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ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness Analysis of a Medial Meniscus Replacement Prosthesis for the Treatment of Patients with Medial Compartment Pain in the United Kingdom

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Abstract

Background The most common intra-articular knee injury is a meniscal tear, which commonly occurs secondary to trauma following twisting or hyperflexion. Treatment options for meniscal tears can either be surgical or non-surgical, and range from rest, exercise, bracing and physical therapy to surgical intervention, including meniscal repair and partial meniscectomy. In patients with persistent pain following loss of meniscus tissue, treatment can include partial replacement or meniscal allograft transplantation. The NUsurface® prosthesis has been developed as a treatment option for patients experiencing persistent knee pain post medial meniscus (MM) surgery.

Objective The aim of this study was to assess the cost effectiveness of MM replacement using NUsurface for the treatment of patients with medial compartment pain following previous partial medial meniscectomy, from a UK health service perspective.

Methods An economic decision-analytic model was developed to assess the cost per quality-adjusted life-year (QALY) gained associated with the introduction of MM replacement using NUsurface compared with non-surgical standard of care, over a lifetime time horizon. The model structure was primarily informed by a previous clinical trial (VENUS) and was developed based on the clinical pathways typically followed by patients with this condition, with treatment pathways and probabilities of clinical progression adjusted depending on whether patients were receiving the intervention or undergoing current practice. A hypothetical cohort of adult patients (mean age of 50 years) was modelled, with clinical data sourced from the VENUS study as well as relevant UK literature. Both deterministic and probabilistic sensitivity analyses were carried out to explore uncertainty in the model results.

Results The base-case probabilistic results indicate that MM replacement using NUsurface is likely to be cost effective across a range of willingness-to-pay (WTP) thresholds (95% probability of being cost effective at the National Institute for Health and Care Excellence (NICE)-recommended £20,000 WTP threshold). Although per-patient costs increase, QALYs are also gained, with the incremental cost per QALY (probabilistic value = £5011) being below £20,000. Deterministic sensitivity analyses indicate that the parameters that have the greatest impact on results are the failure rate in the control group (current practice), utility scores, and the cost of undergoing MM replacement using NUsurface.

Conclusions Based on the analysis presented, MM replacement with the NUsurface prosthetic implant is likely to be a cost-effective use of UK health care service resources compared with current standard care.

1 Introduction

The meniscus is an integral structure within the knee that functions as a load distribution device. Due to the high loads experienced, the meniscus is commonly damaged; in fact, the most common intra-articular knee injury is a meniscal tear, which often occurs due to trauma caused by twisting or hyperflexion of the knee. Traumatic meniscal tears are common in young, active sportspeople following a compression and rotation injury, but meniscal tears can occur at any age, resulting from low-velocity injury, particularly in a middle-aged patient, with activities such as squatting or twisting [1, 2]. A meniscal tear has a number of associated signs and symptoms [3]. A popping sound around the knee joint is the most common early symptom of a tear.

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Key Points for Decision Makers

The NUsurface® prosthesis has been developed to act as a synthetic medial meniscus (MM) replacement in patients experiencing persistent knee pain post MM surgery. This study aimed to explore the cost effectiveness of use of the device in a UK setting, based on its potential to reduce costs for the health care system by delaying the need to progress to knee replacement surgery and improve patient outcomes.

Economic modelling results indicate that introduction of the device leads to an incremental cost per quality-adjusted life-year gained of £5011, and that it has a 95% probability of being cost effective at a £20,000 WTP threshold. In sensitivity analysis, the parameters found to be most impactful on model results were the cost of the device, the failure rate in the control group, the probability of requiring a replacement, and the utility scores of patients in the intervention and control groups.

A robust cost-effectiveness analysis has been performed to demonstrate the potential benefits of the device in a UK setting. Future economic analyses may utilize longer-term clinical evidence on the safety and efficacy of NUsurface from an ongoing, single-arm clinical trial.

Subsequently, common symptoms include effusion, pain, difficulty in straightening the knee or locking, and a feeling of instability or giving way when placed under pressure [4]. Similarly, patients learn avoidance behaviour to protect their damaged meniscus. Meniscal tears have a mean annual incidence of between 60 and 70 people per 100,000 and occur more frequently in males than in females (male-to-female ratio ranging from 2.5:1 to 4:1) [5]. This is likely due to the increased participation of males in activities that are associated risk factors for this type of injury [6]. In England and Wales, meniscal tears are responsible for an estimated 25,000 hospital admissions per year and are associated with a high annual cost [7].

A torn meniscus is typically identified through history and physical examination, with a magnetic resonance imaging study being the best method of detecting and characterizing a tear due to its ability to produce detailed images of both hard and soft tissue within the knee [8, 9]. A meniscal tear can either be treated surgically or non-surgically, with patient management often guided by individual patient characteristics such as age, expectations, activity level, lifestyle, health status, and factors related to the injury itself, such as location, type, and tissue quality [3]. The purpose of both surgical and non-surgical management is to reduce pain, increase function, improve stability, and prevent future damage of the knee [10]. Conservative management will typically involve recommendations to rest the injury, apply ice, compression (with a knee brace, or splint if necessary), and/or exercise and physical therapy to strengthen the affected leg [11]. Lifestyle modification is also often advised with weight reduction and avoidance of aggravating factors. Patients may also be advised to take analgesics, anti-inflammatory medication and/or intra-articular injections, e.g., corticosteroid to manage the associated pain, if required. However, the use of intra-articular corticosteroid injections for pain management has come under scrutiny of late [12, 13], with recent studies indicating that such treatments may not provide long-term pain relief and may have an adverse effect on the cartilage [13].

Where surgical intervention for meniscus dysfunction or injury is required, four main methods are used: meniscal repair (i.e. suturing), meniscectomy (i.e. resection), meniscal scaffold (i.e. resection with suturing in a biodegradable/resorbable scaffold), and meniscal allograft transplant (i.e. total replacement with cadaveric tissue) [3]. Meniscal repair surgery (i.e. suturing) is the most preserving procedure and is conducted when a tear is surgically repairable to prevent progressive arthrosis and long-term functional decline [14]. Subsequent procedures are progressively more destructive to native tissue. In cases where the meniscus cannot be repaired and the patient is not a viable candidate for a successful meniscal scaffold or allograft transplant, the current standard practice is partial meniscectomy. Partial meniscectomy results in changes to the balance of load-bearing in the knee and increasing the load on the articular cartilage [15], predisposing the patient to accelerated cartilage breakdown and osteoarthritis [16]. Partial meniscectomy continues to be a debatable topic in the treatment continuum among older patients as recent studies appear to indicate inconclusive observed differences in outcomes between non-operative treatment and partial meniscectomy in this population [15, 17]. Additionally, a recent consensus statement by the British Association of Surgery for the Knee (BASK) Meniscal Working Group, developed using a modified Delphi process, indicates that the presence of a 'target lesion' such as a displaced flap tear forms the basis of how to select patients for partial meniscectomy, with a focus on removing the mechanical symptoms [18]. Furthermore, clinical studies have also indicated that some patients undergoing arthroscopic resection continue to experience pain, which has a detrimental impact on a patient's quality of life (QoL) [19]. Patients unresponsive to these surgical interventions may ultimately undergo reconstructive techniques such as meniscal scaffolds or allografts, osteotomy (tibial or femoral) or knee replacement to relieve symptoms [19].

