Appendix P: Cost-effectiveness analysis: Prophylaxis strategies for people undergoing elective total hip and elective total knee replacement surgeries

P.1 Introduction

Thrombo-prophylaxis for people admitted to hospital for elective total hip replacement (eTHR) and those admitted for elective total knee replacement (eTKR) has been prioritised for economic modelling. The committee considered the decision to offer prophylaxis for these populations and the choice of the prophylaxis strategy to have substantial economic impact; given the large size of these populations. According to the national joint registry 13th report, in 2015; there were 84,462 hip replacement operations and 94,437 knee replacement operations.[109] The large majority of these operations are elective primary total joint replacement procedures. Hence, the following two review questions were prioritised by the committee for economic modelling:

1. What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing elective hip replacement?

2. What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing elective knee replacement?

For the eTHR population, 32 economic studies, in 35 publications, relating to this review question were identified but were excluded due limited applicability, methodological limitations, a combination of limited applicability and methodological limitations or the availability of more applicable evidence.[41, 103, 104, 125, 149, 228, 234, 257, 267, 269, 352, 354, 374, 381, 587, 620-622, 638, 666, 670, 675, 677, 678, 766, 793, 797, 801, 833, 919, 921, 985, 1017, 1018, 1051] These included 3 NICE TAs, 2 evidence review group [ERG] reports and the CG92 model for standard duration and post discharge prophylaxis. Also, 10 of these publications were previously included in CG46.[41, 103, 104, 228, 234, 267, 354, 374, 587, 793]

Similarly, for the eTKR population, 30 economic studies, in 32 publications, relating to this review question were identified but were excluded due limited applicability, methodological limitations, a combination of limited applicability and methodological limitations or the availability of more applicable evidence.[41, 103, 104, 125, 149, 257, 267, 269, 352, 354, 374, 381, 587, 621, 622, 638, 666, 670, 675, 677, 678, 766, 793, 797, 801, 833, 919, 921, 985, 1017, 1018, 1051] These included the same 3 NICE TAs, 2 evidence review group [ERG] reports and the CG92 model for standard duration and post discharge prophylaxis.

The results of these economic evaluations supported the cost effectiveness of prophylaxis compared to no prophylaxis. The choice of the most cost-effective prophylaxis strategy, however, varied among these studies. Hence, the committee prioritised this area for economic modelling to assess the cost effectiveness of VTE prophylaxis strategies in eTHR and eTKR populations in England.

Methods

P.1.1 Model overview

A cost-utility analysis was undertaken to evaluate the cost effectiveness of the different thrombo-prophylaxis options for people undergoing elective hip or elective knee replacement. A two-stage modelling approach was used, where a decision tree was used to represent the acute phase (up to

90- days post-operatively) and a Markov Chain cohort model was used to represent the long-term (from 90 days post operatively up to lifetime time horizon). The model is used to calculate the lifetime quality-adjusted life years (QALYs) and costs accumulated when using each of the prophylaxis strategies. The analysis was conducted from a UK NHS and personal social services (PSS) perspective, in accordance with the NICE reference case, for interventions with a health focus[673].

P.1.1.1 Population

In line with the clinical review; the model covers two distinct populations: Adults and young people (16 years and over) admitted for eTHR and those admitted for eTKR. These populations were modelled separately due to the differences in their risk of VTE and cohort characteristics. None of the pre-specified subgroups in the clinical review protocol were considered for modelling as the results of the clinical review did not show any heterogeneity to warrant separate analysis.

P.1.1.2 Comparators

The comparators for each population were selected based on the availability of evidence from the clinical review, direct and network meta-analyses (N)MAs and discussion with the committee around which regimens are considered to be relevant to current clinical practice in the UK.

The committee considered LMWHs to be interchangeable; based on a class effect. High and low doses of the pharmacological prophylaxis options were not included in the model; while both standard and extended durations were included. Other comparators in the clinical review that were not included in the model were those that the committee did not consider to be routinely used in current practice in the UK (for example Vit K antagonists (VKAs) and routine use of unfractionated heparin (UFH). Interventions included in the model are outlined in **Table 271** below. Some interventions were not possible to include in the model as they could not be included in the NMAs; as they were not connected to the DVT and PE networks; are listed in **Table 272** below.

Table 271: Interventions included in the model by population

	Elective Total Hip Replacement (eTHR)	Elective Total Knee Replacement (eTKR)
None	No prophylaxis	No prophylaxis
Mechanical only	AES (above-knee) AES (length unspecified)	AES (length unspecified)
	IPCD (length unspecified)	IPCD (length unspecified)
	Foot pump	Foot pump
	Foot pump + AES	Foot pump + AES
Pharmacological Only	LMWH (standard dose; standard duration)	LMWH (standard dose; standard duration)
	LMWH (standard dose; extended duration)	LMWH (standard dose; extended duration)
	Dabigatran	Dabigatran
	Rivaroxaban	Rivaroxaban
	Apixaban	Apixaban
	Aspirin (standard duration)	Aspirin (standard duration)
	LMWH (standard dose, standard duration) followed by aspirin (extended duration)	
Combination- (Pharmacological +	LMWH (standard dose; standard duration) + AES	LMWH (standard dose; standard duration) + AES

	Elective Total Hip Replacement (eTHR)	Elective Total Knee Replacement (eTKR)
mechanical)	LMWH (standard dose; extended duration) + AES	Fondaparinux + AES
	Fondaparinux + AES	

Abbreviations: AES: anti-embolism stockings; eTHR: elective total hip replacement; eTKR: elective total knee replacement; IPCD: intermittent pneumatic compressions device; LMWH:low molecular weight heparin.

Table 272: Interventions not included in the NMAs and the model by population

	Elective Total Hip Replacement (eTHR)	Elective Total Knee Replacement (eTKR)
Mechanical	IPCD + AEs	-
Combination	LMWH (standard dose; standard duration) + IPCD+ AES	Fondaparinux + IPCD + AEs
	Fondaparinux + IPCD+ AES	
	Fondaparinux + IPCD	

Abbreviations: AES: anti-embolism stockings; eTHR: elective total hip replacement; eTKR: elective total knee replacement; IPCD: intermittent pneumatic compressions device; LMWH:low molecular weight heparin.

P.1.1.3 Time horizon, perspective, discount rates used

The analysis follows the standard assumptions of the reference case including discounting at 3.5% for costs and health effects, and incremental analysis is conducted. A sensitivity analysis using a discount rate of 1.5% for costs and health effects was also conducted. Lifetime time horizon was used.

P.1.2 Approach to modelling

We followed a two-stage modelling approach. A decision tree was used to model the acute phase (surgery to 90 days post-operatively) and a Markov Chain was used to model the long-term events beyond 90 days post-operatively. The relative efficacy of the included comparators on the model outcomes was applied during the acute phase of the model, after which progression through the model was treatment-independent and based on epidemiological data for mortality, the incidence of post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH). Uncertainty was explored through probabilistic analysis and one-way sensitivity analyses.

A number of assumptions were made when developing the model. These have been discussed in detail with and agreed by the committee. The key assumptions are outlined below but are also discussed in more detail in subsequent sections of this report:

Assumptions:

1- Asymptomatic DVT is not diagnosed in practice and will not be treated or lead to extra costs or loss in quality of life in the short term.
2- Only one symptomatic event is allowed in the model in the first 90 days; given that the treatment course for these events is 3 months long and once an event is diagnosed; the individual would receive treatments and would no longer be considered to be receiving primary prophylaxis.
3- Those who develop symptomatic proximal DVT or PE will receive treatment. The treatment used was assumed to be either a direct oral anticoagulant (rivaroxaban or apixaban) or LMWH followed by vit-K antagonist (warfarin) in a ratio of 50% each.

4- It was assumed the treatment of VTE events is 100% effective, regardless of which VTE treatment regimen is used and no allowance for recurrence was made in the model. This was decided based on discussions with the committee where it was decided that the rate of recurrence after a provoked VTE is much lower compared to unprovoked VTE event. It was also felt that the prevention of a provoked event will not necessarily lead to prevention of recurrence which might be a result of a previous undiagnosed VTE event or an inherent susceptibility, including thrombophilia.

P.1.2.1 Model structure

A separate model is run for each of the two populations: eTHR and eTKR. This was decided to reflect the difference in baseline VTE and bleeding risks, treatment duration and the characteristics of the target population. However, the structure of the model is the same for both populations. The model consists of a simple decision tree covering the acute phase from admission up to 90 days post-operatively, to cover the period included in the definition of hospital-acquired VTE, followed by a Markov chain for the remaining model time horizon (lifetime in the base case). The structure is repeated for each prophylaxis strategy.

The decision tree consists of the clinical events: DVT (symptomatic proximal, symptomatic distal, asymptomatic proximal and asymptomatic distal), non-fatal PE, fatal PE, Surgical site bleeding, non-surgical site bleeding (gastrointestinal (GI) bleeding, intracranial haemorrhage (ICH)/haemorrhagic stroke, other major bleeding), fatal major bleeding (MB), clinically-relevant non-major bleeding (CRNMB) and heparin-induced thrombocytopaenia (HIT).

Of the VTE events; symptomatic proximal DVT and PE were assumed to always require treatment. Symptomatic distal DVT was assumed to require treatment in 50% of cases. Treatment of DVT and PE was assumed to continue for 3 months, given the provoked nature of the event, and be either a therapeutic dose of an oral anticoagulant (rivaroxaban or apixaban) or a parenteral anticoagulant for 7 days + warfarin for the 3 months. Treatment with either of the two strategies was assumed to be 100% effective and recurrence was not considered. This was based on the committee's expert opinion, given the low rate of recurrence following a provoked VTE event as well as the assumption that prevention of a provoked event does not automatically lead to prevention of the recurrence given that the recurrence could be secondary to any previous VTE event.

Major bleeding (MB) events in the model could be at the surgical site; in which case it would result in return to theatre, or at another site. MB occurring in the GI tract was assumed to require intervention in 13% of cases[666]. ICH/haemorrhagic stroke was assumed to lead to disability.

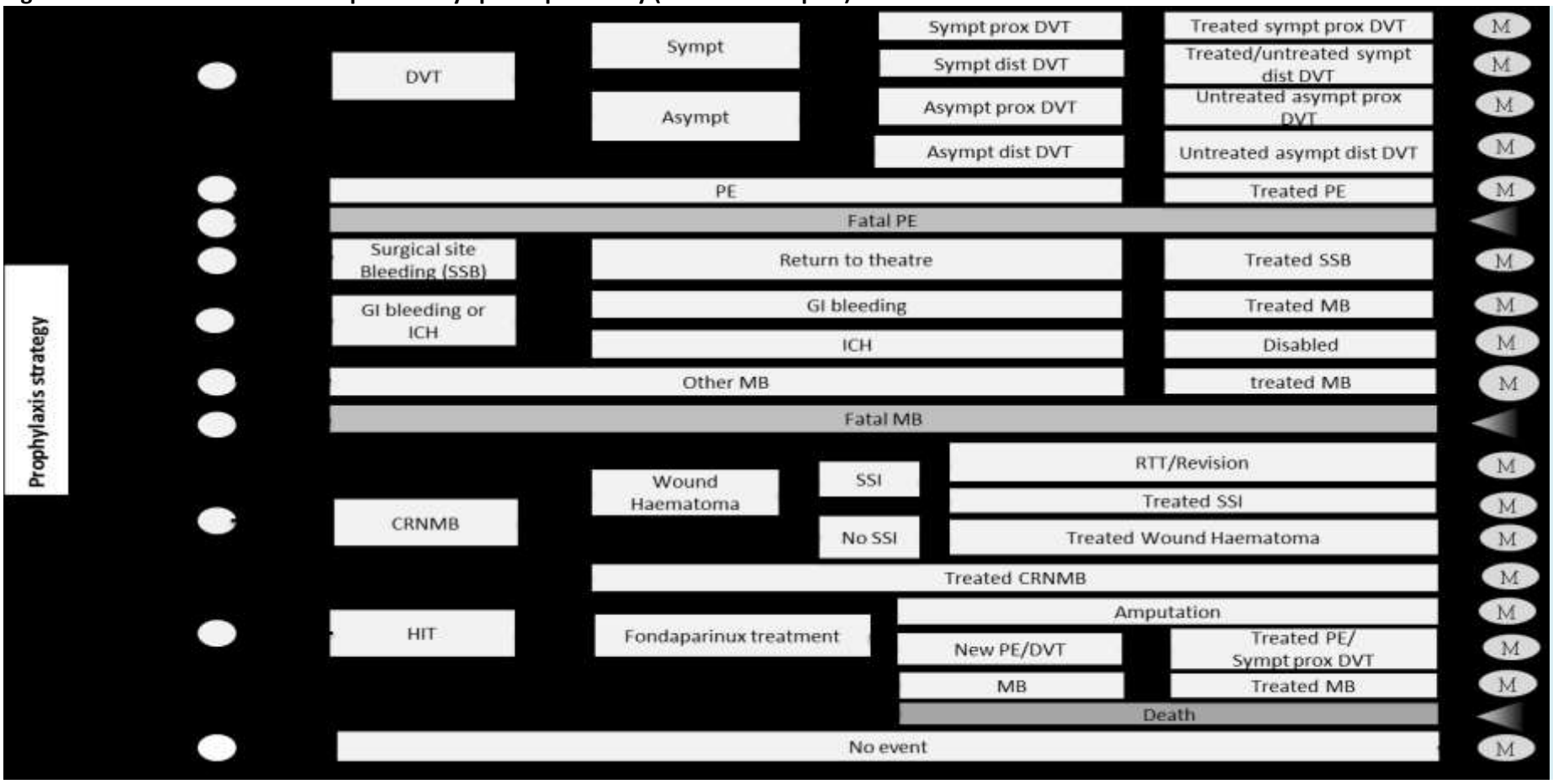
Individuals who develop CRNMB were assumed to either be treated or develop a wound haematoma that could lead to a surgical site infection (SSI). SSIs could either be medically treated or require surgical intervention; which could be either a return to theatre or a revision arthroplasty, in a ratio of 1:1.

Individuals developing HIT were assumed to be treated with a therapeutic dose of fondaparinux. The outcomes of treatment were based on data from two trials; in line with the ACCP 2012 guideline, and include successful treatment, new thrombosis (assumed to be either symptomatic proximal DVT or PE in a ratio of 1:1), major bleeding or death. The structure of the decision tree is presented in **Figure 845**.

