Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
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eMethods. Health Economic Analysis Plan

Here, we describe the methods used in the within-trial cost utility analysis in more detail. We adopted the NHS and personal social services (PSS) perspective in the analysis. Our aim is to provide evidence to UK decision makers concerning the implementation of the intervention in the NHS.

Quality of Life Assessment

Participants were asked to complete the EQ-5D-5L questionnaire at randomisation, 6 weeks post-surgery and at six and twelve months after randomisation, and also at days 0,1,2,3 post-operatively. Responses to EQ-5D-5L questionnaires were converted into utility scores using the cross-walk to the 3-level version (1). QALYs were calculated using the area under the curve approach, which involves estimating the average EQ-5D utility between each follow-up time, and weighting by survival time. Partially completed EQ-5D-5L questionnaires will be considered missing.

Costs Assessment

General

To estimate health care costs, unit cost data were applied to resource use (Appendix 5:Table e1). Cost data were sourced from NHS Reference Costs, English Prescription Cost Analysis, Unit Costs of Health and Social Care (2-4), websites or as self-reported by the participants. All unit costs were inflated, where necessary, to 2018-19 prices using the healthcare and community health services inflation index.

Resource use was obtained from questionnaires at 6 weeks, 6 and 12 months. Here participants were asked to report their use of health and social services, informal care and time-off work, between randomisation and six weeks, six weeks and six months, and six months and twelve months. Data were collected on visits to and from healthcare practitioners (NHS and private), admissions to hospital, medication use, changes to their home and equipment provided or purchased, informal care received, travel costs, social care received, and time away from paid employment and time at work affected by their knee. Each of these components of resource use is described in much greater detail below. Patients’ receipt of the allocated intervention was also recorded.
### eTable 1. Unit Costs (UK 2019 £) of Health Care Services

| Resource use type                     | Unit cost (£) | Source/details                                                                                                                                 |
|---------------------------------------|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Theatre time (per minute)             | 16.49         | Table R142X from Scottish cost tables 2019 (https://beta.isdscotland.org/find-publications-and-data/healthcare-resources/finance/scottish-health-service-costs) |
| Hospital bed day                      | 407           | Weighted average cost per excess bed data for elective HRG HN22 (very major knee procedures) from the NHS Reference Cost schedule 2017-18, where the weights reflect national activity levels. Inflated to 2019. |
| GP – surgery*                         | 39            | Cost GP patient contact consultation: PSSRU 2019-20 (chapter 10, page 125). Average consultation length of 9 minutes (5)                        |
| GP – home*                            | 90            | Cost GP patient contact consultation (including qualification costs and direct care staff costs): PSSRU 2019-20 (chapter 10, page 124). Average consultation length of 9.22 minutes (5); assume average 12 minutes travel time for home visits: PSSRU 2009. |
| GP – telephone*                       | 21            | Cost GP patient contact consultation: PSSRU 2019-20 (chapter 10, page 124). Average consultation length of 5 minutes (5)                             |
| Nurse in GP surgery**                 | 6             | £42 per hour, PSSRU 2019-20 (chapter 10, page 125). Average consultation length of 9.22 minutes (5)                                            |
| Physiotherapist                       | 63            | NHS Reference Cost schedule 2018-19, tab CHS, service code A08A1                                                                                     |
| Occupational therapist                | 83            | NHS Reference Cost schedule 2018-19, tab CHS, currency code A06A1                                                                                  |
| A&E                                   | 192           | NHS Reference Cost schedule 2018-19, tab AE, weighted average of all attendances to a type 1 A&E unit with the exception of dental care and dead on arrival attendances. |
| Outpatient visit                      | 127           | NHS Reference Cost schedule 2018-19, tab total outpatient attendances, weighted average of all service codes                                         |
| Social services                       | 45            | PSSRU 2019-20 (chapter 11, page 138) (social care worker, adult services). Used cost per hour.                                                    |
| Acupuncture/Chiropractor/Osteopath    | 94            | Estimated as average of costs for acupuncture, chiropractor and osteopath sessions. Acupuncture: NHS Reference Cost schedule 2018-19, tab OPROC, service code 191 (pain management), currency code AB23Z Chiropractor: assumed to cost the same as physiotherapy session (£63) Osteopath: assumed to cost the same as physiotherapy session (£63) |

*including direct care staff costs and including qualification costs  
**including qualification costs
Methods for assigning UK-based cost estimates

Intervention and index admission costs

The cost per vial of LB was £241.80 and each participant allocated to the intervention arm received a vial. This cost was provided by the manufacturer. Usual care (UC) arm (i.e. control arm) included use of 100 mg plain bupivacaine (diluted with normal saline) used for peri-articular infiltration. The full cost per vial was applied, even if participants did not receive the protocol stipulated dose because the medication is prepared for the surgery and cannot be re-used if only partially used.

No additional costs for normal saline or plain bupivacaine or use of needles / syringes were taken into consideration as these are minimal, were similar across both the study arms and were assumed to be included in the HRG code. The index hospital stay was converted into a Healthcare Resource Group (HRG) and valued using NHS Reference Costs\(^6\). HRGs are groups of ICD-10 diagnoses and OPCS procedures which use comparable levels of healthcare resources. Based on previous research\(^6\), we used the most common ICD-10 code reported in England for knee replacements: M179 (gonarthrosis, unspecified). We also used the most common OPCS procedure reported in that work that was associated with primary knee replacements: W401 (Primary total prosthetic replacement of knee joint using cement)\(^6\) for total knee replacements, and W581 (Primary resurfacing arthroplasty of joint) and Z845 (Tibiofemoral joint, which the study Chief Investigator confirmed was the most common procedure for unicompartmental knee replacements [UKR] in SPAARK) for all UKRs. Both procedures resulted in the same HRGs (see Appendix 5:Table e2). In England, the large majority of index knee replacements consisted of a single finished consultant episode (FCE) and we assumed the same to apply in this trial. If participants reported post-op complications during their index hospital stay, we coded these as additional secondary ICD-10 diagnosis in the index FCE (finished consultant episode), resulting in differences in the CC scores between patients, which were reflected in the costing. This assumption was also based on the analysis of knee replacements in England\(^6\).

Furthermore, we compared theatre time and length of stay during index admission as well as opioids taken after surgery in the two trial arms. We added cost differences to the HRG-based outlined above. This was done as follows:

- **Length of stay**: we compared the length of stay of each participant with the trial average for the relevant procedure (total or unicompartmental knee replacement). Differences (in days) relative to the trial average were valued using the cost of an excess bed day;  
  Note: the length of stay excluded days in intensive care or high dependency units, which were be costed separately.

- **Theatre time**: we compared theatre time of each participant with the trial average for the relevant procedure (total or unicompartmental knee replacement). Differences (in minutes) relative to the trial average were valued using the average cost per minute in theatre;

- **Opioids**: we valued opioids taken during hospital stay and added these to the total hospital stay costs.

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### eTable 2. Costs for Hospital Admissions Undergoing Knee Replacement

| HRG   | Currency description                                                                 | National average unit cost (EL tab) (reference costs 2018/19) | Cost of excess bed day (reference costs 2017/18) | Cost of excess bed day adjusted to 2018/19 costs |
|-------|--------------------------------------------------------------------------------------|---------------------------------------------------------------|------------------------------------------------|-----------------------------------------------|
| HN22D | Very Major Knee Procedures for Non-Trauma with CC Score 2-3                          | £6,334                                                        | £415                                            | £425                                           |
| HN22E | Very Major Knee Procedures for Non-Trauma with CC Score 0-1                          | £5,882                                                        | £430                                            | £440                                           |

Unit costs were the NHS Reference Cost schedule 2018-19. Excess bed day costs were derived from the NHS Reference Cost schedule 2017-18 and inflated to 2019, as newer versions no longer include information on excess bed day costs.
**GP, community and outpatient visits**

Participants were asked to record their attendances with a GP (surgery, home, or telephone), physiotherapist or occupational therapist (NHS or Private), outpatient clinic (NHS or Private), home care worker or social worker (NHS or Private) and other types of healthcare received as free text (these were allocated to existing resource use categories or additional categories where possible). Information on contacts with accidents and emergency departments were also collected. Participants were asked to report visits as a results of something to do with their knee. We costed all these visits using the national databases (see Appendix 5:Table e3).