Given the limitations associated with existing treatments, there is a clinical need to fill the treatment gap between

arthroscopic meniscal resection and the invasive, end-of-line surgical interventions. The NUsurface® prosthesis (Active Implants LLC, Memphis, TN, USA) has been developed to act as a synthetic medial meniscus (MM) replacement in patients experiencing persistent knee pain post MM surgery [20, 21]. The prosthesis does not require fixation to bone or soft tissue due to its polymer construction material and design. The prosthesis mimics the function of the natural meniscus by redistributing loads transmitted across the knee joint, thereby offering a treatment option between minimally invasive meniscus surgeries and total knee replacement [22–26]. Existing treatment guidelines related to patient management post-resection are weak, however the study by Zaslav et al. has shown the potential for treatment of post-meniscectomy knee symptoms to result in improved patient outcomes [27]. Therefore, this study aims to assess the potential for this novel technique to reduce costs for the health care system by delaying the need to progress to a knee replacement surgery and improve patient outcomes in terms of pain, function, and activities of daily living. In order to explore these economic and clinical implications, we performed a model-based economic evaluation to estimate the cost effectiveness of introducing the MM replacement prosthesis as a treatment option for patients in the UK suffering from medial compartment pain following prior partial meniscectomy.

2 Methods

An economic decision-analytic model was developed to estimate the costs and effectiveness associated with introducing the MM replacement prosthesis into clinical practice for the treatment of patients following prior partial meniscectomy compared with current practice. The current treatment pathways for this patient population and the impact that introducing the intervention would have on the treatment pathways were used as a basis for developing the model structure. Existing clinical guidelines and potential clinical outcomes associated with the intervention were used as a basis for developing the model [28].

Data from the Verifying the Effectiveness of the NUsurface® System (VENUS; ClinicalTrials.gov identifier: NCT02108496) randomized clinical trial, with a 2-year follow-up period, were used as key inputs in informing the effectiveness of the intervention [2, 27]. The trial was also a key source of information in designing the model-based analysis. VENUS was a multi-centred, prospective, randomized, interventional, superiority study in which patients with persistent knee pain following one or more previous partial meniscectomies were randomized to receive either NUsurface or were treated with the non-surgical standard of care. As outlined in the study, existing treatment options are limited (non-surgical treatment options include intra-articular injections of hyaluronic acid and/or corticosteroids; prescription and/or non-prescription oral medications; physical therapy; bracing; etc.) and clinical practice guidelines are weak. The study assessed pain and functional outcomes (knee injury and osteoarthritis outcome score [KOOS] pain and overall) as well as device-related complications at regular follow-up points and was used as a key source of data in populating the model base-case, i.e., use of MM replacement prosthesis. The impact of both treatment strategies on progression to end-stage surgical intervention with replacement, adverse event rate, and QoL were used as a basis for calculating the costs and health outcomes associated with each strategy over the time horizon of the cost-effectiveness analysis. The face validity of the model was confirmed by orthopaedic surgeons involved in this analysis of the investigational device (MS, JM, TS).

The population in the model was a hypothetical cohort of adult patients (mean age of 50 years, based on data from the VENUS randomized clinical trial [27]) who have experienced a meniscal tear, have undergone medial partial meniscectomy 6 months previously (or longer), and are experiencing persistent medial compartment pain and are requesting further treatment. The National Institute for Health and Care Excellence (NICE) in the UK recommends that the time horizon of an economic analysis should be long enough to sufficiently capture all differences in costs and benefits between interventions [29], therefore a lifetime time horizon was used. For costs and benefits occurring after the first year of the model, the UK-recommended discount rate of 3.5% was applied [29]. All costs in the model were considered from a UK National Health Service (NHS) and personal social services (PSS) perspective, and the model was developed in Microsoft Excel (Microsoft Corporation, Armonk, NY, USA). An overview of the model structure is presented in the next section, followed by a detailed overview of all input parameters used in the model.

2.1 Model Overview

A Markov model was developed, consisting of 10 independent health states {post index procedure, post revision surgery, post replacement, post replacement and revision, post removal, post removal and revision, post knee replacement [unicompartmental or partial knee replacement (UKR)/total knee replacement (TKR)], post first UKR/TKR revision, post second UKR/TKR revision and death}. A cycle length of 6 months was applied on the basis of the timing of outcomes reported in the VENUS trial and based on input from clinical experts involved in this research study (MS, JM, TS) [27].

Based on data from the VENUS randomized controlled clinical trial [27], the model included all patients who had

undergone a partial meniscectomy ≥6 months prior to enrolment and were randomized to either undergo non-surgical management (current practice/control arm) or to receive the MM replacement using a NUsurface prosthesis (intervention arm) to help alleviate pain and manage the condition. All patients begin in the model at a point where they are experiencing medial compartment pain following a prior partial meniscectomy procedure ('post index procedure'). Therefore, all patients will start in the 'post index procedure 6m' (6 months) health state. In the intervention arm, it was assumed that patients will undergo the implant procedure at the beginning of the model, however they also start in the 'post index procedure 6m' health state.

Data from the VENUS trial indicated that QoL changes over time following each procedure [27]. Therefore, after the first cycle, patients transit to the 'post index procedure 12m' health state and a different QoL weight is applied. This will be continued until they move to the post index procedure > 24 m health state. Given the impact of any knee surgical treatment on patient QoL, we have assumed that if patients have any surgical treatment, they move back to the initial post-surgical health states, i.e., health states at 6 months. Therefore, if a patient receives an additional surgical treatment within 6 months following a surgical treatment, the patient will remain in the same health state. In the control arm, patients could have a surgery at any time, which would either be a UKR/TKR or non-UKR/TKR surgery; in this event, they will either transit to the post UKR/TKR or post revision 6m health state. Similarly, patients in the intervention arm may need an unplanned arthroscopy or replacement or removal, in which case they will transit to the corresponding health state. Following a device replacement, if patients need an unplanned arthroscopy, he/she will transit to the post replace-revision 6m health state. This enables an estimation of the number of replacements that patients have received.

In any cycle of the model, patients undergoing either strategy can experience what is defined as 'failure', meaning that they progress to subsequent surgical treatment (current practice arm) or undergo a device removal of the prosthesis (intervention arm). In the current practice arm of the model, subsequent surgeries included arthroscopy, tibial osteotomy, osteochondral allograft, and other surgeries except knee replacement. In this event, patients would progress to the 'post revision surgery' health state. Patients will then either remain in this health state over time, progress to a unicompartmental or total knee replacement at any point ('post total or partial knee replacement [TKR or UKR]'), die ('death') or undergo further surgery, in which case they would return to the starting point of the 'post revision surgery' health state. If patients progress to the knee replacement health state, the possibility of undergoing three knee replacements in total (i.e., initial surgery and two subsequent revisions, if required) is modelled, in view of the initial mean age of 50 years at the start of this model.