The long-term part is represented by a Markov model. Individuals enter the model in one of the following states; based on where they end up at the end of the 90 days post-operatively: Well, post-symptomatic proximal DVT, post-symptomatic distal DVT, post-asymptomatic proximal DVT, post-asymptomatic distal DVT, post-PE, amputated post-HIT, disabled post-stroke, post-revision for infection. In the first two years, individuals in a post-VTE state can develop post-thrombotic syndrome (PTS). Those in the post-PE state can also develop chronic thromboembolic pulmonary

hypertension (CTEPH). Those with CTEPH could either undergo a pulmonary endarterectomy (PEA) and be completely cured or have a recurrence after the PEA. Those with non-operable CTEPH or refuse to have the operation were assumed to be treated with lifelong anticoagulation and targeted medical therapy. The first year after the diagnosis of each of PTS or CTEPH is represented in the model by a tunnel state. Additionally, the second year after an operable but recurrent/resistant CTEPH is also represented by a tunnel state to account for the difference in costs from a chronic CTEPH state. Transitioning to death is allowed from any state in the model, to represent all-cause mortality. The structure of the Markov cohort model is illustrated in **Figure 846.**

Figure 845: Model structure up to 90 days post-operatively (Decision tree part)



Abbreviations: Asympt: asymptomatic; Dist: distal; DVT: Deep vein thrombosis; GI: gastrointestinal; HIT: heparin-induced thrombocytopenia; ICH: intracranial haemorrhage; MB: major bleeding; PE: pulmonary embolism; Prox: proximal; RTT: return to theatre; SSB: surgical site bleeding, SSI: surgical site infection; Sympt: symptomatic

Figure 846: Model structure after 90 days post-operatively (Markov model part)

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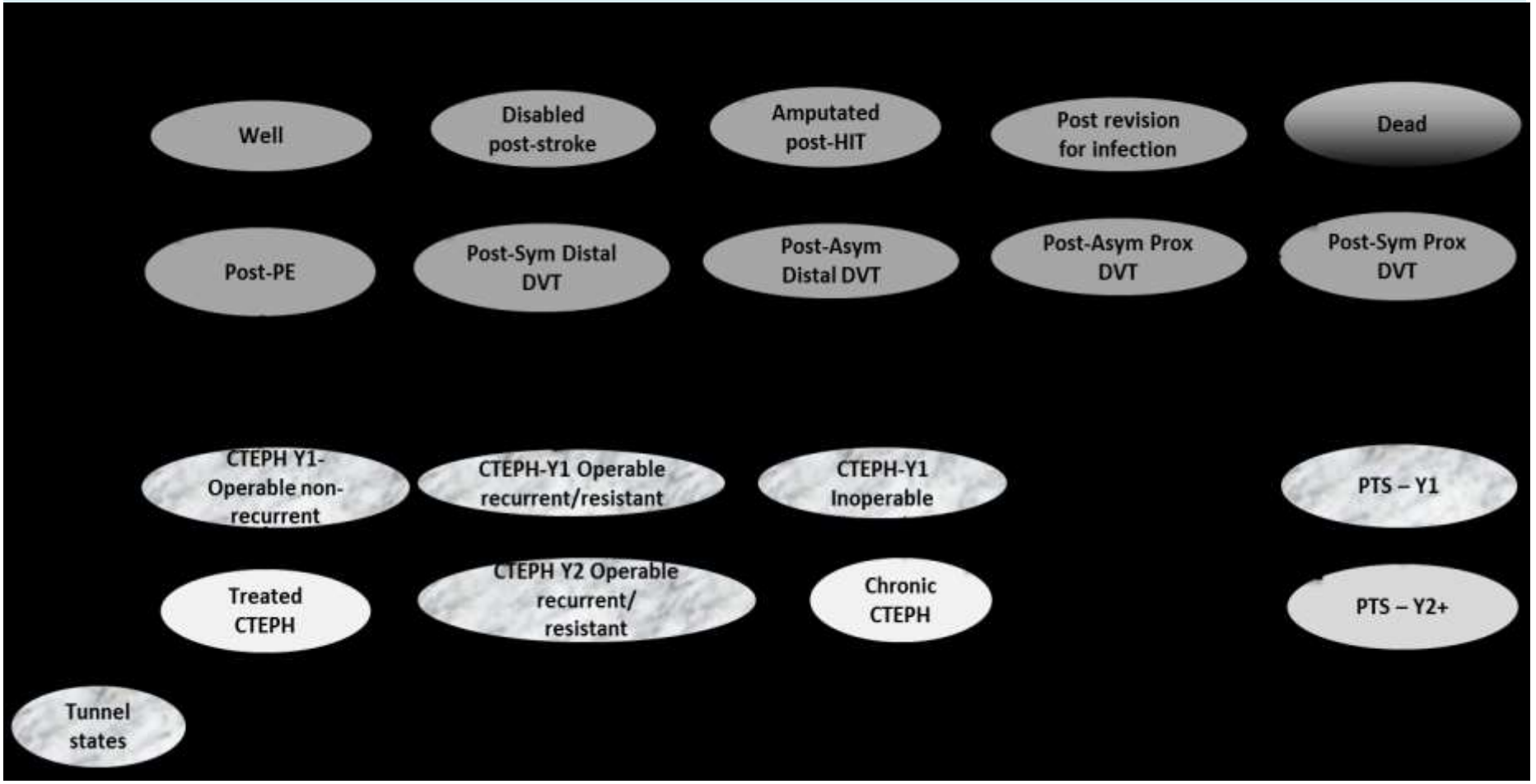


Abbreviations: Asympt: asymptomatic; CTEPH: chronic thrombo-embolic pulmonary hypertension; DVT: Deep vein thrombosis; HIT: heparin-induced thrombocytopenia; PE: pulmonary embolism; Prox: proximal; PTS: post-thrombotic syndrome; Sympt: symptomatic

P.1.2.2 Uncertainty

The model was run probabilistically to take account of the uncertainty around the input parameters' point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 2,500 times for the base case and results were summarised.

The way in which distributions are defined reflects the nature of the data, so for example utilities were given a beta distribution, which is bounded by 0 and 1, reflecting that a quality of life weighting will not be outside this range. All of the variables that were probabilistic in the model and their distributional parameters are detailed in **Table 273** and in the relevant input summary tables in section **P.1.3.1**. Probability distributions in the analysis were parameterised using error estimates from data sources. Where these estimates were not available; the standard error was assumed to be equal to 10% of the mean value.

For the VTE and bleeding event rates which were calculated based on the NMA results, the probability distribution was constructed using the CODA for the probability or the log odds ratio of the respective event from the WinBUGs output in order to maintain the correlation between these parameters.

Table 273: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Utility	Beta	Bounded between 0 and 1. Derived from mean of a domain or total quality of life score and its standard error, using the method of moments. Alpha and Beta values were calculated as follows: $Alpha = mean^2 \times [(1-mean)/SE^2] - mean$ $Beta = Alpha \times [(1-mean)/mean]$
Utility decrements	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and Beta values were calculated as follows: $Alpha = (mean/SE)^2$ $Beta = SE^2/Mean$

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold (which was deemed to be fixed by NICE),
- Drug costs
- The NHS reference costs and the mortality rates from life tables for England and Wales were not varied probabilistically as they are based on national data and therefore the level of uncertainty in the model inputs was considered to be very low and did not warrant incorporation.

In addition, deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change. The sensitivity analyses that were undertaken are described in **section P.1.5**.

P.1.3 Model inputs

P.1.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic reviews undertaken during the development of the guideline, supplemented by additional data sources as required. Model inputs were validated with the clinical members of the committee. A summary of the model inputs used in the base case analysis is provided in **Table 274** below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 274: Summary of base-case model inputs

Input	Data	Source
Population	Adults and young people (16 years and over) undergoing eTHR or eTKR	Guideline scope
Perspective	UK NHS and PSS	NICE reference case –Guidelines Manual[673]
Time horizon	Lifetime	NICE reference case- Guidelines Manual[673]
Discount rate	Costs and outcomes: 3.5%	NICE reference case-Guidelines Manual[673]
Cohort settings		
Start age (years)	eTHR: 68.7 (SD= 11.32) eTKR: 69.3 (SD=9.58)	National Joint Registry Annual Report 2016[109]
Male	eTHR: 40% eTKR: 44%	National Joint Registry Annual Report 2016[109]
BMI (kg/m^2)	eTHR: 28.7 eTKR: 30.9	National Joint Registry Annual Report 2016[109]
Baseline risks - e THR		
DVT (symptomatic and asymptomatic)	5.54%	Calculated based on Jameson 2011[451] and Quinlan 2007[778]
Symptomatic DVT	0.94%	Jameson 2011[451]
Proportion of symptomatic DVTs that are proximal	83.3%	Revankar 2013 [797]based on data from ADVANCE trials
Asymptomatic DVT	4.6%	Calculated based on [451] and Quinlan 2007[778]
Proportion of asymptomatic DVTs that are proximal	26.2%	Revankar 2013 Revankar, 2013 #3341} based on data from ADVANCE trials
Non-fatal PE	0.68%	Jameson 2011[451]
Mortality from PE	17% (1/6)	Randomised controlled trials in our systematic review
Major bleeding at the surgical site	2.29%	Single-arm meta-analysis of the LMWH (standard dose, standard duration) randomised controlled trials in our systematic review
GI and cerebrospinal bleeding	0.72%	Jameson 2011[451]
Other major bleeding	0.2%	Single-arm meta-analysis of the LMWH (standard dose, standard duration) randomised controlled trials in our systematic review
Clinically-relevant non-	2.95%	Single-arm meta-analysis of the LMWH

Input	Data	Source
major bleeding (CRNMB)		(standard dose, standard duration) randomised controlled trials in our systematic review
Wound haematoma as percentage of CRNMB	22.73% (5/22)	Calculated from the LMWH randomised controlled trials in our systematic review
Heparin-induced thrombocytopenia (HIT)	0.17%	Single-arm meta-analysis of the LMWH (standard dose, standard duration) randomised controlled trials in our systematic review
Baseline risk - eTKR		
DVT (symptomatic and asymptomatic)	14%	Calculated based on Jameson 2012[450] and Quinlan 2007[778]
Symptomatic DVT	0.63%	Jameson 2012
Proportion of symptomatic DVTs that are proximal	20%	Revankar 2013 based on data from ADVANCE trials
Asymptomatic DVT	13.37%	Calculated based on Jameson 2012 [450] and Quinlan 2007[778]
Proportion of asymptomatic DVTs that are proximal	8.8%	Revankar 2013[797] based on data from ADVANCE trials
Non-fatal PE	0.45%	Jameson 2012 [450]
Mortality from PE	17%	assumed equal to eTHR as there were no events in the single trial of LMWH (standard dose, standard duration)+ AEs
Major bleeding at the surgical site	0.64%	Single-arm meta-analysis of the LMWH (standard dose, standard duration) randomised controlled trials in our systematic review
GI and cerebrospinal bleeding	0.39%	Jameson 2012 [450]
Other major bleeding	0.2%	Single-arm meta-analysis of the LMWH (standard dose, standard duration) randomised controlled trials in our systematic review
CRNMB	4.15%	Single-arm meta-analysis of the LMWH (standard dose, standard duration) randomised controlled trials in our systematic review
Wound haematoma as percentage of CRNMB	18.97% (11/58)	Calculated from the LMWH randomised controlled trials in our systematic review
HIT	0.92%	Single-arm meta-analysis of the LMWH (standard dose, standard duration) randomised controlled trials in our systematic review
Other parameters		
Proportion requiring return to theatre after surgical site major bleeding	100%	Standard definition of major bleeding and expert opinion
Proportion requiring	13%	CG92 [666]

Input	Data	Source
intervention after GI bleeding		
Surgical site infection due to haematoma	25.77% (25/97)	Wang 2014[988]
Probability of revision/return to theatre due to infection	44% (11/25)	Wang 2014[988]
Long term events		
2-year incidence of PTS after :		
Symptomatic proximal DVT	40%	Kahn 2016[463] & committee Expert opinion
Symptomatic distal DVT	10%	Heit 2001 [412], Botteman 2002 [121]and committee opinion
Asymptomatic proximal DVT	15%	Wille-Jorgensen 2005 [1010]
Asymptomatic distal DVT	3.75%	Heit 2001 [412], Botteman 2002 [121]
Non-fatal PE	15%	Committee expert opinion
Proportion of PTS that is severe	23%	Wolowacz 2009 [1017](average from 8 incidence studies)
2-year incidence of CTEPH after non-fatal PE	3.2% (95% CI: 1.5%–3.1%)	Ende-Verhaar 2017 [287](systematic review of incidence studies)
CTEPH mortality	20%	CG92 [666]
Costs (£)		
Symptomatic proximal DVT	eTHR: £457 eTKR: £457	see section P.1.3.6.2.1
Symptomatic distal DVT	eTHR: £295 eTKR: £295	see section P.1.3.6.2.1
Non-fatal PE	eTHR: £991 eTKR: £992	see section P.1.3.6.2.1
Return to theatre for surgical site bleeding	eTHR: £6,278 eTKR: £6,177	NHS Schedule for Reference Costs 2015-2016 [250](unit cost for primary eTHR) NHS Schedule for Reference Costs 2015-2016[250] (unit cost for primary eTKR
GI bleeding with intervention	£2,409	NHS Schedule for Reference Costs 2015-2016[250]
GI bleeding without intervention	£855	NHS Schedule for Reference Costs 2015-2016[250]
Haemorrhagic Stroke		
acute event-admission	£4,354	Weighted Cost of non-elective long stay admission for stroke with CC score 0-3 to 16+. HRG codes AA35A to AA35F.NHS Schedule for Reference Costs 2015-2016[250]
Acute event- other costs for the first 90 days	£3,255	Three month costs calculated based Weighted average cost of the cost of stroke dependent state and independent state in year 1 from CG144 (VTE management and thrombophilia testing) less the cost of the acute stroke admission.[668] Costs inflated to

