National Institute for Health and Care Excellence

Draft for Consultation

Joint replacement (primary): hip, knee and shoulder

[K] Evidence review for total knee replacement

NICE guideline

Intervention evidence review

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ISBN

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1 Total knee replacement versus partial knee replacement

1.1 Review question: In adults having primary elective knee replacement, what is the clinical and cost effectiveness of total knee replacement versus partial knee replacement?

1.2 Introduction

Knee replacement is an established treatment for people with end-stage arthritis of the knee that have exhausted non-surgical treatment options. Currently over 100,000 knee replacement procedures are performed in the United Kingdom in each calendar year. The National Joint Registry reported a breakdown of 2017 primary knee replacement surgeries, 89% were total knee replacement (TKR), 10% were partial knee replacements (PKR) and, 1% were patellofemoral knee replacements.[44] PKR involves replacement of only the affected area of the knee joint, leaving the non-effected areas behind. It is therefore a less invasive procedure with potentially fewer surgical complications, but leaves behind the remaining joint which may go on to develop symptomatic arthritis in the future with the potential need for future surgery. PKR can also be described as unicompartmental or unicondylar knee replacement (UKR). In contrast TKR replaces all of the knee joint and, while it is more invasive, may reduce the need for further surgery by replacing the entire joint in one operation.

In people with symptomatic arthritis affecting the entire tibiofemoral joint there is general agreement that total knee replacement is the preferred surgical option. However, debate remains as to which is the better procedure for people with arthritis isolated to one part of the tibiofemoral joint. Proponents of partial knee replacement suggest it offers better function, a quicker recovery and is associated with fewer complications. However, these benefits have to be balanced against a conception of a greater failure rate and need for earlier revision surgery. Therefore both options have advantages and potential drawbacks and as a consequence of the way in which these are interpreted there is significant variation in how frequently these two procedures are offered to patients. This review compares these 2 knee replacement procedures to establish which should be offered to people for whom either is a viable option.

1.3 PICO table

For full details, see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults with 1 knee compartment (medial or lateral tibiofemoral) for which knee replacement is offered
Intervention	Medial or lateral tibiofemoral unicompartmental knee replacement
Comparison	Total knee replacement
Outcomes	**Critical** • Mortality: life expectancy • Mortality: 30 day • Quality of life at 6 weeks or earlier, later than 6 weeks up to 1 year, at least 2 years • Patient Reported Outcome Measures (PROMs) at 6 weeks or earlier, later than 6 weeks up to 1 year, at least 2 years

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	• Revision of joint replacement:
	  ○ major – revision of the tibia femoral compartments
	  ○ minor – polyethylene liner/polyethylene exchange
	
	Important
	• Surgical site infection
	  ○ deep
	  ○ superficial
	• Length of stay
	• Reoperation (excluding revision)
	• Major adverse events as described by the studies: for example, VTE, myocardial infarction
	
	To be extracted when not included within a PROM:
	• Function at 6 weeks or earlier, later than 6 weeks up to 1 year, at least 2 years
	• Pain at 6 weeks or earlier, later than 6 weeks up to 1 year, at least 2 years

Study design	Randomised controlled trials (RCTs) (If no well-conducted RCTs are available, then observational studies with multivariate analysis will be investigated.)

1.4 Clinical evidence

1.4.1 Included studies

A search was conducted for randomised trials comparing the effectiveness of medial or lateral tibiofemoral unicompartmental knee replacement versus total knee replacement (TKR).

Two RCTs were included in the review;[31, 45, 47] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix H.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

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1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Kulshrestha 2017[31]	Bilateral medial unicompartmental knee arthroplasty (UKA) (n=40) Versus Bilateral total knee arthroplasty (TKA) (n=40)	Adults with bilateral isolated medial compartment knee arthritis for which knee replacement was offered Age (mean, SD) = 60.96 years (7.55)	PROMS: • Knee Outcome Scale (activities of daily living) after at least 2 years • Oxford knee score after at least 2 years • High Activity Arthroplasty Score after at least 2 years Quality of life (EQ-5D VAS) after at least 2 years	India
Newman 1998[47], Newman 2009[45]	Medial UKA (n=47 and 50 knee replacements) Versus TKA (n=47 and 52 knee replacements)	Adults suitable for unicompartmental knee arthroplasty (UKA) or total knee arthroplasty (TKA) after arthrotomy. Age (mean, range) = 69.7 years(47 to 89)	PROMs: • Bristol Knee Score after at least 2 years Major revision after at least 2 years Minor revision after at least 2 years Length of stay after at least 2 years Adverse events after at least 2 years Function after at least 2 years Pain relief after at least 2 years	UK

See appendix D for full evidence tables.

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1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Medial Unicondylar Knee Arthroplasty (UKA) versus Total Knee Arthroplasty (TKA)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TKA	Risk difference with Medial UKA (95% CI)
Quality of life after at least 2 years Change in EQ-5D - VAS. Scale from 0 to 100.	72 (1 study) 2 years	LOW[1,2] due to risk of bias, imprecision		The mean quality of life in the control groups was 39.4	The mean quality of life in the intervention groups was 3.9 higher (2.06 lower to 9.86 higher)
HAAS score after at least 2 years Change in High Activity Arthroplasty Score. Scale from 0 to 18.	72 (1 study) 2 years	MODERATE[2] due to risk of bias		The mean HAAS score in the control groups was 2.8	The mean HAAS score in the intervention groups was 0.30 higher (0.46 lower to 1.06 higher)
Bristol Knee Score with a rating of excellent (91-100) after at least 2 years	40 (1 study) 15 years	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.36 (0.82 to 2.25)	526 per 1,000	189 more per 1,000 (from 95 fewer to 658 more)
Bristol Knee Score with a rating of excellent or good (81-100) after at least 2 years	40 (1 study) 15 years	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.11 (0.76 to 1.64)	684 per 1000	75 more per 1000 (from 164 fewer to 438 more)
Bristol Knee Score with a rating of excellent or good or fair (71-100 after at least 2 years	40 (1 study) 15 years	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.10 (0.78 to 1.54)	737 per 1000	74 more per 1000 (from 162 fewer to 398 more)
Change in Oxford knee score Scale from 0 to 50 after at least 2 years	72 (1 study) 2 years	MODERATE[2] due to risk of bias		The mean oxford knee score in the control groups was 16.8	The mean oxford knee score in the intervention groups was 0.3 higher (1.94 lower to 2.54 higher)
Change in activities of daily living after at least 2 years	72 (1 study)	LOW[1,2] due to risk of bias,		The mean activities of daily living in the control groups	The mean activities of daily living in the intervention groups was

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TKA	Risk difference with Medial UKA (95% CI)
Knee Outcome Scale (KOS) - ADL. Scale from 0 to 100.	2 years	imprecision		was 47	3 higher (2.32 lower to 8.32 higher)
Major revision (due to tibial component)	91 (1 study) 20 months	VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 7.56 (0.15 to 380.84)	0 per 1,000	20 more per 1,000 (from 40 fewer to 80 more)
Minor revision	91 (1 study) 15 years	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.73 (0.17 to 3.09)	89 per 1,000	24 fewer per 1,000 (from 74 fewer to 186 more)
Length of stay of more than 20 days	102 (1 study) >20 days	LOW[1,2] due to risk of bias, imprecision	RR 0.28 (0.08 to 0.96)	212 per 1,000	152 fewer per 1,000 (from 8 fewer to 195 fewer)
Adverse events, DVT	102 (1 study) 5 years	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.21 (0.03 to 1.72)	96 per 1,000	76 fewer per 1,000 (from 93 fewer to 69 more)

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

1 See appendix F for full GRADE tables.

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1.5 Economic evidence

1.5.1 Included studies

Four health economic studies were identified with the relevant comparison and have been included in this review. [15, 64, 51, 57,] These are summarised in the health economic evidence profile below (Table 4) and the health economic evidence tables in appendix H.

1.5.2 Excluded studies

Three economic studies relating to this review question were identified but were excluded due to methodological limitations [29, 62, 65]. The studies are listed in appendix I, with reasons for exclusion given.

See also the health economic study selection flow chart in appendix G.

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1.5.3 Summary of studies included in the economic evidence review

Table 4: Health economic evidence profile: Unicompartmental knee replacement versus Total knee replacement

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Burn 2018[15] [UK]	Directly applicable[(a)]	Potentially serious limitations[(b)]	A cost-utility analysis using a Markov model. NJR data was used to compare the cost effectiveness of UKR versus TKR for age and sex sub-groups. Lifetime horizon used. Confounders were controlled for using propensity score matching[(c)].	UKR saves £1,355 per 60-75 year old male person[(d)]	UKR gives 0.20 extra QALYs per 60-75 year old male person.	UKR is dominant (less costly and more effective) to TKR for all ages and sex subgroups.	Probabilistic sensitivity analysis showed that UKR had a high probability of being cost effective for all subgroups (72% - 100%). Scenario analysis showed that when the proportion of UKR procedures was <10% UKR was no longer dominant but still cost effective.
Peersman 2014[51] [Belgium]	Partially applicable[(e)]	Potentially serious limitations[(f)]	Markov model utilising registry data to compare the cost-effectiveness of UKR versus TKR conducted from a Belgian healthcare perspective. A lifetime horizon was used.	UKR saves £2,390 per patient	UKR gives 0.04 extra QALYs per patient	UKR is dominant (less costly and more effective) to TKR	Probabilistic sensitivity analysis showed UKR to have 65.1% probability of being cost effective at a WTP threshold of £21,287
Smith 2017[57] [UK]	Partially applicable[(g)]	Potentially serious limitations[(h)]	Cost utility analysis with a Markov model to compare the cost-effectiveness of UKR, TKR (and HTO[(i)]). A UK NHS perspective was taken with a 10-year time horizon.	**40- years old** UKR saves £826 per person **50- years old** UKR saves £826 per person **60- years old**	**40- years old** UKR gives 0.05 less QALYs **50- years old** UKR gives 0.05 less QALYs **60- years old**	**40- years old** TKA costs £16,520 per QALY gained **50- years old** TKA costs £16,520 per QALY gained **60- years old**	Probabilistic sensitivity analysis showed that UKR had a slightly higher probability of being cost effective than TKA for the 60 and 70 year old age groups. For the 40- and 50-year-old age groups TKA had a slightly