**Hospital admissions**

Hospital admissions during the trial follow-up (i.e. admissions subsequent to the index admission) were costed based on the trial’s readmission case report form. This was completed by research staff, and included ICD-10 codes for the hospitalisations, or, if these were not available, details on the reasons for admission, date of admission and discharge, time in intensive care and high dependency unit, and procedures performed during the intervention, were given. We used these data as the primary source for costing relevant admissions during the trial follow-up. Inpatient days beyond the trim point were costed as excess bed days. NHS Reference costs were applied (see Appendix 5:Table e3), and all admissions were assumed to have taken place in an NHS setting.

For hospital admissions recorded without sufficient information to attach an HRG, we valued these using weighted averages of admissions in the relevant trial arm by type (day case, emergency and planned admissions).

This analysis was based on hospital admissions as reported by sites. Patient-reported hospital admissions were monitored to ensure no relevant hospital stays had been missed.
### eTable 3. Cost of Hospital Admissions During Follow-up (2019 Prices)

| HRG   | Currency description                                                                 | Cost of admission (EL) | Cost of excess bed day (costs 2017/18; EL) | Cost of excess bed day (2017/18; EL) adjusted to 2018-19 values | Cost of admission (NEL) | Cost of excess bed day (2017/18; NEL) | Cost of excess bed day adjusted to 2018/19 costs |
|-------|---------------------------------------------------------------------------------------|------------------------|-------------------------------------------|---------------------------------------------------------------|------------------------|--------------------------------------|-----------------------------------------------|
| HD23J | Inflammatory, Spine, Joint or Connective Tissue Disorders, with CC Score 0-2         | £1,187                 | £413                                      | £423                                                          | £1,970                 | £375                                 | £384                                           |
| HD26G | Musculoskeletal Signs or Symptoms, with CC Score 0-3                                  | £2,065                 | £569                                      | £582                                                          | £1,606                 | £333                                 | £341                                           |
| HE81C | Infection or Inflammatory Reaction, due to, Internal Orthopaedic Prosthetic Devices, Implants or Grafts, with CC Score 0-2 | £3,953                 | £288                                      | £295                                                          | £4,089                 | £298                                 | £305                                           |
| HE82D | Other Complications of, Internal Orthopaedic Prosthetic Devices, Implants or Grafts with CC Score 0-1 | £3,005                 | £404                                      | £413                                                          | £2,861                 | £350                                 | £358                                           |
| WH07B | Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 0-1  | £5,483                 | £296                                      | £303                                                          | £5,574                 | £329                                 | £337                                           |
| WH07G | Infections or Other Complications of Procedures, without Interventions, with CC Score 0-1 | £1,606                 | £370                                      | £379                                                          | £2,056                 | £359                                 | £367                                           |

EL: elective admission; NEL: non-elective admission. Unit costs were the NHS Reference Cost schedule 2018-19. Excess bed day costs were derived from the NHS Reference Cost schedule 2017-18 and inflated to 2019, as newer versions no longer include information on excess bed day costs.
Medications

Patients were asked to report any medications taken, whether they were purchased or prescribed, and the dosage, duration, and frequency. Data on dosage, duration, and frequency is often missing. Each self-reported medication was categorised according to its chemical name where possible. Using all data from the 2019 Prescription Cost Analysis(4), the most common medication within each chemical name was identified, and the cost per item prescribed extracted (net ingredient cost per item).

Each medication was classified as likely to be one-off prescription or a long term prescription by physicians. For those drugs considered long-term, we identified the typically number of prescriptions per year based on recommended use and standard pack sizes from the British National Formulary(7).

Equipment and home changes

Participants were asked to report details of any changes to their home/equipment purchased or provided following the index surgery as well as their financial contribution to it. Self-reported equipment types were allocated into a category, and costs attached to each category (see Appendix 5:Table e4); the same unit costs was assumed regardless of whether the equipment was purchased or provided. Home changes were valued using the self-reported financial contribution and published estimates, if appropriate or missing.
## eTable 4. Unit Costs for Equipment (2019 Prices)

| Equipment category       | Cost per item (£) | Source                                      |
|--------------------------|-------------------|---------------------------------------------|
| Arm crutch               | 20.76             | NHS Supply chain                            |
| Bath board               | 16.08             | NHS Supply chain                            |
| Bath lift                | 232.80            | NHS Supply chain                            |
| Bath mat                 | 10.54             | www.completecareshop.co.uk                 |
| Bath sponge              | 2.63              | NHS Supply chain                            |
| Bath step                | 13.14             | NHS Supply chain                            |
| Bath stool/chair         | 21.54             | NHS Supply chain                            |
| Bed cradle               | 19.20             | NHS Supply chain                            |
| Bed raiser               | 18.98             | www.completecareshop.co.uk                 |
| Bed wedge                | 21.84             | NHS Supply chain                            |
| Chair                    | 214.84            | NHS Supply chain                            |
| Chair raises             | 19.98             | www.completecareshop.co.uk                 |
| Chair riser              | 496.07            | NHS Supply chain                            |
| Cold knee wrap           | 26.54             | NHS Supply chain                            |
| Commode                  | 27.60             | NHS Supply chain                            |
| Crutch                   | 9.36              | NHS Supply chain                            |
| Cushion                  | 24.99             | www.completecareshop.co.uk                 |
| Frame                    | 17.91             | NHS Supply chain                            |
| Half step                | 27.23             | www.completecareshop.co.uk                 |
| Knee brace               | 20.14             | NHS Supply chain                            |
| Knee cage                | 74.40             | NHS Supply chain                            |
| Knee massager            | 26.34             | www.completecareshop.co.uk                 |
| Leg lifter               | 6.68              | NHS Supply chain                            |
| Pedal exerciser          | 24.98             | www.completecareshop.co.uk                 |
| Pick up                  | 4.28              | NHS Supply chain                            |
| Rail                     | 8.82              | NHS Supply chain                            |
| Rollator                 | 45.60             | NHS Supply chain                            |
| Mobility scooter         | 722.14            | www.completecareshop.co.uk                 |
| Shoe horn                | 2.56              | NHS Supply chain                            |
| Stick                    | 8.04              | NHS Supply chain                            |
| Stool                    | 29.99             | NHS Supply chain                            |
| Toilet frame             | 21.60             | NHS Supply chain                            |
| Trolley                  | 21.82             | NHS Supply chain                            |
| Toilet seat              | 16.69             | NHS Supply chain                            |
| Urine bottle             | 3.14              | www.completecareshop.co.uk                 |
| Wheelchair               | 133.32            | www.completecareshop.co.uk                 |
| Wiper                    | 3.95              | NHS Supply chain                            |
Travel costs
Participants were asked to report costs of travelling to attend healthcare visits related to their knee.

Social services
Participants were asked to report details on use of social services (meals on wheels, home care, personal care assistant (£24 per hour), laundry services (£10.5 per service) and other), the number of weeks for which they used the service, and whether they were still using it. These are referred to as personal and social services (PSS).

Informal care
Participants were asked to report whether they received unpaid care from family or friends, the number of weeks for which any care was received, the number of hours of care provided per week, whether their carer took time away from paid work, and whether they were still receiving it. Minimum hourly wage (£8.21) were used if carer did not take time away from paid work. Mean hourly wage for all employee jobs (£18.03) were used to value the time of carers who took time away from paid work. Where data on weeks or hours per week of care were missing (but care is reported to have been received), mean imputation was used.

Lost productivity costs
Participants were asked to report whether they had to take time off paid employment due to their knee and, if so, how many days, if they lost pay and, if so, how much pay they have lost. Self-reported occupation were translated into a SOC category (https://onsdigital.github.io/dp-classification-tools/standard-occupational-classification/ONS_SOC_occupation_coding_tool.html) and the days off work were costed using mean hourly wages for all employee jobs by SOC category (see Appendix 5:Table e5).