Input	Data	Source
		2015-2016.
Y1 –dependent state	£29,776	CG144 (VTE management and thrombophilia testing) [668] Costs inflated to 2015-2016
Y1 –independent state	£4,971	CG144 (VTE management and thrombophilia testing) [668] Costs inflated to 2015-2016
Y2+ – dependent state	£15,108	CG144 (VTE management and thrombophilia testing) [668] Costs inflated to 2015-2016
Y2+ – independent state	£1,172	CG144 (VTE management and thrombophilia testing) [668] Costs inflated to 2015-2016
CRNMB (post-discharge)	£242	Committee expert opinion (2 outpatient visits)
Surgical site infection-medically treated	£3,696	NHS Schedule for Reference Costs 2015-2016
Revision surgery for infected joint	eTHR: £19,514 eTKR: £19,203	Kallala 2015 and NHS Schedule for Reference Costs 2015-2016
HIT	£463	NHS Schedule for Reference Costs 2015-2016[250]
Amputation after HIT:		
acute event	£10,300	CG 147 (Lower Limb Peripheral Arterial Disease)[667] adjusted for inflation to 2015-2016 values
Y1	£31,259	CG 147 (Lower Limb Peripheral Arterial Disease) [667] adjusted for inflation to 2015-2016 values
Y2+	£25,987	CG 147 (Lower Limb Peripheral Arterial Disease)[667] adjusted for inflation to 2015-2016 values
PTS		
Mild/Moderate -Year 1	£841	Caprini 2003 [153] converted to 2000 GBP OECD PPP conversion and inflated to 2015-2016 values
Mild/Moderate -Year 2+	£342	Caprini 2003 converted to 2000 GBP OECD PPP)[715] conversion factor and inflated to 2015-2016 values
Severe -Year 1	£3,824	Caprini 2003 converted to 2000 GBP OECD PPP conversion)[715]and inflated to 2015-2016 values
Severe -Year 2+	£1,680	Caprini 2003 converted to 2000 GBP OECD PPP conversion)[715] and inflated to 2015-2016 values
CTEPH		
Operable-Y1	£28,671	see section P.1.3.6.3.1
Recurrent/Resistant- Y1	£29,470	see section P.1.3.6.3.1
Inoperable-Y1	£9,677	see section P.1.3.6.3.1

Input	Data	Source
Recurrent/resistant- Y2	£21,845	see section P.1.3.6.3.1
Chronic-Y2+	£13,967	see section P.1.3.6.3.1
Treated CTEPH	£147	see section P.1.3.6.3.1

Abbreviations: BMI: body mass index; CRNMB: clinically-relevant non-major bleeding; CTEPH: chronic thromboembolic pulmonary hypertension; DVT: deep vein thrombosis; eTHR: elective total hip replacement; eTKR: elective total knee replacement; GI: gastrointestinal; HIT: Heparin-induced thrombocytopenia; LMWH: low molecular weight heparin; PE: pulmonary embolism; PTS: post-thrombotic syndrome; Y1: year 1, Y2+: year 2 and beyond.

P.1.3.2 Initial cohort settings

The cohort characteristics for each of these populations were based on the data reported in the National Joint Registry (NJR) 13th annual report;[109] which were collected up to December 2015 (see **Table 275**)

Table 275: Cohort characteristics based on the National Joint Registry data for operations undertaken in 2015

	THR	TKR
Age (years) (mean)	68.7	69.3
Age (SD)	11.32	9.58
% male	40%	44%
BMI (kg/m2) (mean)	28.7	30.9

Abbreviations: BMI: body mass index; SD: standard deviation; THR: total hip replacement; TKR: total knee replacement.

P.1.3.3 Baseline risk

The baseline risk estimates for VTE and major bleeding events were based on two large observational cohort studies that used the NJR data[450, 451]. In both studies, data from the NJR for England and Wales linked to an administrative database of hospital admissions in the English National Health Service (HES database) were analysed. For the THR population, a total of 108,584 patients operated on between April 2003 and September 2008 were included and followed up for 90 days.[451] Of these, 78.9% received LMWH as the pharmacological prophylaxis (n=85,642) and 72% of them had additional mechanical prophylaxis. The mechanical prophylaxis method used was assumed to be AEs, based on data from NJR for the year 2008,[794] where stockings were the most commonly prescribed mechanical prophylaxis method for THR patients (62%). LMWH was assumed to have been used in the standard dose (40 mg once daily) and duration as the study covered the procedures performed before the publication of CG92 which recommended the use of extended rather than standard duration of LMWH for this population.

For the TKR population, a total of 156,798 patients operated on over the same period were included and followed for 90 days.[450] Of these, 120,639 patients (76.9%) were prescribed LMWH as the pharmacological prophylaxis and 79.5% of them had mechanical prophylaxis. Similar to THR, and based on NJR data, stockings were the most commonly used mechanical prophylaxis method in 2008, where it was used in 66% of patients.[794]

The two studies reported the number of events for symptomatic DVT only and not all DVT which is the outcome analysed in the guideline's DVT NMAs. Hence, we used the ratio of asymptomatic to symptomatic DVT events as reported in Quinlan 2007[778] (symptomatic DVTs = 17% of all DVTs for THR and 4.5% for TKR) to estimate the number of all DVT events that would have been observed in

these studies; based on the reported number of symptomatic DVTs. The results are reported in **Table 276**. The number of DVT events and total number of patients were used to characterise a binomial distribution that was used in the NMA model for the all DVT (symptomatic and asymptomatic) outcome to allow the calculation of the relative risk and the event rate for each of the strategies included in the NMA.

Table 276: Observational study data for the total hip replacement and total knee replacement population on prophylaxis with LMWH (standard dose/standard duration) +AEs and number of all DVT events estimated based on these data

Outcome (a)	Total hip replacement (N= 85642)[451] n (%)	Total knee replacement (N= 156,798)[450] n (%)
DVT (Symptomatic)	806 (0.94%)	762 (0.63%)
PE (non-fatal)	583 (0.68%)	539 (0.45%)
MB (non-surgical site) (b)	620 (0.72%)	465 (0.39%)

Abbreviations: DVT: deep vein thrombosis; MB: major bleeding; OR: odds ratio; PE: pulmonary embolism.
(a) results of the unadjusted analysis
(b) defined as Cerebrovascular accident/gastrointestinal haemorrhage (non-fatal)

It was not possible to find an estimate of baseline risk of surgical site bleeding, other major bleeding and clinically-relevant non-major bleeding from the NJR data or published observational cohort studies of LMWH. Hence, for these outcomes, the baseline risk was calculated using a single arm meta-analysis of LMWH randomised controlled trials included in the major bleeding NMA. The meta-analysis was conducted in WinBUGs version 1.4.3. The results are presented in **Table 277.**

Table 277: Baseline risk of surgical site bleeding, other major bleeding and clinically-relevant non-major bleeding on LMWH (standard dose, standard duration)

Outcome	THR % (SD)	TKR % (SD)
Surgical site bleeding	2.29% (0.025)	0.64% (0.016)
Other major bleeding	0.29% (0.005)	0.20% (0.021)
CRNMB	2.95% (0.013)	4.15% (0.038)

Abbreviations: CRNMB: clinically-relevant non-major bleeding; SD: standard deviation
(c) results of the unadjusted analysis
(d) defined as Cerebrovascular accident/gastrointestinal haemorrhage (non-fatal)

Baseline risk of HIT was based on the results of the systematic review and meta-analysis presented in the full guideline for the pairwise comparison of LMWH (std dose/extd duration) to LMWH (std dose/ std duration). Two trials were identified for the eTHR population,[208, 534] and one for the eTKR population.[208] Based on these trials, the baseline risk of HIT is 0.17% (SE=0.00003) in eTHR and 0.92% (SE= 0.00062) in eTKR.

Mortality during the acute phase was modelled as the consequence of fatal PE, fatal MB and HIT. After the first 90 days and up to 12 years; mortality estimates were based on data from the 2016 NJR report which presented the mortality data by age band up to 12 years post the index operation. A polynomial function was fitted in Microsoft Excel to the reported cumulative mortality to calculate an annual probability of death.[109] Data from the NJR report are presented in Table 278.

Table 278: Mortality data for the first 12 years post primary operation by population

Time since primary operation (months)	Cumulative percentage mortality by population			
	THR		TKR	
	Mean (a)	95% CI	Mean (a)	95% CI

Time since primary operation (months)	Cumulative percentage mortality by population			
	THR		TKR	
	Mean (a)	95% CI	Mean (a)	95% CI
1	0.22	0.21 to 0.23	0.17	0.16 to 0.18
3	0.48	0.47 to 0.50	0.32	0.31 to 0.33
12	1.49	1.46 to 1.52	1.05	1.03 to 1.07
36	4.90	4.85 to 4.96	4.13	4.08 to 4.18
60	9.51	9.43 to 9.59	8.64	8.56 to 8.71
84	15.05	14.95 to 15.16	14.45	14.35 to 14.56
120	24.88	24.70 to 25.06	25.68	25.50 to 25.87
144	28.51	28.28 to 28.74	34.11	33.76 to 34.46

Source: NJR report[109]
(a) Cumulative percentage probability of death weighted by age and sex.

Beyond 12 years post-primary THR or TKR; life tables for England for the years 2013 to 2015 were used as the source of the annual probability of death for males and females. Additionally, disease-specific mortality was modelled for those diagnosed with CTEPH.

P.1.3.4 Relative treatment effects

The between-strategy differences in costs and effects are driven by each strategy's relative risk (RR) reduction for VTE, and its RR increase for major bleeding. For example, the number of DVTs occurring under the rivaroxaban strategy is the baseline risk of DVT (when using the comparator LMWH (std dose/std duration)+ AEs) multiplied by the DVT RR reduction for rivaroxaban compared with LMWH (std dose/std duration) + AEs. The differential effects of treatment are only applied in the acute phase up to 90 days post-operatively (the decision tree part of the model) and treatment effect was not extrapolated beyond this time point. The sources of baseline risks and relative treatment effects are illustrated in **Table 279** and **Table 280**.

Table 279: Source of baseline risk and relative treatment effect for the primary and secondary outcomes in the decision tree part of the model- eTHR population

Outcome	All DVT	PE (non- fatal)	GI bleeding	ICH/ haemorrhagic stroke	SSB	Other MB	CRNMB
LMWH (std,std) + AEs	**BR:** Jameson 2011(b)	**BR:** Jameson 2011(b)	**BR:** Jameson 2011 (b) & proportion of ICH from RCTs in the GL SR		**BR:** RCTs in the GL SR	**BR:** RCTs in the GL SR	**BR:** RCTs in the GL SR
LMWH (std,extd) + AEs	**RR:** DVT NMA	**RR:**PE NMA	**RR:** MB NMA		**RR:**MB NMA	**RR:** MB NMA	**RR:** ITC
Fondaparinux+ AES							**RR:** MB NMA
Foot pump + AES		**RR:**DVT NMA					
IPCD		**RR:**PE NMA					
AEs (above knee)							

Foot pump						
AES						
LMWH (std,std)						**RR:** ITC
LMWH (std,extd)						**RR:** ITC
Aspirin (std duration)			**RR:** Jameson 2011 (a)	**RR:** Jameson 2011(a)	**RR:** Jameson 2011(a)	**RR:** Jameson 2011(a)
LMWH (std, std) +Aspirin (extd duration)	**RR:** PE NMA		**RR:**MB NMA	**RR:** MB NMA	**RR:** MB NMA	**RR:** ITC
Dabigatran	**RR:** DVT NMA					**RR:** pairwise MA of RCTs in GL SR
Apixaban						**RR:** Pairwise MA
Rivaroxaban						Pairwise MA
No prophylaxis						**RR:** MB NMA

Abbreviations: AES: anti-embolism stockings; BR: baseline risk; CRNMB: clinically relevant non-major bleeding; DVT: deep vein thrombosis; eTHR: elective total hip replacement; GI: gastrointestinal; GL: guideline; ICH: intracranial haemorrhage; IPCD: intermittent pneumatic compressions device; ITC: indirect treatment comparison; LMWH :low molecular weight heparin; MA: meta-analysis; MB; major bleeding; NMA: network meta-analysis; RR: relative risk; SR: systematic review; SSB: surgical site bleeding; RCT: randomised controlled trials
Cells highlighted in dark grey indicate a different source of relative risk.to the outcome-specific NMA, ITC or pairwise MA.
(a) Source: Jameson 2011 [451]

Table 280: Source of baseline risk and relative treatment effect for the primary and secondary outcomes in the decision tree part of the model- eTKR population

Outcome	All DVT	PE (non-fatal)	GI bleeding	ICH/ haemorrhagic stroke	SSB	Other MB	CRNMB
LMWH (std,std) + AEs	**BR:** Jameson 2012 (b)	**BR:** Jameson 2012 (b)	**BR:** Jameson 2012 (b) & proportion of ICH from RCTs in the GL SR		**BR:** RCTs in the GL SR	**BR:** RCTs in the GL SR	**BR:** RCTs in the GL SR
Fondaparinux+ AES	**RR:** DVT NMA	**RR:** DVT NMA	**RR:** MB NMA		**RR:** MB NMA	**RR:** MB NMA	**RR:** MB NMA
Foot pump + AES		**RR:** DVT NMA					
IPCD		**RR:** PE NMA					
Foot pump		**RR:** DVT NMA					
AES		**RR:** PE NMA					
LMWH (std,std)							
LMWH (std,extd)							

Aspirin		**RR:** DVT NMA	**RR:** Jameson 2012 (a)	**RR:** Jameson 2012 (a)	**RR:** Jameson 2012 (a)	**RR:** Jameson 2012 (a)
Dabigatran		**RR:** PE NMA	**RR:** MB NMA	**RR:** MB NMA	MB NMA	**RR:** pairwise MA of RCTs in GL SR
Apixaban						**RR:** pairwise MA of RCTs in GL SR
Rivaroxaban						**RR:** pairwise MA of RCTs in GL SR
No prophylaxis						**RR:** MB NMA

Abbreviations: AES: anti-embolism stockings; BR: baseline risk; CRNMB: clinically relevant non-major bleeding; DVT: deep vein thrombosis; eTKR: elective total knee replacement; GI: gastrointestinal; GL: guideline; ICH: intracranial haemorrhage; IPCD: intermittent pneumatic compressions device; LMWH :low molecular weight heparin; MA: meta-analysis; MB; major bleeding; NMA: network meta-analysis; RR: relative risk; SR: systematic review; SSB: surgical site bleeding; RCT: randomised controlled trials.
Cells highlighted in dark grey indicate a different source of relative risk.to the outcome-specific NMA, ITC or pairwise MA.
(a) Source: Jameson 2012[450]

P.1.3.4.1 DVT and PE

The RRs for each of the modelled strategies compared to LMWH (std/std) + AEs were obtained from the NMAs of the all DVT (symptomatic and asymptomatic) and non-fatal PE outcomes (see appendix M for detail). These RRs have been calculated separately for each of the two populations. The absolute risks of each of these events for each prophylaxis strategy are presented in Table 281 and Table 282 below. These were calculated by multiplying the RRs obtained from the NMA by the baseline risk of each event on the model comparator.