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Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
				UKR saves £1,134 per person **70- years old** UKR saves £1,570 per person	UKR gives 0.033[(j)] less QALYs **70- years old** UKR gives 0.015[(j)] less QALYs	TKA costs £34,770 per QALY gained **70- years old** TKA costs £105,810[(k)] per QALY gained	higher probability.
Xie 2010[64] [Singapore]	Partially applicable[(l)]	Potentially serious limitations[(m)]	Cost-utility analysis of a 2-year prospective observational cohort study to compare the cost effectiveness of UKR versus TKR. Conducted from a Singaporean healthcare perspective.	UKR saves £1,100 per patient	UKR gives 0.026 less QALYs per patient	TKR costs £42,307.69 per QALY gained	Probabilistic sensitivity analysis. However, the probabilities for cost effectiveness are only reported for TKR. TKR was 40% cost effective at a WTP threshold of £32,452

Abbreviations: HTO: high tibial osteotomy; ICER: incremental cost-effectiveness ratio; NJR: National Joint Registry; QALY= quality-adjusted life years; TKR: total knee replacement; UKR: unicompartmental knee replacement; WTP: willingness to pay

(a) Markov model using UK registry data with relevant intervention, comparator and cost. QALYs calculated through the EQ-5D questionnaire.

(b) Intervention effects taken from registry data although confounders have been controlled for through propensity score matching. Quality of life scores assumed to remain constant if no subsequent revision or re-revision is required.

(c) Propensity score matching is statistical method used to control for confounders in observational data

(d) The results presented here are for one sub-group as an example, as UKR was dominant in all cases.

(e) A Markov model with a relevant intervention and comparator. QALYs used but not derived from EQ-5D

(f) Cohort is non-randomised registry data. Only incremental costs and outcomes are reported. Source of cohort data is not explicitly stated.1.5% discount rate used for outcomes

(g) A Markov model conducted from a UK NHS perspective with a relevant intervention and comparator. QALYs used but not derived from EQ-5D

(h) A 10-year time horizon used instead of lifetime. Cohort source not specifically cited but appear to be taken from multiple national arthroplasty registries which would have potential confounders

(i) HTO not extracted as it was not included in the scope for this review

(j) More accurate figures have been obtained from the authors and presented here to account for rounding errors in the paper.

(k) The ICER given in the text of the paper for the 70- year old group is given as £14,889, which is incorrect. The authors have provided a corrected figure which is presented here.

(l) Cost-utility analysis using an observational dataset from a Singaporean healthcare perspective. QALYs are used but not derived from EQ-5D

(a) Intervention effect is taken from non-randomised observational data that may have confounding effects present, although differences in demographics were controlled for in a general linear model. A 2-year time horizon may not be long enough for outcomes and associated costs, such as those for revision, to be fully accounted for. The study is conducted from a Singaporean healthcare perspective. There was significant missing utility data at follow-up.

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1.5.4 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 5: UK costs unit costs of UKR and TKR

Item	Unit cost	Resource use	
		UKR	TKR
Hospital bed day	£384.50[(a)]	2-3 days	5 days [(b)]
Revision	£6,642-£14,671[(c)]	12.23% 10-year cumulative revision probability	3.43% 10 year cumulative revision probability

Sources: British National Formulary[25], Alshryda2013[4], National Joint Registry [44]
(a) Average for all elective in patient procedures
(b) Estimate provided by GC knee surgeon and confirmed in literature
(c) HRG HN81A-E, range dependent on complications and co-morbidities

1.6 Evidence statements

1.6.1 Clinical evidence statements

Evidence from 2 RCTs comparing total knee replacement to partial knee replacement.

There was no clinically important difference for after at least 2 years in quality of life (n=72, low quality), high activity arthroplasty score (HAAS) (n=72, moderate quality), Bristol Knee Score (n=40, very low quality), Oxford Knee Score (n=72, moderate quality), and KOS-ADL scale (n=72, low quality).

There was a clinically important benefit of UKA after at least 2 years through the Bristol Knee Score (n=40, very low quality), minor revision at 15 years (n=91, very low quality), length of stay (n=102, low quality), and DVT after 5 years (n=102, very low quality).

There was a clinically important benefit for TKR in terms of major revision at 20 months (n=91, very low quality).

1.6.2 Health economic evidence statements

Two cost-utility analyses found that UKR was dominant (less costly and more effective) compared to TKR. One of these was assessed as being directly applicable with potentially serious limitations whilst the other study was assessed as partially applicable with potentially serious limitations.

One cost-utility analysis found that TKR was not cost effective (£42,308 per QALY gained) compared to UKR in people diagnosed with knee osteoarthritis. The study had a shortest time horizon out of all of the included studies (2- years). This study was assessed as partially applicable with potentially serious limitations.

One cost-utility analysis found that TKR was cost effective (£16,520 per QALY gained) compared to UKR in people who are 50 years old. For 60- and 70- year olds TKA was not cost effective (£34,770 per QALY gained and £105,810 per QALY gained, respectively) compared to UKR. The study had a shorter time horizon than the other included studies (10-year). This study was assessed as partially applicable with potentially serious limitations.

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1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The critical outcomes were mortality, revision of joint replacement (major and minor), quality of life and Patient Reported Outcome Measures (PROMs) at 6 weeks or earlier, later than 6 weeks up to 1 year or after at least 2 years. Revision of joint replacement was separated into major or minor, as they imply different levels and types of revision. Major was classed as revision of the tibia femoral compartments with minor classed as polyethylene liner or polyethylene exchange. The benefits of knee joint replacement operations may not present themselves immediately after surgery; they may take months or years to become apparent. Therefore, multiple time points were necessary to capture this variation in outcomes as rehabilitation occurs.

The important outcomes were deep and superficial surgical site infection, length of stay, reoperation and major adverse events such as venous thromboembolism (VTE) or myocardial infarction (MI).

1.7.1.2 The quality of the evidence

Two studies were included in the review ranging from moderate to very low quality, due to risk of bias or imprecision. The majority of the evidence was rated very low quality.

The committee noted that 1 of the studies is outdated, as it involved implants that are no longer used therefore limiting the applicability of the study's results. The remaining study was also less applicable as it was performed in people having bilateral joint replacement. These surgeries tend to be different from unilateral joint replacement surgery due to more blood loss, increased risk of complications, increased length of stay, prolonged anaesthesia tine, and more complex rehabilitation and recovery.

1.7.1.3 Benefits and harms

Both RCTs addressed the comparison of medial UKR compared to TKR. 1 RCT included people having bilateral joint replacement surgery and the other included people having unilateral joint replacement surgery.

A clinically important benefit for UKR was found for people having a Bristol Knee Score rating of excellent after 5 years and after 15 years, length of stay in hospital of more than 20 days and deep vein thrombosis (DVT) after 5 years.

No clinically important difference was found for all other outcomes which included quality of life after at least 2 years, High-Activity Arthroplasty Score (HAAS) at after at least 2 years, a Bristol Knee Score with a rating of good or better, a Bristol Knee Score of fair or better, major revision after at least 2 years, and minor revision after at least 2 years.

The committee discussed how the revision outcomes for this review were rated as very low quality with low numbers of events. This makes the outcome difficult to use and interpret. It was noted revision rates might be driven by the operation being more straightforward with UKR. A surgeon may therefore recommend revisions more quickly after UKR despite similar pain and function levels in someone who has a TKR. Thus this would obscure benefits of UKR in the studies found.

The committee considered how the National Joint Registry (NJR) data provides a different picture of the revision outcome. It is flawed because the population is different from this

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review in that not all the people having TKRs in the NJR are able to have UKRs instead and also similarly to the above, surgeons may recommend revisions more quickly with UKR because it is more straightforward surgery. The NJR shows people having a UKR have a 12.23% 10-year probability revision rate, compared to a 3.43% 10-year probability revision rate for those having a TKR.[44]

The committee agreed that recovery from UKR tends to be quicker and faster in allowing people to get back to a physically active lifestyle. This procedure is usually associated with less postoperative pain and faster mobilisation, resulting in people often going home on the day or the day after surgery. However UKRs are expected to require revision surgery sooner than TKRs. The committee discussed the importance of a discussion with the person having joint replacement surgery. Factors in the decision mentioned were age, physical activity and co-morbidities. Age is very important in terms of choice of the type of surgery. Younger people have a longer life expectancy and are more likely to require revision surgery in the future and the prospect of a more straightforward revision may influence the decision. A further factor is a person's level of physical activity. Higher levels of physical activity might lead the person to favour surgery with a faster recovery period, and higher activity may increase the likelihood of earlier revision surgery and that will play a role in the discussion. Less active people may not be as motivated by a faster recovery and more interested in the longevity of their joint replacement. These discussions should be combined with clinical factors that may lead a surgeon to recommend TKR over UKR. The surgeon will investigate whether there are symptoms in other knee compartments and whether the cruciate ligaments are functioning and intact. If there were likelihood of the disease spreading to a further compartment or if the cruciate ligaments were thought likely to fail, then the surgeon would recommend TKR. There is currently a grey area around people who have a fraction of wear particularly under the knee cap. Wear on the outside of the knee is a factor that a committee member indicated would strongly oppose UKR. Bringing a host of lifestyle and physiological factors together will drive a person's decision to have a UKR or a TKR, making it crucial that the person undergoing joint replacement surgery engages in discussions with the surgeon to ensure the most appropriate choice of surgery is made.

The committee agreed that this discussion of factors with the person undergoing surgery and then allowing them to decide whether to have UKR or TKR was essential. Therefore, 2 recommendations were made, firstly to have the discussion and secondly to offer the decision of the type of surgery to the person themselves.

It is noted the TOPKAT trial is currently in the process of publishing its results and would be a relevant trial to answer this question.

