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UK poSt Arthroplasty Follow-up rEcommendations (UK SAFE): what does analysis of linked, routinely collected national datasets tell us about mid–late term revision risk after knee replacement?

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ABSTRACT

Objective To identify patients at risk of mid-late term revision of knee replacement (KR) to inform targeted follow-up.

Design Analysis of linked national datasets from primary and secondary care (Clinical Practice Research Datalink (CPRD GOLD), National Joint Registry (NJR), English Hospital Episode Statistics (HES) and Patient Reported Outcome Measures (PROMs)).

Participants Primary elective KRs aged ≥18 years.

Event of interest Revision surgery ≥5 years (mid–late term) postprimary KR.

Statistical methods Cox regression modelling to ascertain risk factors of mid–late term revision. HRs and 95% CIs assessed association of sociodemographic factors, comorbidities, medication, surgical variables and PROMs with mid–late term revision.

Results NJR-HES-PROMs data were available from 2008 to 2011 on 188 509 KR. CPRD GOLD-HES data covered 1995–2011 on 17 378 KR. Patients had minimum 5 years postprimary surgery to end 2016. Age and gender distribution were similar across datasets; mean age 70 years, 57% female. In NJR, there were 8607 (4.6%) revisions, median time-to-revision postprimary surgery 1.8 years (range 0–8.8), with 1055 (0.6%) mid–late term revisions; in CPRD GOLD, 877 (5.1%) revisions, median time-to-revision 4.2 years (range 0.02–18.3), with 352 (2.0%) mid–late term revisions.

Reduced risk of revision after 5 years was associated with older age (HR: 0.95; 95% CI 0.95 to 0.96), obesity (0.70; 0.56 to 0.88), living in deprived areas (0.71; 0.58 to 0.87), non-white ethnicity (0.58; 0.43 to 0.78), better preoperative pain and functional limitation (0.42; 0.33 to 0.53), better 6-month postoperative pain and function (0.33; 0.26 to 0.41) or moderate anxiety/depression (0.73; 0.63 to 0.83) at primary surgery.

Increased risk was associated with male gender (1.32; 1.04 to 1.67); when anticonvulsants (gabapentin and pregabalin) (1.58; 1.01 to 2.47) or opioids (1.36; 1.08 to 1.71) were required prior to primary surgery.

No implant factors were identified.

Conclusion The risk of mid–late term KR revision is very low. Increased risk of revision is associated with patient case-mix factors, and there is evidence of sociodemographic inequality.

Strengths and limitations of this study

- This study is part of a wider programme of work to identify potential patient groups for follow-up after hip and knee replacement and used large national routine datasets from primary and secondary care.
- The linkage of datasets allowed us to explore the impact of multiple risk factors on the mid–late term risk of revision of knee replacement.
- This is one of the first studies to identify predictors of mid–late term revision risk for knee replacement from real-world data and contributes to the discussion on follow-up.
- A limitation of the National Joint Registry–Hospital Episode Statistics–Patient Reported Outcome Measures linked data was limited long-term follow-up due to including data from 2009 onwards but only primary operations up to 2011 to allow for revision rates after 5 years.

INTRODUCTION

Primary knee replacement (KR) surgery is a common elective orthopaedic procedure for the treatment of knee pain due to end stage osteoarthritis (OA). There is good evidence showing that KR is highly clinically effective, reducing symptoms of pain and functional limitations for the vast majority of patients[1–3] and is also cost effective.[4 5] Over 100 000 operations are carried out each year in the UK.[6] The lifetime risk of receiving

knee arthroplasty in the UK is estimated to be 10.8% for women and 8.1% for men.[7] These numbers are projected to increase with an ageing and increasingly obese population, placing a growing public health burden on the National Health Service (NHS) in respect of funding and capacity.[8]

There is significant pressure on hospital trusts to reduce the amount of follow-up appointments due to expanding waiting lists, cancellation of elective surgery and increasing numbers of patients needing primary joint replacement. Although previous British Orthopaedic Association guidelines recommended outpatient follow-up at 1 and 7 years, and every 3 years thereafter, recent guidelines for primary joint replacement in the UK recommend further research on follow-up due to a lack of evidence.[9 10] There is variation across the country in how hospitals organise follow-up services, and many units stopped follow-up after an early postoperative check.[11] Evidence is required on the impact that disinvestment in follow-up services may have on patient safety. There is a need to ensure early detection of patients with failing implants and target follow-up accordingly. In March 2014, the James Lind Alliance and National Institute for Health Research (NIHR) Priority Setting Partnership for Hip and Knee Replacement for Osteoarthritis identified that defining the ideal postoperative follow-up period and the best long-term care model for people with OA and knee replacement was among its top 10 research priorities, highlighting the importance of appropriate follow-up to ensure the health of patients.

The objective of this study was to use nationally available datasets to identify which groups of patients with KR may require follow-up based on their mid–late term revision risk (five or more years post primary surgery). This work forms part of a larger programme of work, UK SAFE, that was designed to address the research question: is it safe to disinvest in mid–late term follow-up of hip and knee replacement?[12] The UK SAFE programme of work took place between 1 December 2016 and 30 November 2020 (protocol provided in online supplemental file 1).

METHODS

Study design

This was a nationwide retrospective cohort study in which national data from primary care (Clinical Practice Research Datalink) and secondary care (National Joint Registry (NJR), Hospital Episode Statistics (HES) and Patient-Reported Outcome Measures) were linked to identify predictors of mid–late term revision of KR.

Sources of data

Clinical Practice Research Datalink (CPRD)-GOLD-HES

The CPRD GOLD comprises the entire computerised medical records of a sample of patients attending general practitioners (GPs) in the UK.[13] It contains information on over 14 million patients registered at over 700 general practices in the UK. With 4.4 million active (alive, currently registered) patients meeting quality criteria, approximately 6.9% of the UK population are included, and patients are broadly representative of the UK general population in terms of age, sex and ethnicity.[14] GPs in the UK play a key role in the delivery of healthcare by providing primary care and referral to specialist hospital services, and each GP practice records this medical information for individual patients. The CPRD is administered by the Medicines and Healthcare products Regulatory Agency. CPRD GOLD records contain all clinical and referral events in both primary and secondary care in addition to comprehensive demographic information, prescription data and hospital admissions. Data are stored using Read codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-10). Read codes are used as the standard clinical terminology system within UK primary care. Only practices that pass quality control are used as part of CPRD GOLD. CPRD ensures patient confidentiality by providing anonymised healthcare records.

CPRD GOLD data were linked to data for all-cause mortality, provided by the Office for National Statistics.[15] CPRD GOLD data were also linked to the Index of Multiple Deprivation (IMD) and to the HES database (described later). CPRD already provide access to HES data for England that is held under the CPRD data Linkage Scheme, available for around 60% of patients in the CPRD GOLD database. Previous research by the CPRD team has shown that linked practices/patients are representative of the CPRD GOLD population as a whole.[16]

NJR–HES–Patient Reported Outcome Measures (PROMs)

Starting in 2003, the National Joint Registry (NJR) collected information on all hip and knee replacements performed each year in both public and private hospitals in England, Wales, Northern Ireland and the Isle of Man.[17] Data are entered into the NJR using forms completed at the time of surgery, and revision operations are linked to primaries using unique patient identifiers. Data recorded in the NJR includes prosthesis and operative information (prosthesis type, approach and thromboprophylaxis); patient information (age, gender, body mass index (BMI), American Society of Anaesthesiologists (ASA) grade); and surgeon and unit information (including caseloads and public/private status).

The HES database holds information on all patients admitted to National Health Service (NHS) hospitals in England, including diagnostic ICD codes providing information about a patient's illness or condition and NHS national clinical procedural codes (OPCS4) for surgery. It covers a smaller geographical area than the NJR and does not include privately funded operations. However, HES provides additional information for every patient (including detailed comorbidity information and deprivation indices) and about every procedure (including length of stay and need for blood transfusion or critical care). Additional records contain details of readmissions,

reoperations and revisions not recorded in the NJR database.

Since April 2009, PROMs data have been collected on all knee replacements performed in public hospitals in England.[18] A health-related quality of life questionnaire (the EuroQol with five domains (EQ-5D-3L)[19]) and a joint-specific outcome score (the Oxford Knee Score (OKS)[20]) are collected preoperatively and at 6 months after surgery, along with patient-reported measures of preoperative disability and postoperative satisfaction.

For this analysis, we used NJR records linked to data from the HES and PROMs databases on all KR operations.

Participants

Anonymised records were extracted for all patients over 18 years of age receiving primary knee replacement surgery. For CPRD GOLD-HES data, the time span covered the years 1995–2017; for NJR–HES–PROMS data, it covered the years 2009–2017. Patients were included if they had primary total knee replacement or unicompartmental knee replacement. We excluded patients that had revision surgery and total joint replacement of unspecified fixation. The following exclusions were made to remove potential case-mix issues: other injuries due to trauma, such as transport accidents and falls; non-elective admissions; and a diagnosis other than primary knee OA. There will be some overlap between patients receiving knee replacement in the two data sources (around 7% of patients between 2009 and 2016); however, these anonymised datasets are analysed independently of each other.

Primary outcome

Early complications (defined as less than 5 years) are often symptomatic and include infection and technical errors.[21] Arthroplasty failure in the longer term (defined as after 5 years), constituting 50% of revision surgery, is usually caused by bearing-surface wear and associated consequences of periprosthetic osteolysis or aseptic loosening and may be asymptomatic until clinical and radiographic failure have occurred.[21 22] The primary outcome was defined as mid–late term revision (defined as more than 5 years postprimary surgery). Revision is defined as the removal, exchange or addition of any of the components of arthroplasty. In the NJR–HES–PROMS linked datasets, operative details are completed using the NJR dataset, rather than the OPCS4 coding used by the HES dataset. The NJR collects operative data using two forms: one for primary operations and the other for revision operations. In both cases, all component labels from the surgery are attached to the form, and it is from these that the component details are collected. Revision operations are linked to primaries using unique patient identifiers and so, two operations on the same knee would be linked using this system. The combination of the separate coding at source and the secondary linkage gives confidence that primary and revision operations are correctly identified. In the CPRD GOLD dataset, subjects with a revision surgery procedure are identified using the Read codes, and for those with HES-linked data OPCS4 codes can be used.