Participants were also asked to report how many days at work were affected by their knee and if so, to rank how much they were affected on a scale of 0 to 10. Participants not in paid employment were asked how many days did their knee affect their ability to carry out usual activities and, if so, to rank how much they were affected on a scale of 0 to 10. The self-reported rank was divided by 10 and multiplied by the number of days reported to ascertain the total days at work of lost productivity. These days were costed using mean hourly wages by SOC for those employed full-time and minimum hourly wage for those unemployed/retired.
| Description                                      | SOC 2010 Code | Unit cost | Source/details                                      |
|--------------------------------------------------|---------------|-----------|----------------------------------------------------|
| Corporate managers and directors                 | 11            | 28.97     | Mean hourly pay (gross) for all employee jobs      |
| Other managers and proprietors                   | 12            | 17.40     |                                                    |
| Science, research, engineering and technology professionals | 21            | 22.99     |                                                    |
| Health professionals                             | 22            | 22.19     |                                                    |
| Teaching and educational professionals           | 23            | 23.91     |                                                    |
| Business, media and public service professionals | 24            | 23.49     |                                                    |
| Science, engineering and technology associate professionals | 31            | 15.56     |                                                    |
| Health and social care associate professionals   | 32            | 14.27     |                                                    |
| Protective service occupations                   | 33            | 18.01     |                                                    |
| Culture, media and sports occupations            | 34            | 17.12     |                                                    |
| Business and public service associate professionals | 35            | 20.33     |                                                    |
| Administrative occupations                       | 41            | 13.68     |                                                    |
| Secretarial and related occupations              | 42            | 11.99     |                                                    |
| Skilled agricultural and related trades          | 51            | 10.89     |                                                    |
| Skilled metal, electrical and electronic trades  | 52            | 15.13     |                                                    |
| Skilled construction and building trades         | 53            | 13.86     |                                                    |
| Textiles, printing and other skilled trades      | 54            | 10.92     |                                                    |
| Caring personal service occupations              | 61            | 10.59     |                                                    |
| Leisure, travel and related personal service occupations | 62            | 11.03     |                                                    |
| Sales occupations                                | 71            | 10.08     |                                                    |
| Customer service occupations                     | 72            | 12.09     |                                                    |
| Process, plant and machine operatives            | 81            | 12.00     |                                                    |
| Transport and mobile machine drivers and operatives | 82            | 12.56     |                                                    |
| Elementary trades and related occupations        | 91            | 10.54     |                                                    |
| Elementary administration and service occupations | 92            | 10.03     |                                                    |
**Missing data**

We followed best practice methods for addressing missing data in cost-effectiveness studies (8). Missing baseline data were imputed using unconditional mean imputation. Data on receipt of allocated interventions and deaths were considered to be complete, and no imputation were performed. For components of resource use where participants provided responses to any questions in the resource diary, we imputed missing values as zero.

We used multiple imputation by chained equations to impute missing data on EQ-5D-5L utility scores, and cost components (except costs related to the allocated intervention), at each follow-up time point. Each missing value was imputed as a function of follow-up period, sex, age, recruitment site, and baseline EQ-5D score, updated EQ-5D score and components of costs, and the imputation model was run separately by randomised treatment. We used predictive mean matching to create a total number of 30 imputed datasets (i.e. the proportion of data missing across all time periods times 100). We imputed costs and EQ-5D-5L utility score in each period. In periods where death was observed we adjusted these. For costs, we assumed that they were incurred linearly over time, such that, if an individual died half way into a period, they incurred half the predicted costs.

**Within-trial analysis**

We reported descriptive statistics (means, SD as a minimum) for resource use, costs, and EQ-5D utilities at each follow-up time point using only complete data. Differences between arms for the EQ-5D-5L utilities were estimated using multi-level mixed effects linear regression models, to allow for multiple follow-ups clustered within participant. The model was adjusted for treatment allocation, an interaction between follow-up time and treatment allocation, recruitment site, and, in the case of EQ-5D, baseline utility score. Clustering by site was accounted for using robust standard errors, using the ‘cluster’ option in Stata. Other outcomes were analysed using simple regression models or t-tests, as appropriate.

Following multiple imputation, we estimated total costs and QALYs for all participants in the SPAARK study from the date of study recruitment until the earliest of death, from study, or the end of follow-up at 1 year. Our analysis followed intent-to-treat principles wherein healthcare resource use, costs and EQ-5D scores were analysed according to treatment allocation, regardless of the treatment actually received. We did not discount total costs and QALYs as the time horizon of the analysis is 12 months.

On each imputed dataset, we estimated mean costs (by type) and QALYs using separate analysis models, as described above. Estimates derived from each imputed dataset were combined using Rubin’s rule to estimate the adjusted mean difference and standard error for each outcome. As a sensitivity analyses, we performed a complete case analysis, including only individuals who provided complete data over the 12 month trial duration.

We estimated the Incremental Cost Effectiveness Ratio (ICER) by dividing the mean cost difference between LB and usual care by the mean QALY difference.

We estimated the joint uncertainty around incremental total costs and QALYs (i.e. the difference between LB and usual care), and in the cost-effectiveness, by bootstrapping 1,000 times from each of the n imputed datasets (creating at least 30,000 bootstraps), running the estimation model on each bootstrapped dataset and extracting the estimated treatment effects. From these bootstrapped results, we calculated the probability that LB was more cost-effective than usual care for different threshold values per QALY gained (9). These were calculated by estimating the proportion of bootstrap replicates with a net monetary benefit (NMB) above 0 for each threshold value, where the NMB was given by the product of the mean difference in QALYs and the threshold value minus the mean difference in costs.
## eTable 6. Stratification Factors at Baseline—Split by Treatment Group and Overall

| Factor     | Intervention (n = 267) | Control (n = 266) | Total (n = 533) |
|------------|------------------------|-------------------|-----------------|
|            | n | %   | n  | %   | n  | %   |
| Centre     |   |     |    |     |    |     |
| Centre 1   | 129 | 48.3 | 129 | 48.5 | 258 | 48.4 |
| Centre 2   | 17  | 6.4  | 14  | 5.3  | 31  | 5.8  |
| Centre 3   | 5   | 1.9  | 5   | 1.9  | 10  | 1.9  |
| Centre 4   | 30  | 11.2 | 33  | 12.4 | 63  | 11.8 |
| Centre 5   | 15  | 5.6  | 16  | 6.0  | 31  | 5.8  |
| Centre 6   | 3   | 1.1  | 3   | 1.1  | 6   | 1.1  |
| Centre 7   | 32  | 12.0 | 33  | 12.4 | 65  | 12.2 |
| Centre 8   | 2   | 0.7  | 1   | 0.4  | 3   | 0.6  |
| Centre 9   | 10  | 3.7  | 10  | 3.8  | 20  | 3.8  |
| Centre 10  | 17  | 6.4  | 16  | 6.0  | 33  | 6.2  |
| Centre 11  | 7   | 2.6  | 6   | 2.3  | 13  | 2.4  |
| **Type of surgery** |   |     |    |     |    |     |
| TKR        | 236 | 88.4 | 235 | 88.3 | 471 | 88.4 |
| UKR        | 31  | 11.6 | 31  | 11.7 | 62  | 11.6 |
eTable 7. Baseline Characteristics of Participants—Split by Treatment Group and Overall

|                      | Intervention (n=267) | Control (n=266) | Total (n=533) |
|----------------------|----------------------|-----------------|---------------|
| **Age**<sup>1</sup>  | 68.9 (10.1), (39.4, 91.4), 267 | 69.0 (9.3), (43.5, 90.5), 266 | 69.0 (9.7), (39.4, 91.4), 533 |
| **BMI**<sup>1</sup>   | 32.0 (6.4), (9.2, 49.7), 263 | 31.6 (5.9), (10.0, 53.9), 263 | 31.8 (6.1), (9.2, 53.9), 526 |
| **Gender**<sup>2</sup>|                      |                 |               |
| Male                 | 116 (43.4)           | 130 (48.9)      | 246 (46.2)    |
| Female               | 151 (56.6)           | 136 (51.1)      | 287 (53.8)    |
| **Knee**<sup>2</sup> |                      |                 |               |
| Left                 | 115 (43.1)           | 114 (42.9)      | 229 (43.0)    |
| Right                | 149 (55.8)           | 151 (56.8)      | 300 (56.3)    |
| **ASA Grade**<sup>2</sup>|                    |                 |               |
| I                    | 18 (7.0)             | 17 (6.7)        | 35 (6.8)      |
| II                   | 187 (72.8)           | 174 (68.2)      | 361 (70.5)    |
| III                  | 52 (20.2)            | 64 (25.1)       | 116 (22.7)    |