1.7.2 Cost effectiveness and resource use

The economics evidence overall favoured UKR in being cost effective. All 4 studies presented found that UKR is cost saving compared to TKR. However, the impact on health outcomes was variable compared to TKR.

The NJR and clinical review provided conflicting evidence of if there is a difference in revision rate between UKR and TKR. The committee agreed that the NJR data, which suggested that there is a difference in revision rate, gave a better overall picture although it was observational data so could be prone to confounding effects. Although UKR is likely to have a higher revision rate than TKR, if revision is required, it is often but not always a simpler operation. As it is a potentially simpler procedure, there may be less resistance in offering it, driving the difference in revision rate, but this is only anecdotal. Observational data from the NJR shows people having a UKR have a 12.23% 10-year probability revision rate, compared to a 3.43% 10-year probability revision rate for those having a TKR. Offering UKR to younger people is therefore likely to have a greater resource impact on the NHS than in older patients, as they will require more revisions overall.

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The cost of revision may be partially offset by a reduced length of stay (LOS) for people receiving UKR. The committee agreed that TKR LOS is more likely to be the 4.07 days reported in the Getting It Right First Time (GIRFT) national report, as opposed to the 5 days which was presented in the evidence review. UKR can be expected to have 1–2 days LOS less than TKR.

There is evidence that the volume of UKRs that a surgeon does can improve outcomes, and therefore the cost-effectiveness of the procedure. If the surgeon is well practised in UKR, then the time it takes to do the procedure is likely to be similar to TKR. Therefore, there is unlikely to be a difference in resource use during surgery itself. There is also geographical variation at present in terms of how often UKRs are offered to people, which may have resource use implications.

Overall, the committee agreed that the recommendations are likely to save money given that:

1. The evidence suggests UKR saves money compared with TKR
2. TKR make up the majority of current practice and the recommendation is likely to result in more UKR operations.

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Appendices

Appendix A: Review protocols

Table 6: Review protocol: total knee versus partial knee replacement

ID	Field	Content
0.	PROSPERO registration number	Not yet registered
1.	Review title	Clinical and cost effectiveness of total knee and partial knee joint replacement
2.	Review question	In adults having primary elective knee replacement, what is the clinical and cost effectiveness of total knee replacement versus partial knee replacement?
3.	Objective	In people with unicompartmental knee damage, both full knee replacement and partial knee replacement are surgical options. This review seeks to assess which is most clinically and cost effective.
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) 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.
5.	Condition or domain	Total and partial knee joint replacement

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ID	Field	Content
	being studied	
6.	Population	Inclusion: Adults with 1 knee compartment (medial or lateral tibiofemoral) for which knee replacement if offered Exclusion: Adults having joint replacement as immediate treatment following fracture. Adults having revision joint replacement. Adults having joint replacement as treatment for primary or secondary cancer affecting the bones. Randomisation by leg when undertaking bilateral replacement
7.	Intervention/Exposure/Test	Knee replacement: medial or lateral tibiofemoral
8.	Comparator/Reference standard/Confounding factors	Total knee replacement
9.	Types of study to be included	Randomised controlled trials
10.	Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	Mortality: life expectancy (time to event) Mortality: 30 day (dichotomous) Quality of life at 6 weeks or earlier, later than 6 weeks up to 1 year, at least 2 years (continuous) Patient Reported Outcome Measures (PROMs) at 6 weeks or earlier, later than 6 weeks up to 1 year, at least 2 years (continuous) Revision of joint replacement (time to event): major – revision of the tibia femoral compartments minor – polyethylene liner/polyethylene exchange
13.	Secondary outcomes (important outcomes)	Surgical site infection (dichotomous): deep superficial

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ID	Field	Content
		Length of stay (continuous) Reoperation (excluding revision) Major adverse events as described by the studies: for example, VTE, myocardial infarction To be extracted when not included within a PROM: Function at 6 weeks or earlier, later than 6 weeks up to 1 year, at least 2 years (continuous). Pain at 6 weeks or earlier, later than 6 weeks up to 1 year, at least 2 years (continuous)
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer 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. For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) 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.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome.

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ID	Field	Content	
		Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, 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 outcome. If the population included in an individual study includes children aged under 12, it will be included if the majority of the population is aged over 12, and downgraded for indirectness if the overlap into those aged less than 12 is greater than 20%. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.	
17.	Analysis of sub-groups	Compartment for which replacement is offered: medial lateral tibia femoral Age: working age non-working age Fixed and mobile bearing Surgeon volume: 12 or fewer per year 13 or more per year Knees operated: Bilateral Unilateral	
18.	Type and method of	☒	Intervention

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ID	Field	Content			
	review	☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	15/11/18			
22.	Anticipated completion date	31/07/19			
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 TBC 5e Organisational affiliation of the review			

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ID	Field	Content
		National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: Mr Carlos Sharpin [Guideline lead] Mr Alex Allen [Senior Systematic Reviewer] Ms Rafina Yarde [Systematic reviewer] Mr Robert King [Health economist] Ms Agnès Cuyàs [Information specialist] Ms Eleanor Priestnall [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: [NICE guideline webpage].
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	Total knee, unicompartmental, medial, arthroplasty, partial, lateral tibiofemoral, knee replacement
33.	Details of existing review of same topic by	N/A

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ID	Field	Content	
	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	

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Table 7: 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 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 2003, abstract-only studies and studies from low or middle-income countries (e.g. most non-OECD countries) or the USA will also be excluded. 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).[43] **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,

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	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 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 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.

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Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[43]

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the searches where appropriate.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 01 May 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 01 May 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 5 of 12 CENTRAL to 2019 Issue 5 of 12	None

Medline (Ovid) search terms

1.	arthroplasty, replacement, knee/
2.	((joint* or knee*) adj3 (replace* or prosthe* or endoprosthe* or implant* or arthroplast*)).ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case report/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/

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19.	exp Rodentia/
20.	(rat or rats or mouse or mice).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	(Total and (partial or unicompartment* or unicondylar or compartment* or resurf* or re-surf* or patell*)).ti,ab.
25.	(partial and (Total or unicompartment* or unicondylar or compartment* or resurf* or re-surf* or patell*)).ti,ab.
26.	((unicompartment* or unicondylar or compartment*) and (Total or partial or resurf* or re-surf* or patell*)).ti,ab.
27.	((resurf* or re-surf* or patell*) and (Total or partial or unicondylar or unicompartment* or compartment*)).ti,ab.
28.	((medial or lateral) adj3 (compart* or unicompart* or unicondylar)).ti,ab.
29.	or/24-28
30.	23 and 29
31.	randomized controlled trial.pt.
32.	controlled clinical trial.pt.
33.	randomi#ed.ti,ab.
34.	placebo.ab.
35.	randomly.ti,ab.
36.	Clinical Trials as topic.sh.
37.	trial.ti.
38.	or/31-37
39.	Meta-Analysis/
40.	exp Meta-Analysis as Topic/
41.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
42.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
43.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
44.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
45.	(search* adj4 literature).ab.
46.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
47.	cochrane.jw.
48.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
49.	or/39-48
50.	Epidemiologic studies/
51.	Observational study/
52.	exp Cohort studies/
53.	(cohort adj (study or studies or analys* or data)).ti,ab.
54.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
55.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
56.	Controlled Before-After Studies/
57.	Historically Controlled Study/

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58.	Interrupted Time Series Analysis/
59.	(before adj2 after adj2 (study or studies or data)).ti,ab.
60.	or/51-60
61.	exp case control study/
62.	case control*.ti,ab.
63.	or/62-63
64.	61 or 64
65.	Cross-sectional studies/
66.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
67.	or/66-67
68.	61 or 68
69.	61 or 64 or 68
70.	30 and (38 or 49 or 69)

1 **Embase (Ovid) search terms**

1.	knee replacement/
2.	((joint* or knee*) adj3 (replace* or prosthe* or endoprosthe* or implant* or arthroplast*)).ti,ab.
3.	or/1-2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.
9.	or/4-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animal/ not human/
13.	nonhuman/
14.	exp Animal Experiment/
15.	exp Experimental Animal/
16.	animal model/
17.	exp Rodent/
18.	(rat or rats or mouse or mice).ti.
19.	or/11-18
20.	3 not 19
21.	limit 20 to English language
22.	(Total and (partial or unicompartment* or unicondylar or compartment* or resurf* or re-surf* or patell*)).ti,ab.
23.	(partial and (Total or unicompartment* or unicondylar or compartment* or resurf* or re-surf* or patell*)).ti,ab.
24.	((unicompartment* or unicondylar or compartment*) and (Total or partial or resurf* or re-surf* or patell*)).ti,ab.
25.	((resurf* or re-surf* or patell*) and (Total or partial or unicondylar or unicompartment* or compartment*)).ti,ab.
26.	((medial or lateral) adj3 (compart* or unicompart* or unicondylar)).ti,ab.
27.	or/22-26

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28.	21 and 27
29.	random*.ti,ab.
30.	factorial*.ti,ab.
31.	(crossover* or cross over*).ti,ab.
32.	((doubl* or singl*) adj blind*).ti,ab.
33.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
34.	crossover procedure/
35.	single blind procedure/
36.	randomized controlled trial/
37.	double blind procedure/
38.	or/29-37
39.	systematic review/
40.	meta-analysis/
41.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
42.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
43.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
44.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
45.	(search* adj4 literature).ab.
46.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
47.	cochrane.jw.
48.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
49.	or/39-48
50.	Clinical study/
51.	Observational study/
52.	family study/
53.	longitudinal study/
54.	retrospective study/
55.	prospective study/
56.	cohort analysis/
57.	follow-up/
58.	cohort*.ti,ab.
59.	58 and 59
60.	(cohort adj (study or studies or analys* or data)).ti,ab.
61.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
62.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
63.	(before adj2 after adj2 (study or studies or data)).ti,ab.
64.	or/51-57,60-64
65.	exp case control study/
66.	case control*.ti,ab.
67.	or/66-67
68.	65 or 68
69.	cross-sectional study/

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70.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
71.	or/70-71
72.	65 or 72
73.	65 or 68 or 72
74.	28 and (38 or 49 or 73)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Arthroplasty, Replacement, Knee] this term only
#2.	((joint* or knee*) near/3 (replace* or prosthe* or endoprosthe* or implant* or arthroplast*)):ti,ab
#3.	(OR #1-#2)
#4.	(Total and (partial or unicompartment* or unicondylar or compartment* or resurf* or re-surf* or patell*)):ti,ab
#5.	(partial and (Total or unicompartment* or unicondylar or compartment* or resurf* or re-surf* or patell*)):ti,ab
#6.	((unicompartment* or unicondylar or compartment*) and (Total or partial or resurf* or re-surf* or patell*)):ti,ab
#7.	((resurf* or re-surf* or patell*) and (Total or partial or unicondylar or unicompartment* or compartment*)):ti,ab
#8.	((medial or lateral) near/3 (compart* or unicompart* or unicondylar)):ti,ab
#9.	(OR #4-#8)
#10.	#3 AND #9

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the joint replacement population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional health economics searches were run in Medline and Embase.