Predictors

Secondary care predictors

The patient level characteristics available in NJR and HES include: age, gender, BMI, area deprivation, rurality, ethnicity, Charlson comorbidity index[23] (calculated from HES using ICD10 codes), ASA grade. Data from the NJR provide additional information on surgical and operative factors: whether or not a minimally invasive technique was used; annual surgeon volume/case load, operative time, grade of operating surgeon, surgical approach, patient position, implant fixation, type of mechanical or chemical thromboprophylaxis and unit type (public, private, independent sector treatment centre). Data from the PROMs database provide additional information on symptoms of pain, function and health related quality of life preoperatively and at 6 months postsurgery. Pain and function are measured using the OKS. The EQ-5D-3L consists of five questions (assessing mobility, self-care, ability to conduct usual activities, degree of pain/discomfort and degree of anxiety/depression), ranging from 1 (best state) to 3 (worst state). EQ-5D-3L can be expressed as an overall index (graded from −0.594 to 1), or as ordinal responses for each category.

Primary care predictors

The CPRD GOLD database includes information on: age, gender, BMI, joint replaced (hip/knee), year of joint replacement operation, recorded diagnosis of OA (yes/no), fracture presurgery (yes/no), calcium and vitamin D supplements, use of bisphosphonates, use of selective oestrogen receptor modulators, oral glucocorticosteroid therapy, smoking status and alcohol intake recorded closest to the date of the primary surgery, region of UK, comorbid conditions registered by the physician from the following list (asthma, malabsorptive syndromes, inflammatory bowel disease, hypertension, hyperlipidaemia, ischaemic heart disease, stroke, chronic obstructive pulmonary disease, chronic kidney failure, neoplasms, diabetes), use of drugs that can affect fracture risk (proton pump inhibitors, antiarrhythmics, anticonvulsants, antidepressants, anti-Parkinson drugs, statins, thiazide diuretics and anxiolytics).

Sample size

We included all patients receiving planned elective primary surgery for knee OA. For the NJR–HES–PROMs data, this covered the years 2009–2016 (as our requested linked HES data was from 2008 onwards, and earlier years of data were not available to us). For the CPRD GOLD-HES, this spanned the years 1995–2016. For both datasets, we excluded patients receiving a primary knee replacement after 2011 to ensure all patients had at least 5-year follow-up, as we were not interested in revisions occurring in the early period up to 5 years after the

primary replacement surgery. The sample was created from all available data that satisfied these criteria.

Statistical analysis methods

Survival analysis was used to model time to revision. To identify patients most likely to require revision, proportional hazards regression modelling was used to identify preoperative, perioperative and postoperative predictors of mid–late term revision. The date of the first incidence of a subject's knee replacement was used as the start time. The event of interest in all time-to-event models was the first recorded revision operation. Linearity of continuous predictors was assessed using fractional polynomial regression modelling. Proportionality assumptions were checked using Schoenfeld residuals. Missing data were handled by using multiple imputation methods using the Imputation by Chained Equations procedure.[24] SEs were calculated using Rubin's Rules. We include all predictor variables in the multiple imputation process, together with the outcome variable (Nelson Aalen estimate of survival time and whether or not the patient had the outcome) as this carried information about missing values of the predictors.

For the CPRD GOLD-HES primary care, we generated 10 imputed datasets for KR. Data were imputed for the variables BMI, deprivation index, smoking and drinking risk factors. For secondary care NJR–HES–PROMS dataset, we generated a single imputed dataset for KR. Variables imputed were BMI, deprivation index, rurality, ethnicity, OKS baseline scores and EQ-5D-3L item for anxiety and depression. We ran univariate Cox regression models. Risk factors with a p value <0.20 were selected for a multivariable model. Backward selection of variables was used to identify variables to keep in the final model risk factors with at least one category with a p value <0.05. For the CPRD GOLD-HES primary care dataset, we present two final models: one with medication use as yes/no variables and the other model with daily defined doses (DDDs) calculated from 1 year prior to the primary surgery and divided in tertiles. In addition, we conducted sensitivity analyses using a Fine-Gray competing risk model to account for the competing risk of death.

Patient and public involvement

Members of the NIHR Leeds Biomedical Research Centre and Bristol public and patient involvement groups (PPI) were involved in developing the UK SAFE research question and work programme based on experiences of arthroplasty and preferences for care. The steering committee includes a PPI coapplicant who has contributed to interpretation of the results and will be involved in production of the final report that is disseminated to the public, patients and NHS staff.

RESULTS

This study has been reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology checklist (online supplemental file 2).

Table 1 Stages of patient selection for inclusion in study: primary care data

Included	Excluded
Patients with primary knee replacement in CPRD GOLD (64 071)	
→	Outcome (knee revision) and index event (primary surgery) outside England: 5397 (8.4%); Wales 6982 (10.9%)
→	Outcome (knee revision) and index event: 31 395 (42.9%)
Patients with primary knee replacement in CPRD GOLD linked to HES and used in survival analysis (22 836)	
→	Primary surgery after 2011 (allowing for 5 years of follow-up): 5458 (23.9%)
Patient with primary knee replacement used in the survival analysis (17 378)	

CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics.

Participants

For the CPRD GOLD-HES dataset, 64 071 sets of data were available, and table 1 shows the steps towards 17 378 participants. Construction of the NJR–HES–PROMs dataset commenced with 84 1 212 records in the NJR and 188 509 participants after exclusions (table 2).

Summary statistics for patients in the CPRD GOLD-HES and the NJR-HES-PROMs linked datasets are provided (online supplemental file 3, tables A,B. The CPRD GOLD-HES linked data covered a longer time period between 1995 to 2011; the NJR-HES-PROMs data were available 2009–2011. The characteristics of patients in the full CPRD dataset compared with those in the CPRD-HES linked data were similar with no evidence of any selection bias (online supplemental file 3, table C). Both datasets allowed a minimum of 5-year follow-up to end 2016. The age and gender distribution of patients was similar across both datasets, with a mean age of 70 years at time of knee replacement and 57% female. An extensive range of patient case-mix, surgical, operative factors and primary care prescribing data was available for analysis.

The CPRD GOLD-HES dataset had a longer time to revision. There were 877 (5.1%) revisions, with median time to revision of 4.2 years (range 0.02–18.3 years) and 352 (2.0%) were mid–late term revisions.

In the NJR-HES-PROMs data, there were 8607 (4.6%) knee replacement revisions with a median time to revision of 1.8 years (range 0–8.8 years); this included 1055 (0.6%) mid–late term revisions.

Table 2 Stages of patient selection for inclusion in study: hospital data

Included		Excluded
Patients with primary knee replacement in National Joint Registry (841 212)		
	→	Primary surgery before 2008 (no data available in HES) (169 776; 20.2%)
	→	Primary surgery after 2011 (allowing for 5 years of follow-up) (414 832; 49.4%)
	→	Without primary surgery date (1037; 0.1%)
	→	A diagnosis other than primary knee osteoarthritis (2940; 0.4%)
	→	Non-elective surgeries (535; 0.06%)
	→	Without information on type of admission (63 416; 7.5%)
Patient with primary knee replacement used in the survival analysis (188 509)		

HES, Hospital Episode Statistics.

Predictors of mid–late term revision

Patient demographics

Older age at the time of primary KR was associated with a lower risk of mid–late revision (tables 3 and 4). The effect of age was linear and the association was strong where, for a 1-year increase in age at surgery, the risk of outcome reduced by 5%, and this finding was consistent across the CPRD GOLD-HES and NJR–HES–PROMs datasets. The effect of gender was that males had an increased risk of mid–late revision compared with females. This was only observed in the CPRD GOLD-HES data, where males had a 24% increased risk of revision, while the effect size was weaker and non-significant in the NJR-HES-PROMs dataset.

The effect of obesity on outcome was demonstrated in the NJR–HES–PROMs dataset, where compared with those of normal BMI, underweight patients were at increased risk of revision and obese patients at reduced risk of mid–late revision. The effect of IMD deprivation in the NJR–HES–PROMs dataset showed that patients in the most deprived areas were less likely to receive mid–late term revision; there was no such association with obesity or deprivation observed in the CPRD GOLD-HES dataset. An association with ethnicity was observed only in the NJR–HES–PROMs dataset, where patients of non-white ethnicity were less likely to be revised mid–late term.

Implant factors (NJR–HES–PROMs dataset)

None of the implant related factors were associated with an increased mid–late revision risk.

Preoperative and 6-month follow-up PROMs (table 4)

There was a clear linear trend with the preoperative and 6-month postoperative OKS, where patients with the most pain and functional limitations at the time of surgery, and at 6 months after surgery, were substantially more likely to require mid–late term revision. Patients with preoperative anxiety/depression were found to be less likely to receive a mid–late revision operation.

Primary care comorbidities and medication use (table 3)

Through the CPRD GOLD-HES dataset, we were able to investigate comorbidities recorded prior to surgery and medication use. There was no effect of preoperative comorbidity for KR. With medication use, oral glucocorticoid steroid therapy was associated with a lower risk of revision, whereas use of antiarrhythmics and anticonvulsants placed patients at a higher risk.

For the pain medication use, an increased revision risk was observed in those patients requiring opiates. When examining effects of medication use in more detail, by looking at DDDs calculated from the 1 year prior to the primary surgery and divided into tertiles, the effect of opioids was only significant in the highest DDD tertile of >600 DDD.

The sensitivity analysis for the competing risk of death is presented (tables 3 and 4).