In the intervention arm of the model, patients experiencing 'failure' progress to the 'post removal' health state since removal of the device in the intervention arm constitutes a clinical trial failure. If patients experience an unplanned arthroscopy, they move to the 'post revision surgery' health state. In the intervention arm, the possibilities of requiring a replacement procedure ('post replace'), requiring a replacement in combination with an unplanned arthroscopy ('post replace and revision') and the possibility of undergoing a removal in combination with any one of the surgical interventions outlined previously ('post removal and revision') are also modelled. Patients in these health states can progress back and forth between health states over the model time horizon, unless they are in one of the 'post removal' health states, in which case patients will have had the prosthesis removed and cannot undergo a subsequent replacement. As in the current practice arm, patients may progress to the 'post total or partial knee replacement (TKR or UKR)' health state, or to the post removal-revision health state or die at any point. Therefore, the probability of death from other causes in each cycle is also modelled.

In addition to the core treatment pathways that were modelled and described above, the probabilities of experiencing a range of clinical complications associated with each treatment strategy were also considered. These will be described in further detail in the next section. An outline of the model structure is presented in Fig. 1.

2.2 Model Inputs

All inputs included in the model are presented in the following section. Where appropriate, distributions were assigned to model parameter values to allow for a probabilistic analysis to be carried out.

2.2.1 Clinical Effectiveness Parameters

The clinical effectiveness of each treatment strategy was based on the progression or non-progression of patients to subsequent surgical treatment, and knee replacement procedures if required. As described previously, progression from the initial health state to surgical treatment/device removal in each arm of the model ended therapy and was defined as a 'failure'. The 6-monthly failure rates associated with MM replacement using the NUsurface prosthesis and the conventional treatment strategy were derived from the VENUS clinical trial [27] (up to 24 months based on the 2-year follow-up duration of the trial). In order to understand details around 'time to events', i.e., time to failure and longer-term outcomes, parametric survival analyses were undertaken, the methods of which are outlined in Sect. 2.2.2.

The potential surgical treatments that patients in either arm of the model could progress to are outlined in Sect. 2.1. The percentage of patients requiring knee replacement (arthroplasty) on a yearly basis, in each arm of the model, were derived from a previous systematic review [30] and from the VENUS clinical trial [27]. The annual failure rate associated with a knee replacement arthroplasty (i.e., reoperation/revision) was derived from a previous clinical study comparing medial versus lateral arthroscopic partial meniscectomy on stable knees [31] and a cost-effectiveness analysis of meniscal repair versus partial meniscectomy [32], with this rate declining over time. Failure rates associated with a revision knee arthroplasty procedure were derived from the same two studies. Clinical probabilities of events related to the prosthesis were considered in the model and these included repositioning of the prosthesis, replacement of the prosthetic implant, unplanned arthroscopy, and deep vein thrombosis. The 6-monthly probabilities of each event were derived from the VENUS clinical trial [27]. Complications associated with surgical procedures, including arthroscopy, arthroplasty and high tibial osteotomy, were also considered in the model and are presented in Table 1.

2.2.2 Parametric Survival Analysis

Parametric survival analyses were conducted to explore the 'failure' rate for patients undergoing current practice and for those receiving the intervention, i.e., probability of progressing to surgical treatment at different time points in the model. For the intervention arm, these analyses were carried out to estimate the probability of undergoing device removal, repositioning, replacement, unplanned arthroscopy, and progression to knee replacement health states at different time points in the model. These recognized techniques involve exploring the relationship between the survival of a patient, a distribution, and explanatory variables to estimate the probability of an event occurring over a defined time horizon.

Failure in the control group is defined as having any surgical intervention (except arthroplasty). The surgical interventions include arthroscopy, tibial osteotomy, osteochondral allograft, and posterolateral compartment reconstruction. Failure in the intervention arm is defined as having device removal. The failure percentage is the likelihood of having surgical treatment in each cycle, which was estimated in the parametric survival analysis utilizing data from the VENUS clinical trial [27] and was applied until the patient transitions to the arthroplasty health states.

Multiple different hazard functions were sampled for failure in the control group based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values, and the exponential distribution was the best fit; therefore the transition probability is constant over time. This assumption was confirmed by the clinicians involved in this research study (MS, JM, TS), who agreed that the patterns were clinically plausible. The parametric survival models were all conducted based on the NICE Decision Support Unit (DSU) recommendations for conducting survival analysis. Due to

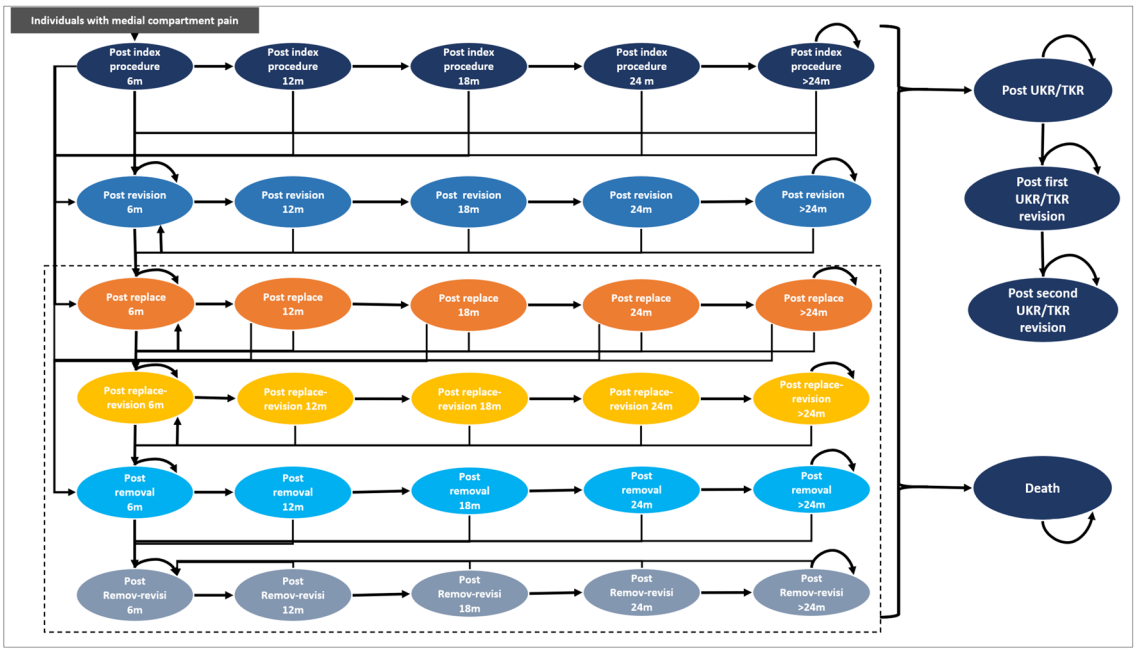

Fig. 1 Structure of the decision-analytic model (dashed section applies to the intervention arm only). *Remov-revisi* performing revision surgeries post removal, *TKR* total knee replacement, *UKR* unicompartmental knee replacement

the nature of the intervention (NUsurface) and treatment pathway in the control group, as well as post-implant outcomes (removal, replacement, repositioning), we could not define identical failure or events that apply to both treatment arms; therefore, individual survival curves were fitted. This method provides the most robust estimates of long-term pattern and probabilities of events over the long-term.

In electronic supplementary material (ESM) Appendix 1, details of each parametric survival analysis conducted, which include the selected distribution and figures representing patient survival, are presented.