<sup>1</sup> Summaries are mean (SD), (range), N

<sup>2</sup> Summaries are n (%)
Table 8. Primary and Secondary Outcome Measures at Baseline—Split by Treatment Group and Overall

|        | Intervention | Control | Total |        |        |
|--------|--------------|---------|-------|--------|--------|
|        | n            | Mean (SD) | Median (IQR) | Range | n      | Mean (SD) | Median (IQR) | Range |
| QoR-40 | 25 (7)       | 183.3 (12.8) | 187.0 (178.0, 192.0) | (104.0, 200.0) | 24 (9) | 184.2 (12.0) | 189.0 (180.0, 192.0) | (133.0, 199.0) | 50 (6) | 183.7 (12.4) | 188.0 (179.0, 192.0) | (104.0, 200.0) |
| Pain VAS (0-10) | 25 (6) | 5.6 (2.5) | 6.0 (4.0, 7.1) | (0.0, 10.0) | 25 (2) | 5.2 (2.6) | 5.0 (3.0, 7.0) | (0.0, 10.0) | 50 (8) | 5.4 (2.5) | 6.0 (4.0, 7.0) | (0.0, 10.0) |
| OKS    | 26 (3)       | 17.5 (6.8) | 17.0 (13.0, 22.0) | (0.0, 36.0) | 25 (4) | 19.2 (7.4) | 19.0 (14.0, 25.0) | (4.0, 40.0) | 51 (7) | 18.4 (7.1) | 18.0 (13.0, 23.0) | (0.0, 40.0) |
| AKS    | 23 (9)       | 53.6 (20.8) | 51.0 (38.0, 68.0) | (12.0, 112.0) | 23 (2) | 58.1 (21.2) | 58.5 (42.0, 73.0) | (11.0, 131.0) | 47 (1) | 55.8 (21.1) | 55.0 (40.0, 71.0) | (11.0, 131.0) |
eTable 9. Details of Surgery and Complications Experienced During Surgery Summarized by Treatment Group

|                                      | Intervention | Control |
|--------------------------------------|--------------|---------|
| Participants with surgery form       | 258<sup>1</sup> | 256<sup>2</sup> |
| Time from randomisation to surgery (days; n, median, IQR, range) | 258, 0.0, (0.0, 5.0), (0.0, 63.0) | 256, 0.0, (0.0, 7.0), (0.0, 90.0) |
| Time in theatre (minutes; n, median, IQR, range) | 258, 111.0, (90.0, 129.0), (35.0, 270.0) | 256, 116.0, (90.0, 131.0), (45.0, 276.0) |
| TKR performed, n (%)                 | 229 (88.8)  | 232 (90.6) |
| Missing                              | 0 (0.0)     | 0 (0.0)   |
| Type of surgery different from planned at randomisation, n (%) | 11 (4.3)  | 9 (3.5)   |
| Number of anaesthetists present (n, median, IQR, range) | 258, 1.0, (1.0, 1.0), (0.0, 4.0) | 256, 1.0, (1.0, 1.0), (1.0, 3.0) |
| Number of surgeons present (n, median, IQR, range) | 258, 2.0, (2.0, 2.0), (0.0, 4.0) | 256, 2.0, (1.0, 2.0), (0.0, 4.0) |
| Number of nursing staff present (n, median, IQR, range) | 258, 3.0, (2.0, 4.0), (0.0, 8.0) | 256, 3.0, (2.0, 4.0), (0.0, 7.0) |
| ASA Grade, n (%)                     |             |         |
| Grade I                              | 18 (7.0)    | 17 (6.6) |
| Grade II                             | 187 (72.5)  | 174 (68.0) |
| Grade III                            | 52 (20.2)   | 64 (25.0) |
| Missing                              | 1 (0.4)     | 1 (0.4)   |
| Anaesthetic used, n (%)              |             |         |
| General                              | 4 (1.6)     | 9 (3.5)   |
| Neuraxial - spinal                   | 214 (82.9)  | 210 (82.0) |
| Neuraxial - epidural                 | 3 (1.2)     | 2 (0.8)   |
| Block - femoral                      | 11 (4.3)    | 11 (4.3)  |
| Block - sciatic                      | 2 (0.8)     | 0 (0.0)   |
| Block - adductor canal               | 23 (8.9)    | 24 (9.4)  |
| Block - lumbar plexus                | 0 (0.0)     | 0 (0.0)   |
| Missing                              | 1 (0.4)     | 0 (0.0)   |
| Patients with complications during surgery, n (%) | 1 (0.4)  | 3 (1.2)   |
| Total no. of complications during surgery, n (%) | 1 (0.4)  | 3 (1.2)   |

<sup>1</sup>8 participants withdrew from the intervention arm before surgery; 1 patient had their surgery delayed due to the COVID-19 pandemic

<sup>2</sup>8 participants withdrew from the control arm before surgery; 2 patients had their surgeries delayed due to the COVID-19 pandemic
| Questionnaire                                                                 | Intervention (n = 267) | Control (n = 266) |
|-------------------------------------------------------------------------------|-----------------------|-------------------|
|                                                                               | n    | %    | n    | %    |
| **Total**                                                                     | 10   | 3.7  | 13   | 4.9  |
| **Before surgery**                                                            |       |      |      |      |
| Consultant no longer participating in study.                                  | 2    | 0.7  | 1    | 0.4  |
| Knee replacement surgery cancelled.                                           | 0    | 0.0  | 0    | 0.0  |
| Knee replacement surgery postponed.                                           | 0    | 0.0  | 1    | 0.4  |
| Knee replacement surgery postponed. No longer eligible to receive IMP (ASA Grade III & contralateral knee). | 1    | 0.4  | 0    | 0.0  |
| No longer eligible to receive IMP (ASA Grade III).                            | 1    | 0.4  | 1    | 0.4  |
| Patient became anxious and left prior to surgery                               | 1    | 0.4  | 0    | 0.0  |
| Patient felt length of recovery would affect work.                             | 1    | 0.4  | 0    | 0.0  |
| Patient relisted as PFJ replacement +/- total knee - no guarantee of TKR.     | 0    | 0.0  | 1    | 0.4  |
| Personal reason (no further details).                                         | 2    | 0.7  | 2    | 0.8  |
| Study closing at site before patient will be seen again in November 2019.     | 0    | 0.0  | 1    | 0.4  |
| **Day 0**                                                                     |       |      |      |      |
| Day 0                                                                         | 0    | 0.0  | 1    | 0.4  |
| Felt angry at level of post pain. Thought study involvement was to blame.     | 0    | 0.0  | 1    | 0.4  |
| **Day 1**                                                                     |       |      |      |      |
| Day 1                                                                         | 0    | 0.0  | 0    | 0.0  |
| **Day 2**                                                                     |       |      |      |      |
| Day 2                                                                         | 0    | 0.0  | 1    | 0.4  |
| Personal reason (no further details).                                         | 0    | 0.0  | 0    | 0.0  |
| **Day 3**                                                                     |       |      |      |      |
| Day 3                                                                         | 2    | 0.7  | 1    | 0.4  |
| No longer eligible to receive IMP (ASA Grade III).                            | 1    | 0.4  | 0    | 0.0  |
| No longer wants to complete questionnaires. Scrub nurse dropped the IMP at time of surgery. | 1    | 0.4  | 0    | 0.0  |
| Struggling to complete questionnaires due to partial blindness.               | 0    | 0.0  | 1    | 0.4  |
| **6 weeks**                                                                   |       |      |      |      |
| Pt moving house - too busy to complete questionnaires. Pt broke ankle and finds it too difficult to answer the questions just about pain in her knee. | 0    | 0.0  | 1    | 0.4  |
| **6 months**                                                                  |       |      |      |      |
| 6 months                                                                       | 0    | 0.0  | 0    | 0.0  |
| **12 months**                                                                 |       |      |      |      |
| 12 months                                                                      | 0    | 0.0  | 1    | 0.4  |
| Personal reason (no further details).                                         | 0    | 0.0  | 1    | 0.4  |
# eTable 11. Details of Interventions Received Split by Randomized Treatment Group

| Intervention                                           | Intervention | Control |
|--------------------------------------------------------|--------------|---------|
| Received allocated intervention as planned*            | 238          | 251     |
| Didn’t receive allocated intervention as planned       | 29           | 15      |
| Withdrawn before surgery                               | 8            | 8       |
| Received alternate trial treatment                      | 7            | 0       |
| Did not receive all syringes as planned                | 10           | -       |
| Did not receive IMP or control                         | 3            | 5       |
| Surgery delayed due to COVID-19                        | 1            | 2       |