DISCUSSION

The risk of a mid–late revision operation (≥5 years) after primary knee replacement surgery is very low. Within our CPRD GOLD-HES primary care dataset, we had up to 20 years patient follow-up from the start point of 5 years after the primary operation and even then, the mid–late revision rate was only 2.0%. In this study, it was the patient case-mix factors that were associated with mid–late term revision surgery. Patients at increased risk were those who were younger, male gender, not obese, living in affluent areas, of white ethnicity, not anxious or depressed at primary surgery. Those with worse pain and functional scores at primary surgery were at higher risk for mid–late revision than those with better scores.

Strengths of this study include the use of large national routine datasets where the NJR data are mandatory and have near complete coverage, and the CPRD GOLD data is nationally representative in respect of UK population demographic characteristics. Large sample sizes afforded us the ability to identify predictors of a rare long-term outcome such as revision surgery. A limitation of the NJR–HES–PROMs linked data was limited long-term follow-up

Table 3 Cox regression model identifying risk factors for revision after 5 years of primary total knee and unicompartmental replacement: primary care data

Risk factors (reference category)	Patients undergoing KR (n=17 378)			Patients undergoing KR with missing dose for bisphosphonates and opioids excluded (n=14 470)	
	Crude analysis	Adjusted analysis (Drug yes/no)	Adjusted competing risk analysis (Drug yes/no)	Adjusted analysis (Drug DDD)	Adjusted competing risk analysis (Drug DDD)
	HR (95% CI) P value	HR (95% CI) P value	HR (95% CI) P value	HR (95% CI) P value	HR (95% CI) P value
Year of primary KR (2010–2011)					
1995–1999	4.63 (1.98 to 10.81); **p<0.01**	5.39 (2.28 to 12.75); **p<0.01**	6.60 (2.82 to 15.44); p<0.01	8.10 (2.52 to 25.98); **p<0.01**	10.16 (3.20 to 32.29); p<0.01
2000–2004	3.24 (1.42 to 7.41); **p=0.01**	3.65 (1.59 to 8.40); **p<0.01**	4.33 (1.90 to 9.87); p<0.01	5.49 (1.73 to 17.37); **p<0.01**	6.64 (2.12 to 20.83); p=0.001
2005–2009	2.36 (1.04 to 5.36); **p=0.04**	2.42 (1.06 to 5.52); **p=0.04**	2.77 (1.22 to 6.28); p=0.015	3.45 (1.10 to 10.86); **p=0.03**	4.04 (1.29 to 12.65); p=0.017
Age at primary KR (continuous variable)	0.93 (0.92 to 0.94); **p<0.01**	0.93 (0.92 to 0.94); **p<0.01**	0.93 (0.92 to 0.93] ; p<0.01	0.93 (0.92 to 0.94); **p<0.01**	0.92 (0.92 to 0.93); p<0.01
Sex (woman)					
Man	1.26 (1.02 to 1.55); **p=0.03**	1.24 (1.00 to 1.53); p=0.06	1.18 (0.95 to 1.46); p=0.13	1.32 (1.04 to 1.67); p=**0.02**	1.26 (1.00 to 1.60); p=0.054
Body mass index (normal)					
Underweight					
Overweight	1.02 (0.71 to 1.45); p=0.93	0.97 (0.67 to 1.42); p=0.89	1.01 (0.69 to 1.47); p=0.96	0.98 (0.65 to 1.46); p=0.91	1.01 (0.68 to 1.51); p=0.97
Obese class I (moderately obese)	1.25 (0.86 to 1.80); p=0.24	1.06 (0.71 to 1.57); p=0.79	1.08 (0.73 to 1.60); p=0.71	1.09 (0.69 to 1.70); p=0.72	1.11 (0.71 to 1.73); p=0.66
Obese class II and higher	1.35 (0.91 to 2.00); p=0.14	1.03 (0.65 to 1.63); p=0.90	1.03 (0.65 to 1.64); p=0.90	0.97 (0.58 to 1.63); p=0.90	0.97 (0.57 to 1.63); p=0.89
Region (East Midlands)					
East of England	0.83 (0.49 to 1.41); p=0.49	0.95 (0.56 to 1.61); p=0.84	0.94 (0.55 to 1.59); p=0.82		
London	0.81 (0.46 to 1.43); p=0.47	0.96 (0.54 to 1.71); p=0.90	0.94 (0.53 to 1.66); p=0.83		
North East	0.28 (0.08 to 0.95); **p=0.04**	0.27 (0.08 to 0.91); **p=0.04**	0.27 (0.08 to 0.91); p=0.035		
North West	0.88 (0.53 to 1.47); p=0.63	0.93 (0.56 to 1.55); p=0.78	0.91 (0.55 to 1.52); p=0.73		
South Central	0.81 (0.48 to 1.36); p=0.42	0.93 (0.55 to 1.57); p=0.79	0.91 (0.54 to 1.52); p=0.71		
South East Coast	1.08 (0.64 to 1.82); p=0.77	1.37 (0.82 to 2.29); p=0.23	1.33 (0.80 to 2.23); p=0.28		
South West	0.86 (0.51 to 1.44); p=0.56	1.01 (0.60 to 1.70); p=0.97	0.98 (0.58 to 1.65); p=0.95		
West Midlands	0.74 (0.44 to 1.26); p=0.26	0.79 (0.46 to 1.33); p=0.37	0.78 (0.46 to 1.31); p=0.34		
Yorkshire and The Humber	0.87 (0.46 to 1.65); p=0.68	0.88 (0.47 to 1.66); p=0.70	0.87 (0.46 to 1.63); p=0.67		
Drugs prior to primary KR					
Oral glucocorticosteroid therapy	0.75 (0.56 to 1.02); p=0.07	0.72 (0.53 to 0.99); **p=0.04**	0.69 (0.50 to 0.94); p=0.02		

Continued

Table 3 Continued

Risk factors (reference category)	Patients undergoing KR (n=17 378)			Patients undergoing KR with missing dose for bisphosphonates and opioids excluded (n=14 470)	
	Crude analysis	Adjusted analysis (Drug yes/no)	Adjusted competing risk analysis (Drug yes/no)	Adjusted analysis (Drug DDD)	Adjusted competing risk analysis (Drug DDD)
	HR (95% CI) P value	HR (95% CI) P value	HR (95% CI) P value	HR (95% CI) P value	HR (95% CI) P value
Drugs that can affect fracture risk prior to primary KR					
Antiarrhythmics	1.35 (0.97 to 1.87); p=0.08	1.41 (1.00 to 1.98); **p=0.05**	1.36 (0.97 to 1.92); p=0.078		
Anticonvulsants	1.72 (1.11 to 2.68); **p=0.02**	1.58 (1.01 to 2.47); **p=0.04**	1.50 (0.96 to 2.34); p=0.076		
Painkillers/anti-inflammatory drugs					
Total opiates	1.40 (1.13 to 1.73); **p<0.01**	1.36 (1.08 to 1.71); **p=0.01**	1.32 (1.05 to 1.65); p=0.019		
DDDs 1 year prior to primary KR					
Bisphosphonates (no dose)					
<140 DDD	0.25 (0.03 to 1.79); p=0.17			0.40 (0.06 to 2.91); p=0.37	0.36 (0.05 to 2.59); p=0.31
≥140 to 340 DDD	1.47 (0.73 to 2.96); p=0.28			2.44 (1.12 to 5.36); **p=0.03**	2.10 (0.96 to 4.60); p=0.063
>340 DDD	0.55 (0.14 to 2.21); p=0.40			1.08 (0.26 to 4.54); p=0.92	0.96 (0.23 to 4.06); p=0.95
Dose missing	1.23 (0.51 to 2.95); p=0.65				
Opioids total (no dose)					
<85 DDD	1.45 (0.95 to 2.21); p=0.09			1.33 (0.86 to 2.06); p=0.20	1.30 (0.84 to 2.01); p=0.25
≥85 to 365 DDD	1.36 (0.97 to 1.90); p=0.07			1.27 (0.90 to 1.79); p=0.17	1.22 (0.86 to 1.72); p=0.26
>365 DDD	1.85 (1.20 to 2.85); **p=0.01**			1.67 (1.08 to 2.59); **p=0.02**	1.53 (0.99 to 2.38); p=0.056
Dose missing	1.28 (0.95 to 1.72); p=0.10				

HR represents number of times to have a revision after 5 years compared with the reference group. A value >1 indicates that the group has higher risk for revision.
Variables included in the final regression model are those with at least one category with a p value <0.05 for the 10 imputed datasets in a backward selection.
Body mass index and sex were force-entered into all models. 'Total opiates' includes benzomorphan derivatives, diphenylpropylamine derivatives, morphinan derivatives, natural opium alkaloids, oripavine derivatives, phenylpiperidine derivatives and other opioids.
DDD, daily defined dose; KR, total and unicompartmental knee replacement.

due to including data from 2009 onwards but only primary operations up to 2011 to allow for revision rates after 5 years. This was to allow us to explore the impact of preoperative PROMs data, which has only been collected since 2009. Strengths of NJR data are detailed surgical and hospital factors available in the data. A limitation is that there have been changes in anaesthesia and surgical techniques over time that may no longer reflect current orthopaedic practice. The strength of our CPRD GOLD dataset was over 20 years of follow-up and the ability to capture a wide range of primary and hospital factors. There were missing data for some of the variables in our data, and this required us to use imputation to account for this in our analyses.