2.2.3 Utilities

The health state utility values associated with being in the post index procedure health state, i.e., post partial meniscectomy, at different time points were derived from the VENUS clinical trial [27]. The UK-based value set was used to convert the five-digit EQ-5D-3L codes to utility scores. These values differed depending on whether or not the patient received the intervention, with the utility value typically being higher in the intervention arm at the different time points. The health state utility values before and following a total knee replacement were derived from research conducted by the NHS into patient-reported outcome measures for hip and knee replacement procedures in England [33]. These values were the same in both the intervention and control arms of the model. The complications that were modelled were assumed not to incur disutilities, as the utility decrements associated with complications were implicitly captured in the utility values used in the model. All utility values included in the model are presented in Table 1.

2.2.4 Costs

All costs were estimated in UK pound sterling (£) for the 2020 price year. Where costs were derived from a source prior to 2020, they were inflated accordingly using the Personal Social Services Research Unit (PSSRU) inflation indices [34]. Costs included in the model were the initial cost of the procedure, the device cost, and the number of affected knees. These data were derived from the manufacturer of the intervention [21], as well as the NHS reference costs [35]. The non-surgical cost of managing pain for patients with the condition was included for each strategy in the model, with this cost based on a range of different resources required and the resource use rate. A relative risk was assigned to calculate the probability of patients in the intervention arm requiring the specified resources, and therefore a differing pain management cost was calculated for patients receiving the prosthesis. This relative risk was derived from a previous study looking at knee pain and osteoarthritis in the general population and the factors that influence patients to consult [36]. These costs included items such as primary and secondary health care utilization (general practitioner [GP], practice nurse, physiotherapist, NHS consultant, knee-related investigations); non-pharmacological treatments, including physical therapy, electrotherapy, and bracing; pharmacological treatments, including over-the-counter analgesics, weak, moderate, and strong combination opioid agents (alone or in combination), non-steroidal anti-inflammatory drugs, and intra-articular corticosteroid injections. These costs were derived from a range of sources, including the NHS Reference Costs, British National Formulary and the Unit Costs of Health and Social Care [34, 35, 37]. The unit cost of each of the items included in the model was based on the overall cost of each item and the percentage of patients who would utilize that specific resource. For many of these items (including primary and secondary health care resource use and use of pharmacological treatments), the patient utilization percentages were derived from a previous cost-utility analysis focusing on interventions to improve the effectiveness of exercise therapy among adults with knee osteoarthritis [38]. For others (including non-pharmacological treatment and intra-articular injection resource use), percentages were unavailable, therefore assumptions were made based on expert clinical input, and unit costs were calculated.

Prosthesis-related and non-prosthesis-related adverse event costs were also included in the model. Adverse event costs, including the cost of deep venous thrombosis, pulmonary embolism, infection, and non-union requiring revision, were considered in the model [35, 47]. Finally, the costs associated with further surgical procedures were considered. Patients in the model had the potential to receive arthroscopy, device repositioning, device replacement, device removal, knee arthroplasty, revision knee arthroplasty, tibial osteotomy, and chondral allograft. All of the aforementioned costs were derived from the NHS reference costs [35]. All costs included in the model, as well as relevant distributions, are presented in Table 1.

2.3 Analysis

A cost-utility analysis was conducted, with the outcome of interest being the cost per quality-adjusted life-year (QALY) gained associated with the introduction of MM replacement using the NUsurface prosthesis for the treatment of patients with medial compartment pain following previous surgery. Both deterministic and probabilistic sensitivity analyses (PSA) were carried out to explore uncertainty in the model results. In the deterministic analysis, model parameter values were varied to explore the impact this had on the model output.

For the PSA, a Monte Carlo simulation was conducted to account for the uncertainty present in the model.

Table 1 Parameters included in the economic model

Variables	Mean	Distribution	Lower limit/alpha	Upper limit/beta/lambda	Source
Clinical effectiveness parameters					
Failure rate per 6 months (control arm)	7.46%	Multivariate normal	NA	NA	VENUS clinical trial [27]
Failure rate per 6 months (MM replacement using NUsurface prosthesis)	2.45%	Multivariate normal	NA	NA	VENUS clinical trial [27]
Percentage of patients who need knee arthroplasty per year (control arm)	2.62%	Beta	32.4 (alpha)	1205.0 (beta)	Winter et al., 2017 [30]
Percentage of patients who need knee arthroplasty per year (MM replacement using NUsurface prosthesis)	1.60%	Multivariate normal	NA	NA	VENUS clinical trial [27]
Failure rate of knee arthroplasty per year (years 1–4)	1.9%	Beta	15.1 (alpha)	778.3 (beta)	Feeley et al., 2016 [32]; Chatain et al., 2003 [31]
Failure rate of knee arthroplasty per year (years 5–9)	1.0%	Beta	15.2 (alpha)	1506.1 (beta)	Feeley et al., 2016 [32]; Chatain et al., 2003 [31]
Failure rate of knee arthroplasty per year (year 10)	0.9%	Beta	15.2 (alpha)	1676.8 (beta)	Feeley et al., 2016 [32]; Chatain et al., 2003 [31]
Failure rate of knee arthroplasty per year (years 11+)	0.6%	Beta	15.3 (alpha)	2530.4 (beta)	Feeley et al., 2016 [32]; Chatain et al., 2003 [31]
Failure rate of revised knee arthroplasty per year	3.0%	Beta	9.8 (alpha)	316.8 (beta)	Feeley et al., 2016 [32]; Chatain et al., 2003 [31]
Implant-related adverse events (clinical events post MM replacement using NUsurface prosthesis)					
Deep vein thrombosis rate per 6 months	1.50%	Multivariate normal	NA	NA	VENUS clinical trial [27]
Prosthesis repositioning rate per 6 months	2.43%	Multivariate normal	NA	NA	VENUS clinical trial [27]
Prosthesis replacement rate per 6 months	12.42%	Multivariate normal	NA	NA	VENUS clinical trial [27]
Unplanned arthroscopy rate per 6 months	1.73%	Multivariate normal	NA	NA	VENUS clinical trial [27]
Adverse event (clinical events post arthroscopy)					
Deep vein thrombosis rate per 6 months	0.41%	Beta	4.3 (alpha)	1029.2 (beta)	Thorlund et al., 2015 [39]
Pulmonary embolism rate per 6 months	0.08%	Beta	552.8 (alpha)	708,112.5 (beta)	Abram et al., 2018 [40]
Infection rate per 6 months	0.14%	Beta	863.2 (alpha)	638,539.1 (beta)	Abram et al., 2018 [40]
Adverse event (clinical events post arthroplasty)					
Deep vein thrombosis rate per 6 months	1.20%	Beta	6.1 (alpha)	498.6 (beta)	Bannister et al., 2010 [41]
Pulmonary embolism rate per 6 months	0.80%	Beta	3.4 (alpha)	418.6 (beta)	Bannister et al., 2010 [41]
Infection rate per 6 months	2.90%	Beta	0.4 (alpha)	11.8 (beta)	Bannister et al., 2010 [41]
Adverse event (clinical events post high tibial osteotomy)					
Deep vein thrombosis rate per 6 months	3.50%	Beta	20.2 (alpha)	556.5 (beta)	Atrey et al., 2012 [42]
Pulmonary embolism rate per 6 months	0.08%	Beta	552.8 (alpha)	708,112.5 (beta)	Abram et al., 2018 [40]
Infection rate per 6 months	3.50%	Beta	24.9 (alpha)	687.0 (beta)	Woodacre et al., 2016 [43]; Atrey et al., 2012 [42]
Non-union requiring revision rate per 6 months	4.30%	Beta	9.3 (alpha)	207.5 (beta)	Woodacre et al., 2016 [43]