* Participants are classed as having received their allocated intervention if for those randomised to Liposomal bupivacaine + bupivacaine hydrochloride all six syringes of Liposomal bupivacaine were administered as planned, and those who were randomised to Bupivacaine hydrochloride only received this
**eTable 12. Analysis of Coprimary Outcomes at Primary End Points (ITT Population)**

| Outcome                  | Intervention | Control | Adjusted diff (97.5% CI) | P-value |
|--------------------------|--------------|---------|--------------------------|---------|
|                          | n            | Mean (SD) | n            | Mean (SD) |              |            |
| QoR 40 (72 hours)        | 234          | 184.72 (13.93) | 219          | 184.41 (15.31) | 0.54 (-2.05, 3.13) | 0.643  |
| Pain (AUC 6-72 hours) *  | 226          | 361.8 (307.7)  | 218          | 383.2 (306.3)  | -21.5 (-46.8, 3.8) | 0.057  |

* To calculate the AUC, categorical covariates were set as the most commonly occurring group (TKR for surgery type, female for gender, no for preoperative opiate use) and as the median value for continuous covariates (70.1 years for age and 6 for baseline pain VAS scores)
eTable 13. Analysis of Coprimary Outcomes at Primary End Points (PP Population)

| Outcome               | Intervention      | Control          | Adjusted diff (97.5% CI) | P-value |
|-----------------------|-------------------|------------------|--------------------------|---------|
|                       | n | Mean (SD) | n | Mean (SD) |              |         |
| QoR 40 (72 hours)     | 218 | 184.81 (14.01) | 215 | 184.38 (15.37) | 0.52 (-2.14, 3.17) | 0.663 |
| Pain (AUC 6-72 hours)*| 211 | 359.0 (296.2) | 213 | 380.6 (299.6) | -21.6 (-47.4, 4.2) | 0.060 |

* To calculate the AUC, categorical covariates were set as the most commonly occurring group (TKR for surgery type, female for gender, no for preoperative opiate use) and as the median value for continuous covariates (70.2 years for age and 6 for baseline pain VAS scores)
| Outcome  | Timepoint | Intervention n | Mean (SD) | Control n | Mean (SD) | Adjusted diff (97.5% CI) | P-value |
|----------|-----------|----------------|-----------|------------|-----------|--------------------------|---------|
| QoR-40   | 6 hours   | 236            | 180.5 (15.2) | 234        | 180.1 (14.8) | 0.98 (-2.06, 4.02)       | 0.471   |
|          | 24 hours  | 243            | 176.0 (16.1) | 237        | 177.4 (14.5) | -0.19 (-3.20, 2.82)      | 0.890   |
|          | 48 hours  | 239            | 180.5 (16.3) | 232        | 180.7 (15.0) | 0.71 (-2.32, 3.75)       | 0.599   |
|          | 72 hours  | 234            | 184.7 (13.9) | 219        | 184.4 (15.3) | 0.41 (-2.68, 3.49)       | 0.768   |
|          | 6 weeks   | 202            | 176.9 (18.5) | 207        | 178.1 (15.9) | -0.51 (-3.73, 2.71)      | 0.721   |
|          | 6 months  | 191            | 182.5 (19.0) | 184        | 181.5 (17.5) | 1.27 (-2.06, 4.61)       | 0.393   |
|          | 12 months | 184            | 182.0 (17.7) | 175        | 183.3 (17.7) | -0.98 (-4.40, 2.43)      | 0.519   |
| Pain VAS | 6 hours   | 244            | 4.1 (3.0)   | 241        | 4.7 (3.0)   | -0.54 (-1.07, -0.02)     | 0.021   |
|          | 24 hours  | 247            | 5.9 (2.5)   | 242        | 6.0 (2.4)   | -0.12 (-0.64, 0.41)      | 0.620   |
|          | 48 hours  | 245            | 5.0 (2.4)   | 234        | 5.2 (2.4)   | -0.36 (-0.88, 0.17)      | 0.131   |
|          | 72 hours  | 244            | 4.3 (2.4)   | 223        | 4.5 (2.3)   | -0.27 (-0.80, 0.26)      | 0.256   |
|          | 6 weeks   | 200            | 3.9 (2.5)   | 204        | 4.1 (2.3)   | -0.33 (-0.90, 0.24)      | 0.198   |
|          | 6 months  | 190            | 2.8 (2.6)   | 193        | 2.6 (2.4)   | 0.06 (-0.52, 0.64)       | 0.820   |
|          | 12 months | 187            | 2.2 (2.4)   | 179        | 2.2 (2.4)   | -0.13 (-0.73, 0.46)      | 0.611   |
| Pain VAS | Summary measures AUC (6-72 hours) | 236 | 333.0 (131.5) | 217 | 345.3 (122.6) | -19.9 (-45.6, 5.8) | 0.082 |
eTable 15. Oral Morphine Equivalent Daily and Cumulative Opiate Use by Treatment Group

|                | Intervention |                        | Control | Adj diff (95% CI) | p-value |
|----------------|--------------|-------------------------|---------|-------------------|---------|
|                | Summary      | N                       | Summary |                   |         |
| Daily opiate use (mg)^1 |               |                          |         |                   |         |
| Day 0          | 33.1 (29.6), 20 (20, 40), (0, 200) | 257 | 33.6 (28.0), 20 (20, 40), (0, 186) | 255 | - | - |
| Day 1          | 51.1 (35.7), 41 (30, 70), (0, 198) | 256 | 51.5 (47.3), 40 (22, 70), (0, 530) | 252 | - | - |
| Day 2          | 30.1 (29.9), 20 (10, 40), (0, 200) | 229 | 31.1 (44.9), 20 (10, 40), (0, 520) | 217 | - | - |
| Day 3          | 20.1 (29.2), 10 (0, 21), (0, 220) | 137 | 23.8 (52.3), 10 (0, 20), (0, 510) | 130 | - | - |
| Cumulative opiate use from day 0 to 3 (mg)^2 | Best-case^3 | 126.5 (88.9) | 233 | 127.4 (132.6) | 226 | -3.06 (-22.32, 16.19) | 0.76 |
|                | Worst-case^4 | 135.6 (91.4) | 233 | 139.2 (135.9) | 226 | -6.83 (-26.09, 12.42) | 0.49 |

1 Summaries are mean (SD), median (IQR), (min, max). Opioids were converted to oral morphine equivalent doses using standardized conversion tables
2 Summaries are mean (SD)
3 For participants discharged prior to day 3, it is assumed they took no opioids following discharge
4 For participants discharged prior to day 3, it is assumed they took the maximum daily dose of the opioids prescribed at discharge until discharge
etTable 16. Analysis of OKS and AKSS Secondary Outcome

| Scale                  | Timepoint | Intervention | Control | Adjusted diff (95% CI) | P-value |
|------------------------|-----------|--------------|---------|------------------------|---------|
|                        |           | Mean (SD)    | n       | Mean (SD)              | n       |
| OKS                    | 6 weeks   | 25.8 (9.6)   | 207     | 26.1 (8.6)             | 216     | 0.43 (-1.23, 2.10) | 0.610  |
|                        | 6 months  | 34.3 (10.0)  | 199     | 34.3 (9.3)             | 199     | 0.56 (-1.14, 2.25) | 0.518  |
|                        | 12 months | 36.3 (9.4)   | 191     | 36.3 (9.0)             | 185     | 0.58 (-1.15, 2.30) | 0.513  |
| AKSS – Expectations    | 6 weeks   | 8.5 (3.2)    | 209     | 8.3 (2.9)              | 218     | 0.18 (-0.41, 0.77) | 0.549  |
|                        | 6 months  | 9.2 (3.3)    | 198     | 9.0 (3.0)              | 199     | 0.20 (-0.40, 0.81) | 0.508  |
|                        | 12 months | 9.5 (3.5)    | 192     | 9.7 (3.0)              | 180     | -0.14 (-0.76, 0.48)| 0.659  |
| AKSS – Satisfaction    | 6 weeks   | 24.0 (9.1)   | 209     | 24.4 (8.1)             | 217     | 0.09 (-1.59, 1.78) | 0.915  |
|                        | 6 months  | 27.7 (9.8)   | 199     | 28.4 (8.7)             | 200     | -0.38 (-2.09, 1.34)| 0.666  |
|                        | 12 months | 29.4 (9.9)   | 194     | 30.0 (9.0)             | 180     | -0.13 (-1.89, 1.62)| 0.881  |
| AKSS – Function        | 6 weeks   | 57.3 (19.6)  | 207     | 60.3 (18.2)            | 212     | -1.45 (-5.23, 2.33)| 0.452  |
|                        | 6 months  | 60.3 (22.1)  | 189     | 61.0 (22.3)            | 193     | 2.38 (-1.52, 6.28) | 0.232  |
|                        | 12 months | 65.5 (22.1)  | 190     | 64.9 (22.1)            | 178     | 2.92 (-1.05, 6.89) | 0.149  |