One of the aims of our study was to provide an evidence base for any group of patients in need of routine

Table 4 Cox regression model identifying risk factors of revision after 5 years of primary total knee and unicompartmental replacement: hospital data

	Patients undergoing KR (n=188 509)		
Risk factors (reference category)	Crude analysis HR (95% **CI**); p value	Adjusted analysis HR (95% **CI**); p value	Adjusted analysis competing risks HR (95% **CI**); p value
Year of primary KR (2008)			
2009	0.91 (0.78 to 1.06); p=0.23	0.90 (0.77 to 1.05); p=0.20	0.88 (0.75 to 1.03); p=0.10
2010	0.82 (0.68 to 0.98); **p=0.03**	0.82 (0.69 to 0.99); p=0.037	0.77 (0.64 to 0.92); p=0.004
2011	0.83 (0.64 to 1.07); p=0.15	0.83 (0.65 to 1.07); p=0.15	0.69 (0.54 to 0.87); p=0.002
Age at primary KR (continuous variable)	0.94 (0.9–0.9); **p<0.01**	0.95 (0.95 to 0.96); p<0.01	0.95 (0.94 to 0.95); p<0.01
Sex (women)			
Men	1.08 (1.0–1.2); p=0.23	1.13 (0.99 to 1.28); p=0.074	1.09 (0.95 to 1.24); p=0.21
Body mass index (normal)			
Underweight	1.96 (0.96 to 4.01); p=0.07	2.31 (1.13 to 4.73); p=0.022	2.22 (1.08 to 4.56); p=0.029
Overweight	1.04 (0.85 to 1.28); p=0.68	0.91 (0.74 to 1.11); p=0.35	0.92 (0.75 to 1.13); p=0.45
Obese class I (moderately obese)	1.02 (0.83 to 1.25); p=0.87	0.74 (0.60 to 0.91); p=0.004	0.75 (0.61 to 0.92); p=0.007
Obese class II and higher	1.20 (0.96 to 1.49); p=0.10	0.70 (0.56 to 0.88); p=0.002	0.71 (0.56 to 0.88); p=0.002
IMD (quintiles), at primary KR (less deprived 20%)			
Less deprived 20%–40%	0.87 (0.72 to 1.05); p=0.14	0.84 (0.70 to 1.01); p=0.06	0.84 (0.70 to 1.01); p=0.058
Less deprived 40%–60%	0.91 (0.75 to 1.10); p=0.32	0.78 (0.64 to 0.94); p=0.01	0.77 (0.64 to 0.93); p=0.008
More deprived 20%–40%	0.94 (0.78 to 1.14); p=0.55	0.79 (0.65 to 0.96); p=0.016	0.78 (0.64 to 0.94); p=0.01
Most deprived 20%	0.87 (0.71 to 1.06); p=0.17	0.71 (0.58 to 0.87); p=0.001	0.70 (0.58 to 0.86); p=0.001
Ethnicity (white)			
Non-white	0.68 (0.5 to 0.9); **p=0.01**	0.58 (0.43 to 0.78); p<0.01	0.59 (0.44 to 0.80); p=0.001
OKS, baseline score (0–10 points) (0=poor, 48=good)			
(11–14 points)	0.82 (0.7 to 1.0); **p=0.03**	0.85 (0.70 to 1.02); p=0.073	0.85 (0.71 to 1.02); p=0.087
(15–19 points)	0.69 (0.6 to 0.8); **p<0.01**	0.71 (0.60 to 0.85); p<0.01	0.73 (0.61 to 0.87); **p<0.01**
(20–24 points)	0.51 (0.4 to 0.6); **p<0.01**	0.55 (0.44 to 0.68); p<0.01	0.56 (0.45 to 0.69); **p<0.01**
(25–48 points)	0.37 (0.3 to 0.5); **p<0.01**	0.42 (0.33 to 0.53); p<0.01	0.43 (0.34 to 0.54); **p<0.01**
OKS, 6-month score (0–10 points) (0=poor, 48=good)			
(11–14 points)	0.72 (0.61 to 0.86); p<0.01	0.81 (0.67 to 0.96); p=0.016	0.81 (0.68 to 0.97); p=0.019
(15–19 points)	0.53 (0.44 to 0.63); p<0.01	0.59 (0.49 to 0.72): p<0.01	0.60 (0.50 to 0.72); p<0.01
(20–24 points)	0.43 (0.35 to 0.52); p<0.01	0.48 (0.39 to 0.59); p<0.01	0.48 (0.39 to 0.59); p<0.01
(25–48 points)	0.29 (0.23 to 0.36); p<0.01	0.33 (0.26 to 0.41); p<0.01	0.33 (0.26 to 0.42); p<0.01
EQ-5D-3L Anxiety Depression, 3 months or closer to primary KR (I am not anxious or depressed)			
I am moderately anxious or depressed	1.02 (0.9 to 1.2); p=0.78	0.73 (0.63 to 0.83); p<0.01	0.72 (0.63 to 0.82); p<0.01
I am extremely anxious or depressed	1.26 (0.9 to 1.7); p=0.14	0.67 (0.49 to 0.91); p=0.01	0.65 (0.48 to 0.89); p=0.007

HR represents number of times to have a revision after 5 years compared with the reference group. A value >1 indicates that the group has higher risk for revision.
Variables included in the final regression model are those with at least one category with a p value <0.05 for a single imputed dataset in a backward selection.
Body mass index and sex were force-entered into all models.
Bold figures represent results with p values <0.05 in the final regression model
EQ-5D-3L, EuroQol five domains; IMD, Index of Multiple Deprivation; KR, total and unicompartmental knee replacement; OKS, Oxford Knee Score.

follow-up after KR. Our findings were consistent with a previous study using data from the CPRD GOLD in which the authors demonstrated an instantaneous risk of revision (risk of revision following a given period of implant survival) by age and gender subgroups.[25] The smoothed hazard plots consistently showed higher revision risks for men and younger patients at all timepoints. These graphs also showed that the trends in time to revision surgery were similar across all age bands, except for the most elderly patient groups in whom follow-up is limited by life expectancy. Males and younger patients were at a consistently higher revision risk over the whole follow-up, and these factors did not influence timing of when revision occurred. In our previous work, we have shown that younger age, males and obesity are risk factors for revision hip and knee replacement.[26] Our finding in respect of age is consistent with this existing literature, as is the effect of males, showing that these effects are also seen in mid–late term, and the results were unchanged by the competing risk of death. For obesity, the opposite effect was seen in the present study where this now had a protective effect on risk of mid–late revision, although the cause of this effect was not clear. With regard to deprivation, it has previously been shown that those in the most deprived areas are less likely to receive revision knee replacement surgery,[27] and this is disappointingly consistent with what we observed and may reflect inequalities in access to revision surgery. Alternatively, it could be that obese patients or those of non-white ethnicity are more likely to be having revision surgery in the early term at less than 5 years, and hence these groups are under-represented for mid–late term revisions. However, the effect of deprivation and that of obesity were only present in the secondary care dataset, which requires further investigation.

There have been previous studies looking at the effects of medication use on revision risk, particularly for medications associated with bone and fracture risk. It has been suggested that postoperative statin use reduces revision risk for hip replacement.[28] The effects seen here in our study showed that, in crude unadjusted analyses, statins reduced the risk for knee replacement revision, but this was attenuated in the full regression model, which may be explained by the association of statin use with obesity. Bisphosphonate use has also been suggested to reduce revision risk,[29] but we saw an opposite effect for high DDD users. They had increased revision risk, which may be associated with the reason for revision as Danish studies have shown that, although bisphosphonates reduced overall all-cause revision, the risk of revision for infection was increased.[30]

The findings of this study suggest that patients receiving a mid–late revision surgery are a healthier, affluent group of patients of white ethnicity. It is unclear to what extent this represents need for revision surgery as this group may be more active, healthier, with lifestyle effects; or, is this a reflection of the known measurement error in using revision surgery as an outcome measure for the success of surgery? This patient group may simply be better able to navigate the care pathway (as for the primary operation), or reflect biases in patient–surgeon decision making, and may not be representative of those requiring revision surgery. There will always be patients in pain and functional difficulty that do not seek help from their GP or surgeon. It is of major interest to better understand why patient demographic characteristics seem to play a role in knee revision surgery.

The findings in respect of pain were interesting: in the secondary care data, although pain and function at or 6 months after primary surgery were associated with reduced risk of revision, those with the poorest scores were more likely to undergo revision. In primary care data, preoperative pain medication was the only risk factor of interest other than healthy patient case-mix selection effects that are unlikely to be informative for extended follow-up. Use of oral glucocorticoid steroid therapy may be a surrogate marker for chronic health conditions and was associated with a lower risk of revision in our data. This may reflect reduced functional goals or expectations in this patient group, with less likelihood of proceeding to revision surgery, or a reluctance to proceed with surgery due to an increased risk of infection. Anticonvulsants (gabapentin and pregabalin) and opioid use preoperatively were associated with an increased mid–late revision risk. Although opioids may be recommended for controlling pain due to osteoarthritis before primary surgery,[31] they may also be indicative of chronic pain and/or opioid related comorbidities, and two-thirds of patients have been shown to continue to use opioids postsurgery.[29 32] This group of patients often experience a mixed picture of pain and may have high levels of dissatisfaction after surgery, leading them to seek further surgical solutions for persistent pain.[33 34] Use of anticonvulsants prior to primary surgery is suggestive of existing neuropathic pain or multisite joint pain. Postsurgery, this group of patients may experience sensitisation subsequent to chronic pain and/or additional neuropathic components, leading to more severe symptoms that places them at greater risk of revision. Further work would be required to investigate whether patients with neuropathic or chronic pain after primary KR would benefit from closer monitoring and follow-up, particularly if they are then at further increased risk of mid–late revision.

In this study, there was an opportunity to examine unique datasets for predictors of mid–late term revision risk for KR surgery. We have reported the results for KR in this study, but it is of interest that in the wider programme of work (UK SAFE[12]), the predictors of revision were different for hips and knees with age being the main consistent finding. The patient factors we identified as predictive of mid-late term revision risk after KR may reflect inequalities in access to revision surgery, or there may be other factors not captured within this study; this requires further investigation. In addition, further work is needed to determine if targeted follow-up is required for those patients with worse pain and function preprimary

and/or postprimary surgery, or higher levels of preoperative pain medication (opioids and anticonvulsants) due to their increased risk of mid–late term revision. The findings from this study have implications for future provision of follow-up services for patients with a KR.