Table 1 (continued)

Variables	Mean	Distribution	Lower limit/alpha	Upper limit/beta/lambda	Source
Health utility					
Post index procedure [1.5 months] (control arm)	0.69	Beta	271.10 (alpha)	120.30 (beta)	VENUS clinical trial [27]
Post index procedure [1.5 months] (MM replacement using NUsurface prosthesis)	0.61	Beta	200.50 (alpha)	129.40 (beta)	VENUS clinical trial [27]
Post index procedure [6 months] (control arm)	0.72	Beta	155.90 (alpha)	60.70 (beta)	VENUS clinical trial [27]
Post index procedure [6 months] (MM replacement using NUsurface prosthesis)	0.76	Beta	277.80 (alpha)	87.40 (beta)	VENUS clinical trial [27]
Post index procedure [12 months] (control arm)	0.78	Beta	387.40 (alpha)	110.10 (beta)	VENUS clinical trial [27]
Post index procedure [12 months] (MM replacement using NUsurface prosthesis)	0.79	Beta	170.00 (alpha)	45.40 (beta)	VENUS clinical trial [27]
Post index procedure [24 months] (control arm)	0.77	Beta	245.10 (alpha)	75.80 (beta)	VENUS clinical trial [27]
Post index procedure [24 months] (MM replacement using NUsurface prosthesis)	0.79	Beta	134.10 (alpha)	35.80 (beta)	VENUS clinical trial [27]
Post index procedure [>24 months] (control arm)	0.79	Beta	67.80 (alpha)	19.40 (beta)	VENUS clinical trial [27]
Post index procedure [>24 months] (MM replacement using NUsurface prosthesis)	0.87	Beta	125.50 (alpha)	18.70 (beta)	VENUS clinical trial [27]
Post total knee replacement (control arm)	0.77	Beta	11,635.10 (alpha)	3475.40 (beta)	NHS Digital [33]
Post total knee replacement (MM replacement using NUsurface prosthesis)	0.77	Beta	11,635.10 (alpha)	3475.40 (beta)	NHS Digital [33]
Post revision of total knee replacement (control arm)	0.63	Beta	3700.00 (alpha)	2173.00 (beta)	NHS Digital [33]
Post revision of total knee replacement (MM replacement using NUsurface prosthesis)	0.63	Beta	3700.00 (alpha)	2173.00 (beta)	NHS Digital [33]
Costs					
Prosthetic implant costs					
Cost of procedure	£1715	Normal			NHS Reference Costs [35]
Device price	£4000	Normal			Active Implants [21]
Number of knees treated	1	Fixed	NA	NA	Assumption
Health care professional visits					
GP visits, including prescription costs (primary care)	£73	Fixed	NA	NA	PSSRU [34]
Practice nurse visits (primary care)	£14	Fixed	NA	NA	PSSRU [34]
Physiotherapist visits	£67	Fixed	NA	NA	PSSRU [34]
NHS consultant visits	£123	Fixed	NA	NA	NHS reference costs [35]
Knee-related investigations and treatment	£341	Fixed	NA	NA	PSSRU [34]
Non-pharmacological treatments					
Supervised physical therapy	£804	Fixed	NA	NA	PSSRU [34]
Electrotherapy (TENS)	£35	Fixed	NA	NA	NHS reference costs [35]
Bracing	£263	Fixed	NA	NA	NHS reference costs [35]

Table 1 (continued)

Variables	Mean	Distribution	Lower limit/alpha	Upper limit/beta/lambda	Source
Pharmacological treatments					
Simple analgesics	£68	Fixed	NA	NA	British National Formulary [37]
Weak combination opioids	£92	Gamma	75.00 (alpha)	450.00 (lambda)	British National Formulary [37]
Moderate combination opioids	£68	Fixed	NA	NA	British National Formulary [37]
Strong combination opioids	£110	Fixed	NA	NA	British National Formulary [37]
NSAIDs and COX-2 inhibitors	£132	Fixed	NA	NA	British National Formulary [37]
Intra-articular injections					
Intra-articular corticosteroid injections	£43	Fixed	NA	NA	British National Formulary [37]
Intra-articular hyaluronic acid injections	£57	Fixed	NA	NA	British National Formulary [37]
Cost of surgical interventions and other treatments for complications					
Arthroscopy	£3158	Normal			NHS reference costs [35]
Prosthesis repositioning	£572	Normal			NHS reference costs [35]
Prosthesis replacement	£4572	Normal			NHS reference costs [35]
Permanent prosthetic implant removal	£572	Normal			NHS reference costs [35]
Knee arthroplasty	£6352	Normal			NHS reference costs [35]
Revision knee arthroplasty	£14,371	Normal			Mistry et al., 2019 [44]
Tibial osteotomy	£3880	Normal			NHS reference costs [35]
Chondral allograft	£16,502	Normal			Mistry et al., 2019 [44]
Meniscal allograft transplant	£8738	Normal			NHS reference costs [35]
Unicompartmental knee replacement	£6352	Normal			NHS reference costs [35]
Medial meniscectomy and autologous chondrocyte implantation	£21,497	Normal			NICE TA477 [45]
Meniscectomy medial and lateral	£3158	Normal			NHS reference costs [35]
Treatment following total knee replacement	£263	Normal			Dakin et al., 2012 [46]
Deep vein thrombosis treatment	£2438	Normal			Bamber et al., 2015 [47]
Venous thromboembolism prophylaxis following knee replacement and other surgeries	£1	Fixed	NA	NA	British National Formulary [37]
Pulmonary embolism treatment	£5306	Normal			Bamber et al., 2015 [47]
Infection treatment with further surgery and admission	£3880	Normal			NHS reference costs [35]
Non-union requiring revision	£3880	Normal			NHS reference costs [35]
Probabilities and relative risks related to resource use (annual)					
Number of patients undergoing GP visits (primary care)	0.95	Gamma	0.20 (alpha)	5.60 (beta)	Kigozi et al., 2016 [38]
Number of patients undergoing practice nurse visits (primary care)	0.13	Gamma	0.00 (alpha)	3.90 (beta)	Kigozi et al., 2016 [38]
Number of patients undergoing physiotherapist visits	0.21	Gamma	0.00 (alpha)	7.90 (beta)	Kigozi et al., 2016 [38]
Number of patients undergoing NHS consultant visits	0.70	Gamma	0.10 (alpha)	7.60 (beta)	Kigozi et al., 2016 [38]
Number of patients undergoing knee-related investigations and treatment	0.14	Beta	86.00 (alpha)	528.30 (beta)	Kigozi et al., 2016 [38]

Table 1 (continued)