Table 9: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 01 May 2019	Exclusions Health economics studies
Embase	2014 – 01 May 2019	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 01 May 2019 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	arthroplasty/ or arthroplasty, replacement/ or arthroplasty, replacement, hip/ or arthroplasty, replacement, knee/ or arthroplasty, replacement, shoulder/ or hemiarthroplasty/
2.	joint prosthesis/ or hip prosthesis/ or knee prosthesis/ or shoulder prosthesis/
3.	((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)).ti,ab.

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4.	or/1-3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	Economics/
26.	Value of life/
27.	exp "Costs and Cost Analysis"/
28.	exp Economics, Hospital/
29.	exp Economics, Medical/
30.	Economics, Nursing/
31.	Economics, Pharmaceutical/
32.	exp "Fees and Charges"/
33.	exp Budgets/
34.	budget*.ti,ab.
35.	cost*.ti.
36.	(economic* or pharmaco?economic*).ti.
37.	(price* or pricing*).ti,ab.
38.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
39.	(financ* or fee or fees).ti,ab.
40.	(value adj2 (money or monetary)).ti,ab.
41.	or/25-40
42.	24 and 41

1 **Embase (Ovid) search terms**

1.	*arthroplasty/ or *replacement arthroplasty/ or *hip replacement/ or *knee replacement/ or *shoulder replacement/ or *hemiarthroplasty/
2.	*joint prosthesis/ or *hip prosthesis/ or *knee prosthesis/ or *shoulder prosthesis/

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3.	((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)).ti,ab.
4.	or/1-3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language
23.	health economics/
24.	exp economic evaluation/
25.	exp health care cost/
26.	exp fee/
27.	budget/
28.	funding/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/23-35
37.	22 and 36

1 NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR arthroplasty
#2.	MeSH DESCRIPTOR arthroplasty, replacement
#3.	MeSH DESCRIPTOR arthroplasty, replacement, hip
#4.	MeSH DESCRIPTOR arthroplasty, replacement, knee

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#5.	MeSH DESCRIPTOR arthroplasty, replacement, shoulder
#6.	MeSH DESCRIPTOR hemiarthroplasty
#7.	MeSH DESCRIPTOR joint prosthesis
#8.	MeSH DESCRIPTOR hip prosthesis
#9.	MeSH DESCRIPTOR knee prosthesis
#10.	MeSH DESCRIPTOR shoulder prosthesis
#11.	(((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)))
#12.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11) IN NHSEED
#13.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11) IN HTA

1

2

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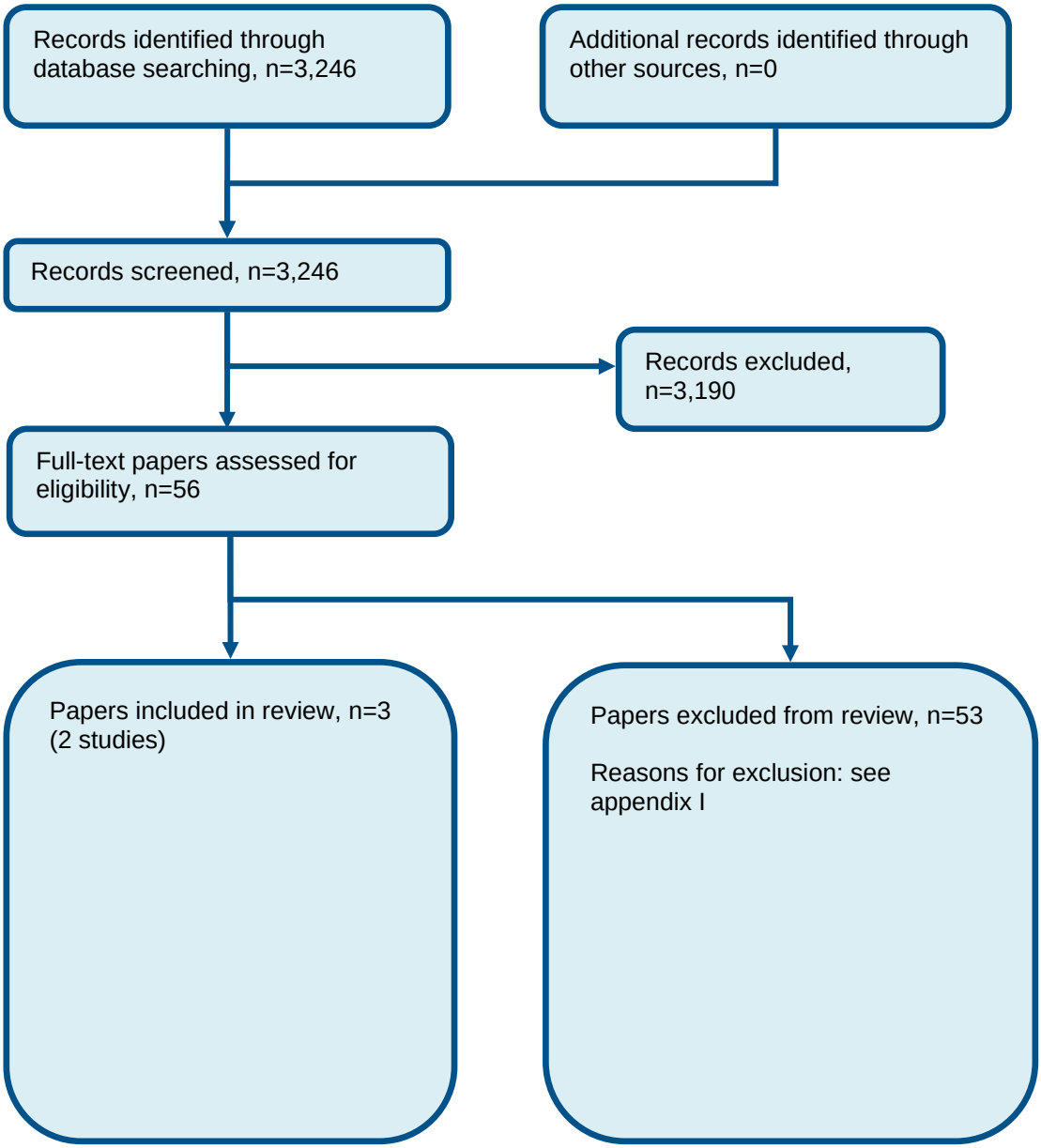
Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of total knee versus partial knee replacement



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1 Appendix D: Clinical evidence tables

Study	Kulshrestha 2017[31]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=80)
Countries and setting	Conducted in India
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 year FU
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion included the following: medial compartment osteoarthritis with a complete loss of joint space observed on anteroposterior or lateral radiographs of both knees. No clinical or functional anterior cruciate ligament (ACL) laxity in any knee. Radiographically normal lateral compartment joint space in both knees. A less than 15° correctable varus deformity in both knees.
Exclusion criteria	Fixed varus deformity in any knee, a more than 10° fixed flexion deformity in any knee, currently having or a history of inflammatory/infective joint disease, the presence of other lower limb or joint pathologies, patellofemoral arthritis with the involvement of the lateral facet of any knee, a history of previous knee surgery, an inability to participate in follow-up.
Age, sex and family origin	Age - Mean (SD): 60.96 (7.55). Sex (M:F): 16 male, 56 female. Family origin: N/A
Further population details	1. Age: Not elderly ~<75 years old (study defined) 2. Indication: Osteoarthritis 3. Specific implant:
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Medial/lateral knee replacement - Medial. UKA - All were performed through a limited medial parapatellar incision, without entering the rectus tendon. After exposure, the surgeons examined the integrity of the ACL, assessed for any arthritic changes in the lateral knee compartment and lateral patellofemoral joint. In case of any evidence of arthritis in theses compartments or loss of ACL, the surgery was converted to TKA on one or both sides, depending on the findings. . Duration 2 years FU. Concurrent medication/care: All surgeries were simultaneously performed on the right and left sides by 2 surgical teams, but a tourniquet was used only on 1 side. All surgeries were performed under single shot spinal anesthesia.

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	At induction, all patients received weight-adjusted and comorbidity adjusted doses of cefazolin or cefuroxime and an aminoglycoside. In all patients, one more dose of antibiotic was repeated at 8 hours after surgery. All patients received tranexamic acid at induction and 1 repeated dose at 3 hours after surgery. . Indirectness: No indirectness Further details: 1. Method of selective resurfacing: (n=40) Intervention 2: Total knee replacement. TKA - All surgeries in the TKA group were performed through a midline skin incision, followed by medial parapatellar arthrotomy. Duration 2 years FU. Concurrent medication/care: All surgeries were simultaneously performed on the right and left sides by 2 surgical teams, but a tourniquet was used only on 1 side. All surgeries were performed under single shot spinal anesthesia. At induction, all patients received weight-adjusted and comorbidity adjusted doses of cefazolin or cefuroxime and an aminoglycoside. In all patients, one more dose of antibiotic was repeated at 8 hours after surgery. All patients received tranexamic acid at induction and 1 repeated dose at 3 hours after surgery. Indirectness: No indirectness Further details: 1. Method of selective resurfacing:
Funding	No funding (No financial support was received from any outside agency.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MEDIAL versus TOTAL KNEE REPLACEMENT

Protocol outcome 1: Quality of life at later than 2 years
- Actual outcome: EQ-5D (VAS) at 2 years at 2 years; Group 1: mean 43.3 (SD 13.9); n=36, Group 2: mean 39.4 (SD 11.8); n=36
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UKA - 33.3, TKA - 31.4; Group 1 Number missing: 4, Reason: 4 patients in whom 1 knee underwent UKA and the other TKA were dropped and not included in analysis. ; Group 2 Number missing: 4, Reason: 4 could not attend FU visits due to relocation.