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eTable 17. Analysis of Categorical Secondary Outcomes

| Timepoint               | Intervention | Control | Difference (95% CI) | Unadj. | Adj. |
|-------------------------|--------------|---------|---------------------|--------|------|
|                         | n   | %      | n   | %      |         |        |
| **Fitness for discharge** |    |        |    |        |         |        |
| Day 0                   | 5   | 1.9    | 0   | 0      | 0.91 (0.42, 2.00) | 0.96 (0.44, 2.11) |
| Day 1                   | 20  | 7.5    | 31  | 11.7   | 0.50 (0.21, 1.23) | 0.51 (0.20, 1.25) |
| Day 2                   | 77  | 28.8   | 70  | 26.3   | 1.01 (0.52, 1.97) | 1.04 (0.53, 2.02) |
| Day 3                   | 66  | 24.7   | 64  | 24.1   | 0.91 (0.42, 2.00) | 0.96 (0.44, 2.11) |
| **Complications**       |    |        |    |        |         |        |
| Participants            | 22  | 8.2    | 25  | 9.4    | 0.84 (0.44, 1.61) | 0.95 (0.48, 1.86) |
| Missing                 | 9   | 3.4    | 10  | 3.8    | -       | -      |

The number of patients not experiencing complications was 236 in the intervention arm and 231 in the control arm.
eTable 18. Clavien-Dindo Classification of Surgical and Inpatient Complications by Treatment Arm

| Clavien-Dindo Classification | Intervention | Control | Total |
|-----------------------------|--------------|---------|-------|
| **Inpatient Complications** |              |         |       |
| I                           | 14           | 20      | 34    |
| II                          | 10           | 16      | 26    |
| III-a                       | 3            | 2       | 5     |
| III-b                       | 1            | 0       | 1     |
| IV-a                        | 0            | 0       | 0     |
| IV-b                        | 0            | 0       | 0     |
| V                           | 0            | 0       | 0     |
| **Surgical Complications**  |              |         |       |
| I                           | 1            | 2       | 3     |
| II                          | 0            | 0       | 0     |
| III-a                       | 0            | 0       | 0     |
| III-b                       | 0            | 1       | 1     |
| IV-a                        | 0            | 0       | 0     |
| IV-a                        | 0            | 0       | 0     |
| IV-a                        | 0            | 0       | 0     |
eTable 19. Summary of Serious Adverse Events (SAEs) Including SARs/SUSARs

|                                | Intervention | Control | Total |
|--------------------------------|--------------|---------|-------|
| Number of SUSARS               | 0            | 0       | 0     |
| Number of SARS                 | 0            | 0       | 0     |
| Number of SAEs                 | 30           | 28      | 58    |
| Number of participants with SAEs| 26           | 26      | 52    |
| Average number of SAEs per participants (for those with at least one SAE) | 1.2          | 1.1     | 1.1   |
| Number of participants without SAE, SAR or SUSAR | 241         | 240     | 481   |
| Number of deaths               | 3            | 0       | 3     |
| Number of AEs                  | 51           | 56      | 107   |
| Number of participants with AEs | 43           | 44      | 87    |
eTable 20. Sensitivity Analysis for Pain VAS Coprimary Outcome (ITT Population)

| Outcome | Timepoint       | Intervention | Control | Adjusted diff (97.5% CI) | P-value |
|---------|-----------------|--------------|---------|--------------------------|---------|
|         |                 | n            | Mean (SD) | n            | Mean (SD) |           |         |
| Pain VAS| Summary measures| 267          | 355.3 (146.7) | 266          | 375.5 (137.4) | -26.3 (-53.4, 0.9) | 0.030   |
eTable 21. Missing Data on Resource Use and EQ-5D Utility by Treatment Allocation in Each Follow-up Period

| Follow-up time      | Healthcare resource use data | EQ-5D-5L utility data |
|---------------------|------------------------------|-----------------------|
|                     | Intervention | Control | Intervention | Control |
| Baseline            | 265 (99%)    | 262 (98%) | 262 (98%)    | 249 (94%) |
| Post operation: day 0* | n/a         | n/a      | 246 (92%)    | 236 (89%) |
| Post operation: day 1* | n/a         | n/a      | 247 (93%)    | 240 (90%) |
| Post operation: day 2* | n/a         | n/a      | 249 (93%)    | 232 (87%) |
| Post operation: day 3* | n/a         | n/a      | 244 (91%)    | 219 (82%) |
| 6 weeks*            | 210 (81%)    | 218 (85%) | 208 (78%)    | 217 (82%) |
| 6 months            | 201 (75%)    | 200 (75%) | 198 (74%)    | 197 (74%) |
| 1 year              | 194 (73%)    | 187 (70%) | 191 (72%)    | 182 (68%) |

*Note: only expected for participants who underwent surgery

Self-reported healthcare resource use is classed as missing if no EQ-5D-5L questions, no resource use, and no personal costs were reported.
eTable 22. EQ-5D-5L Utility Scores, EQ-5D-Visual Analog Scale Score (VAS), and Quality-Adjusted Life-Years (QALYs) by Treatment Allocation (Imputed Data)

|                      | Intervention n=267 | Control n=266 | Treatment effect | p-value |
|----------------------|--------------------|---------------|------------------|---------|
| **EQ-5D-5L utility**¹ |                    |               |                  |         |
| Baseline             | 0.431 (0.238)      | 0.458 (0.231) |                  |         |
| day of surgery*      | 0.146 (0.017)      | 0.144 (0.018) | 0.006 (-0.040, 0.052) | 0.797  |
| 1 day post surgery*  | 0.324 (0.018)      | 0.340 (0.018) | -0.013 (-0.063, 0.038) | 0.623  |
| 2 days post surgery* | 0.444 (0.016)      | 0.449 (0.017) | -0.001 (-0.038, 0.035) | 0.944  |
| 3 days post surgery* | 0.518 (0.015)      | 0.543 (0.015) | -0.021 (-0.080, 0.037) | 0.476  |
| 6 weeks post surgery*| 0.636 (0.015)      | 0.637 (0.013) | 0.003 (-0.039, 0.045)  | 0.885  |
| 6 months             | 0.723 (0.015)      | 0.738 (0.013) | -0.011 (-0.055, 0.033) | 0.627  |
| 1 year               | 0.754 (0.016)      | 0.766 (0.014) | -0.007 (-0.052, 0.037) | 0.747  |
| **EQ-VAS**¹          |                    |               |                  |         |
| Baseline             | 70.9 (18.8)        | 70.2 (19.5)   |                  |         |
| day of surgery*      | 68.7 (1.2)         | 68.7 (1.2)    | -0.4 (-3.0, 2.2)  | 0.745  |
| 1 day post surgery*  | 66.2 (1.3)         | 67.8 (1.2)    | -1.7 (-4.4, 0.9)  | 0.205  |
| 2 days post surgery* | 70.2 (1.2)         | 71.3 (1.1)    | -1.4 (-4.1, 1.2)  | 0.291  |
| 3 days post surgery* | 72.6 (1.2)         | 73.3 (1.2)    | -1.2 (-4.7, 2.4)  | 0.520  |
| 6 weeks post surgery*| 73.7 (1.4)         | 75.0 (1.2)    | -2.0 (-5.0, 1.1)  | 0.205  |
| 6 months             | 77.0 (1.4)         | 78.5 (1.3)    | -2.5 (-6.5, 1.6)  | 0.232  |
| 1 year               | 79.0 (1.5)         | 79.9 (1.3)    | -1.4 (-5.8, 3.0)  | 0.544  |
| **QALY**²            |                    |               |                  |         |
| Baseline to 6 months³| 0.320 (0.093)      | 0.323 (0.081) | -0.001 (-0.022, 0.020) | 0.927  |
| 6 to 12 months       | 0.368 (0.108)      | 0.375 (0.095) | -0.004 (-0.028, 0.020) | 0.693  |
| Baseline to 12 months| 0.689 (0.187)      | 0.698 (0.164) | -0.005 (-0.048, 0.038) | 0.793  |

¹Differences between treatment arms are obtained from multilevel mixed-effects models, adjusted for baseline utility, type of surgery performed (total vs. partial knee replacement); robust standard errors were used to account for clustering by site; a time by treatment interaction was included in the model; the follow-up time point was used as a categorical variable.