Only where an intervention was in one of the NMAs but not in the other, it was agreed with the committee that the OR will be assumed the same as for the outcome for which data are available. This was based on an assumption of proportionality of effect on both VTE outcomes (DVT and PE). In the eTHR population, this was the case for only two interventions LMWH (std/std) followed by aspirin and foot pump+AES. For LMWH (std/std) followed by aspirin, no data were available for the outcome DVT (symptomatic and asymptomatic) and the OR obtained from the PE NMA was used instead. This assumption has also been tested in a sensitivity analysis (see section P.1.5), as the committee thought that the estimate obtained from the PE network was highly imprecise with very wide credible intervals. For the eTKR population, four interventions were not in the PE NMA and ORs from the DVT network were used instead. These were: fondaparinux+AES, foot pump, foot pump + AES and aspirin.

In the model, we apply the RR for all DVT to both symptomatic and asymptomatic DVT. Thus, if a certain strategy was shown to reduce DVTs by 60% then in the model the incidence of both symptomatic and asymptomatic DVT will be reduced by 60%.

Table 281: Absolute risk (95% CrI) of all DVT (symptomatic and asymptomatic) and non-fatal PE applied in the model for elective total hip replacement (eTHR)

Strategy	DVT (symptomatic and asymptomatic)	Non-fatal PE
1) LMWH (std,std) + AEs	5.54% (%5.39 to %5.70)	0.68% (%0.63 to %0.74)
2) LMWH (std,extd)+ AEs	4.03% (%0.53 to %14.34)	0.15% (%0.00 to %0.94)

Strategy	DVT (symptomatic and asymptomatic)	Non-fatal PE
3) Fondaparinux+ AES	3.25% (%0.46 to %11.43)	1.15% (%0.09 to %5.12)
4) Foot pump + AES	14.66% (%1.99 to %46.06)	1.48%(b)
5) IPCD	33.06% (%5.56 to %76.99)	5.28% (%0.15 to %31.35)
6) AEs (above knee)	8.30% (%0.87 to %48.85)	10.21% (%0.00 to %88.30)
7) Foot pump	28.01% (%2.41 to %78.81)	21.94% (%0.11 to %98.05)
8) AES	12.05% (%4.35 to %25.55)	1.18% (%0.08 to %5.46)
9) LMWH (std,std)	20.30% (%3.41 to %56.46)	2.47% (%0.18 to %12.53)
10) LMWH (std,extd)	9.76% (%0.97 to %36.66)	0.45% (%0.00 to %3.19)
11) Aspirin (std duration)	26.26% (%1.56 to %80.91)	36.63% (%0.35 to %99.62)
12) LMWH (std, std) + Aspirin (extd duration)	0.05%(a)	0.11% (%0.00 to %0.77)
13) Dabigatran	18.91% (%2.05 to %60.30)	3.56% (%0.13 to %20.41)
14) Apixaban	9.81% (%0.55 to %43.30)	2.01% (%0.05 to %12.24)
15) Rivaroxaban	4.00% (%0.27 to %18.33)	1.20% (%0.01 to %7.82)
16) No prophylaxis	40.42% (%9.59 to %81.09)	8.80% (%0.83 to %37.52)

Abbreviations: AES: anti-embolism stockings; CrI: credible interval; DVT: deep vein thrombosis; eTHR: elective total hip replacement; extd: extended; IPCD: intermittent pneumatic compressions device; LMWH:low molecular weight heparin; PE: pulmonary embolism; std: standard

a) *Not in DVT NMA. Point estimate calculated based on the assumption that the relative effectiveness for the PE outcome compared to LMWH (std,std) + AES will be the same for the DVT.*

b) *Not in PE NMA. Point estimate calculated based on the assumption that the relative effectiveness for the DVT outcome compared to LMWH (std,std)+ AES will be the same for the PE.*

Table 282: Absolute risk (95% CrI) of DVT (symptomatic and asymptomatic) and non-fatal PE applied in the model for elective total knee replacement (eTKR)

Strategy	DVT (symptomatic and asymptomatic)	Non-fatal PE
1) LMWH (std,std) + AEs	14.00% (%13.81 to %14.20)	0.45% (%0.41 to %0.49)
2) Fondaparinux+ AES	12.51% (%3.76 to %27.50)	0.36% (a)
3) Foot pump + AES	18.96% (%9.45 to %33.25)	0.58%(a)
4) IPCD	21.23% (%7.04 to %42.74)	1.92% (%0.00 to %18.60)
5) Foot pump	8.38% (%1.12 to %26.89)	0.20% (a)
6) AES	29.97% (%15.13 to %48.19)	2.48% (%0.007 to %20.33)
7) LMWH (std,std)	9.22% (%2.98 to %20.08)	1.94% (%0.00 to %19.44)
8) LMWH (std,extd)	7.83% (%1.80 to %20.51)	0.87% (%0.000 to %6.25)

Strategy	DVT (symptomatic and asymptomatic)	Non-fatal PE
9) Aspirin	15.28% (%3.64 to %37.46)	0.43% (a)
10) Dabigatran	9.10% (%2.78 to %20.49)	5.06% (%0.00 to %60.15)
11) Apixaban	5.31% (%1.54 to %12.44)*	4.35% (%0.000 to %49.77)
12) Rivaroxaban	4.32% (%1.17 to %10.42)*	1.45% (%0.00 to %13.84)
13) No prophylaxis	34.21% (%13.98 to %58.93)	4.47% (%0.002 to %46.25)

Abbreviations: AES: anti-embolism stockings; CrI: credible interval; DVT: deep vein thrombosis; eTKR: elective total knee replacement; extd: extended; IPCD: intermittent pneumatic compressions device; LMWH: low molecular weight heparin; PE: pulmonary embolism; std: standard

a) *Not in PE network. Point estimate calculated based on the assumption that the relative effectiveness for the DVT outcome compared to LMWH (std,std)+ AES will be the same for the PE.*

P.1.3.4.2 Bleeding events

The main safety outcome included in the model is major bleeding. The odds ratios (ORs) for the included interventions compared to LMWH (std,std)+AEs were calculated from the NMA for non-fatal major bleeding. In the model, we use these ORs and the relevant baseline risk on LMWH (std,std)+AEs to calculate the absolute risk of each of the major bleeding events in the model (surgical site bleeding, stroke, GI bleeding , other major bleeding and fatal major bleeds). These ORs were also used to calculate the absolute risk of CRNMB when an intervention did not have trial data for this outcome. Wound haematoma and subsequent surgical site infection were modelled as consequences of CRNMB based on epidemiological data.

In the major bleeding NMA, we assumed that the major bleeding rate for mechanical only strategies is the same as for the no prophylaxis strategy and these were treated as one intervention (see appendix M for the full NMA report). This was considered reasonable on biological grounds. The absolute risks of the bleeding events on each prophylaxis strategy are presented in Table 283 and Table 284 below.

Table 283: Absolute risk of the major bleeding and CRNMB events applied in the model for elective total hip replacement (eTHR)

Strategy	GI bleeding + ICH	SSB	Other major bleeding	CRNMB
1) LMWH (std,std) + AEs	0.72%	0.94%	0.30%	3.04%
2) LMWH (std,extd)+ AEs	0.77%	0.70%	0.23%	3.04%
3) Fondaparinux+ AES	1.40%	1.57%	0.51%	4.98%
4) Foot pump + AES	0.34%	0.36%	0.12%	1.18%
5) IPCD	0.34%	0.36%	0.12%	1.18%
6) AEs (above knee)	0.34%	0.36%	0.12%	1.18%
7) Foot pump	0.34%	0.36%	0.12%	1.18%
8) AES	0.34%	0.36%	0.12%	1.18%
9) LMWH (std,std)	0.72%	0.94%	0.30%	3.04%
10) LMWH (std,extd)	0.77%	0.70%	0.23%	3.04%
11) Aspirin (std duration)	0.79% (a)	1.03%	0.33%	3.29%
12) LMWH (std, std) + Aspirin (extd duration)	0.80%	0.10%	0.03%	1.64%

Strategy	GI bleeding + ICH	SSB	Other major bleeding	CRNMB
13) Dabigatran	1.19%	1.34%	0.43%	3.48%
14) Apixaban	1.17%	1.16%	0.37%	2.75%
15) Rivaroxaban	0.95%	0.99%	0.32%	3.68%
16) No prophylaxis	0.34%	0.36%	0.12%	1.18%

Abbreviations: AEs: anti-embolism stockings; DVT: deep vein thrombosis; extd: extended; LMWH: low molecular weight heparin; PE: pulmonary embolism; std: standard

(a) Source: Jameson 2011 [451]

Table 284: Absolute risk of the major bleeding and CRNMB events applied in the model for elective total knee replacement (eTKR)

Strategy	GI bleeding + ICH	SSB	Other major bleeding	CRNMB
17) LMWH (std,std) + AEs	0.39%	0.94%	0.21%	4.89%
18) Fondaparinux+ AES	4.20%	5.85%	1.34%	25.11%
19) Foot pump + AES	0.36%	0.88%	0.19%	4.58%
20) IPCD	0.36%	0.88%	0.19%	4.58%
21) Foot pump	0.36%	0.88%	0.19%	4.58%
22) AES	0.36%	0.88%	0.19%	4.58%
23) LMWH (std,std)	0.39%	0.94%	0.21%	4.89%
24) LMWH (std,extd)	0.43%	0.14%	0.03%	6.77%
25) Aspirin	0.38% (a)	0.93%	0.21%	4.84%
26) Dabigatran	0.44%	0.95%	0.21%	5.46%
27) Apixaban	0.34%	0.69%	0.15%	3.78%
28) Rivaroxaban	0.64%	1.33%	0.29%	5.83%
29) No prophylaxis	0.42%	0.88%	0.19%	4.58%

Abbreviations: AEs: anti-embolism stockings; DVT: deep vein thrombosis; extd: extended; LMWH: low molecular weight heparin; PE: pulmonary embolism; std: standard

(a) Source: Jameson 2012[450]

P.1.3.4.3 Complications of mechanical prophylaxis

Given the established evidence that some patients find stockings uncomfortable [985], this discomfort might cause patients to wear the stockings incorrectly (especially thigh-length stockings) – this might mean that the effectiveness estimated under trial conditions will not be replicated in practice. For this reason we included in the model the cost of nurse time for checking that mechanical prophylaxis options that require fitting and monitoring are fitted correctly. This will also ensure that complications can be avoided

P.1.3.5 Utilities

For economic evaluation, a specific measure of health-related quality of life (HRQoL) known as utility is required to calculate QALYs. Utilities indicate the preference for health states on a scale from 0 (death) to 1 (perfect health). The NICE reference case specifies that the preferred way for this to be assessed is by the EQ-5D instrument.

A systematic review of the literature was conducted to identify utility inputs to use in the model. Additionally, we examined the sources used in the economic evaluations retrieved in our main guideline economic search and existing NICE TAs.

P.1.3.5.1 Up to 90 days after surgery

For baseline utility values, we used EQ-5D-3L index values reported in the UK 2014-2015 PROMS programme.[683]The PROMS programme collects EQ-5D-3L data pre- and 6 months post-operatively for eTHR and eTKR patients.

The post-operative EQ-5D-3L index values reported in the PROMS data represents the utility at 6-12 months. We assumed that this value would be reached at the mean of the two time points (9 months). We also assumed a linear increase from the pre-operative utility score over the 6 months (180 days) to calculate the utility score at 90 days (the point of entry to the Markov model).

Bleeding events

We found three sources for the utility values for major bleeding events. We used the values reported by Locadia et al. 2004 for the major bleeding related outcomes (GI bleeding and stroke) as this study used time trade-off (TTO) for preference elicitation.[573] The relative utility decrements for the study population (mean age 55 years) were calculated and applied to the baseline utility in our model. These are listed in **Table 285.**

Table 285: Utility values for bleeding events and their sources

Event	Utility decrement	Source
Gastrointestinal bleeding	-32% (b)	Locadia 2004[573]
Haemorrhagic stroke-acute phase	-65%(b)	Locadia 2004[573]
CRNMB/Wound haematoma	-0.03 (c)	Sullivan 2011[927]

Abbreviations: CI: Confidence interval; CRNMB: clinically-relevant non-major bleeding.
(a) Calculated based on a SE of 10% around the mean
(b) time trade off (TTO). Relative utility decrement.
(c) EQ-5D. Absolute utility decrement

For those who develop other events during this period, an event-specific (Dis)utility was applied. The (dis)utilities and their sources are outlined in **Table 286.** The (dis)utilities for all events were applied as event-based after which the individual's quality of life would recover and continue on the post-operative linear improvement trajectory to achieve the utility value at 90-days post-operatively; except for surgical site infection that requires return to theatre or revision where it was assumed that the utility at 90 days post-operatively would be equal to that of post-infected revision/return to theatre for surgical site infection. This value was calculated based on data from Baker 2013, which reported on the QoI of individuals who had two-stage TKR revision for infection.[65]. The relative utility decrement and post-revision improvement reported in this study were assumed to be the same as for eTHR population (see **Table 286**). The timing of events, for the purpose of calculating QALYs, it was assumed that DVT and any adverse events (AEs) take place on day 7 while PE events take place on day 21. This was based on committee estimates. Data from Warwick 2007 were used in sensitivity analysis.[993]

Table 286: Base case (dis-)utility values for events up to 90 days

	Mean (dis-)utility	SE(a)	Source
No event (baseline utility at 90 days)	THR: 0.579 (BLU-THR)	0.057	PROMS 2014-2015[683]
	TKR: 0.582 (BLU-TKR)	0.058	PROMS 2014-2015[683]
Asymptomatic DVT- Distal	THR: 0.579 (BLU-THR)	0.057	PROMS 2014-2015[683]
Asymptomatic DVT- Proximal	TKR: 0.582 (BLU-TKR)	0.058	PROMS 2014-2015[683]
Symptomatic DVT- Proximal	-14%		Cohen 2014[192]
Symptomatic DVT- Distal	-14%		Assumption: equal to the disutility for symptomatic DVT-