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Patient consent for publication Not applicable.

Ethics approval The CPRD Group has obtained ethical approval from a National Research Ethics Service Committee (NRES) for all purely observational research using anonymised CPRD data; namely, studies that do not include patient involvement. The study has been approved by Independent Scientific Advisory Committee for MHRA Database Research (protocol number 11_050AMnA2RA2). For the NJR, before personal data and sensitive personal data are recorded, express written patient consent is provided. The NJR records patient consent as either 'Yes', 'No' or 'Not Recorded'. With support under Section 251 of the NHS Act 2006, the Ethics and Confidentiality Committee (now the Health Research Authority Confidentiality Advisory Group) allows the NJR to collect patient data where consent is indicated as 'Not Recorded'. Section 251 support (17/CAG/0030) and NHS Digital approval (DARS-NIC-172121-G0Z1H-v0.11) were obtained for the NJR-HES-PROMS dataset analysis.

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Data availability statement Data may be obtained from a third party and are not publicly available. Access to data is available from the National Joint Registry for England and Wales, Northern Ireland and the Isle of Man, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data access applications can be made to the National Joint Registry Research Committee. Access to linked Hospital Episode Statistics and PROMs data is available through data applications to NHS Digital.

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Towards UK poSt Arthroplasty Follow-up rEcommendations (UK SAFE): protocol for an evaluation of the requirements for arthroplasty follow-up, and the production of consensus-based recommendations

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ABSTRACT

Introduction Hip and knee arthroplasties have revolutionised the management of degenerative joint diseases and, due to an ageing population, are becoming increasingly common. Follow-up of joint prostheses is to identify problems in symptomatic or asymptomatic patients due to infection, osteolysis, bone loss or potential periprosthetic fracture, enabling timely intervention to prevent catastrophic failure at a later date. Early revision is usually more straight-forward surgically and less traumatic for the patient. However, routine long-term follow-up is costly and requires considerable clinical time. Therefore, some centres in the UK have curtailed this aspect of primary hip and knee arthroplasty services, doing so without an evidence base that such disinvestment is clinically or cost-effective.

Methods Given the timeline from joint replacement to revision, conducting a randomised controlled trial (RCT) to determine potential consequences of disinvestment in hip and knee arthroplasty follow-up is not feasible. Furthermore, the low revision rates of modern prostheses, less than 10% at 10 years, would necessitate thousands of patients to adequately power such a study. The huge variation in follow-up practice across the UK also limits the generalisability of an RCT. This study will therefore use a mixed-methods approach to examine the requirements for arthroplasty follow-up and produce evidence-based and consensus-based recommendations as to how, when and on whom follow-up should be conducted. Four interconnected work packages will be completed: (1) a systematic literature review; (2a) analysis of routinely collected National Health Service data from five national data sets to understand when and which patients present for revision surgery; (2b) prospective data regarding how patients currently present for revision surgery; (3) economic modelling to simulate long-term costs and quality-adjusted life years associated with different follow-up care models and (4) a Delphi-consensus process, involving all stakeholders, to develop a policy document which includes a stratification algorithm to determine appropriate follow-up care for an individual patient.

Ethics and Dissemination Favourable ethical opinion has been obtained for WP2a (RO-HES) (220520) and WP2B (220316) from the National Research Ethics Committee. Following advice from the Confidentiality Advisory Group (17/CAG/0122), data controllers for the data sets used in WP2a (RO-HES) – NHS Digital and The Phoenix Partnership – confirmed that Section 251 support was not required as no identifiable data was flowing into or out of these parties. Application for approval of WP2a (RO-HES) from the Independent Group Advising on the Release of Data (IGARD) at NHS Digital is in progress (DARS-NIC-147997). Section 251 support (17/CAG/0030) and NHS Digital approval (DARS-NIC-172121-G0Z1H-v0.11) have been

Strengths and limitations of this study

- ► Our mixed-methods approach allows us to address a question that would not be feasible to answer with a randomised controlled trial.
- ► Our study will capture data from a mixture of teaching hospitals, district general hospitals and hospitals with a special interest in joint replacement and with a geographical spread, increasing the generalisability of our results.
- ► Our economic model will be populated with routinely collected National Health Service (NHS) data of patients attending primary and hospital care in the UK, ensuring that our analysis is based on actual patient use of services, outcomes such as health-related quality of life and costs to the NHS.
- ► While our analysis is based on data sources that reflect clinical practice in England only, we believe key cost-effectiveness findings are likely to be informative for decision-making in the whole of the UK.

obtained for WP2a (NJR-HES-PROMS). ISAC (11_050MnA2R2) approval has been obtained for WP2a (CPRD-HES).

INTRODUCTION

Arguably, total hip arthroplasty (THA) and total knee arthroplasty (TKA) are the most successful surgical interventions performed in modern times. Due to an ageing population, and an obesity epidemic, hip and knee replacement procedures increase annually, rising from less than 20 000/year in the UK in 1978 to around 200 000/year in 2017.[1] The current follow-up requirements are estimated at 500 000–1 000 000 annual outpatient attendances. With limitless resources, every patient undergoing a joint arthroplasty would incur routine lifetime follow-up. The rationale for follow-up is to ensure timely detection of complications or arthroplasty failure, such as aseptic loosening, osteolysis and potential periprosthetic fracture. The cost of revision for aseptic loosening is 35% lower than that for periprosthetic fractures and has a lower incidence of complications which impact recovery.[2] However, while routine long-term follow-up of joint prostheses may support timely revision for patients with asymptomatic complications, improving long-term health outcomes, it is also costly both clinically and financially.

Orthopaedic services are already one of the poorest performers across the National Health Service (NHS) by failing to meet waiting list targets, with an estimated 8000 orthopaedic NHS breaches each month.[3] With a rapidly ageing population and medical advances that mean less stringent criteria for surgery eligibility,[4] there is no sign that demand will recede in coming years and orthopaedic services will soon reach breaking point. To reduce the burden on orthopaedic services, evidence-based consensus guidelines are required to establish how, when and on whom follow-up should be conducted.

British Hip Society (BHS) and British Orthopaedic Association (BOA) guidelines recommend outpatient follow-up at 1 and 7 years, and every 3 years thereafter for Orthopaedic Data Evaluation Panel 10A (ODEP-10A) implants, with more frequent follow-up for novel implants.[5] However, recent work revealed considerable diversity across the UK in arthroplasty follow-up pathways, in timing, how follow-up is conducted and which health professionals are involved.[6]While some centres followed-up patients beyond 10 years, others did not have an established follow-up policy and in some centres follow-up services have been curtailed or stopped entirely after an early postoperative check.[6] Notably, we do not know whether long-term follow-up is cost-effective or whether disinvestment is safe for patients.

This project aims to determine the consequences of disinvestment in hip and knee arthroplasty follow-up. Given the timeline from joint replacement to revision, with a 7% revision rate for THA and 4% revision rate for TKA at 14 years, conducting a randomised controlled trial to address this question is not feasible. Moreover, the huge variation in follow-up practice across the UK limits the generalisability of the results of an RCT. We will therefore use a mixed-methods approach to comprehensively evaluate the requirements for arthroplasty follow-up and will use this evidence to inform the development of consensus-based recommendations and a policy document which includes a stratification algorithm to determine appropriate follow-up for individual patients. Disinvestment is a complex and often contentious issue. We plan to make use of published recommendations[7] to ensure that the results of this work are understood and considered as a genuine attempt to use the best evidence available to ensure that the NHS gets value for money and that patients remain safe.

METHODS AND ANALYSIS

Study objectives

A. Identify who needs follow-up and when this should occur for primary THA, TKA and unicompartmental knee arthroplasty (UKA) surgery by making use of routinely collected NHS data.
B. Understand the patient journey (in primary and secondary care) to revision surgery by recruiting patients admitted for elective and emergency hip and knee revision surgery.
C. Establish how and when patients are identified for revision, why some patients are missed from regular follow-up and present acutely with fracture around the implant (periprosthetic fracture), by using prospective and retrospective data.
D. Identify the most appropriate and cost-effective follow-up pathway to minimise potential harm to patients by undertaking cost-effectiveness modelling.
E. Provide evidence-based and consensus-based recommendations on how follow-up of primary THA and TKA should be conducted.

Design

This is a mixed-methods study using a variety of data sources consisting of four interconnected work packages (WP): (1) a systematic literature review; (2a) analysis of routinely-collected NHS data to understand when and which patient present for revision surgery; (2b) prospective data regarding how patients currently present for revision surgery collected on around 455 patients prior to elective or emergency revision surgery; (3) economic modelling to simulate long-term costs and quality adjusted life years associated with different follow-up models; (4) a Delphi-consensus process, incorporating all previous WPs and involving all stakeholders, to develop a policy document which includes a stratification algorithm to determine appropriate follow-up for an individual patient.

WP1: systematic review

The aim of the review is to evaluate different models of routine long-term follow-up care after TKA/THA/UKA. This systematic review will establish a robust evidence base

for the cost-effectiveness modelling (WP3) and consensus guideline development (WP4).

Registration

This systematic review will be undertaken following Cochrane Collaboration methods[8] and reported in accordance with Preferred Reporting Items for Systematic Review and Meta-analyses guidelines.[9] It has been prospectively registered with PROSPERO (CRD42017053017).

Searches

A comprehensive literature search will be undertaken with the aim of retrieving all relevant literature, published or unpublished, which evaluated the effectiveness of long-term follow-up after primary TKA/THA/UKA. A range of information sources will be searched: BIOSIS, CINAHL, ClinicalTrials.gov, The Cochrane Library, Embase, Health Management Information Consortium, IDEAS (RePEC), Ovid Medline(R), ProQuest Dissertations and Theses, PsycINFO, PubMed and Web of Science. Reference lists of included studies will be reviewed for potentially relevant articles. A sample search strategy is detailed in the online supplementary appendix A. No date or language restrictions will be applied.