²Differences between treatment arms are obtained from regression models, adjusted for baseline utility, type of surgery performed (total vs. partial knee replacement); robust standard errors were used to account for clustering by site.

³The QALY data for the baseline to six months period included EQ-5D-5L utility data collected at days zero, one, two, three and 42 days (6 weeks) post-operatively for participants who received their surgery. This is because these assessments varied in terms of their timing from randomisation.

*=data only expected for those who had surgery

Missing baseline data were mean-imputed.
eTable 23. Details of the Index Procedure (Only Including Participants Who Received the Surgery)

|                                | Intervention (n=267) | Control (n=266) | Treatment effect* |
|--------------------------------|----------------------|-----------------|------------------|
|                                | n                    | mean (SD) | median (IQR) | range    | n         | mean (SD) | median (IQR) | range    | Difference (95% CI) | p-value |
| Participants receiving surgery¹| 258/267 (97%)        |           |             |          | 256/266 (96%) |           |             |          | -2.4 (-8.1, 3.3) | 0.408   |
| Time in theatre (minutes)      | 25/8                 | 111.5 (33.0)| 111 (90, 129)| 35, 270  | 25/6      | 113.9 (32.6)| 116 (90, 131)| 45, 276  | -2.4 (-8.1, 3.3) | 0.408   |
| Length of stay (days)          | 25/8                 | 4.1 (1.8)  | 4 (3, 5)    | 1, 15    | 25/6      | 4.1 (2.4)  | 4 (3, 5)    | 1, 22    | -0.1 (-0.5, 0.3) | 0.642   |
| Cost of surgery and length of stay (£)* | 25/8       | 5939.0 (956.1)| 5808 (5354, 6360)| 4112, 11365 | 25/6      | 6012.4 (1188.4)| 5800 (5360, 6366)| 4145, 14412 | -73.4 (-260.2, 113.5) | 0.441   |
| Cost of the LB drug (£)⁴      | 25/8                 | 232.4 (46.8)| 242 (242, 242)| 0, 242  | 25/6      | 0.0 (0.0)  | 0 (0, 0)    | 0, 0     | 232.4 (226.7, 238.2) | 0.000   |
| Cost for Opioids (£)           | 25/8                 | 3.3 (2.7)  | 3 (1, 4)    | 0, 21    | 25/6      | 3.2 (2.9)  | 2 (1, 4)    | 0, 28    | 0.2 (-0.3, 0.7) | 0.486   |
| Total cost of hospital stay (£) | 25/8                | 6174.8 (961.7)| 6039 (5577, 6591)| 4357, 11611 | 25/6      | 6015.6 (1189.6)| 5802 (5361, 6373)| 4145, 14425 | 159.2 (-28.2, 346.6) | 0.096   |

¹treatment effects obtained from t-test
The cost for the hospital stay includes: HRG cost, and adjustment for length of stay, critical care bed days (ICU/HDU), adjustment for theatre time and cost of Liposomal bupivacaine if appropriate.

¹showing n/N (%)

**including procedure costs, adjustment for length of stay and time in theatre
⁴The cost of the bupivacaine hydrochloride is assumed to be included in the HRG code for the primary procedure cost.
eTable 24. Summary of Cost (£) Component Over the 1-Year Follow-up (Imputed Data)

| Cost Component                        | Intervention Mean (SE) | Control Mean (SE) | Treatment effect Mean (SE) | p-value  |
|---------------------------------------|------------------------|-------------------|---------------------------|----------|
| Total NHS and PPS costs (over one year) | 6779.8 (112.0)         | 6757.2 (147.7)    | 22.4 (-410.0, 454.9)      | 0.908    |
| Primary hospital stay (excluding intervention & opioid costs) | 5738.8 (87.3)          | 5786.4 (100.2)    | -47.6 (-290.1, 194.9)     | 0.700    |
| Intervention¹                          | 224.6 (3.8)            | 0.0 (0.0)         | 224.6 (211.6, 237.6)      | <0.001   |
| Opioids                                | 3.2 (0.2)              | 3.0 (0.2)         | 0.2 (-0.1, 0.5)           | 0.262    |
| All hospital readmissions              | 89.3 (31.8)            | 118.7 (51.3)      | -29.5 (-146.1, 87.1)      | 0.577    |
| Primary care (NHS)                     | 658.5 (43.4)           | 718.6 (44.6)      | -60.1 (-193.0, 72.8)      | 0.310    |
| Equipment (NHS)                        | 12.9 (1.4)             | 14.2 (1.9)        | -1.3 (-6.0, 3.4)          | 0.502    |
| Prescribed medication for knee         | 43.8 (4.4)             | 36.9 (4.4)        | 7.0 (-6.7, 20.6)          | 0.269    |
| Personal social services               | 8.6 (5.1)              | 79.4 (38.3)       | -70.8 (-147.1, 5.5)       | 0.064    |
| Total non-NHS costs (over one year)    | 1068.1 (195.1)         | 1012.1 (198.6)    | 56.0 (-515.4, 627.3)      | 0.817    |
| Healthcare resource use (private)      | 58.8 (14.6)            | 53.7 (14.0)       | 5.1 (-35.1, 45.2)         | 0.775    |
| Equipment (private)                    | 121.1 (41.6)           | 79.4 (37.8)       | 41.7 (-66.7, 150.2)       | 0.374    |
| Over the counter medication for knee   | 10.4 (3.6)             | 4.5 (1.0)         | 5.9 (-3.4, 15.1)          | 0.181    |
| Other medication                       | 76.7 (12.8)            | 66.8 (9.2)        | 9.9 (-20.0, 39.7)         | 0.461    |
| Travel costs                           | 23.3 (3.6)             | 27.8 (3.4)        | -4.5 (-17.7, 8.8)         | 0.460    |
| Informal care                          | 618.5 (176.4)          | 648.2 (184.8)     | -29.8 (-572.0, 512.4)     | 0.899    |
| Productivity loss                      | 159.4 (53.6)           | 131.7 (41.6)      | 27.7 (-88.1, 143.5)       | 0.549    |
| Societal costs (over one year)         | 7847.9 (227.5)         | 7769.3 (256.4)    | 78.4 (-690.5, 847.3)      | 0.816    |

Note: missing baseline values mean imputed
Note: treatment effects obtained from linear regression model adjusted for type of surgery performed (total vs. partial knee replacement) and baseline values (where available); robust standard errors were used to account for clustering by site.

*sum of NHS and non-NHS cost
Table 25. Life-Years, Quality-Adjusted Life-Years, Health Care Costs, and Cost-effectiveness for the Base-Case Analysis at 1 Year Following Multiple Imputation

|                              | Intervention Mean (SE) | Control Mean (SE) | Difference (Intervention vs control) Mean difference (95% CI) |
|------------------------------|------------------------|------------------|---------------------------------------------------------------|
| N                            | 267                    | 266              | -                                                             |
| Life-years¹                  | 1.0 (0.0)              | 1.0 (0.0)        | 0.0 (0.0, 0.0)                                                |
| QALYs²                       | 0.689 (0.187)          | 0.698 (0.164)    | -0.005 (-0.048, 0.038)                                        |
| Total NHS & PSS costs (including intervention)* | £6779.8 (112.0)       | £6757.2 (147.7)  | £22.4 (-410.0, 454.9)                                         |
| LB drug costs*               | £224.6 (3.8)           | £0.0 (0.0)       | £224.6 (211.6, 237.6)                                         |
| Total non-NHS costs*         | £1068.1 (195.1)        | £1012.1 (198.6)  | £56.0 (-515.4, 627.3)                                         |
| Total societal costs*        | £7847.9 (227.5)        | £7769.3 (256.4)  | £78.4 (-690.5, 847.3)                                         |