Protocol outcome 2: Patient Reported Outcome Measures (PROMs) at later than 2 years
- Actual outcome: KOS-ADLS at 2 years at 2 years; Group 1: mean 50 (SD 9.8); n=36, Group 2: mean 47 (SD 13); n=36
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UKA - 40.4, TKA - 42.9; Group 1 Number missing: 4, Reason: 4 patients in whom 1 knee underwent UKA and the other TKA were dropped and not included in analysis. ; Group 2 Number missing: 4, Reason: 4 could not attend FU visits due to relocation.
- Actual outcome: Oxford score at 2 years at 2 years; Group 1: mean 17.1 (SD 4.1); n=36, Group 2: mean 16.8 (SD 5.5); n=36
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UKA - 24.8, TKA - 23.2; Group 1 Number missing: 4, Reason: 4 patients in whom 1 knee underwent UKA and the other TKA were dropped and not included in analysis. ; Group 2 Number missing: 4, Reason: 4 could not attend FU visits due to relocation.
- Actual outcome: HAAS score at 2 years at 2 years; Group 1: mean 3.1 (SD 1.6); n=36, Group 2: mean 2.8 (SD 1.7); n=36
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

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Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UKA - 9.1, TKA - 8.9; Group 1 Number missing: 4, Reason: 4 patients in whom 1 knee underwent UKA and the other TKA were dropped and not included in analysis. ; Group 2 Number missing: 4, Reason: 4 could not attend FU visits due to relocation.	
Protocol outcomes not reported by the study	Mortality: life expectancy at time to event; Mortality at within 30 days; Quality of life at 6 weeks or earlier; Quality of life at later than 6 weeks up to 1 year; Patient Reported Outcome Measures (PROMs) at 6 weeks or earlier; Patient Reported Outcome Measures (PROMs) at later than 6 weeks up to 1 year; Major revision: tibia femoral compartments at time to event; Minor revision: secondary patella resurfacing at time to event; Deep surgical site Infection at before JR is revised; Superficial surgical site infection at before JR is revised; Length of stay at in hospital; Reoperation at 6 weeks or earlier; Reoperation at later than 6 weeks up to 1 year; Reoperation at later than 2 years ; Major adverse events as described by the studies (for example, VTE, myocardial infarction) at before JR is revised; Function at 6 weeks or earlier; Function at later than 6 weeks up to 1 year; Function at later than 2 years ; Pain at 6 weeks or earlier; Pain at later than 6 weeks up to 1 year; Pain at later than 2 years

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Study (subsidiary papers)	Newman 1998[47] (Newman 2009[45])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=100)
Countries and setting	Conducted in United Kingdom
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 5 years FU
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Unicompartmental tibiofemoral osteoarthritis with 'normal' other compartments, Intact cruciate ligaments, Flexion deformity ≤15°, Varus/valgus deformity ≤15°
Exclusion criteria	N/A
Recruitment/selection of patients	Patients likely to be suitable for unicompartmental replacement gave consent to participate in the trial.
Age, sex and family origin	Age - Mean (range): 69.7 (47 to 89). Sex (M:F): 38 male, 56 female. Family origin: N/A
Further population details	1. Age: Not elderly ~<75 years old (study defined) 2. Indication: Osteoarthritis 3. Specific implant:
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Medial/lateral knee replacement - Medial. UKR - We used a standard technique with a medial parapatellar incision and arthrotomy. For UKR, the varus or the valgus deformity was deliberately under corrected in order not to load the contralateral compartment. (St Georg Sled; Waldemar Link, Hamburg, Germany). The St Georg Sled has a metal femoral component, which is rounded in both the AP and lateral planes, and a totally flat tibial component, which was used without metal backing. Duration 5 years FU. Concurrent medication/care: In both groups, all components were fixed using Palacos cement with gentamicin. The postoperative care and rehabilitation were identical in both groups with mobilisation of both the knee and the patient beginning on the second postoperative day. Routine anticoagulation was not used, but all patients received three perioperative doses of antibiotic. Indirectness: No indirectness Further details: 1. Method of selective resurfacing: (n=52) Intervention 2: Total knee replacement. TKA - the appropriate soft-tissue release was carried out and the patella resurfaced routinely. The manufacturers' guidelines regarding the use of instruments and implants were followed. No uncemented components were used. Duration 5 years FU. Concurrent medication/care: In both groups all components were fixed using Palacos cement with gentamicin. The

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	postoperative care and rehabilitation were identical in both groups with mobilisation of both the knee and the patient beginning on the second postoperative day. Routine anticoagulation was not used, but all patients received three perioperative doses of antibiotic. Indirectness: No indirectness Further details: 1. Method of selective resurfacing:
Funding	Study funded by industry (The authors received financial assistance from one of the manufacturers for the provision of secretarial help to the unit)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MEDIAL versus TOTAL KNEE REPLACEMENT

Protocol outcome 1: Mortality: life expectancy at time to event
- Actual outcome: Mortality at 5 years at 5 years; Group 1: 4/50, Group 2: 5/52
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 4 died, 1 lost to FU; Group 2 Number missing: 6, Reason: 5 died, 1 lost to FU
- Actual outcome: Mortality at 15 years at 15 years; Group 1: 23/52, Group 2: 20/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 23, Reason: 23 died; Group 2 Number missing: 20, Reason: 20 died

Protocol outcome 2: Patient Reported Outcome Measures (PROMs) at later than 2 years
- Actual outcome: Bristol knee score - excellent score (90 - 100), at 5 years at 5 years; Group 1: 34/45, Group 2: 26/46
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UKR -54.7, TKR - 57.2; Group 1 Number missing: 5, Reason: 4 died, 1 lost to FU; Group 2 Number missing: 6, Reason: 5 died, 1 lost to FU
- Actual outcome: Bristol knee score - excellent score (91 - 100), at 15 years at 15 years; Group 1: 15/21, Group 2: 10/19
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UKR -54.7, TKR - 57.2; Group 1 Number missing: 23, Reason: 23 died; Group 2 Number missing: 20, Reason: 20 died
- Actual outcome: Bristol knee score - excellent or good score (80 - 100), at 5 years at 5 years; Group 1: 39/45, Group 2: 38/46
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UKR -54.7, TKR - 57.2; Group 1 Number missing: 5, Reason: 4 died, 1 lost to FU; Group 2 Number missing: 6, Reason: 5 died, 1 lost to FU
- Actual outcome: Bristol knee score - excellent or good or fair score (70 - 100), at 5 years at 5 years; Group 1: 42/45, Group 2: 43/46
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UKR -54.7, TKR - 57.2; Group 1 Number missing: 5, Reason: 4 died, 1 lost to FU; Group 2 Number missing: 6, Reason: 5 died, 1 lost to FU
- Actual outcome: Bristol knee score - excellent or good score (81 - 100), at 15 years at 15 years; Group 1: 16/21, Group 2: 13/19
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UKR -54.7, TKR - 57.2; Group 1 Number missing: 23, Reason: 23 died;

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Group 2 Number missing: 20, Reason: 20 died - Actual outcome: Bristol knee score - excellent or good or fair score (71 - 100), at 15 years at 15 years; Group 1: 17/21, Group 2: 14/19 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UKR -54.7, TKR - 57.2; Group 1 Number missing: 23, Reason: 23 died; Group 2 Number missing: 20, Reason: 20 died Protocol outcome 3: Major revision: tibia femoral compartments at time to event - Actual outcome: Revision due to tibial component at 20 months at 5 years; Group 1: 1/45, Group 2: 0/46; Comments: The tibial component was replaced because of aseptic loosening at 20 months and remains very satisfactory three years later Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 4 died, 1 lost to FU; Group 2 Number missing: 6, Reason: 5 died, 1 lost to FU Protocol outcome 4: Minor revision: secondary patella resurfacing at time to event - Actual outcome: Revision at 57 and 60 months at 5 years; Group 1: 1/45, Group 2: 1/46; Comments: UKR - one knee revised to TKR at 57 months for recurrent haemarthrosis. TKR - one knee was revised for aseptic loosening at 60 months. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 4 died, 1 lost to FU; Group 2 Number missing: 6, Reason: 5 died, 1 lost to FU - Actual outcome: Revision at 15 years at 15 years; Group 1: 3/46, Group 2: 4/45 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 23, Reason: 23 died; Group 2 Number missing: 20, Reason: 20 died Protocol outcome 5: Length of stay at in hospital - Actual outcome: Length of stay of more than 20 days at 5 years; Group 1: 3/50, Group 2: 11/52 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 4 died, 1 lost to FU; Group 2 Number missing: 6, Reason: 5 died, 1 lost to FU Protocol outcome 6: Major adverse events as described by the studies (for example, VTE, myocardial infarction) at before JR is revised - Actual outcome: Deep vein thrombosis at 5 years; Group 1: 1/50, Group 2: 5/52 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 4 died, 1 lost to FU; Group 2 Number missing: 6, Reason: 5 died, 1 lost to FU	
Protocol outcomes not reported by the study	Mortality at within 30 days; Quality of life at 6 weeks or earlier; Quality of life at later than 6 weeks up to 1 year; Quality of life at later than 2 years ; Patient Reported Outcome Measures (PROMs) at 6 weeks or