Criteria for selection of studies

All study designs will be included which (1) consider the clinical and/or cost effectiveness of routine long-term (>5 years) follow-up care after primary THA, TKA or UKA; (2) describe patient safety issues associated with routine follow-up or (3) consider the acceptability of new care pathways from the perspective of the patient and/or practitioner. Studies will be excluded if they do not report specific patient-related outcome measures or appropriate health utility measures.

Selection of studies

Titles/abstracts of identified studies will be screened for eligibility by one experienced reviewer with a random selection (25%) independently screened by a second. Potential studies will be retrieved in full text and reviewed against the inclusion/exclusion criteria independently by the same two reviewers, with a third reviewer used to settle any disputes.

Data extraction

Data will be extracted by a single reviewer using a standardised proforma capturing (1) purpose and design; (2) methodological characteristics; (3) information relating to quality assessment and (4) outcome data relating to the clinical and cost-effectiveness of routine long-term follow-up care.

Quality assessment

The Cochrane Risk of Bias assessment tool will be used for experimental studies,[10] and the Newcastle-Ottawa scales for cohort and case–control studies.[11] Qualitative literature will be assessed using critical interpretive synthesis.[12] Economic evaluations will be assessed using the Drummond checklist.[13] Studies will be evaluated independently by two reviewers, with a third to settle any disputes. Studies at high risk of bias will not be excluded and conclusions will incorporate observed biases.

Evidence synthesis

The design, methodological characteristics, study quality and main findings will be summarised in narrative and tabular form. We anticipate substantial heterogeneity among included studies precluding the use of meta-analysis techniques.

WP2a: Analysis of routinely collected NHS data

This WP will use routinely collected NHS data to determine when revision happens and to identify patients most likely to require revision in order to target when and on whom follow-up should occur.

Data sources

Data from five national datasets will be used: (1) Clinical Practice Research Database (CPRD),[14] (2) ResearchOne (RO),[15] (3) Hospital Episode Statistics (HES),[16] (4) National Joint Registry (NJR)[17] and (5) patient reported outcome measures (PROMs).[18]

Three linked data sets will be constructed for analysis: (a) CPRD–HES–PROMS, which preexists at the University of Oxford, (b) RO–HES will be constructed and analysed at the University of Leeds. Linkage will be undertaken by NHS Digital on the basis of pseudonyms generated from NHS numbers by the data providers. (c) NJR–HES–PROMS will be constructed and analysed at the University of Oxford. Linkages will be undertaken by NHS Digital, using an agreed set of common patient identifiers, including NHS number. Data sets (a) and (b) provide a primary care view (eg, prior diagnoses, prescribing) and include different, representative patient populations for cross-validation; data set (c) provides a secondary care view (eg, surgeon, procedure details).

Data analysis

The primary outcome of the analysis will be mid-late term revision (>5 years post-primary surgery), defined as the removal, exchange or addition of any of the components of arthroplasty. Exposures will include secondary care predictors, including patient level characteristics recorded in NJR and HES (eg, age, body mass index (BMI)), surgical and operative factors and symptoms of pain, function and health-related quality of life preoperatively and 6 months post-surgery from PROMS, and primary care predictors, including patient demographics, comorbidities and use of drugs which can affect fracture risk. Survival analysis will be used to model time to revision.[19 20] The smoothed Nelson-Aalen cumulative hazard rate will be examined to identify any peak in the mid-long term risk of revision. Cox proportional hazards regression modelling will be used to identify preoperative, perioperative and postoperative predictors of mid-late term revision, for example, age, BMI, comorbidities, implant type, surgeon skill and postoperative problems. Competing risk

regression will be used, since mortality can be regarded as a competing risk for revision surgery.[21 22] To account for clustering within the data (such as patients nested within hospitals), a multilevel survival model will be fitted by extending the survival regression model to include a frailty term with a Gaussian distribution.[23]

WP2b part 1: multicentre observational prospective cohort

Prospective data collection from patients undergoing revision surgery.

Objectives:

- Identify all recent (previous 12 months) medical appointments and advice sessions related to the index joint in primary and secondary care.
- Establish if the patient has been seen by orthopaedic health professionals from 12 months after primary surgery until this hospital admission, that is, was the revision directed by routine follow-up.

Design

A multicentre, observational, single visit, prospective cohort study of patients admitted for revision hip or knee surgery.

Population

Patients presenting for elective and emergency revision surgery of a primary THA, TKA or UKA and who are able and willing to provide written informed consent will be included in the study. Patients will be excluded if they have had previous revision surgery; metal-on-metal primary joint replacement or hip hemiarthroplasty. Participants will be recruited from a sample of hospitals selected to provide geographical spread and representation of teaching hospitals, district general hospitals and hospitals with a special interest in joint replacement

Data collection

A participant case report form (CRF) will capture details of follow-up after primary surgery and pathway to current revision surgery, including symptom state. An investigator CRF will extract data from medical notes including demographics (age, gender, diagnosis leading to primary surgery, medical history), general practitioner and hospital appointments, details of primary and revision surgery (including implant type, complications, length of stay). The participant CRF will be piloted with the Leeds Biomedical Research Centre Patient and Public Involvement (PPI) group and the investigator CRF with two research nurses to ascertain the comprehension, usability and completeness of data subsequently extracted.

Sample size

We will use stratified sampling to recruit centres of varying size and anticipate that the average number of patients per centre will be 45 (based on NJR records and information from prospective centres). We initially anticipated the recruitment of 25 centres. With a recruitment rate of 60%, this gave 27 recruited patients from 25 centres (n=675). We do not know the intraclass correlation coefficient (ICC) for our primary outcome ('Was the revision a result of routine follow-up?'), but we anticipate it to be in the region of 0.01–0.05. To be conservative, we use ICC=0.05. This gives a design factor of 2.3 and hence an effective sample size of 293 after accounting for clustering within centre. The enrolment of 35 centres reduced the design factor to 1.6 and the total sample size required to 455. From previous research,[6] we estimate that the rate of our primary outcome is 20% so that the effective number of events will be 58. Hence, we will have sufficient power for our logistic regression to robustly estimate the coefficients of up to five potential risk factors derived from our brief patient survey.[24]

Analysis

The primary outcome will be 'revision identified through routine follow-up', and this will be modelled through a multilevel logistic regression model, with a centre-level random intercept of particular interest. The size of the centre-level effect will be assessed as the proportion of variance explained and will also be assessed through a likelihood ratio test. Up to five factors from the patient questionnaire will be explored as fixed effects at the patient level. This will adjust for case mix. Factors that are found to be both clinically and statistically significant could potentially contribute to a stratified approach to follow-up.

WP2b part 2: qualitative study

Building on previous work highlighting the changes in follow-up practice,[6] this WP aims to explore the rationale and motivating factors behind these changes, the facilitators and the evidence considered when implementing new pathways, including no follow-up.

Sampling

A sample of n=20–30 orthopaedic practitioners and/or unit managers will be recruited. Purposive sampling via sampling matrix will recruit participants with different experiences of a range of follow-up pathways while reflecting NHS trust type, geographical area (urban, rural); socioeconomic area (low/high socioeconomic status) and diverse ethnicity. Some selection criteria are likely to be nested (eg, hospital type, geographical area) and care will be taken to ensure that all viewpoints are represented.

Data collection

Semistructured, telephone interviews following a topic guide refined from the literature review and expert opinion (clinician coapplicants/advisors and PPI members). The researcher will probe pertinent initial responses and expand on issues raised. Interviews will be recorded and transcribed verbatim.

Data analysis

The guiding approach will be framework analysis.[25] Data analysis will comprise five stages: (1) data familiarisation;

(2) identifying the thematic framework; (3) indexing; (4) charting and (5) mapping and interpreting. The process of familiarisation enables the researcher to identify emerging themes or issues in the data. Little is known about why NHS trusts have chosen to either withdraw follow-up care or change the way it is delivered. The evidence generated from the literature review and input from our clinical coapplicants will be used to help identify and refine the thematic framework. Themes are flexible and can be modified in the light of new data, and a process of constant comparison will be undertaken across themes and cases.

WP3

As previous work conducted by members of our team has identified considerable heterogeneity in current follow-up pathways,[6] our cost-effectiveness analysis will compare the relative costs and quality-adjusted life years associated with having follow-up compared with not having follow-up. A third hypothetical scenario of a virtual follow-up will be considered.

Comparators

Both the findings from our systematic review and the prospective cohort will inform the criteria to be used to identify patients as having or not having follow-up. The 7-year reference point for a follow-up currently suggested by BHS and BOA guidelines is likely to be incorporated. Patients having an orthopaedic outpatient appointment around the reference point(s) following a primary arthroplasty will be used to group patients in the CPRD–HES–PROMS data set into the follow-up and no follow-up groups. Joint-specific revision procedures will be identified by OPCS-4 codes as reported in the Admitted Patient Care data set within HES, with corresponding linked records to primary care and PROMS.

Model structure

To identify the most appropriate modelling approach for the question and data at hand, we will conduct a series of preliminary analysis to determine if a cohort-level or patient-level decision analytic model should be employed. Previous models examining the long-term cost-effectiveness of hip and knee replacements have used cohort Markov models.[26 27] Analyses will include associations between patients' characteristics and revision rates, health utilities and costs and whether the risk for revision depends on the time patients stay unrevised after their primary. Regardless of the chosen model type, the key health state or event will be revision arthroplasty, with death and complications also considered. The model will be designed to cover patients' lifetime and analysed from an NHS and Personal Social Services perspective, with discounting of costs and outcomes as per current guide to the methods of technology appraisal.[28]

Model inputs

WP2 data sets will be used to quantify primary and hospital healthcare resource use for comparator groups of follow-up care models through estimation of NHS costs and health-related quality of life (HRQoL). The economic model will simulate long-term costs and quality adjusted life years (QALYs) associated with each care model. Primary care costs will include consultations, and hospital costs will be derived by grouping hospital episodes into Health Resource Groups, a set of casemix groupings utilising similar levels of healthcare resources. Panel data regression analysis[29–31] will be used to estimate hospital costs conditional on patient characteristics and comorbidities. QALYs and transition probabilities will be derived from the linked data sets and published literature as needed. The hypothetical costs of virtual follow-up will be based on similar virtual clinic alternatives previously studied and NHS X-ray-associated costs.

