Wrong comparator (comparing to something other than whether the person goes on to need joint replacement surgery)
Riddle 2012[78]	Does not adjust for BMI in multivariate analysis
Riddle 2013[79]	Reports outcomes as growth curve parameters, no mention of a multivariate analyses
Riddle 2013[76]	Wrong comparator (comparing to something other than whether the person goes on to need joint replacement surgery)
Riddle 2015[77]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Riddle 2020[75]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Schiphof 2019[80]	Wrong comparator (comparing to something other than whether the person goes on to need joint replacement surgery)
Tambascia 2016[81]	Wrong comparator (comparing to something other than whether the person goes on to need joint replacement surgery)
Teirlinck 2019[82]	Systematic review; references checked
Teng 2017[83]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Tolpadi 2020[84]	Wrong study type (case control study)
Turcotte 2021[85]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
van de Sande 2006[86]	Systematic review; not relevant PICO
Vinciguerra 1995[87]	Not available
Wang 2009[88]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)
Wang 2020[89]	Wrong comparator (comparing to something other than whether the person goes on to need joint replacement surgery)
Weigl 2021[90]	Does not adjust for age and BMI in a multivariate analysis
Wijn 2020[91]	Does not adjust for age and BMI in a multivariate analysis
Zeng 2019[92]	Wrong comparator (comparing to something other than whether the person goes on to need joint replacement surgery)
Zeni 2010[93]	Wrong prognostic variable (radiographic or clinical factors that were not included in the protocol)

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 19: Studies excluded from the health economic review

Reference	Reason for exclusion
Dakin 2012[21]	Excluded as rated not applicable. Study is not relevant to the review question as it assesses the cost effectiveness of joint replacement surgery.
Mari 2016[56]	Excluded as rated not applicable. Study is not relevant to the review question as it assesses the cost effectiveness of joint replacement surgery.
Medical Advisory Secretariat 2005[58]	Excluded as rated not applicable. Study is not relevant to the review question as it assesses the cost effectiveness of joint replacement surgery.
Mujica Mota 2013[62]	Excluded as rated not applicable. Study is not relevant to the review question as it assesses the cost effectiveness of joint replacement surgery.
Mujica Mota 2017[61]	Excluded as rated not applicable. Study is not relevant to the review question as it assesses the cost effectiveness of joint replacement surgery.

Appendix K – Research recommendations – full details

K.1 Research recommendation

What are the most important indicators that someone with osteoarthritis (including shoulder osteoarthritis) would benefit from joint replacement? For example:

- presence of night pain
- non-response to non-pharmacological interventions
- joint instability symptoms
- presence of flares
- numerical summary scores.

K.1.1 Why this is important

Although joint replacement is demonstrated to be an effective treatment for end-stage osteoarthritis, there are few data on the relative importance of the various clinical features of the disease as indications for referral for surgery. It is important to understand which of these features should action a referral for surgery.

K.1.2 Rationale for research recommendation

Importance to 'patients' or the population	Little is known about which clinical features of osteoarthritis, aside from the key features of pain and loss of function, are important in triggering a referral to surgery. Given the potential important effect that surgical intervention could have in improving quality of life, this is of concern to people with osteoarthritis.
Relevance to NICE guidance	This question was considered in the guideline and insufficient data was identified for the committee to make a firm recommendation based on the factors available. If this information is available in the future updates to this guideline then this may allow for more certainty to be provided.
Relevance to the NHS	Data answering this question would create clearer understanding on the importance of different clinical features when considering a referral for surgery.
National priorities	This is not an area of national priority
Current evidence base	Limited evidence was identified in this review for some of the prognostic variables identified in the protocol. No evidence was available for those stated in the question. Further evidence investigating the range of moderators would be important to gain a complete understanding.
Equality considerations	The committee noted that osteoarthritis research in general does not appear to represent the diverse population of people with osteoarthritis. They agreed that any further research should be representative of the population, including

	people from different family backgrounds, and socioeconomic backgrounds, disabled people, and people of different ages and genders. Future work should be done to consider the different experiences of people from diverse communities to ensure that the approach taken can be made equitable for everyone

K.1.3 Modified PICO table

Population	Inclusion: • Adults (age ≥16 years) with osteoarthritis affecting any joint attending GP with symptomatic osteoarthritis Exclusion: • Children (age <16 years) • People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, diseases of childhood that may predispose to osteoarthritis, medical conditions presenting with joint inflammation and malignancy). • Studies with an unclear population (e,g, type of arthritis, proportion of participants with osteoarthritis) • Spinal osteoarthritis
Index/Prognostic variable	• Presence of night pain • Non-response to pharmacological interventions • Non-response to non-pharmacological interventions (including exercise, weight loss, physiotherapy or other non-pharmacological interventions) • Longer duration of symptoms • Joint instability symptoms • Presence of flares • Numerical summary scores (such as the Oxford Knee, Hip and Shoulder scores, EQ-5D)
Confounding factors	• Age • Body mass index • Smoking status • Multimorbidity • Socio-economic factors
Outcome	Progression to surgical intervention
Study design	Prospective cohort study
Timeframe	2 years

Additional information	Including a multivariate analysis investigating the association of all of the prognostic variables and confounding factors.