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	earlier; Patient Reported Outcome Measures (PROMs) at later than 6 weeks up to 1 year; Deep surgical site Infection at before JR is revised; Superficial surgical site infection at before JR is revised; Reoperation at 6 weeks or earlier; Reoperation at later than 6 weeks up to 1 year; Reoperation at later than 2 years ; Function at 6 weeks or earlier; Function at later than 6 weeks up to 1 year; Function at later than 2 years ; Pain at 6 weeks or earlier; Pain at later than 6 weeks up to 1 year; Pain at later than 2 years

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Appendix E: Forest plots

E.1 Medial UKA versus TKA

Figure 2: Quality of life (EQ-5D - VAS), 2 years

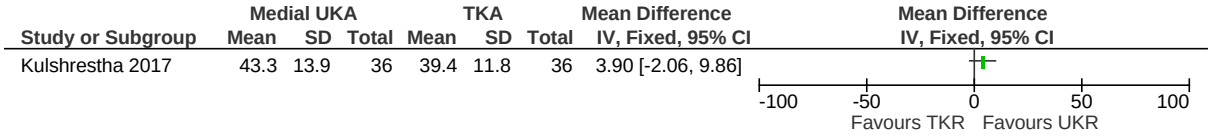

Figure 3: High Activity Arthroplasty Score, 2 years, 0-18

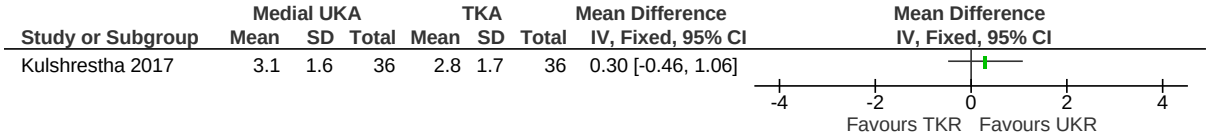

Figure 4: Bristol Knee Score, 15 years

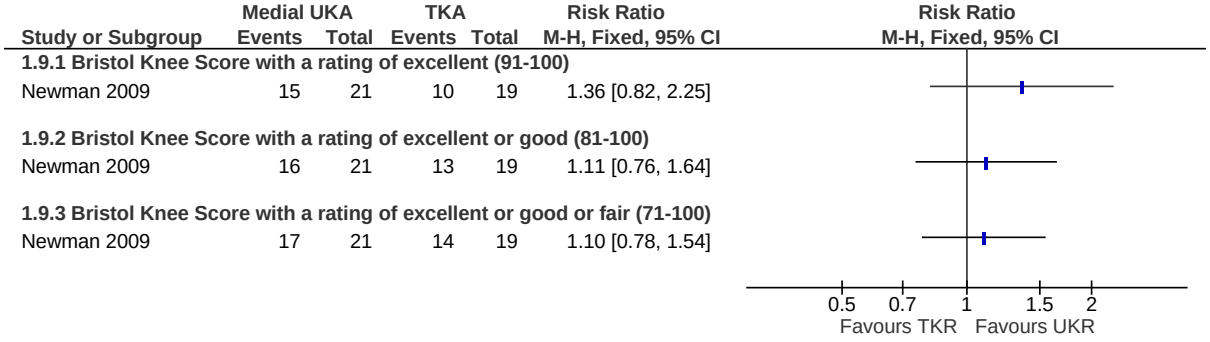

Figure 5: Oxford knee score, 2 years, 0-50

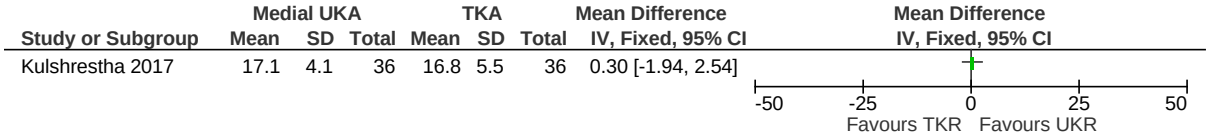

Figure 6: Knee outcome scale - activities of daily living (KOS-ADL), 2 years, 0-100

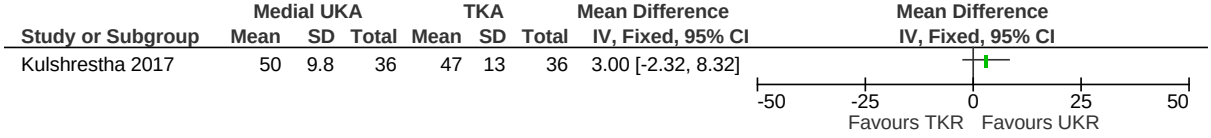

Figure 7: Major revision (due to tibial component) at 20 months

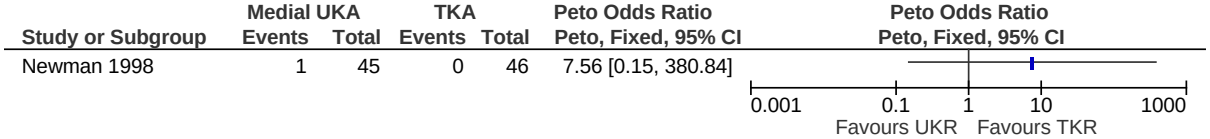

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Figure 8: Minor revision at 15 years

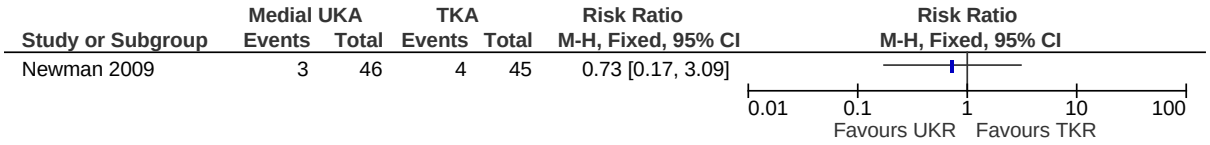

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Figure 9: Length of stay of more than 20 days

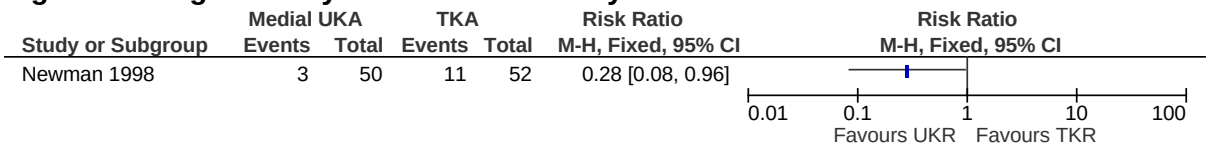
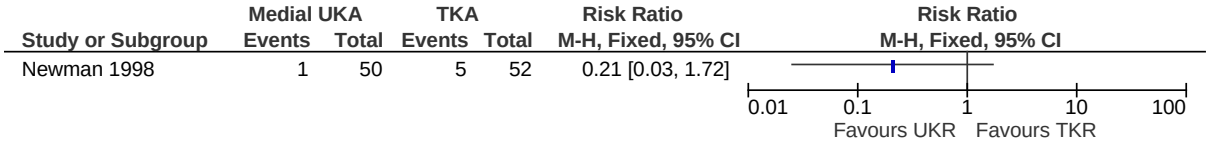


Figure 10: Adverse events, DVT, 5 years



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1 Appendix F: GRADE tables

2 Table 10: Clinical evidence profile: Medial UKA versus TKA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Medial UKA	TKA	Relative (95% CI)	Absolute		
Quality of life (follow-up 2 years; measured with: Change in EQ-5D - VAS; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	36	36	-	MD 3.9 higher (2.06 lower to 9.86 higher)	⊕⊕OO LOW	CRITICAL
HAAS score (follow-up 2 years; measured with: change in High Activity Arthroplasty Score; range of scores: 0-18; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36	36	-	MD 0.30 higher (0.46 lower to 1.06 higher)	⊕⊕⊕O MODERATE	CRITICAL
Bristol Knee Score with a rating of excellent (91-100) (follow-up 15 years; assessed with: Bristol Knee Score)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	15/21 (71.4%)	10/19 (52.6%)	RR 1.36 (0.82 to 2.25)	189 more per 1000 (from 95 fewer to 658 more)	⊕OOO VERY LOW	CRITICAL
Bristol Knee Score with a rating of excellent or good (81-100) (follow-up 15 years)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	16/21 (76.2%)	13/19 (68.4%)	RR 1.11 (0.76 to 1.64)	75 more per 1000 (from 164 fewer to 438 more)	⊕OOO VERY LOW	CRITICAL
Bristol Knee Score with a rating of excellent or good or fair (71-100) (follow-up 15 years)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	17/21 (81%)	14/19 (73.7%)	RR 1.10 (0.78 to 1.54)	74 more per 1000 (from 162 fewer to 398 more)	⊕OOO VERY LOW	CRITICAL
Change in Oxford knee score (follow-up 2 years; measured with: Oxford Knee Score; range of scores: 0-50; Better indicated by higher values)												
1	randomised	serious[2]	no serious	no serious	no serious	none	36	36	-	MD 0.3 higher (1.94	⊕⊕⊕O	CRITICAL

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	trials		inconsistency	indirectness	imprecision					lower to 2.54 higher)	MODERATE	
Change in Activities of daily living (follow-up 2 years; measured with: Knee Outcome Scale (KOS) - ADL; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	36	36	-	MD 3 higher (2.32 lower to 8.32 higher)	⊕⊕OO LOW	CRITICAL
Major revision (due to tibial component) (follow-up 20 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/45 (2.2%)	0/46 (0%)	Peto OR 7.56 (0.15 to 380.84)	20 more per 1000 (from 40 fewer to 80 more)	⊕OOO VERY LOW	CRITICAL
Minor revision (follow-up 15 years)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	3/46 (6.5%)	4/45 (8.9%)	RR 0.73 (0.17 to 3.09)	24 fewer per 1000 (from 74 fewer to 186 more)	⊕OOO VERY LOW	CRITICAL
Length of stay of more than 20 days (follow-up >20 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	3/50 (6%)	11/52 (21.2%)	RR 0.28 (0.08 to 0.96)	152 fewer per 1000 (from 8 fewer to 195 fewer)	⊕⊕OO LOW	IMPORTANT
Adverse events, DVT (follow-up 5 years)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/50 (2%)	5/52 (9.6%)	RR 0.21 (0.03 to 1.72)	76 fewer per 1000 (from 93 fewer to 69 more)	⊕OOO VERY LOW	IMPORTANT