Analysis

Cost-effectiveness analyses will be performed separately for relevant patient subgroups based on gender, age and other potential covariates for which data may be available. As with all economic models, a number of assumptions will be made, and their plausibility and potential impact discussed, relating to model structure and input parameters for transition probabilities, health utilities and costs, including the cost of periprosthetic fractures if no reference is found for these in the literature. Sensitivity analyses will be conducted to explore the uncertainty associated with key assumptions and model parameters and the implications of using different estimates discussed.

WP4: Delphi-consensus process

This WP will use the collective evidence from WP1–3 to inform a consensus process to determine appropriate follow-up care pathways for hip and knee arthroplasty.

Evidence gathered from WP1–3 will feed into a consensus panel workshop. We intend to use methods employed by the National Institute for Health and Care Excellence (NICE) in both the technology assessment committees and Guideline Development Groups. The expert stakeholders invited to attend will have a special interest in patient follow-up after hip or knee replacement surgery. Participants will include patients, orthopaedic surgeons, arthroplasty practitioners, NHS managers and commissioners, manufacturers and representatives of the major orthopaedic bodies (including BOA, BHS and BASK). The purpose of this exercise is to consider the evidence and obtain agreement for future care pathways, supported by the evidence of their effectiveness and cost-effectiveness, to be recommended and adopted across the NHS. Following the NICE consensus model all participants will receive summaries of the main research findings in advance. There will be presentations from the work-stream leaders to outline the evidence for consideration.

Robert *et al*[7] demonstrate that decommissioning is often about more than the 'evidence' and that withdrawal of previously available services is often seen as being driven by the wrong kind of evidence, based on cost data and

political priorities and not on what patients and service users value.[7] It is a complex issue, perhaps as contentious as NICE decisions when they do not fund an effective intervention because it exceeds the threshold. However, NICE investment decisions are made with the explicit understanding that, with no increase in the budget, there must be some displacement of other healthcare technologies.[32] We plan to make use of the recommendations for engagement and the use of evidence outlined in Robert *et al* to ensure the results of this work are understood and considered as a genuine attempt to use the best evidence available to ensure that the NHS gets value for money and that patients remain safe.

Patient and public involvement

Members of the NIHR Leeds BRC, Oxford and Bristol PPI groups are involved in UK SAFE. The PPI co-applicant is a member of the study steering committee and contributes across all WPs. Two independent PPI advisors sit on the Independent Advisory Group. Specific areas where lay involvement will be pivotal include the interpretation of results of the systematic review, the expert panel discussion and consensus process, study oversight (steering group), preparation of patient material and study results and contribution to reports and newsletters for patients and NHS staff.

ETHICS AND DISSEMINATION

All studies will be conducted in accordance with the principles of Good Clinical Practice, and the UK Policy Framework for Health and Social Care Research, 2018. Favourable ethical opinion has been obtained for WP2a (RO-HES) (220520) and WP2B (220316) from the National Research Ethics Committee. Following advice from the Confidentiality Advisory Group (17/CAG/0122), data controllers for the data sets used in WP2a (RO–HES)—NHS Digital and The Phoenix Partnership—confirmed that Section 251 support was not required as no identifiable data was flowing into or out of these parties. Application for approval of WP2a (RO–HES) from the Independent Group Advising on the Release of Data (IGARD) at NHS Digital is in progress (DARS-NIC-147997). Section 251 support (17/CAG/0030) and NHS Digital approval (DARS-NIC-172121-G0Z1H-v0.11) have been obtained for WP2a (NJR-HES-PROMS). ISAC (11_050MnA2R2) approval has been obtained for WP2a (CPRD–HES).

At the end of the project, outputs will be disseminated nationally in the form of an executive summary statement of the agreed pathway/s through appropriate NHS Networks, NICE, the NHS England Elective Orthopaedics Sub-committee, the NHS Institute for Innovation and Improvement and professional societies, including BHS, BOA, BASK, Arthroplasty Care Practitioners Association and the NJR. Dissemination will be key to developing a culture of 'finding the best way of doing something and doing it everywhere' to significantly reduce wastage of clinical resources and optimise NHS spend. We will put forward the consensus statement to each society's AGM for adoption as a resolution. Internationally, dissemination platforms are in place through the International Society of Arthroplasty Registers (ISAR) and the European Federation of National Associations of Orthopaedics and Traumatology. A lay summary of the project will be produced for study participants. Findings will also be presented at relevant orthopaedic and methodological conferences, such as the BOA and the Exploiting Existing Data for Health Research conference. The chief investigator and co-applicants will be named as authors on main publications, and an appropriate first author agreed through discussion. Other key individuals will be included as authors or contributors as appropriate, at the discretion of the Senior Management Group. Any disputes relating to authorship will be resolved by the Steering Committee.

The Chair and Independent members of the Steering Committee will be acknowledged, but will not qualify for full authorship, in order to maintain their independence. Individual collaborators must not publish data concerning their participants' which are directly relevant to the questions posed in the study until the main results of the study have been published.

CONCLUSION

This research will deliver the first research-supported, best-for-patient, joint-specific, cost-effective recommendations for follow-up pathways, providing a gold standard for clinical excellence and follow-up advice for patients, surgeons, purchasers and the NHS as a whole. Value is not limited to the UK, but has substantial global impact potential.

The impact of this work will be to reduce the burden on patients and the NHS in terms of outpatient visits and clinical tests that do not add benefit, while optimising detection of potential problems. From an NHS perspective, this work will provide managers with economic and clinical information on arthroplasty follow-up to inform service planning and delivery, and the role of arthroplasty practitioners in this service, with the potential to reduce geographical disparity through NHS trusts modelling their service provision on a national evidence-based guideline; provide orthopaedic surgeons with guidance on follow-up, including patient and economic considerations of factors involved; produce arthroplasty follow-up guidelines for adoption by the relevant specialist societies and information for their members. From a patient perspective, this work will help to inform patients about follow-up practice, empower them to make choices about future healthcare relating to their joint arthroplasty and provide reassurance that their follow-up pathway is appropriate

The outputs of this project, in terms of evidence-based support for timing of follow-up and identification of the most cost-effective follow-up model, fit directly within the

NHS framework for improving outcomes from elective procedures. Rationalising current diversity of follow-up practices should enable substantial savings for the NHS. We envisage outputs to be readily applicable to the wider NHS, not only hip and knee but also other joint replacements. With the committed support of key national and international organisations already in place, we anticipate that these guidelines will be positively received and that implementation will be widespread.

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Supplementary file II: STROBE checklist

STROBE. Strengthening the reporting of observational studies in epidemiology. Available at: https://www.strobe-statement.org/. [Last accessed 29 September 2021].

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6,8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6,8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6,8,9
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Supp File 3: Tables A&B
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13,14,15,16,17
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13,14,15,16,17
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19, 20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Supplementary file III: Additional results

Table A. Descriptive statistics for the CPRD-HES linked datasets

	Knee Replacement
Year of primary	
1995-1999	995 (5.7%)
2000-2004	4486 (25.8%)
2005-2009	8415 (48.4%)
2010-2011	3482 (20.0%)
Age at primary	69.4 (SD 9.2)
Sex	
Female	9963 (57.3%)
Male	7415 (42.7%)
Body mass index	
Underweight	48 (0.4%)
Normal	2204 (16.2%)
Overweight	5239 (38.6%)
Obese Class I (Moderately obese)	3777 (27.8%)
Obese Class II and higher	2306 (17.0%)
Index of Multiple Deprivation (IMD) quintiles	
Least deprived	3890 (22.4%)
2	4145 (23.9%)
3	3918 (22.6%)
4	3078 (17.7%)
Most deprived	2328 (13.4%)
Region	
East Midlands	706 (4.1%)
East of England	2003 (11.5%)
London	1464 (8.4%)
North East	434 (2.5%)
North West	2551 (14.7%)
South Central	2605 (15.0%)
South East Coast	2144 (12.3%)
South West	2386 (13.7%)
West Midlands	2320 (13.4%)
Yorkshire & The Humber	765 (4.4%)
Smoker	
Ex-smoker	5122 (34.6%)
Non-smoker	8310 (56.2%)
Current	1368 (9.2%)
Alcohol	

Ex-smoker	322 (2.7%)
No	2242 (18.8%)
Yes	9371 (78.5%)
Recorded diagnosis of hip OA	6841 (39.4%)
Hip Fracture prior primary surgery	119 (0.7%)
Fracture in pelvis, proximal/humerus, wrist/forearm, spine or rib	537 (3.1%)
Comorbidities	
asthma	1713 (9.9%)
malabsorption	42 (0.2%)
inflammatory bowel disease	128 (0.7%)
hypertension	6106 (35.1%)
hyperlipidaemia	2223 (12.8%)
ischaemic heart disease	1685 (9.7%)
myocardial infarction	345 (2.0%)
stroke/cerebrovascular disease	585 (3.4%)
chronic pulmonary disease	498 (2.9%)
chronic kidney failure	1277 (7.4%)
cancer	1446 (8.3%)
diabetes	1774 (10.2%)
Drugs which can affect fracture risk prior primary surge	
Calcium and vitamin D supplements	1377 (7.9%)
Bisphosphonates	1161 (6.7%)
Selective oestrogen receptor modulators	33 (0.2%)
Oral glucocorticosteroid therapy	3521 (20.3%)
Drugs prior primary surgery	
Proton pump inhibitors	7586 (43.7%)
Anti-arrhythmics	1700 (9.8%)
Anticonvulsants	865 (5.0%)
Antidepressants	5875 (33.8%)
Anti-Parkinson drugs	305 (1.8%)
Statins	5697 (32.8%)
Thiazide diuretics	8498 (48.9%)
Anxiolitics	3406 (19.6%)
Painkillers/anti-inflammatory drugs	
NSAIDs	15406 (88.7%)
NSAID cox	3155 (18.2%)
Paracetamol	14438 (83.1%)
Partial Opiates	13334 (76.7%)
Total Opiates	6459 (37.2%)
Steroid iFuse Implant System® Minimally Invasive Arthrodesis (iMIA)	5401 (31.1%)
DDDs (daily defined dose) 1-year prior surgery	