Variables	Mean	Distribution	Lower limit/alpha	Upper limit/beta/lambda	Source
Percentage of patients undergoing supervised physical therapy	50.00	Beta	50.00 (alpha)	50.00 (beta)	Assumption based on expert clinical input
Percentage of patients undergoing electrotherapy (TENS)	50.00	Beta	50.00 (alpha)	50.00 (beta)	Assumption based on expert clinical input
Percentage of patients undergoing bracing	50.00	Beta	50.00 (alpha)	50.00 (beta)	Assumption based on expert clinical input
Percentage of patients undergoing simple analgesics	17.00	Beta	82.70 (alpha)	394.30 (beta)	Kigozi et al., 2016 [38]
Percentage of patients undergoing weak combination opioids	7.00	Beta	92.70 (alpha)	1171.00 (beta)	Kigozi et al., 2016 [38]
Percentage of patients undergoing moderate combination opioids	1.00	Beta	99.30 (alpha)	14,800.70 (beta)	Kigozi et al., 2016 [38]
Percentage of patients undergoing strong combination opioids	8.00	Beta	92.00 (alpha)	1058.00 (beta)	Kigozi et al., 2016 [38]
Percentage of patients undergoing NSAIDs and COX-2 inhibitors	11.00	Beta	89.30 (alpha)	748.20 (beta)	Kigozi et al., 2016 [38]
Percentage of patients undergoing intra-articular corticosteroid injections	20.00	Beta	80.00 (alpha)	320.00 (beta)	Assumption based on expert clinical input
Percentage of patients undergoing intra-articular hyaluronic acid injections	0.00	Fixed	NA	NA	Assumption based on expert clinical input
Relative risk of non-surgical resource use for pain management in the intervention arm	0.50	Beta	0.50 (alpha)	0.50 (beta)	Bedson et al., 2007 [36]

NA not available, *MM* medial meniscus, *GP* general practitioner, *NHS* National Health Service, *TENS* transcutaneous electrical nerve stimulation, *NSAIDs* non-steroidal anti-inflammatory drugs, *COX-2* cyclooxygenase 2, *PSSRU* Personal Social Services Research Unit, *NICE* National Institute for Health and Care Excellence

Distributions were assigned to model parameters, which allowed for a plausible value for each distribution to be selected when the simulation was run. A large number of iterations of the model were run (10,000) and a distribution of results from the model was produced. Probabilistic output, including cost-effectiveness acceptability curves (CEACs) and cost-effectiveness planes, were produced to display these results and are presented in the next section. The base-case analysis presents these probabilistic results to allow for uncertainty to be explored.

Several scenario analyses have also been performed to explore the impact of key model parameter variation on the cost-effectiveness results.

3 Results

This section presents the results of the economic analysis; base-case results are presented first, followed by results of the sensitivity analyses.

3.1 Base-Case Analysis

Results from the base-case probabilistic analysis, presented in Table 2, indicate that the introduction of MM replacement using the NUsurface prosthesis leads to an incremental cost per QALY gained of £5011, which is below the NICE willingness-to-pay (WTP) threshold of £20,000, indicating that the intervention is likely to be cost effective. Although average costs per patient increase (+£6589), QALYs gained per patient increase also (+1.31). Results from the probabilistic analysis are presented in Fig. 2. The cost-effectiveness plane presented in Fig. 2 shows that most iterations of the analysis result in the intervention increasing costs but also increasing benefits, while the CEAC presented in Fig. 2 indicates that the intervention has a high probability of being cost effective across all WTP thresholds presented. As shown in Table 2, at a £20,000 WTP threshold, the intervention has a 95.1% probability of being cost effective.

Table 2 Base-case probabilistic results

Base-case probabilistic results	Current practice	MM replacement using NUsurface® prosthesis
Cost (£)	32,239	38,828
Incremental cost per patient (£)	6589	
QALYs	20.46	21.77
Incremental QALYs per patient	1.31	
Incremental cost per QALY gained (£)	5011	
Probability of being cost effective at £20,000 WTP threshold	95.1%	
Probability of being cost saving	1.7%	

MM medial meniscus, *QALYs* quality-adjusted life-years, *WTP* willingness-to-pay

3.2 Sensitivity Analysis

A number of sensitivity analyses were also conducted in order to explore individual parameter variation and the impact that these variations had on the model results. The tornado diagram, shown in Fig. 3, presents the impact of 25% parameter variations (increases and decreases) on the incremental cost of the intervention (base-case value = £6,349,826). In Fig. 4, the impact of parameter variations on the net monetary benefit (NMB) of the intervention is shown (base-case value = £14,917,225). The NMB represents the value of the intervention in monetary terms and is calculated as (incremental benefit × threshold) – incremental cost. Each individual variation represents a one-way sensitivity analysis, with all other parameters in the model kept at their base-case value.

Results from Fig. 3 indicate that the parameters with the biggest impact on incremental costs were the failure rate in the control group, cost of NUsurface, and the probability of requiring a replacement. When the cost of a replacement procedure is reduced by 25%, the intervention is less cost-incurring than in the base-case analysis. Similarly, when the replacement rate is reduced by 25%, the intervention is less cost-incurring. The parameter variations with the biggest impact on NMB were the utility scores of patients beyond 24 months in the intervention and control groups, the cost of NUsurface, and the failure rate in the control group.

3.3 Scenario Analysis

Scenario analyses, with variations in the percentage of patients in each arm requiring knee arthroplasty per year, the time horizon of the analysis, and the utility of patients in the intervention arm post-24 months, have also been performed. When scenario analyses were explored by applying different assumptions about the failure rate in the intervention and control groups, the time horizon and the utility scores, the estimated ICER showed that the intervention remained cost effective in all cases, other than when the time horizon of the analysis was shortened to 5 years, where results showed an ICER of £22,022. These findings indicate that MM replacement using NUsurface prosthesis is a cost-effective intervention in almost all scenarios explored. Results of these analyses are presented in ESM Appendix 2, Table S7.

4 Discussion

Meniscal tears are widely recognized as a cause for pain and have the potential to lead to early-onset osteoarthritis [28]. One of the most common procedures used to rectify the issue, partial meniscectomy, as well as non-operative therapies, may not improve symptoms, resulting in deterioration in knee function and the potential for eventual knee replacement surgery, either partial or total [28]. Therefore, the meniscal tear is associated with high health care costs and a substantial disease burden [32]. A novel prosthetic device, the NUsurface prosthesis, developed and designed to act as an artificial meniscus for patients still experiencing pain following meniscectomy, has the potential to reduce the number of patients progressing to end-of-line treatments. In this analysis, we sought to assess the cost effectiveness of introducing this technology in the UK health care system.

Results indicate that the intervention improves QoL over the lifetime of patients and although costlier on an individual patient basis, it is a cost-effective use of NHS resources given that the incremental cost per QALY gained (£5011) is below the NICE WTP threshold of £20,000 per QALY. The base-case analysis shows an increase in QALYs of 1.31 per patient with NUsurface, with an increase in costs of £6,589. The QALY gain is driven by the difference in QoL between patients in the intervention and control arms at 6, 12, 24 and post 24 months, plus procedure-related mortality (see Table 1). Data from the VENUS trial [27] indicate that patients have a higher quality-of-life at regular follow-up time points following use of NUsurface compared with