	Mean (dis-)utility	SE(a)	Source
(requiring treatment)			proximal
Symptomatic DVT- Distal (not requiring treatment)	-7%		Assumption: equal to the 50% of the disutility for symptomatic DVT-proximal
Non-fatal PE	-19%		Cohen 2014[192]
Warfarin treated DVT or PE	-0.012		Marchetti 2001 [609] & Edoxaban TA354 [674]company submission
Major bleeding (surgical site, GI with or without intervention, other)	-32%		Locadia 2004[573]
ICH/acute stroke	-65%		Locadia 2004[573]
Pre- aseptic revision surgery	THR: 0.399	0.039	PROMS 2014-2015[683]
	TKR: 0.329	0.033	PROMS 2014-2015[683]
Post-aseptic revision surgery	THR: 0.538	0.054	PROMS 2014-2015[683]
	TKR: 0.459	0.046	PROMS 2014-2015[683]
Post-reoperation for surgical site MB	THR: 0.538	0.054	Assumed equal to post-aseptic revision
	TKR: 0.459	0.046	Assumed equal to post-aseptic revision
CRNMB (including wound haematoma)	-0.03		Sullivan 2011[927]
Surgical site infection	-66%		Baker 2013[65] for TKR, assumed the same for THR
Post-infected revision/return to theatre for surgical site infection	-30%		Baker 2013[65]for TKR, assumed the same for THR
HIT	-0.0712		Gould 1999 [355]
Post-HIT amputation	-0.28		Beaudet 2014, T1D GL[82]
Post-HIT thrombosis	-16.5%		Assumed average of PE and symptomatic proximal DVT dis-utilities
Post-HIT MB	-32%		Assumed equal to Major bleeding (surgical site, GI with or without intervention, other)
Fatal MB Fatal PE Death due to HIT	0.000		

Abbreviations: CRNMB: clinically-relevant non-major bleeding; GI: gastrointestinal; HIT: heparin-induced thrombocytopaenia; ICH: intracranial haemorrhage; MB: major bleeding; PE : pulmonary embolism; SE: standard error; THR: total hip replacement; TKR: total knee replacement.

(a) Where not reported; SE was calculated as 10% of the mean

P.1.3.5.2 > 90 days after surgery

For patients who have no event during the first part of the model, and progress to enter the "*well*" state in the Markov model, quality of life was adjusted for ageing as time passes in the model using age- and sex- specific disutility calculated from Kind 1998. [495]

The same utility value and aging disutility were used for individuals in the post-treated and post-untreated VTE health states ("*post- PE", "post-symptomatic proximal DVT", "post-symptomatic distal*

DVT", "post-asymptomatic proximal DVT", and "post-asymptomatic distal DVT"). For the remaining health states in the Markov model, the (dis)utilities and their sources are outlined in **Table 287**.

Table 287: Base case (dis-)utility values for the Markov model health states (more than 90 days after surgery)

	Mean (dis-)utility	SE(a)	Source	duration
Post stroke (disabled)	-10%		Lunde 2013 [586] 345 Stroke patients in Norway who had ischaemic/haemorrhagic or TIA	lifetime
Mild to Moderate PTS	-0.02		Lenert 1997 [548]	lifetime
Severe PTS	-0.07		Lenert 1997[548]	lifetime
CTEPH-Year 1	-26%		Meads 2008 [627]	Operable or inoperable (3 months) Recurrent/resistant (12 months)
CTEPH - Year 2- recurrent resistant Chronic CTEPH	22%		Meads 2008[627]	Utility improvement after medical treatment applied to CTEPH-Year 1 utility value Chronic CTEPH utility applied lifetime
Post-HIT amputation	-0.28		Beaudet 2014 [82], T1D GL[669]	Lifetime

Abbreviations: HIT: heparin-induced thrombocytopaenia; SE: standard error; T1D: Type 1 diabetes
a) Where not reported; SE was calculated as 10% of the mean

P.1.3.6 Resource use and costs

P.1.3.6.1 Prophylaxis strategies

The cost of the prophylaxis strategies included in the models was calculated based on the dose and duration of each of its components (pharmacological and/or mechanical). Additionally, the cost of administration and monitoring, where required, were included.

The total costs of each prophylaxis strategy are presented in

Table 288 for eTHR and eTKR populations. For a breakdown of the costs of the mechanical prophylaxis options, see **Table 289** and **Table 290** for the eTHR and eTKR populations; respectively. The unit costs of all pharmacological prophylaxis options are presented in **Table 291**. A breakdown of the costs of the pharmacological prophylaxis options including drug, administration and monitoring costs are also presented in **Table 292** and **Table 293** for the eTHR and eTKR populations; respectively. In calculating the costs of pharmacological prophylaxis options, oral administration was assumed to incur no costs. It was also assumed that there will be no drug wastage. A sensitivity analysis has been undertaken taking wastage into account (see section P.1.5).

Table 288: Total costs of each prophylaxis strategy in the eTHR and eTKR models

Population and strategy	Total costs of pharmacological prophylaxis (I)	Total costs of mechanical prophylaxis (II)	Total intervention cost (I+II)
THR			
1. LMWH (std,std) + AEs	£138	£31	£169
2. LMWH (std,extd)+ AEs	£387	£31	£419
3. Fondaparinux+ AES	£83	£31	£115
4. Foot pump + AES	£0	£91	£91
5. IPCD	£0	£42	£42
6. AEs (above knee)	£0	£34	£34
7. Foot pump	£0	£59	£59
8. AES	£0	£31	£31
9. LMWH (std,std)	£138	£0	£138
10. LMWH (std,extd)	£387	£0	£387
11. Aspirin (std duration)	£0	£0	£0
12. LMWH (std, std) + Aspirin (extd duration)	£115	£0	£115
13. Dabigatran	£80	£0	£80
14. Apixaban	£59	£0	£59
15. Rivaroxaban	£74	£0	£74
16. No prophylaxis	£0	£0	£0
TKR			
1. LMWH (std,std) + AEs	£111	£31	£142
2. Fondaparinux+ AES	£97	£31	£128
3. Foot pump + AES	£0	£91	£91
4. IPCD	£0	£42	£42
5. Foot pump	£0	£59	£59
6. AES	£0	£31	£31
7. LMWH (std,std)	£111	£0	£111
8. LMWH (std,extd)	£355	£0	£355
9. Aspirin	£0	£0	£0
10. Dabigatran	£34	£0	£34
11. Apixaban	£23	£0	£23
12. Rivaroxaban	£25	£0	£25
13. No prophylaxis	£0	£0	£0

Abbreviations: AEs: anti-embolism stockings; eTKR: elective total knee replacement; eTHR: elective total hip replacement; extd: extended; IPCD: intermittent pneumatic compression devices; LMWH: low molecular weight heparin; std: standard

Table 289: Total costs of mechanical prophylaxis options - eTHR

Mechanical Prophylaxis	Price per pair (a) (I)	Prophylaxis duration (days) (b)	Number of Pairs (c) (II)	Total cost of consumables (Pairs)(d) (III)	Total Cost of fitting and monitoring (e) (IV)	Total Cost (f)
IPCD						
Knee length	£21.34	8.5	2	£43	£15	£58
Thigh length	£31.67	8.5	2	£63	£15	£78
Any length	£26.50(g)	8.5	2	£53	£15	£68
AES						
Knee length	£3.86	7	1	£4	£18	£22
Thigh length	£6.63	26	4	£27	£18	£45
Full length	£9.12	26	4	£37	£18	£55
Any length	£6.54 (g)	10.5	2	£13	£18	£31
Foot pump						
Foot Pump	£44.23 (h)	7	1	£44	£15	£60

Abbreviations: AEs: anti-embolism stockings; eTHR: elective total hip replacement; IPCD: intermittent pneumatic compression.

(a) Average price of sizes small to medium of IPC sleeves with vascular refill detection or stockings. Source: NHS supply chain catalogue 2015-2016[685]

(b) Average duration in the RCTs included in the NMA

(c) Calculated based on life expectancy of 7 days per pair and the duration of prophylaxis

(d) Calculated as (I) X (II).

(e) Cost of fitting was calculated based on average time required for fitting of IPCD/Foot pump and AEs of 5 minutes and 10 minutes, respectively. This was assumed to be completed by a band 5 hospital-based nurse (£35 per hour).[224] Cost of monitoring was assumed to require 5 minutes daily while in hospital. Similarly, this was assumed to be completed by a band 5 hospital-based nurse (£35 per hour).[224]

(f) Calculated for the duration of prophylaxis as the sum of (III) and (IV).

(g) Calculated as average of all lengths.

(h) Source: Price used in CG92 model was adjusted for inflation using the PSSRU hospital & community health services (HCHS) index.[224]

Table 290: Total costs of mechanical prophylaxis options - eTKR

Mechanical Prophylaxis	Price per pair (a) (I)	Prophylaxis duration (days) (b)	Number of Pairs (c) (II)	Total cost of consumables (Pairs)(d) (III)	Total Cost of fitting and monitoring (e) (IV)	Total Cost (f)
IPCD						
Knee length	£21.34	6	1	£21	£15	£37
Thigh length	£31.67	6	1	£32	£15	£47
Any length	£26.50 (g)	6	1	£27	£15	£42
AEs						
Knee length	£3.86	10.5	2	£8	£18	£26
Thigh length	£6.63	10.5	2	£13	£18	£31
Full length	£9.12	10.5	2	£18	£18	£36
Any length	£6.54 (g)	10.5	2	£13	£18	£31
Foot pump						
Foot Pump	£44.23 (h)	4	1	£44	£15	£59

Abbreviations: AEs: anti-embolism stockings; eTKR: elective total knee replacement; IPCD: intermittent pneumatic compression.

(a) Average price of sizes small to medium of IPC sleeves with vascular refill detection or stockings. Source: NHS supply chain catalogue 2015-2016.[685]
(b) Average duration in the RCTs included in the NMA
(c) Calculated based on life expectancy of 7 days per pair and the duration of prophylaxis
(d) Calculated as (I) X (II).
(e) Cost of fitting was calculated based on average time required for fitting of IPCD/Foot pump and AEs of 5 minutes and 10 minutes, respectively. This was assumed to be completed by a band 5 hospital-based nurse (£35 per hour).[224] Cost of monitoring was assumed to require 5 minutes daily while in hospital. Similarly, this was assumed to be completed by a band 5 hospital-based nurse (£35 per hour).[224]
(f) Calculated for the duration of prophylaxis as the sum of (III) and (IV).
(g) Calculated as average of all lengths.
(h) Source: Price used in CG92 model was adjusted for inflation using the PSSRU hospital & community health services (HCHS) index.[224]

Table 291: Unit costs of pharmacological prophylaxis

Drug	Preparation	strength	Mg or IU/ unit	Units / pack	Cost/ pack (£)	Cost/ unit (£)	Units / day	Cost/ day (£)	Cost/ month (£)
Enoxaparin sodium	solution for injection pre-filled syringes	40mg/ 0.4ml	40	10	£30.27 (a)	£3.03	1	£3.0	£92
Dalteparin sodium	Solution for injection- pre-filled syringes	5,000 units/ 0.2ml	5,000	10	£28.23 (b)	£2.82	1	£2.8	£86
Tinzaparin sodium	Solution for injection- pre-filled syringes	3500units /0.35ml	3,500	10	£27.71 (b)	£2.77	1	£2.8	£84
Tinzaparin sodium	Solution for injection- pre-filled syringes	4500units /0.45ml	4,500	10	£35.63 (b)	£3.56	1	£3.6	£108
Fondaparinux sodium	solution for injection pre-filled syringes	2.5 mg/ 0.5ml	2.5	10	£43.95 (c)	£4.40	1	£4.4	£134
Dabigatran etexilate	capsules	110 mg	110	60	£65.90 (a)	£1.10	1	£1.1	£33
Dabigatran etexilate	capsules	110 mg	110	60	£65.90 (a)	£1.10	2	£2.2	£67
Dabigatran etexilate	capsules	150 mg	150	60	£65.90 (a)	£1.10	1	£1.1	£33
Dabigatran etexilate	capsules	75 mg	75	60	£65.90 (a)	£1.10	1	£1.1	£33
Rivaroxaban	tablets	10 mg	10	30	£63.00 (a)	£2.10	1	£2.1	£64
Apixaban	tablets	2.5 mg	2.5	60	£57.00 (a)	£0.95	2	£1.9	£58
Aspirin	tablets	300 mg	300	32	£3.35 (a)	£0.10	1	£0.1	£3

(a) NHS Drug tariff July 2016[682]
(b) British National Formulary[458]
(c) eMIT/CMU[207]

Table 292: Total costs of pharmacological prophylaxis for the eTHR population

Drug	Dose	RCT duration (a)	Licensed duration (b)	Initiation	Cost category	Total costs
LMWH (standard duration)	**(c)**	**16**	**N/A**	**Post-op**	Drug cost	£41.14
					Administration costs	£91.30
					Monitoring tests	£47.47
					Total cost	**£179.91**
LMWH (standard duration)	**(c)**	**11**	**N/A**	**Pre-op**	Drug cost	£25.85
					Administration costs	£37.40
					Monitoring tests	£32.37
					Total cost	**£95.61**
LMWH (extended duration)	**(c)**	**33**		**Pre-op**	Drug cost	£92.81
					Administration costs	£242.73
					Monitoring tests	£51.79
					Total cost	**£387.33**
Fondaparinux sodium (standard duration)	**2.5 mg once daily (dose is weight based)**	**8**	**N/A**	**post-op**	Drug cost	£30.77
					Administration costs	£26.77
					Monitoring tests	£25.89
					Total cost	**£83.42**
Dabigatran etexilate	**Dose is age-based (75 to 110 mg once to twice daily)**	**32**	**27-34**	**post-op**	Drug cost	£67.00
					Administration costs	£0.00
					Monitoring tests	£12.95
					Total cost	**£79.94**
Rivaroxaban	**10 mg once daily**	**35**	**35**	**post-op**	Drug cost	£73.50
					Administration costs	£0.00
					Monitoring tests	£0.00
					Total cost	**£73.50**
Apixaban	**2.5 mg once**	**32**	**32-38**	**post-op**	Drug cost	£58.90