Calcium and vitamin D supplements	
No dose	16001 (92.1%)
<120 DDD	281 (1.6%)
>=120 to 340 DDD	503 (2.9%)
>340 DDD	222 (1.3%)
Dose missing	371 (2.1%)
Bisphosphonates	
No dose	16217 (93.3%)
<140 DDD	229 (1.3%)
>=140 to 340 DDD	374 (2.2%)
>340 DDD	260 (1.5%)
Dose missing	298 (1.7%)
Selective oestrogen receptor modulators	
No dose	17345 (99.8%)
<280 DDD	8 (0.1%)
>=280 to 390 DDD	8 (0.1%)
>390 DDD	0 (0%)
Dose missing	17 (0.1%)
Oral glucocorticosteroid therapy	
No dose	13857 (79.7%)
<30 DDD	493 (2.8%)
>=30 to 280 DDD	458 (2.6%)
>280 DDD	316 (1.8%)
Dose missing	2254 (13.0%)
Proton pump inhibitors (no dose)	
No dose	9792 (56.4%)
<85 DDD	1376 (7.9%)
>=85 to 365 DDD	2847 (16.4%)
>365 DDD	995 (5.7%)
Dose missing	2368 (13.6%)
Anti-arrhythmics (no dose)	
No dose	15678 (90.2%)
<170 DDD	159 (0.9%)
>=170 to 365 DDD	241 (1.4%)
>365 DDD	158 (0.9%)
Dose missing	1142 (6.6%)
Anticonvulsants	
No dose	16513 (95.0%)
<85 DDD	132 (0.8%)
>=85 to 365 DDD	212 (1.2%)
>365 DDD	111 (0.6%)
Dose missing	410 (2.4%)
Antidepressants	

No dose	11503 (66.2%)
<85 DDD	786 (4.5%)
>=85 to 365 DDD	1418 (8.2%)
>365 DDD	565 (3.3%)
Dose missing	3106 (17.9%)
Anti-Parkinson drugs	
No dose	17073 (98.2%)
<200 DDD	36 (0.2%)
>=200 to 600 DDD	90 (0.5%)
>600 DDD	41 (0.2%)
Dose missing	138 (0.8%)
Statins	
No dose	11681 (67.2%)
<280 DDD	1248 (7.2%)
>=280 to 370 DDD	2522 (14.5%)
>370 DDD	1383 (8.0%)
Dose missing	544 (3.1%)
Thiazide diuretics	
No dose	8880 (51.1%)
<225 DDD	1678 (9.7%)
>=225 to 390 DDD	2826 (16.3%)
>390 DDD	1565 (9.0%)
Dose missing	2429 (14.0%)
Anxiolitics	
No dose	13972 (80.4%)
<30 DDD	367 (2.1%)
>=30 to 350 DDD	531 (3.1%)
>350 DDD	344 (2.0%)
Dose missing	2164 (12.5%)
NSAIDs	
No dose	1972 (11.4%)
<60 DDD	2428 (14.0%)
>=60 to 300 DDD	4602 (26.5%)
>300 DDD	2352 (13.5%)
Dose missing	6024 (34.7%)
NSAID cox	
No dose	14223 (81.8%)
<60 DDD	355 (2.0%)
>=60 to 280 DDD	553 (3.2%)
>280 DDD	267 (1.5%)
Dose missing	1980 (11.4%)
Paracetamol	
No dose	2940 (16.9%)

<40 DDD	2796 (16.1%)
>=40 to 200 DDD	5521 (31.8%)
>200 DDD	2425 (14.0%)
Dose missing	3696 (21.3%)
Opioids mix	
No dose	4044 (23.3%)
<30 DDD	2074 (11.9%)
>=30 to 180 DDD	4002 (23.0%)
>180 DDD	1976 (11.4%)
Dose missing	5282 (30.4%)
Opioids total	
No dose	10919 (62.8%)
<200 DDD	995 (5.7%)
>=200 to 600 DDD	1916 (11.0%)
>600 DDD	871 (5.0%)
Dose missing	2677 (15.4%)
Steroid IMIA	
No dose	11977 (68.9%)
<55 DDD	1292 (7.4%)
>=55 DDD	597 (3.4%)
Dose missing	3512 (20.2%)

Table B. Descriptive statistics for the NJR-HES-PROMs linked dataset

	Knee Replacement
Year of primary	
2008	33504 (17.8%)
2009	45928 (42.1%)
2010	52460 (70.0%)
2011	56617 (100.0%)
Age at primary knee replacement	69.9 (SD 9.3)
Sex	
Female	106812 (56.7%)
Male	81697 (43.3%)
Body mass index	30.9 (SD 5.5)
Index of Multiple Deprivation (IMD) quintiles	
Least deprived	40247 (21.6%)
2	42721 (22.9%)
3	35839 (19.2%)
4	34691 (18.6%)
Most deprived	33119 (17.8%)
Rurality, at primary	
urban >=10,000	140202 (74.5%)
town and fringe	22366 (11.9%)
village/isolated	25618 (13.6%)
ethnicity	
white	161079 (92.9%)
non-white	12237 (7.1%)
Number comorbidities at primary (none)	
None	141570 (75.1%)
Mild	38083 (20.2%)
Moderate	6875 (3.7%)
Severe	1981 (1.1%)
ASA grade	
P1 - Fit and healthy	20087 (10.7%)
P2 - Mild disease not incapacitating	138997 (73.7%)
P3 - P5	29425 (15.6%)
Minimally invasive (no)	
No	176683 (93.7%)
Yes	11826 (6.3%)
Surgical volume per consultant	
<=10 operations	5312 (2.8%)
11-50	58102 (30.8%)
51-75	42101 (22.3%)
76-100	33558 (17.8%)

101-150	32381 (17.2%)
>150	17055 (9.1%)
Surgeon experience	
<8 training years	44650 (23.7%)
Consultant (≥8 training years)	143859 (76.3%)
Surgical approach (knee)	
Lateral parapatellar	1756 (0.9%)
Medial parapatellar	175112 (92.9%)
Mid-Vastus	5710 (3.0%)
Sub-Vastus	2300 (1.2%)
Other	3631 (1.9%)
Primary graft femur	
No	186951 (99.2%)
Yes	1558 (0.8%)
Implant fixation	
Cementless	9429 (5.0%)
cemented	177031 (94.0%)
Hybrid	1947 (1.0%)
Primary graft tibia	
No	187679 (99.6%)
Yes	830 (0.4%)
Type of primary implant	
UKR	13266 (7.0%)
TKR	175243 (93.0%)
Type of mechanical thromboprophylaxis	
None	16746 (8.9%)
Any	171763 (91.1%)
Type of chemical thromboprophylaxis	
None	13239 (7.0%)
Aspirin only	16356 (8.7%)
LMWH (+/-Other)	134648 (71.4%)
Other (no LMWH)	24266 (12.9%)
Unit type	
Public hospital	153780 (81.6%)
Independent sector - hospital	24716 (13.1%)
Independent sector - treatment centre	10013 (5.3%)
OKS, baseline score	18.0 (SD 7.8)
EQ-5D Anxiety Depression	
I am not anxious or depressed	65123 (62.4%)
I am moderately anxious or depressed	32676 (31.3%)
I am extremely anxious or depressed	3710 (3.6%)

Table C. Descriptive statistics comparing patients in the full CPRD dataset to those with linked HES data for the CPRD-HES linked datasets

Year of primary (2010-2011)	CPRD (n=37,906)	CPRD-HES (n=17,378)
	3118 (8.2%)	995 (5.7%)
	10011 (26.4%)	4486 (25.8%)
	17920 (47.3%)	8415 (48.4%)
	6857 (18.1%)	3482 (20.0%)
Age at primary (continuous variable)		
	69.6 (SD 9.7)	69.4 (SD 9.2)
Sex (Woman)		
	16328 (43.1%)	7415 (42.7%)
Body mass index		
	120 (0.4%)	48 (0.4%)
	5201 (18.0%)	2204 (16.2%)
	11427 (39.6%)	5239 (38.6%)
	7739 (26.8%)	3777 (27.8%)
	4364 (15.1%)	2306 (17.0%)
Index of Multiple Deprivation (IMD) quintiles, at primary		
	7254 (24.5%)	3890 (22.4%)
	7111 (24.0%)	4145 (23.9%)
	6548 (22.1%)	3918 (22.6%)
	5031 (17.0%)	3078 (17.7%)
	3725 (12.6%)	2328 (13.4%)
Region		
	2244 (5.9%)	706 (4.1%)
	4547 (12.0%)	2003 (11.5%)
	3436 (9.1%)	1464 (8.4%)
	1033 (2.7%)	434 (2.5%)
	5066 (13.4%)	2551 (14.7%)
	5537 (14.6%)	2605 (15.0%)
	4894 (12.9%)	2144 (12.3%)
	4738 (12.5%)	2386 (13.7%)
	4589 (12.1%)	2320 (13.4%)
	1822 (4.8%)	765 (4.4%)
Smoker		
	10576 (33.4%)	5122 (34.6%)
	18106 (57.2%)	8310 (56.2%)
	2971 (9.4%)	1368 (9.2%)
Drink alcohol		
	634 (2.5%)	322 (2.7%)
	4657 (18.2%)	2242 (18.8%)
	20367 (79.4%)	9371 (78.5%)