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

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Appendix G: Health economic evidence selection

Figure 11: Flow chart of health economic study selection for the guideline

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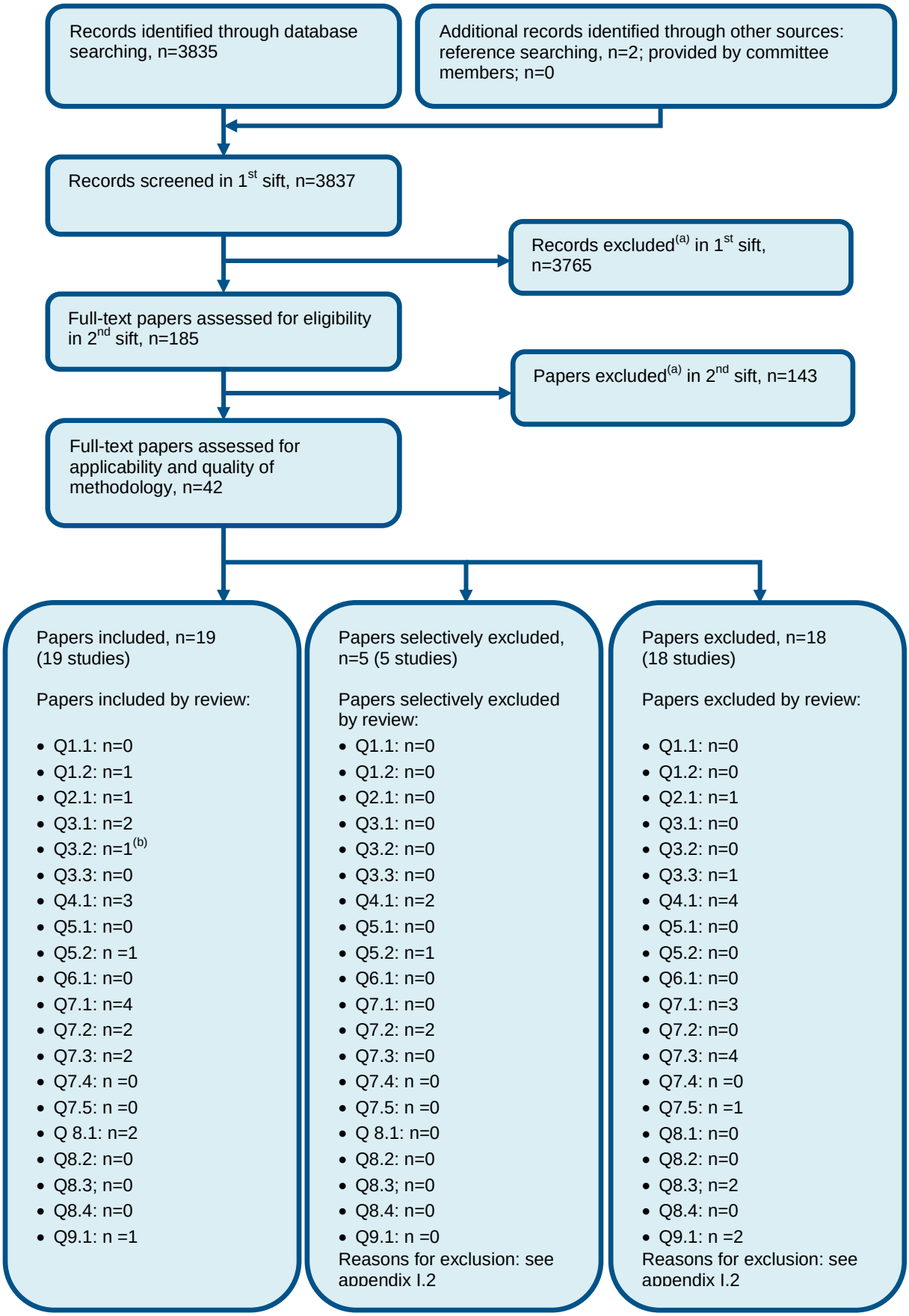

a) Non-relevant population, intervention, comparison, design or setting; non-English language
b) One study was applicable to both Q3.1 and Q3.2

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Appendix H: Health economic evidence tables

Study	Burn 2018[15]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Probabilistic decision model **Approach to analysis:** A Markov model using propensity score matched[(a)] registry data **Perspective:** UK NHS **Time horizon**: lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** Patients in the NJR who received either a UKR or TKR between 2003 and 2012 **Cohort settings:** Subgroup analyses by age <65, 65-75 and 75+ year olds and sex (male and female) **Intervention 1:** TKR **Intervention 2:** UKR	**Total costs (mean per 60-75 year old male patient[(b)]):** Intervention 1: £13,307 Intervention 2: £11,952 Incremental (2−1): UKR saves £1,355 per person (95% CI: -1610 to --1122; p=NR) **Currency & cost year:** Costs were estimated and also presented here in 2014 pounds sterling **Cost components incorporated:** Revision, re-revision, primary care utilisation	**QALYs (mean per 60-75 year old male patient [(b)]):** Intervention 1: 8.61 Intervention 2: 8.81 Incremental (2−1): UKR gives 0.20 extra QALYs per person (95% CI: 0.01 to 0.39; p=NR)	UKR is dominant to TKR for all age and sex sub-groups. **Analysis of uncertainty:** A probabilistic sensitivity analysis showed that UKR had a 100% probability of being cost effective in all subgroups except males <60 years old (87%) and females <60 years old (72%). A scenario analysis showed that the cost effectiveness of UKR was sensitive to the proportion of UKR procedures, which are carried out. When the proportion of UKR was <10% it was no longer dominant but still cost effective (ICER = £3,000 per QALY gained).
Data sources				
Health outcomes: NJR data linked to Hospital Episode Statistics and the Office for National statistics informed the effectiveness **Quality-of-life weights:** EQ-5D was taken from PROMs data and propensity score matched to patients in the model who had their procedures prior to 2009, as this was when recording of quality-of-life started. **Cost sources:** Primary procedures and revision costs taken from HRG codes and the 2014/2015 National Tariff Payment System. Cost of re-revision was assumed to be the same as the cost of an initial revision.				
Comments				
Source of funding: Research was part funded by Zimmer Biomet and supported by the NIRH and the Oxford BRC **Limitations:** Intervention effects not taken from registry data although confounders have been controlled for through propensity score matching. Quality of life scores assumed to remain constant if no subsequent revision or re-revision is required.				
Overall applicability:[(c)] Directly applicable	**Overall quality:**[(d)] Potentially serious limitations			

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Abbreviations: 95% CI= 95% confidence interval; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NIRH: National Institute for Health Research; NJR: National Joint Registry; NR= not reported; BRC: Oxford Biomedical Research Centre; QALYs= quality-adjusted life years; TKR: total knee replacement; UKR unicompartmental knee replacement
(a) Propensity score matching is statistical method used to control for confounders in observational data
(b) The results presented here are only for one sub-group as an example, as UKR was dominant in all cases.
(c) Directly applicable / Partially applicable / Not applicable
(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Peersman 2014[51]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Probabilistic decision model **Approach to analysis:** Markov model utilising registry data to compare the cost-effectiveness of UKA versus TKA **Perspective:** Belgian Healthcare **Time horizon:** lifetime **Discounting:** Costs: 3%; Outcomes: 1.5%	**Population:** Knee arthroplasty patients on the Finnish arthroplasty registry 1990 to 2002[(a)] **Cohort settings:** Start age: NR but subgroup analysis by age reported Male: N/R **Intervention 1:** TKR **Intervention 2:** UKR	**Total costs (mean per patient):** Only incremental costs reported Incremental (2−1): UKA saves £2,390 per patient (95% CI: NR; p=NR) **Currency & cost year:** 2014 Euros (presented here as 2014 UK pounds[(b)]) **Cost components incorporated:** Hospital stay, drugs, healthcare professionals, postoperative assessments, rehabilitation, revisions	**QALYs (mean per patient):** Only incremental QALYs reported Incremental (2−1): UKR gives 0.04 extra QALYs per patient (95% CI: NR; p=NR)	UKR is dominant to TKR in the base case and for all age and sex sub-groups. **Analysis of uncertainty:** Probabilistic sensitivity analysis showed UKR to have 65.1% probability of being cost effective at a WTP threshold of £21,287.
Data sources				
Health outcomes: QALYs taken from the literature, one of which used quality of well-being index scores. Revision rates taken from unpublished Swedish Knee arthroplasty register. **Quality-of-life weights:** Cited from 3 papers in the literature, none of which use EQ-5D **Cost sources:** sourced from the Belgian National Institute for Health and Disability Insurance				
Comments				
Source of funding: Unrestricted grant from Biomet Europe BV **Limitations:** Source of cohort data is not explicitly stated but appears to be Finnish registry data. Cohort is non-randomised registry data. Quality of life weights are taken from other papers, which do not use EQ-5D. Only incremental costs and outcomes are reported. A discount rate of 1.5% was used for the outcomes.				