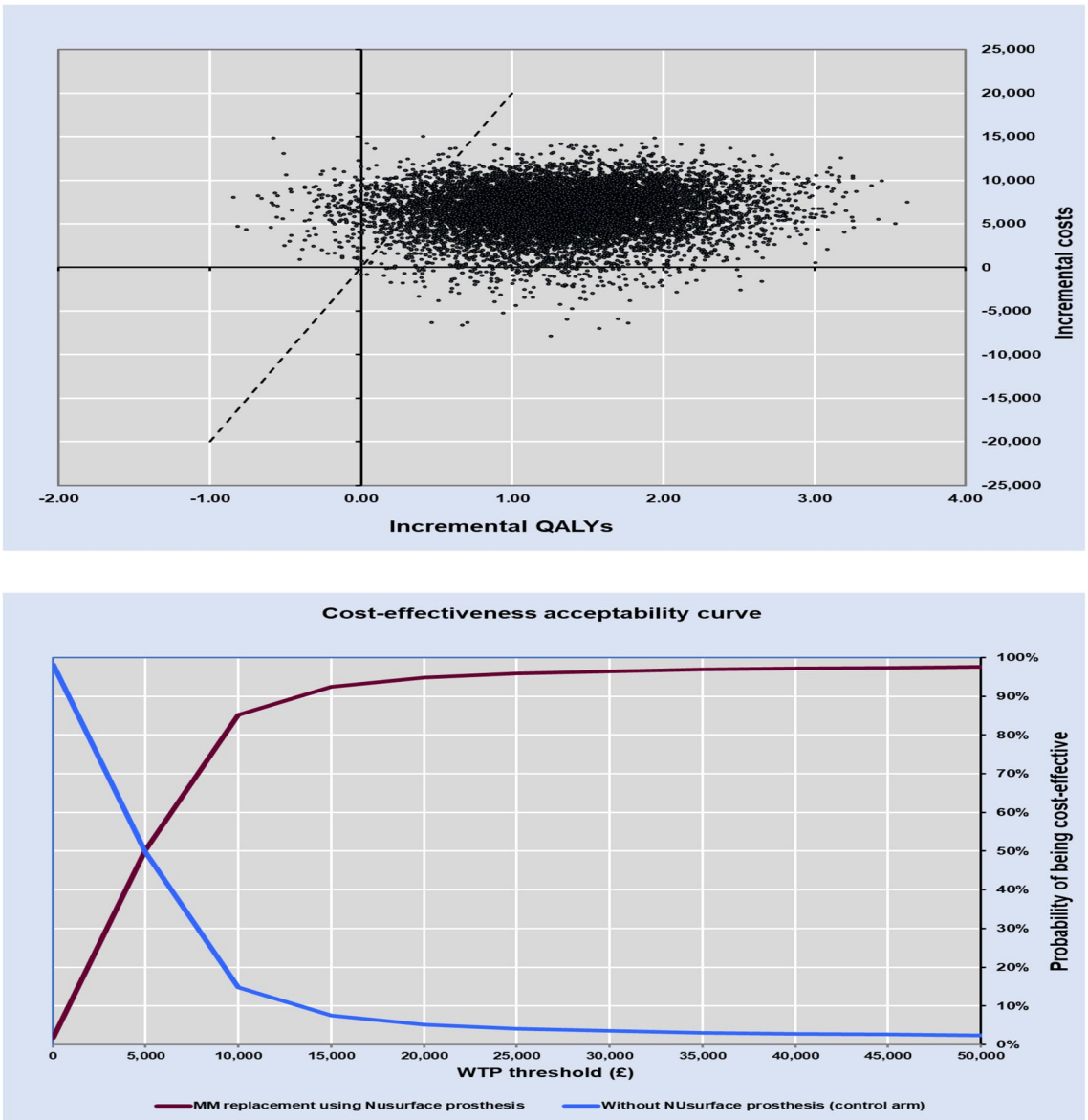

Fig. 2 **a** Scatter plot at £20,000 WTP threshold, and **b** cost-effectiveness acceptability curve at various WTP thresholds (£0–£50,000). *WTP* willingness-to-pay, *QALYs* quality-adjusted life-years, *MM* medial meniscus

use of the non-surgical standard of care. In this study, it is reported that osteoarthritis outcome scores (as measured by the KOOS) were significantly greater following use of the intervention, compared with the control group. Similarly, KOOS-assessed QoL scores were significantly greater in the intervention arm at follow-up. The higher number of surgeries among patients in the control arm, as well as associated procedure-related death (Table 1), were further drivers of this difference in QALYs over the lifetime. It is also worth noting that conservative cost estimates were used for some of the surgical procedures included in the analysis, such as meniscal allograft transplant, which led to a conservative estimate of the ICER.

Results of the analysis also indicated that in the intervention arm, the per patient cost of device replacement was higher than the initial cost of NUsurface implantation. This was due to the fact that among those retaining the device, replacement with a new device would be required on average every 3.5 years; therefore, over the long-term, the average cost per patient of replacement exceeds the average cost of the original procedure. The potential of the prosthesis to be cost effective was robust to most of the scenario analyses conducted, with the ICER only exceeding £20,000 when the time horizon of the analysis was reduced to 5 years. Shortening the duration of the analysis means that the longer-term clinical benefits associated with the intervention are

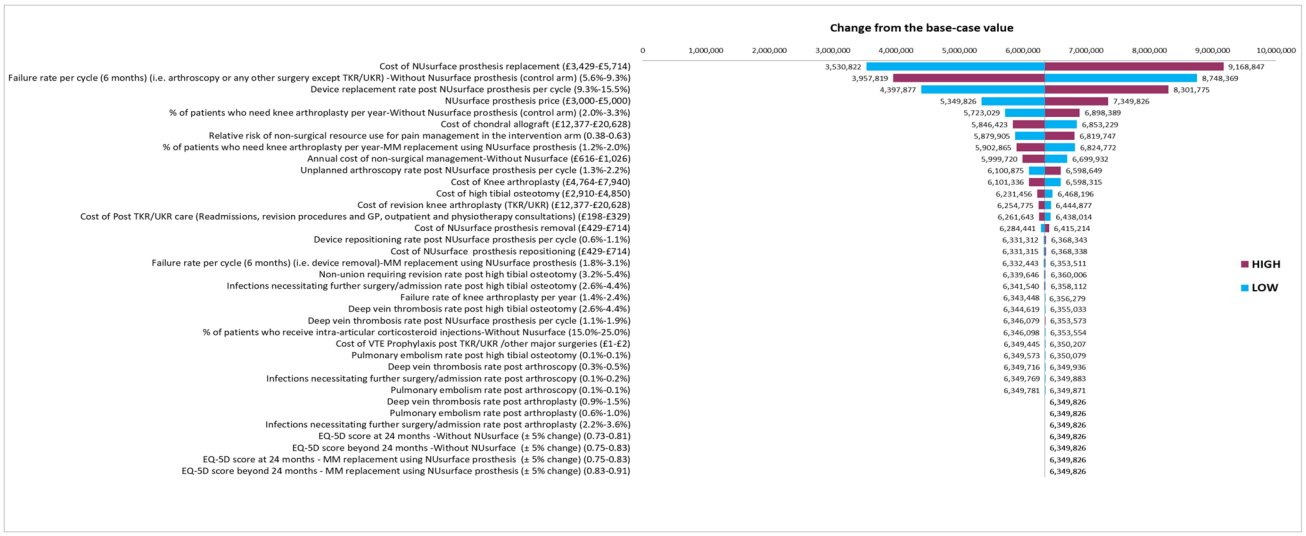

Fig. 3 Tornado diagram showing the impact of changing the input parameters by ±25% on the estimated incremental cost. *TKR* total knee replacement, *UKR* unicompartmental knee replacement, *MM* medial meniscus, *GP* general practitioner, *VTE* venous thromboembolism