Drug	Dose	RCT duration (a)	Licensed duration (b)	Initiation	Cost category	Total costs
	daily					
					Administration costs	£0.00
					Monitoring tests	£0.00
					Total cost	**£58.90**
Aspirin	**100 mg daily (d)**	**7**	**N/A**	**post-op**	Drug cost	£0.24
					Administration costs	£0.00
					Monitoring tests	£0.00
					Total cost	**£0.24**
LMWH (10 days)+ Aspirin (28 days)	**LMWH: (c) Aspirin: 100 mg daily (d)**	**38**	**N/A**	**Postop**	Drug cost	£29.71
					Administration costs	£53.17
					Monitoring tests	£32.37
					Total cost	**£115.25**

(a) average duration in the relevant randomised controlled trials included in the NMAs. For LMWH, this is the average for across all the trials of all included drugs (enoxaparin, tinzaparin and daltparin)
(b) Source: British National Formulary British National Formulary[458]
(c) Enoxaparin: 40 mg once daily, tinzaparin: 3500 units/day, dalteparin:5000IU/day
(d) Dose as used in the included trials

Table 293: Total costs of pharmacological prophylaxis for the eTKR population

Drug	Dose	RCT duration (a)	Licensed duration (b)	Initiation	Cost category	Total costs
LMWH (standard duration)	**(c)**	10	N/A	Post-op	Drug cost	£28.74
					Administration costs	£53.17
					Monitoring tests	£32.37
					Total cost	**£114.27**
LMWH (standard duration)	**(c)**	10	N/A	Pre-op	Drug cost	£28.74
					Administration costs	£46.20
					Monitoring tests	£32.37
					Total cost	**£107.30**
LMWH (extended duration)	**(c)**	30	N/A	Post-op	Drug cost	£83.34
					Administration costs	£220.37
					Monitoring tests	£51.79

Drug	Dose	RCT duration (a)	Licensed duration (b)	Initiation	Cost category	Total costs
					Total cost	**£355.49**
Fondaparinux sodium	**2.5 mg once daily (dose is weight based)**	11	N/A	Post-op	Drug cost	£43.95
					Administration costs	£53.17
					Monitoring tests	£0.00
					Total cost	**£97.12**
Dabigatran etexilate	**Dose is age-based (75 to 110 mg once to twice daily)**	11	9	Post-op	Drug cost	£20.87
					Administration costs	£0.00
					Monitoring tests	£12.95
					Total cost	**£33.81**
Rivaroxaban	**10 mg once daily**	13	14	Post-op	Drug cost	£25.20
					Administration costs	£0.00
					Monitoring tests	£0.00
					Total cost	**£25.20**
Apixaban	**2.5 mg once daily**	12	10 to 14	Post-op	Drug cost	£22.80
					Administration costs	£0.00
					Monitoring tests	£0.00
					Total cost	**£22.80**
Aspirin	**100 mg daily (d)**	14	N/A	Post-op	Drug cost	£0.49
					Administration costs	£0.00
					Monitoring tests	£0.00
						£0.49

(a) average duration in the relevant randomised controlled trials included in the NMAs. Fir LMWH, this is the average for across all the trials of all included drugs (enoxaparin, tinzaparin and daltparin)
(b) Source: British National Formulary British National Formulary[458]
(c) Enoxaparin: 40 mg once daily, tinzaparin: 3500 units/day, dalteparin:5000IU/day
(d) Dose as used in the included trials

P.1.3.6.2 Decision tree events (up to 90 days post-operatively)

P.1.3.6.2.1 Pulmonary Embolism (PE) and symptomatic DVT treatment

Micro-costing was undertaken to calculate the cost of treating non-fatal PE and symptomatic proximal DVT episodes, as the committee felt that the NHS reference costs did not reflect recent advances in current practice where both DVT and PE are generally treated on outpatient basis and if

a hospital admission is required for PE, this would be either a short stay or day case admission. Additionally, the committee wanted to reflect the fact that PE events occurring in hospital pre-discharge would only require, on average, one excess bed day and unlikely to result in a delay in discharging patients.

The total cost of diagnosis and treatment for these VTE events was, thus, calculated to include the following cost categories: diagnosis, drug treatment and other resources. Unit costs were taken from standard NHS sources: NHS Electronic Drug Tariff,[682] NHS Schedule for Reference Costs 2015-2016[250], British National Formulary (June 2016)[458], eMIT/CMU,[207] and Unit Costs of Health and Social Care 2016.[224]

Diagnosis:

The pathways for objective confirmation of the diagnosis of symptomatic DVT and PE were based on NICE guideline CG144.[668] costs of diagnosing symptomatic DVT and PE are presented in **Table 294** and **Table 295**; respectively. A weighted average cost for events occurring in-hospital (pre-discharge) and those occurring in community (post-discharge) was calculated for each event on the assumption that 25% of events occur post-discharge.

For DVT; the weighted average cost was calculated to be £62 for proximal and £92 for distal DVT. For PE; events occurring post-discharge were assumed to require an inpatient admission and hence, diagnosis costs if occurring post-discharge were assumed to be £0 as diagnostic investigations would be included in the cost of the admission episode.

Table 294: Diagnosis costs for symptomatic DVT

	Units used	Breakdown of Resources used per unit	Unit cost	Source for unit cost	Total cost	% of patients		Weighted average cost
						In hospital	Post-discharge	
Wells Score	1	10 minutes of registrar time.	£10.06 [£60.33 per hour (weighted average cost of all working hours, including qualification)]	PSSRU 2016[224]	£10.06	100%	0% (assumed to be completed as part of a GP or ED visit)	
DDi-laboratory based	1	One DDi test	£20.79 [£207.88 per pack of 10]	Supply chain catalogue 2015-2016[685]	£31.65	7% (proximal DVT)[353] 100% (distal DVT)	7% (proximal DVT)[353] 100% (distal DVT)	
		5 minutes of a laboratory technician time	£2.00 [£24 per hour (allied health professional)]	PSSRU 2016				
		10 minutes of a hospital-based clinical support worker (nursing)-band 2	£3.83 [£23 per hour of patient contact(including qualification)]	PSSRU 2016[224]				
		5 minutes of a registrar time	£5.03 [£60.33 per hour (weighted average cost of all working hours, including qualification)]	PSSRU 2016[224]				
Proximal Leg Vein Ultrasound (PLV-US)-direct access	1	Leg ultrasound for less than 20 minutes for each leg.	Direct access: £55.12 per test Outpatient: £52.20 per test [weighted average of Leg ultrasound for less than 20 minutes for each leg with	National Schedule of Reference Costs - Year 2015-2016[250]	£55.12 £52.20	100%	50% 50%	

			and without contrast (currency codes RD41Z and RD40Z respectively)]					
						In-hospital	**Post-discharge**	**Weighted average (a)**
					Proximal DVT	£64.47	£55.87	£62.32
					Distal DVT	£93.90	£85.31	£91.75

Abbreviations: DDi: D-Dimer, DVT: deep vein thrombosis.

a) Calculated based on a proportion of DVTs happening in hospital of 75% while 25% would be diagnosed post discharge.

Table 295: Costs of diagnosing PE events occurring in-hospital (pre-discharge)

	Units used	Breakdown of Resources used per unit	Unit cost	Source for unit cost	Total cost	% of patients In-hospital
Chest X-ray	1	Direct Access Plain Film	£30.26[HRG code DAPF]	National Schedule of Reference Costs - Year 2015-2016 [250]	£30.26	100%
Two level PE Wells Score	1	10 minutes of registrar time.	£10.06 [£60.33 per hour (weighted average cost of all working hours, including qualification)]	PSSRU 2016[224]	£10.06	100%
DDi-laboratory based	1	One DDi test	£20.79 [£207.88 per pack of 10]	Supply chain catalogue 2015-2016[685]	£31.65	75%
		5 minutes of a laboratory technician time	£2.00 [£24 per hour (allied health professional)]	PSSRU 2016[224]		
		10 minutes of a hospital-based clinical support worker (nursing)-band 2	£3.83 [£23 per hour of patient contact(including qualification)]	PSSRU 2016[224]		
		5 minutes of a registrar time	£5.03 [£60.33 per hour (weighted average cost of all working hours, including qualification)]	PSSRU 2016[224]		
CTPA	1	Computerised Tomography Scan of one area, with post contrast only,	£102.01 [weighted average cost of HRG codes RD21A(19 years and over) and RD21B (between 6 and 18 years)	National Schedule of Reference Costs - Year 2015-2016[250]	£102.01	90%
V/Q Spect	1	Single Photon Emission Computed Tomography (SPECT)	£263.56 [weighted average cost of HRG codes RN08A (19 years and over) and RN08B (between 6 and 18 years)	National Schedule of Reference Costs - Year 2015-2016[250]	£263.56	5%
V/Q planar	1	Lung Ventilation or Perfusion Scan, 19 years	£245.77 [weighted average cost of HRG codes RN18A (19 years and over)	National Schedule of Reference Costs - Year	£245.77	5%

	Units used	Breakdown of Resources used per unit	Unit cost	Source for unit cost	Total cost	% of patients In-hospital
		and over	and RN18B (between 6 and 18 years)	2015-2016[250]		
					Total	£181.33

Drug treatment:
Strategies for the treatment of DVT and PE were based on CG144, the recent edoxaban technology appraisal for VTE treatment and secondary prevention (TA354) and the committee expert opinion. [674] The committee advised that the duration of the treatment course for symptomatic DVT and PE would be 3 months, given that hospital acquired VTE is a provoked event. Three strategies for treatment were considered to be the standard recommended treatment pathways.

The first strategy (Strategy 1) is the traditional approach to treatment where a parenteral anticoagulant is given from diagnosis for up to day 7; overlapping with an oral Vit. K antagonist (warfarin). The parenteral anticoagulants considered were LMWHs (enoxaparin, dalteparin or tinzaparin), UFH or fondaparinux. The Vit K antagonist is then continued up to 3 months. The second strategy (Strategy 2) involves using the direct acting oral anticoagulants (DOACs) rivaroxaban or apixaban from day 0 up to 3 months. The third strategy (Strategy 3) involves the use of a parenteral anticoagulant for 7days followed by one of the two DOACs: dabigatran or edoxaban for the remainder of the 3 months treatment duration.

The cost of each strategy was calculated using the following doses:

- LMWHs (for 7 days):
    - Dalteparin : 15,000-unit (0.6-mL) syringe.
    - Tinzaparin : 14,000-unit (0.7-mL) syringe.
    - Enoxaparin : 100-mg (1-mL, 10 000-units) syringe.
- UFH: 5,000 units/mL:5-mL amp.
- Fondaparinux: body-weight under 50 kg, 5 mg every 24 hours; body-weight 50–100 kg, 7.5 mg every 24 hours; body-weight over 100 kg, 10 mg every 24 hours
- Warfarin: on average 5 mg twice daily
- Rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily)
- Apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily)
- Dabigatran (150 mg twice daily, or 110 mg twice daily for patients >80 years of age) following acute phase parenteral anticoagulation
- Edoxaban (60 mg once daily) following acute-phase parenteral anticoagulation

The unit costs for these drug regimens are presented in **Table 296.**

The costs of administration, monitoring and follow-up, where applicable, were also included (see **Table 297**). The cost of anticoagulation clinics was also included in strategy 1 where a Vit K antagonist is used. Self-administration of parenteral treatments was considered to occur in a similar proportion of patients to that used for calculating the cost of the parenteral prophylaxis interventions (80%). The cost of nurse education for self-administration and the costs of sharps bins were included for these patients. For patients requiring nurse administration, the cost of nurse time was included.

The committee advised that the first two of these are the most commonly used in practice; hence; a weighted average cost of treatment was calculated as the weighted average of these two strategies in a ratio of 1:1 in the base case analysis. The total cost of each strategy is presented in **Table 298**.

Table 296: Drug costs for VTE treatment regimens

Drug	Preparation	Mg or IU/ unit	Units/ pack	Cost/ pack (£)	Cost/ unit (£)	Cost/ mg or IU (£)	Units/ day	Cost/ day (£)	Cost/ month (£)
Parenteral anticoagulants									
LMWHs									
Enoxaparin sodium	solution for injection pre-filled syringes	100	10	£72.3 (a)	£7.23	£0.07	1	£7.23	£219.91
Dalteparin sodium	Solution for injection- pre-filled syringes	15,000	5	£42.34 (b)	£8.47	£0.001	1	£8.47	£257.57
Tinzaparin sodium	solution for injection- pre-filled syringes	14,000	6	£49.98 (b)	£8.33	£0.001	1	£8.33	£253.37
Unfractionated heparin (UFH)									
Heparin sodium	solution for injection- ampoules	5,000	10	£13.89 (c)	£1.39	£0.0003	1	£1.39	£42.25
Pentasaccharide									
Fondaparinux sodium	solution for injection pre-filled syringes	5	10	£84.22 (c)	£8.42	£1.68	1	£8.42	£256.17
Fondaparinux sodium	solution for injection pre-filled syringes	7.5	10	£86.92 (c)	£8.69	£1.16	1	£8.69	£264.38
Fondaparinux sodium	solution for injection pre-filled syringes	10	10	£89.38 (c)	£8.94	£0.89	1	£8.94	£271.86
Vit K antagonists									
Warfarin sodium	tablets	5	28	£0.82(a)	£0.03	£0.01	2	£0.06	£1.78
Direct-acting Oral Anticoagulants (DOACs)									
Rivaroxaban	tablets	15	28	£58.80(a)	£2.10	£0.14	2	£4.20	£127.75
Rivaroxaban	tablets	20	28	£58.80(a)	£2.10	£0.11	1	£2.10	£63.88
Apixaban	tablets	5	28	£26.60 (b)	£0.95	£0.19	4	£3.80	£115.58
Apixaban	tablets	5	56	£53.20 (b)	£0.95	£0.19	2	£1.90	£57.79

Drug	Preparation	Mg or IU/ unit	Units/ pack	Cost/ pack (£)	Cost/ unit (£)	Cost/ mg or IU (£)	Units/ day	Cost/ day (£)	Cost/ month (£)
Dabigatran etexilate	capsules	150	60	£65.90 (a)	£1.10	£0.01	2	£2.20	£66.82
Edoxaban (as tosilate)	tablets	60	28	£51.80 (b)	£1.85	£0.03	1	£1.85	£56.27