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Overall applicability:[c] Partially applicable	**Overall quality:**[d] Potentially serious limitations

Abbreviations: CI= 95% confidence interval; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; QALYs= quality-adjusted life years; WTP: willingness to pay
(b) The cohort source is not explicitly stated in the paper but it appears that Finnish registry data has been used
(c) Converted using 2014 purchasing power parities[49]
(d) Directly applicable / Partially applicable / Not applicable
(e) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Smith 2017**[57]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model to compare the cost-effectiveness of UKR, TKR (and HTO[a]). **Perspective:** UK NHS **Time horizon**: 10 years postoperatively **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** Patients with medial compartment knee osteoarthritis requiring TKR, UKR or HTO **Cohort settings:** Separate models ran for patients 40, 50, 60 and 70 years of age Male: NR **Intervention 1:** TKA **Intervention 2:** UKA	**Total costs (mean per person):** **40- years old** Intervention 1: £6,815 Intervention 2: £,5,989 Incremental (2-1): UKR saves £826 **50- years old** Intervention 1: £6,815 Intervention 2: £5,989 Incremental (2-1): UKR saves £826 **60- years old** Intervention 1: £6,813 Intervention 2: £5,679 Incremental (2-1): UKR saves £1,134 **70- years old** Intervention 1: £5,235 Intervention 2: £6,825 Incremental (2-1): UKR saves £1,570 (95% CI: NR; p = NR) **Currency & cost year:** 2013 pounds sterling presented here as the same **Cost components incorporated:**	**Total QALYs (mean per person):** **40- years old** Intervention 1: 6.54 Intervention 2: 6.50 Incremental (2-1): UKR gives 0.05 less QALYs **50- years old** Intervention 1: 6.54 Intervention 2: 6.49 Incremental (2-1): UKR gives 0.05 less QALYs **60- years old** Intervention 1: 6.43 Intervention 2: 6.40 Incremental (2-1): UKR gives 0.033[b] less QALYs **70- years old** Intervention 1: 6.10 Intervention 2: 6.08 Incremental (2-1): UKR gives 0.015[b] less	**ICER (Intervention 2 versus Intervention 1):** 40- years old TKA costs £16,520 per QALY gained 50- years old TKA costs £16,520 per QALY gained 60- years old TKA costs £34,770 per QALY gained 70- years old TKA costs £105,810[c] per QALY gained **Analysis of uncertainty:** Probabilistic sensitivity analysis showed that UKR had the greatest probability of being cost effective for the 60- and 70-year-old age groups (34.9% and 36.7%, respectively). For the 40- and 50-year-old groups TKA had a greater probability of being cost effective (33.0% and 34.8%,

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		Length of hospital stay , implant costs, revisions, cement mix difference where relevant	QALYs (95% CI: NR; p = NR)	respectively). The model was highly sensitive to changes in utility and to a lesser extent in costs and revision rates
Data sources				
Health outcomes: A systematic review was conducted to find appropriate literature. It was assumed outcomes for UKR and TKR were the same so differences were driven by 5- and 10-year revision rates. Revision rates were estimated from multiple national registry databases **Quality-of-life weights:** Sourced from multiple papers in the literature. EQ-5D was not used in these papers with one using SF-12. **Cost sources:** Primary and revision arthroplasty components were obtained from the NJR. Hospital based costs were obtained from the KAT trial				
Comments				
Source of funding: NR **Limitations:** QALYs not calculated using the EQ-5D questionnaire. A 10-year time horizon used instead of lifetime. Cohort source not specifically cited but appear to be taken from multiple national arthroplasty registries which would have potential confounders				
Overall applicability:[(d)] Partially applicable		**Overall quality:**[(e)] Potentially serious limitations		

Abbreviations: EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HTO: high tibial osteotomy; ICER: incremental cost-effectiveness ratio; KAT: Knee Arthroplasty Trial; NJR: National Joint Registry; NR: not reported; QALYs: quality-adjusted life years; TKR: total knee replacement; UKR unicompartmental knee replacement

(a) HTO is not covered in the protocol so the results for this arm have not been presented

(b) More accurate figures have been obtained and presented here from the authors to account for rounding errors in the paper.

(c) The ICER given in the text of the paper for the 70- year old group is given as £14,889, which is incorrect. The authors have provided a corrected figure which is presented here.

(d) Directly applicable / Partially applicable / Not applicable

(e) Minor limitations / Potentially serious limitations / Very serious limitations

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Study	Xie 2014[64]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Within-trial analysis **Approach to analysis:** Costs and QALYs compared for UKR and TKR based on a 2-year prospective observational cohort study. **Perspective:** Singaporean healthcare perspective(a) **Follow-up**: 2 year **Discounting:** Costs: N/A; Outcomes: 3%	**Population:** Patients diagnosed with knee osteoarthritis undergoing TKR or UKR at Singapore General Hospital in 2003 **Cohort characteristics:** TKR and UKR Mean age: 66.8 and 63.3 Male: 19.6% and 25.0% **Intervention 1:** TKR**Intervention 2:** UKR	**Total costs (mean per patient):** Intervention 1: £5,541 Intervention 2: £4,441 Incremental (2−1): UKR saves £1,100 per patient (95% CI: NR; p<0.001) **Currency & cost year:** 2008 US dollars presented here as 2008 pounds sterling(b) **Cost components incorporated:** Health professional costs, tests or investigations, implants, medication, physiotherapy, ward costs, distributed overhead costs	**Mean QALY change from baseline** Intervention 1: 0.053 Intervention 2: 0.028 Incremental (2−1): UKR gives 0.026 less QALYs (95% CI: -0.021 to 0.074; p=NR)	**ICER (Intervention 2 versus Intervention 1):** TKR costs £42,307.69 per QALY gained. **Analysis of uncertainty:** Non-parametric bootstrapping of 3000 samples was done to estimate the 95% CIs of the ICER. However, probabilities of cost effectiveness are only reported for TKR at different WTP thresholds. TKR had 40% probability of being cost effective at £32,452.
Data sources				
Health outcomes: Patient level outcomes recorded during the observational study **Quality-of-life weights:** Patients filled out the SF-36 questionnaire at baseline, 6 months and 2-years. **Cost sources:** Individual patient resource use obtained from the hospital administrative database				
Comments				
Source of funding: NR **Limitations:** Intervention effect is taken from non-randomised observational data that may have confounding effects present, although differences in demographics were controlled for in a general linear model. A 2-year time horizon may not be long enough for outcomes and associated costs, such as those for revision, to be fully accounted for. The study is conducted from a Singaporean healthcare perspective. There was significant missing utility data at follow-up.				
Overall applicability:(c) Partially applicable **Overall quality:**(d) Potentially serious limitations				

Abbreviations: EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; QALYs= quality-adjusted life years; TKR: total knee replacement; UKR: unicompartmental knee replacement

(a) The perspective is described as societal in the paper but indirect costs are not included and the breakdown of costs is

(b) Converted using 2008 purchasing power parities[49]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

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1 Appendix I: Excluded studies

I.1 2 Excluded clinical studies

3 **Table 11: Studies excluded from the clinical review**

Study	Exclusion reason
Abdel 2018[1]	Incorrect interventions
Ackroyd 2005[2]	Incorrect study design. Abstract
Ahn 2017[3]	multivariate analysis not used
Amin 2006[5]	Incorrect study design
Argenson 2008[6]	Incorrect study design
Arirachakaran 2015[7]	Systematic review with different inclusion criteria however included studies were checked for this review
Aslam 2017[8]	Inappropriate comparison
Baker 2012[9]	Not review population. not enough data on type of UKA
Beard 2013[10]	Protocol
Berend 2009[11]	Inappropriate comparison
Biazzo 2019[12]	Incorrect study design
Braito 2016[13]	Incorrect study design
Brown 2012[14]	multivariate analysis not used
Burn 2017[16]	Incorrect study design
Callahan 1995[17]	Inappropriate comparison
Cameron 1988[18]	Incorrect study design. not enough information given about UKR type
Confalonieri 2009[19]	Incorrect study design
Costa 2011[20]	Incorrect study design
Dalury 2009[21]	multivariate analysis not used
Engh 2014[22]	Inappropriate comparison
Fisher 2010[23]	Inappropriate comparison. Multivariate analysis not used. UKA type not specified
Horikawa 2015[24]	multivariate analysis not used
Kim 2017[26]	Incorrect study design
Kleeblad 2018[27]	Inappropriate comparison. Systematic review with different inclusion criteria however included studies were checked for this review
Kooner 2017[28]	Inappropriate comparison
Koskinen 2008[29]	Incorrect study design
Köster 2016[30]	Unavailable
Larsen 2012[32]	Incorrect interventions
Laurencin 1991[33]	multivariate analysis not used. not enough data given on type of UKA
Liddle 2014[34]	not enough data on type of UKA
Liddle 2015[35]	type of UKA not specified. Incorrect study design
Liebs 2013[36]	Inappropriate comparison
Longo 2015[37]	Systematic review with different inclusion criteria however included studies were checked for this review

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Study	Exclusion reason
Lyons 2012[38]	multivariate analysis not used
Manzotti 2007[39]	multivariate analysis not used
Matthews 2013[40]	not enough data on type of UKA. Incorrect study design
Morrison 2011[41]	Incorrect interventions
Myers 2006[42]	Incorrect study design. Not review population
Newman 1994[46]	Incorrect study design. Abstract
Ode 2018[48]	multivariate analysis not used
Parratte 2015[50]	Inappropriate comparison
Radmer 2006[52]	Unavailable
Rodriguez-merchan 2014[53]	Systematic review with different inclusion criteria however included studies were checked for this review
Shah 1998[54]	Incorrect study design. Abstract
Shankar 2016[55]	multivariate analysis not used
Siman 2017[56]	Incorrect study design
Swanson 1985[58]	Incorrect interventions
Von keudell 2014[59]	Incorrect study design. Incorrect interventions
Walton 2006[60]	multivariate analysis not used. Incorrect study design
Weale 1999[61]	Incorrect study design. Abstract
Witjes 2016[63]	Systematic review with different inclusion criteria however included studies were checked for this review
Xie 2010[64]	Incorrect study design
Zuiderbaan 2017[66]	multivariate analysis not used

I.21 Excluded health economic studies

2 **Table 12: Studies excluded from the health economic review**

Reference	Reason for exclusion
Yang 2003[65]	This study was assessed as partially applicable with very serious limitations due to unclear methodology
Koskinen 2008[29]	This study was assessed as partially applicable with very serious limitations due to the use of registry data from 1980 not reflecting current practice.
Willis-owen 2009[62]	This study was assessed as partially applicable with very serious limitations due to a lack of adjusted data

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