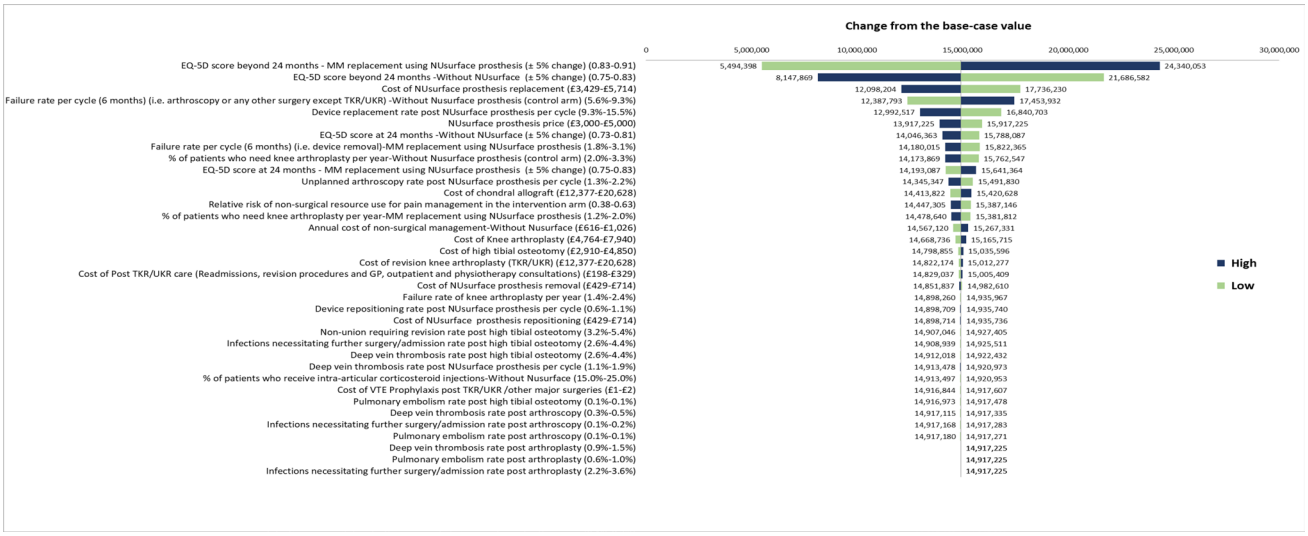

Fig. 4 Impact of changing the input parameters by ±25% on the estimated Net Monetary Benefit – EQ-5D scores are changed by ± 5%. *MM* medial meniscus, *TKR* total knee replacement, *UKR* unicompartmental knee replacement, *GP* general practitioner, *VTE* venous thromboembolism

not captured. However, the reported ICER of £22,022 from this analysis was still within the commonly accepted WTP range of £20,000–£30,000 per QALY.

Previous work has been carried out exploring the economic impact of treating meniscal tear patients with meniscectomy compared with non-surgical management. Hershman et al. carried out a single-centre, prospective, observational study over a 24-month period in the US to evaluate the direct treatment costs associated with carrying out a meniscectomy on patients compared with non-surgical treatment [48]. Based on their analysis involving 50 patients, they found that direct costs among those patients who received a meniscectomy were higher on average than among the non-surgical cohort ($4562 [SD $1151] compared with $1792 [SD $1576]) [45]. Notably, costs increased significantly among those patients who went on to have total knee arthroplasty ($32,197 [SD $169]), highlighting the sharp increase in costs for those patients who progress to end-of-line treatments. Similarly, Barnds et al. conducted a cost comparison among meniscal tear patients receiving arthroscopic partial meniscectomy and non-surgical care [49], and found that costs among those patients undergoing

meniscectomy were significantly higher ($3843 vs. $411). Findings from these studies highlight the costs associated with a meniscal tear, particularly when patients progress to total knee replacement procedures.

Not only are the costs associated with a deficient or dysfunctional meniscus significant but the long-term effectiveness of one of the most common procedures, the meniscectomy, has been questioned. Katz et al. conducted a randomized controlled trial among 351 patients with a symptomatic meniscal tear to compare the effectiveness of arthroscopic partial meniscectomy with non-surgical therapy. Their assessments at 6- and 12-month timepoints showed that there was no significant improvement in pain and functional status among those patients who underwent surgery [50]. These findings were comparable with a smaller, randomized controlled trial comparing partial meniscectomy with physical therapy among this patient population, where it was shown that the two groups had comparable functional outcomes at 6 months [51, 52]. Krych et al. also carried out a comparative study over 2 years to explore the efficacy of partial meniscectomy compared with non-surgical treatment among a group of patients with MM posterior root tears, and found that between the two groups, there was no significant difference in pain scores, failure rates or progression to arthroplasty [53]. The literature suggests that an effective treatment for patients continuing to experience pain following meniscectomy would be beneficial and could potentially result in significant cost savings for the health care service by reducing the number of patients requiring costly, end-of-line treatments.

4.1 Strength and Limitations

Most of the clinical data surrounding use of the intervention, including data on the failure rate of the intervention, the clinical complication rate for patients receiving the prosthesis, and the utility values of patients following surgical implantation, were all derived from one randomized controlled clinical trial that looked at 2-year outcomes in an evaluation of the clinical superiority of the NUsurface prosthesis to non-surgical controls [27]. Additional clinical evidence from a separate, ongoing, single-arm trial ($n = 115$) studying the safety and efficacy of MM replacement using NUsurface prosthesis through 5-year follow-up ('Safety Using NUsurface' study [SUN]; ClinicalTrials.gov identifier: NCT02483988), will be able to provide additional evidence, beyond the available 2-year randomized controlled trial evidence evaluated in this cost-effectiveness study, upon the conclusion of that trial. It is worth noting that there was an information gap related to the use and costs for some of the non-surgical care included in the base-case model that are not available from the information used to populate the model. To address these information gaps, we relied on clinical expert opinion and data from a UK-based study [38]. An additional limitation of the analysis is that given that this economic analysis was performed from the NHS and PSS perspective, treatment options such hyaluronic acid injections, which are commonly administered through private care in the UK, are not represented in the base-case model. Despite this, we believe that this robust cost-effectiveness model based on comparative 2-year randomized controlled trial data enables exploration of the intervention's potential cost effectiveness in a UK setting, in what is the first analysis of its kind. Moreover, the estimated cost per QALY is a conservative estimate due to the application of conservative cost estimates for some of the surgical procedures, such as meniscal allograft transplant.

5 Conclusions

Introduction of the NUsurface prosthesis as a treatment option for patients continuing to experience medial compartment knee pain post previous partial meniscectomy is likely to be a cost-effective use of health care resources in the UK.

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Declarations

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Conflict of interest Mehdi Javanbakht, Atefeh Mashayekhi and Eoin Moloney are employees of Optimax Access Ltd, which received funds from Device Access to conduct the study. Device Access (Mehdi Javanbakht) and Angeline Carlson received funds from Active Implants LLC during the conduct of this study. Martyn Snow, James Murray and Tim Spalding have no relevant conflicts of interest.

Author contributions MJ was responsible for developing and populating the economic model and drafting the final version of the paper. All authors provided inputs for the model, and read and approved the final draft of the manuscript.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material All data and material relevant to the analysis are presented in the outlined publication or supplementary material.

Code availability Model code may be made available following written request to the authors.

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