Abbreviations: DOACs: directly-acting oral anticoagulants; IU: international unit; LMWH: low molecular weight heparin; UFH: unfractionated heparin;
(a) NHS Electronic Drug Tariff[682]
(b) British National Formulary (June 2016)[458]
(c) eMIT/CMU[207]

Table 297: Administration and monitoring costs for drugs used for VTE treatment

Treatment	Tests required	total Cost of tests per 3 months treatment	Nurse time associated with administering and monitoring prophylaxis	Cost of Nurse education of self-injection	Cost of nurse time per day of hospital stay	Cost of nurse time per day in community	Cost of Sharps bin	Other costs	Total cost of monitoring and administration	
									Sympt DVT	PE
LMWH	Full blood count: baseline then every 2-4 days until day 14 (BCSH guidelines, Keeling 2006 [481])	£29.13	2-3 minutes per injection	£4.40	£1.83	£8.80	£2.21	-	£97.34	£90.37
UFH	Full blood count: baseline (plus the day after start if previous exposure to UFH) then alternate days from day 4-14 (BCSH guidelines, Keeling 2006[481])	£29.13	2-3 minutes per injection	£4.40	£5.50	£26.40	£2.21	-	£220.54	£199.64
Warfarin	prothrombin time (PT) once at the start, International Normalised	£97.10	10-20 minutes per day	-	£11.00	-	-	£116.91 (a)	£97.10	£108.10

Treatment	Tests required	total Cost of tests per 3 months treatment	Nurse time associated with administering and monitoring prophylaxis	Cost of Nurse education of self-injection	Cost of nurse time per day of hospital stay	Cost of nurse time per day in community	Cost of Sharps bin	Other costs	Total cost of monitoring and administration	
									Sympt DVT	PE
	Ratio (INR) tests: approximately 3 per week during hospital stay then less frequently at least once every 12 weeks									
Fondaparinux	-	-	2-3 minutes per injection	£4.40	£1.83	£8.80	£2.21	-	£68.21	£12.95
Apixaban	-	-	-	-	-	-	-	-	-	-
Dabigatran	Baseline liver and renal function test	£12.95	-	-	-	-	-	-	£12.95	£12.95
Edoxaban	Baseline liver and renal function test	£12.95	-	-	-	-	-	-	£12.95	£12.95
Rivaroxaban	-	-	-	-	-	-	-	-	-	-

Abbreviations: DVT: deep vein thrombosis; LMWH: low molecular weight heparin; PE: pulmonary embolism; UFH: unfractionated heparin;
(a) Anticoagulation clinic costs (1 first visit and 3 monthly follow-up visits)

Table 298: Total costs for each VTE treatment strategy

Drug class	Drug	% of patients	Days on treatment	Drug cost per treatment course - PE/DVT	Monitoring and administration for period of treatment- PE	Monitoring and administration for period of treatment- DVT	Total costs	
							PE	DVT
Strategy 1							**£372.18**	**£368.85**
Parentral Anticoagulant		100%						

Drug class	Drug			% of patients	Days on treatment	Drug cost per treatment	Monitoring and administration for period of	Monitoring and administration for period of	Total costs	
LMWH	enoxaparin	dalteparin	tinzaparin							
	45% (a)	27% (a)	18% (a)	90%(b)	7	£49.27(b)	£90.37	£97.34	£139.65	£149.65
UFH				5% (b)	7	£9.72	£199.64	£220.54	£209.36	£230.26
Fondaparinux				5% (b)	7	£60.84	£61.24	£68.21	£122.09	£129.05
Vit K antagonist	Warfarin			100%	84	£4.92	£225.01	£214.01	£229.93	218.93
Strategy 2									**£196.70**	**£196.70**
Direct-acting oral anticoagulants (DOACs)	Apixaban			50%	84	£172.90	£0.00	£0.00	£172.90	£172.90
	Rivaroxaban			50%	84	£220.50	£0.00	£0.00	£220.50	£220.50
Strategy 3									**£311.00**	**£318.66**
Parentral Anticoagulant				100%						
LMWH	enoxaparin	dalteparin	tinzaparin							
	45% (a)	27% (a)	18% (a)	90%(b)	7	£49.27(b)	£90.37	£97.34	£139.65	£149.65
UFH				5% (b)	7	£9.72	£199.64	£220.54	£209.36	£230.26
Fondaparinux				5% (b)	7	£60.84	£61.24	£68.21	£122.09	£129.05
Direct-acting oral anticoagulants (DOACs)	Dabigatran			50%	77	£169.14	£12.95	£12.95	£182.09	£182.09
	Edoxaban			50%	77	£142.45	£12.95	£12.95	£155.40	£155.40

Abbreviations: DOACs: directly-acting oral anticoagulants; DVT: deep vein thrombosis; LMWH: low molecular weight heparin; PE: pulmonary embolism; UFH: unfractionated heparin; VTE: venous thromboembolism

(a) Proportions expert opinion as reported in TA354 [674]

(b) Proportions expert opinion as reported in TA354 [674]

(c) Average cost of the three LMWHs weighted by the probability of prescribing each of them.

Other resources:

For symptomatic DVT events diagnosed pre-discharge, no extra resources were included. In case of PE, an excess bed day was included for all patients as well as a critical care admission for 10% of patients. For events occurring post discharge, it was assumed that a visit to either the GP or the emergency department will be required during which initial assessment will be undertaken. The cost of an ambulance transfer was included for patients who will require an emergency department visit. The cost of short stay admission was also included for all patients diagnosed with PE and 50% of patients diagnosed with a symptomatic proximal DVT (see **Table 299** and **Table 300**).

Table 299: Resource use for PE events

	% of Patients		
Resource item	**In-hospital**	**Post-discharge**	**unit cost**
Emergency department visit	0%	80%	£222(a)
GP visit	0%	20%	£36 (b)
PE admission short stay	0%	100%	£499 (c)
Critical care unit stay	10%	10%	£1,021(d)
Ambulance	0%	80%	£236 (e)
Excess bed days-Hip	100%	0%	£333 (f)
Excess bed days-knee	100%	0%	£335 (g)
Total	**In-hospital**	**Post-discharge**	**Weighted average cost**
eTHR	£435.10	£975.46	**£570.19**
eTKR	£437.01	£975.46	**£571.63**

Abbreviations: eTHR: elective total hip replacement; eTKR: elective total knee replacement; GP: general practitioner; PE: pulmonary embolism.

(a) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average cost of Type 01 and Type02 admitted emergency department HRG codes VB01Z to VB09Z.

(b) PSSRU 2016[224]

(c) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average cost of non-elective short stay for "Pulmonary Embolus with Interventions", codes DZ09J to DZ09N, DZ09P and DZ09Q.

(d) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average cost of adult Critical Care, 0 to 6 or more organs Supported, codes XC01Z to XC01Z.

(e) NHS Schedule for Reference Costs 2015-2016[250]. "See and treat and convey", code ASS02.

(f) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average cost of elective inpatient excess bed days for "Very Major Hip Procedures for Non-Trauma" CC score 0 to 10+, codes HN12A to HN12F.

(g) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average cost of elective inpatient excess bed days for "Very Major knee Procedures for Non-Trauma" CC score 0 to 8+, codes HN22A to HN22E.

Table 300: Resource use for symptomatic DVT events

	% of Patients		
Resource item	**In-hospital**	**Post-discharge**	**unit cost**
Emergency department visit	0%	50%	£222(a)
GP visit	0%	50%	£36 (b)
DVT admission short stay	0%	50% (proximal) 0% (distal)	£403 (d)
Ambulance	0%	50%	£236 (e)
Total	**In-hospital**	**Post-discharge**	**Weighted average cost**
Symptomatic proximal	£0.00	£448.85	**£112.21**
Symptomatic distal	£0.00	£247.21	**£61.80**

Abbreviations: DVT: deep vein thrombosis; eTHR: elective total hip replacement; eTKR: elective total knee replacement; GP: general practitioner.

(a) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average cost of Type 01 and Type02 admitted emergency department HRG codes VB01Z to VB09Z.
(b) PSSRU 2016[224]
(c) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average cost of non-elective short stay for "Deep Vein Thrombosis" CC score 0 to 12+, codes YQ51A to YQ51E.
(d) NHS Schedule for Reference Costs 2015-2016[250]. "See and treat and convey", code ASS02.

In clinical practice there would be no diagnosis or treatment costs associated with asymptomatic DVT (proximal and distal). Hence, the costs of these events were assumed to be £0. Similarly, in line with CG92 model assumptions; the incremental treatment cost of fatal pulmonary embolism (and fatal bleeding) was assumed to be £0 - on the one hand treatment of the event would generate additional health service costs but on the other hand the treatment costs for the illness they were admitted will be curtailed.

P.1.3.6.2.2 Major bleeding

The cost of managing major bleeding was calculated based on the site of bleeding and the need to re-operate. Antidote costs were not explicitly incorporated.

For **gastro-intestinal bleeding**, it was assumed that an intervention would be required in 13% of cases, based on a review of five fondaparinux and dabigatran trials.[666] The cost for managing a GI bleed that requires an intervention was based on the NHS schedule for Reference costs 2015-2016 HRG codes FZ38J to FZ38L (Gastrointestinal Bleed with Single Intervention, with CC Score 0-4 to 8+) for non-elective short stay, non-elective long stay and elective long stay. This was £2,409. The cost for managing a GI bleed that does not require an intervention was based on the NHS schedule for Reference costs 2015-2016 HRG codes FZ38M to FZ38P (Gastrointestinal Bleed without Interventions, with CC Score 0-4 to 9+) for non-elective short stay, non-elective long stay and elective long stay98890. This was £855.[250]

For **surgical site bleeding**, it was assumed that it will lead to a return to theatre in 100% of cases based on the definition in the trials that reported it. The cost was considered to be equal to that of the primary operation: £6,278 for eTHR and £6,178 for eTKR. For eTHR, the cost was the weighted average of HRG codes HN12A to HN12F (Very Major Hip Procedures for Non-Trauma with CC Score from 0-1 to 10+) and for eTKR, the cost was the weighted average of HRG codes HN22A to HN22E (Very Major Knee Procedures for Non-Trauma with CC Score from 0-1 to 8+).

For **intracranial haemorrhage/haemorrhagic stroke**, the cost of the acute event management was calculated as the weighted average cost for the HRG codes AA35A to AA35F (Stroke with CC Score 0-3 to 16+), non-elective long stay, to be £4,354. Other costs during the first 90 days were calculated as the average of managing a patient with stroke in the first year for a dependent state and for an independent state for 90 days out of the full year. This was £3,255. Hence, the total cost for managing the stroke event in the first 90 days was calculated to be £7,609.

For **bleeding at any other site**, the cost was assumed to be the same as for GI bleeding that does not require an intervention (£855).[250]

P.1.3.6.2.3 Clinically-relevant non-major bleeding

The cost of managing a CRNMB that is diagnosed post-discharge was assumed to be the cost of two outpatient visits-trauma and orthopaedics. The first visit cost was calculated to be £133, which is a weighted average cost of consultant-led and non-consultant-led, for a non-admitted face to face attendance, first visit. The follow-up visit cost was calculated to be £108.3, which is a weighted average cost of consultant-led and non-consultant-led, for a non-admitted face to face attendance, follow-up visit. Hence, the total cost of managing a CRNMB event was £241.6. For events that occur in-hospital; no extra cost was factored in and hence; the cost was assumed to be £0.

For CRNMB events that lead to a **surgical-site infection**, however, the cost of medically managing the surgical site infection was calculated to be £3,696. This was the weighted average cost of HRG codes HD25D (Infections of Bones or Joints, with CC Score 0-1 to 13+) for non-elective short, non-elective long and elective inpatient stays. For surgical site infections that will require surgical intervention, the cost was assumed to be a weighted average of the cost of a return to theatre and that of a revision for infection.

The cost of a **return to theatre** was assumed to be the same as a primary operation (£6,278 for eTHR and £6,178 for eTKR). The cost of a **revision for infection** was calculated based on published UK data which reported that the cost of a two-stage revision for TKR was £30,011 (cost year 2013). In the same study, the cost of a primary TKR was reported to be £9,655 which was higher than the cost or a primary eTKR in our model. Hence, it was decided that rather than using the cost of a revision directly from the study and adjusting for inflation that a ratio of the cost of the revision for infection to that of the primary operation in the same study be used instead. This ratio was calculated to be 3.11 (£30,011/£9,655). This ratio was, thus, applied to the cost of primary eTKR in the model (£6,178) to calculate the cost of the revision for infection (£19,203). Based on the committee's expert opinion, it was considered appropriate to apply this ratio also to the eTHR primary operation cost to calculate the cost of the revision for infection for eTHR. Hence, the cost of a revision for infection for eTHR was calculated as £6,278*3.11 to be £19,514.

P.1.3.6.2.4 Heparin-induced thrombocytopenia (HIT)

The cost of HIT was included in the model only for people receiving prophylaxis strategies that included LMWH. A weighted average cost for a HIT episode was then calculated based on a ratio of 75:25 for in-hospital to post-discharge diagnosis.

HIT events diagnosed in-hospital (pre-discharge) were assumed to be treated as an episode of thrombocytopenia with CC score 0-1 (HRG code SA12K). The national unit cost for this episode is £395. For events diagnosed post-discharge, it was assumed that either a visit to the GP (£36 for a visit of 9.9 minutes long),[224]or the emergency department (£222),[250] will also be required, in a ratio of 1:1, in addition to the hospital admission episode cost. The cost of diagnostic tests (4T clinical scoring and immunoglobulin assay) was also included. The cost of completing 4T clinical scoring was assumed to be that of 5 minutes of a registrar's time (costed at £60 per hour; £5.1 for 5 minutes). The cost of an immunoglobulin assay was £6, the national average unit cost of an immunology test (HRG code DAPS06). Hence, the total cost of visits and diagnosis was calculated to be an extra £134.3 for post-discharge diagnosis of HIT and the total cost would be £530. Hence, the weighted average cost of a HIT event in the model was £463.