Incremental cost-effectiveness ratios (ICER)**

|                              |                        |                  | Dominated*                                                   |
|------------------------------|------------------------|------------------|--------------------------------------------------------------|
| Total NHS & PSS costs        | -                      | -                | Dominated*                                                   |
| Total societal costs          |                        |                  | Dominated*                                                   |
| Probability of cost-effectiveness at willingness to pay threshold of £20,000 per QALY (NHS & PSS perspective) | -                      | -                | 37%                                                          |

¹All but three participants in the intervention arm who died prior to the one-year follow-up were followed up for one year. Means and SD are provided.
²Differences derived from linear regression model of each treatment allocation against each outcome adjusted for recruitment site and, for QALYs, baseline utility score.
³Dominated: Intervention is less effective but more costly than control.
⁴Differences derived unadjusted linear regression models.
Abbreviations: CI—confidence interval; PSS—personal and social services; QALY—quality adjusted life year; SE—standard error
eTable 26. Total NHS and PSS Costs (Including Intervention) in US Dollars

|                          | Original prices (£) | GDP PPPs** 2019 (x1.45) | Health PPPs** 2017 (x1.33) | Exchange rate** 2019 (x1.28) |
|--------------------------|---------------------|--------------------------|---------------------------|-----------------------------|
| **Intervention, mean (SE)** | £6779.8 (112.0)     | $9830.7 (162.4)          | $9017.1 (149.0)           | $8678.1 (143.4)             |
| **Control, mean (SE)**    | £6757.2 (147.7)     | $9797.9 (214.2)          | $8987.1 (196.4)           | $8649.2 (189.1)             |
| **Mean difference*, 95% CI** | £22.4 (-410.0, 454.9) | $32.5 (-594.5, 659.6)   | $29.8 (-545.3, 605.0)    | $28.7 (-524.8, 582.3)      |

*Differences derived unadjusted linear regression models.

**PPPs and exchange rate obtained from OECD

Abbreviations: CI – confidence interval; PSS – personal and social services; SE – standard error
eTable 27. Previous RCT Comparing 266-mg Liposomal Bupivacaine Against Periarticular Infiltration With Local Anesthetic

| Author          | NCT number      | Intervention/Control (n) | Intervention | Control | Pain Assessment                           | Opioid Assessment                                                                 | Post Operative Routine Opioids | Mean cumulative inpatient opioid mg (SD): Intervention | Mean cumulative inpatient opioid mg (SD): Control |
|-----------------|-----------------|--------------------------|--------------|---------|-------------------------------------------|----------------------------------------------------------------------------------|-------------------------------|-------------------------------------------------------|-----------------------------------------------|
| Bramlett 2012   | NCT00485693     | 25/35                    | 266mg LB     | 150mg BHCl | No difference                             | No difference                                                                  | No                            | NS                                                     | NS                                             |
| Schroer 2015    | Not stated      | 58/53                    | 266mg LB + 75mg BHCl | 150mg BHCl | No difference                             | No difference                                                                  | Yes                           | 52 (32)                                               | 54 (33)                                       |
| Jain 2016       | Not stated      | 63/62                    | 266mg LB     | 75mg BHCl | No difference                             | No difference                                                                  | Yes                           | NS                                                     | NS                                             |
| Schwarzkopf 2016| Not stated      | 20/18                    | 266mg LB + 100mg BHCl | 250mg RHCl | No difference                             | Yes                                                                            | NS                            | NS                                                     | NS                                             |
| Collis 2016     | Not stated      | 54/51                    | 266mg LB     | 250mg RHCl | No difference                             | No difference                                                                  | Yes                           | NS                                                     | NS                                             |
| Snyder 2016     | NCT02299349     | 35/35                    | 266mg LB     | 400mg RHCl | Lower pain VAS with LB (PACU, d1, d2)     | Lower mean opioid with LB (PACU, d3)                                           | Not stated                    | NS                                                     | NS                                             |
| Barrington 2017 | Not stated      | 40/38                    | 266mg LB + 125mg BHCl | 250mg RHCl | Lower pain VAS with LB (6h, 12h)          | No difference                                                                  | No                            | 71 (93)                                               | 75 (85)                                       |
| DeClaire 2017   | NCT02808728     | 47/49                    | 266mg LB + BHCl | RHCl     | No difference                             | No difference                                                                  | Not stated                    | 98 (43)                                               | 90 (59)                                       |
| Amundson 2017   | NCT02223364     | 55/55                    | 266mg LB + 125mg BHCl | 200mg - 400mg Ropivacaine | No difference                             | No difference                                                                  | Yes                           | NS                                                     | NS                                             |
| Alijanipour 2017| NCT02060591     | 87/75                    | 266mg LD     | 50mg BHCl    | No difference                             | No difference                                                                  | No                            | 110(50-185)\(^2\)                                   | 90(45-180)\(^2\)                             |
| clinicaltrials.gov 2017 | NCT02682498 | 18/20                     | 266mg LB     | 250mg RHCl | No difference                             | No difference                                                                  | Not stated                    | NS                                                     | NS                                             |
| Mont 2018       | NCT02713490     | 70/69                    | 266mg LB + 100mg BHCl | 100mg BHCl | Lower pain VAS AUC with LB (12 to 48)  | Lower cumulative opioid with LB (0 to 48)                                      | No                            | 21 (9)\(^3\)                                        | 94 (39)\(^3\)                                 |
| Suarez 2018     | Not stated      | 52/52                    | 266mg LB + 75mg BHCl | 75mg BHCl | No difference                             | Higher mean opioid with LB (d1)                                                | No                            | NS                                                     | NS                                             |

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| Study               | Duration | Dose 1 | Dose 2 | Comparator | Pain Outcome | Statistic 1 | Statistic 2 |
|---------------------|----------|--------|--------|------------|--------------|-------------|-------------|
| Schumer 2018       | Not stated | 67/64  | 266mg LB + BHCl | BHCl       | No difference | No difference | Yes         | NS          | NS          |
| Zlotnicki 2018      | Not stated | 38/40  | 266mg LB | 100mg BHCl | Lower pain VAS with LB (d1) | No difference | Yes         | NS          | NS          |
| Hyland 2019         | Not stated | 30/29  | 266mg LB | 40mg RHCl  | No difference | No difference | Yes         | 275 (121)   | 305 (143)   |
| clinicaltrials.gov 2019 | NCT02543801 | 59/59  | 266mg LB | RHCl       | No difference | No difference | Not stated  | 52 (28)\(^4\) | 50 (22)\(^4\) |

\(^1\) Oral Morphine Equivalent  \(^2\) Median (IQR)  \(^3\) 0 to 72 hours  \(^4\) 0 to 48 hours
eFigure 1. Forest Plot Showing the Treatment Effect of the Intervention vs Control Based on the QoR-40 Coprimary Outcome Between Recruitment Sites
A pattern-mixture model is used to extend a linear regression allowing for a clustering effect for recruitment site. Model is further adjusted for type of surgery (TKR vs UKR), baseline QoR-40 scores, participant age at randomisation and gender.
Scatter plot of estimated joint density of incremental costs and QALYs of LB relative to control obtained by bootstrap re-sampling from each of the 30 imputed datasets, running the regression models on each bootstrapped dataset and extracting the estimated incremental costs and QALYs. The dashed line indicates the willingness to pay threshold at £20,000 per QALY gained. Bootstrapped results falling below this line are deemed cost-effective. From the bootstrapped results, we calculated the probability that LB was more cost-effective than control for different threshold values per QALY gained. 

Abbreviations: PSS – personal and social services; QALY – quality adjusted life year
Figure 4. Cost-effectiveness Acceptability Curve for the NHS and Personal and Social Services Perspective and the Societal Perspective for the Base Case Analysis (Imputed Data)

Figure plots the probability (y-axis) that LB intervention is cost-effective compared to control for different willingness to pay thresholds per QALY gain (x-axis). Probability captures the joint uncertainty in incremental costs and QALYs of LB compared to control and was obtained by estimating the proportion of bootstrapped results that were cost-effective for each threshold value. The interpretation is that, given a willingness to pay threshold of £20,000 per QALY gained, the probability that LB is cost-effective compared to control is 0.37 and from a NHS&PSS and a societal perspective, respectively. 

Abbreviations: LB - liposomal bupivacaine; PSS – personal and social services; QALY – quality adjusted life year

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