For individuals who are successfully treated, no other costs were included. However, for those who develop new thrombosis, major bleeding or amputation; event-specific costs were also included. For a **new thrombosis**, the cost was calculated as the average of the cost of managing a symptomatic proximal DVT and that of managing a PE. For a **major bleeding**, the average cost of GI bleeding with and without intervention was used (£1,632). The cost of an **amputation** event was based on the NHS Schedule for Reference Costs 2015-2016 unit costs for amputation of single limb with CC scores 0-9 and 10+ (HRG codes YQ22A and YQ22B, weighted average of non-elective short, non-elective long and elective inpatient stay) to be £10,300.

P.1.3.6.3 Markov model Health states (> 90 days post-operatively

P.1.3.6.3.1 Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

For chronic thromboembolic pulmonary hypertension (CTEPH) we derived a yearly cost for first and subsequent years post diagnosis. We have estimated the cost of CTEPH by adding together the cost of diagnosis and treatment for year one and ongoing treatment for subsequent years. The diagnosis and treatment pathway was based on the European Society of Cardiology and European Respiratory

Society guidelines (2015),[332] NHS England clinical commissioning policy for targeted therapies for use in pulmonary hypertension in adults,[911] and a published analysis of an international registry of newly diagnosed patients with CTEPH.[245] This was supplemented by the committee's expert input.

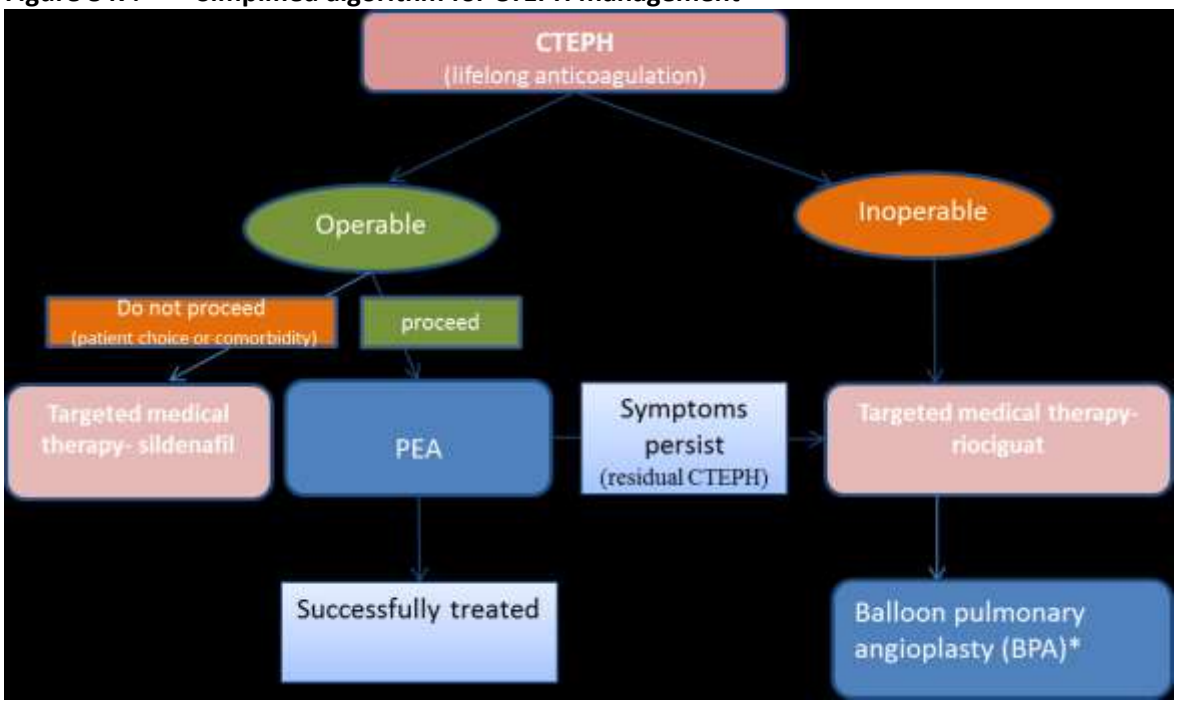
Diagnosis: The detailed costing of diagnosing CTEPH is presented in **Table 301.** It was based on the algorithm recommended by the European Society of Cardiology and European Respiratory Guidelines (2015) and the committee's expert opinion. [332]

Table 301: Costs of diagnosing CTEPH

Item	% of patients	Resource used	units	unit cost	source
Clinical examination	100%	GP visit	1	£36	PSSRU 2016[224], 9.9 minutes.
	100%	Outpatient visit- Non-consultant led	1	£63	NHS Reference Costs 2015-2016 (non-consultant led respiratory medicine outpatient visit; service code 340) [250]
V/Q scan	100%	Diagnostic imaging-Outpatient	1	£274	NHS Reference Costs 2015-2016 (weighted average cost of of Lung Ventilation or Perfusion Scan, 18 years and under and 19 years and over; HRG codes: RN18A, RN18B)[250]
Referral/ outpatient visit	100%	Outpatient visit-consultant led	1	£192	NHS Reference Costs 2015-2016 (consultant led respiratory medicine outpatient visit; service code 340)[250]
CTPA	100%	Diagnostic imaging-Outpatient	1	£104	NHS Reference Costs 2015-2016 (weighted average cost of Computerised Tomography Scan of one area, with post contrast only, 19 years and over and 18 years and under; HRG codes RD21A and RD21B)[250]
Right heart catheterisation	100%	Test	1	£1,051	NHS Reference Costs 2015-2016 (weighted average cost of "Standard Cardiac Catheterisation with CC Score 0-1 to 10-12"; HRG codes EY43B to EY43F [Day cases]) [250]
Pulmonary angiogram/ angiography	20%	Test	1	£1,477	NHS Reference Costs 2015-2016 (weighted average cost of "Percutaneous Transluminal Angioplasty, including Stenting, of Intracranial or Extracranial Blood Vessel"; HRG codes YA10Z to YA 12Z) [250]
MRI pulmonary angiogram	80%	Test	1	£135	NHS Reference Costs 2015-2016 (weighted average cost of "Magnetic Resonance Imaging Scan"; HRG codes : RD01A, RD01B, RD02A, RD02B, RD03Z) [250]
			Total	**£2,123**	

Management: A simplified management algorithm was also constructed and costed based on the aforementioned sources (See **Figure 847**). In this algorithm, all patients with CTEPH were considered to continue long-term anticoagulation. Patients are assessed for operability and those considered operable (60%) would undergo pulmonary endarterectomy (PEA) surgery. Patients who are inoperable or continue to have residual symptoms after surgery and those who refuse surgery would receive targeted medical therapy in accordance with the Clinical Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults,[911] in addition to supportive therapy. New York Heart Association (NYHA) functional classification class I-II patients are assumed to receive supportive therapy only (39%).[245]

Figure 847: Simplified algorithm for CTEPH management



Abbreviations: BPA: Balloon pulmonary angioplasty CTEPH: chronic thromboembolic pulmonary hypertension; PEA: pulmonary endarterectomy.

a) *Based on the European Society of Cardiology and European Respiratory Society guidelines (2015),[332] NHS England clinical commissioning policy for targeted therapies for use in pulmonary hypertension in adults,[911] and a published analysis of an international registry of newly diagnosed patients with CTEPH[245] supplemented by the committee's expert input.*

b) **Not commissioned by the NHS.*

Anticoagulation: The cost of anticoagulation was calculated based on prescribing warfarin sodium tablets in a dose of 5mg on average. The annual cost of warfarin was thus calculated to be £10.66. Additionally, the annual cost of anticoagulation clinics, prothrombin time (once at the start of treatment) and INR testing were included. According to the BNF; INR testing is recommended to be undertaken daily or on alternate days in early days then less frequently and at least every 12 weeks after that, however; according to the committee, in clinical practice it is likely to be less frequently [3 to 4 days after a dose change] hence its cost might be an over-estimate. The total costs were £152.4 in year 1 and £28.1 in subsequent years. The costs of anticoagulation clinic visits were £42.3 for the first visit and £24.9 for subsequent follow-up visits.

Table 302: Costs of anticoagulation prescribing and management

category	Y1	Y2+
Warfarin (a)	£10.66	£10.66

category	Y1	Y2+
Monitoring tests (b)	£152.43	£28.05
Follow-up (c)	£315.87	£107.77
Total	**£478.96**	**£146.48**

Abbreviations: Y1: year 1; Y2+: years 2 to life time
(a) Average daily dose 5 mg (prescribed as 5mg tablets, 28 tablets per pack at an average price of £.82)
(b) PT once at the start, INR testing daily or alternate days in early days then less frequently and at least every 12 weeks. Source: British National Formulary[458]
(c) Y1 once a month, Y2 once every 12 weeks)

Pulmonary endarterectomy: the cost of the PEA operation was based on the costs provided by Papworth hospital, The UK's only designated PEA centre. This was reported to be £23,579.

Targeted medical therapy: According to the Clinical Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults,[911] patients with potentially operable CTEPH, those unsuitable for surgery due to co-morbidity and those who refuse surgery would be started on monotherapy with generic sildenafil (an oral phosphodiesterase type 5 inhibitors (PDE5I)), while patients with residual CTEPH post-PEA would routinely be prescribed the newly licensed soluble guanylate cyclase stimulator; riociguat. Balloon pulmonary angioplasty (BPA) might also be offered to some CTEPH patients, however; it is not currently funded by the NHS.

The yearly cost of each of the treatment options available for patients with CTEPH and the percentage of patients receiving each option in the year of diagnosis (Y1) and thereafter (Y2+) are presented in **Table 303**. These percentages were based on the NHS Clinical Commissioning Policy for year 1 and on data from the analysis of the international registry data in Delcroix 2016.[245] The number and costs of outpatient visits required for those prescribed riociguat are presented in **Table 304.** In practice; patients may not need so many follow up appointments and up titration in dose every 2 weeks can be done at home in a telephone consultation with nurse. For people prescribed sildenafil in year 1, the frequency of outpatients visits is assume to be once every 12 weeks. In Years 2+, follow-up for both drugs would occur at the same frequency (once every 12 weeks).

Based on these costs; and the percentage of total cost of both drug treatments and outpatient visits are in year 1 is £7,527 and in years 2+ is £19,212.

Table 303: Targeted medical therapy costs for patients with CTEPH in the first and subsequent years after diagnosis

Class	Drug	Annual drug cost (a)	% of patients	
			Year 1	Year 2 + (b)
Phosphodiesterase type 5 inhibitors (PDE5I)		**£154**	**87% (a)**	**28%**
	Sildenafil generic (for dose escalation 25-100mg three times daily)	£154		
Endothelin receptor antagonist (ERAs)/ Soluble guanylate cyclase stimulator		**£25,168(c)**		**39%**
	Bosentan (62.5mg – 125mg twice daily)	£23,500		
	Ambrisentan (5-10mg once daily)	£23,500		
	Macitentan (10mg once daily)	£27,672		
	Riociguat (dose as per titration – usually 2.5mg three times daily)(d)	£26,000	**13.1% (a)**	
Intravenous prostanoids		**£35,300 (d)**	**0.0%**	**3%**
	epoprostenol (dose titrated to response)	£35,000		
	Iloprost (5micrograms up to 9-times daily)	£35,600		
Dual Therapy		**£25,322**	**0.0%**	**30%**

Class	Drug	Annual drug cost (a)	% of patients	
			Year 1	Year 2 + (b)
	Sildenafil +ERA (e)	£25,322		
Total cost			**£3,527**	**£18,575**

(a) Source: Clinical Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults.[911] Not including home care costs.
(b) Source: Published analysis of an international registry of newly diagnosed patients with CTEPH.[245]
(c) Average of the annual costs of all ERAs.
(d) Average annual cost of IV prostanoids.
(e) According to the commissioning policy; dual therapy will only be funded in combinations involving a PDE5I unless there are exceptional circumstances.

Table 304: Outpatient visits for patients with residual CTEPH post-PEA surgery starting on riociguat

Year	Weeks	frequency	First/Follow-up	Unit cost	Total cost outpatient visits
1	2	every 2 weeks	First	£191.54 (a)	£191.54
1	2	every 2 weeks	Follow-up	£146.23 (b)	£146.23
1	2	every 2 weeks	Follow-up	£146.23 (b)	£146.23
1	2	every 2 weeks	Follow-up	£146.23 (b)	£146.23
1	44	every 4 weeks	Follow-up	£146.23 (b)	£1,618.09
Total-Y1					**£2,239**
Total-Y2	**52**	**every 12 weeks**	**Follow-up**	**£146.23** (b)	**£634**

(a) NHS Schedule for reference costs 2015-2016[250]; "Respiratory medicine" Service code 340; weighted average of HRG codes for outpatient first visit (HRG codes WF01B, WF01D, WF02B, WF02D)
(b) NHS Schedule for reference costs 2015-2016[250]; "Respiratory medicine" Service code 340; weighted average of HRG codes for outpatient follow-up visit (HRG codes WF01A, WF01C, WF02A, WF02C)

Supportive therapy: According to Schweikert 2015 and the committee's expert opinion ;[871] the main supportive therapy currently used is diuretics in 59% of patients and supplemental oxygen in only 25%. Based on CG92, the diuretic used was assumed to be furosemide at an average dose of 40 mg per day; with an annual cost of £9.

Primary and secondary care resources: The associated with primary and secondary care resource use were included. The utilisation of these resources varied according to the functional class.

For NYHA class II, one outpatient visit and one day ward assessment were included annually at a cost of £147 (consultant led, follow-up visit, respiratory medicine; service code 340) and £332 (heart failure or shock, HRG code EB03A; Day case), respectively. For NYHA class III and IV; 1 outpatient visit and 2 day ward assessment visits. Repeated hospitalisation (4 episodes per year) were also included for NYHA class IV at a unit cost of £2,849 (heart failure or shock, HRG code EB03A; elective inpatient). A weighted average cost was calculated for the three functional classes based on the proportion of each class among CTEPH patients, as reported in Schweikert 2014. [871] The total cost of primary and secondary care resources used are presented in **Table 305**.

Table 305: Primary and secondary care resource use costs by NYHA class

Functional class	% of patients (a)	outpatient visits (b)	day ward assessment (b)	Hospital admissions (b)	outpatient visit unit cost (c)	day ward assessment unit cost (d)	Admission unit cost (e)	total cost
II	27%	1	1	0	£146	£332	£3,144	£478
III	59%	1	2	0				£810
IV	14%	1	2	4				£13,385

Functional class	% of patients (a)	outpatient visits (b)	day ward assessment (b)	Hospital admissions (b)	outpatient visit unit cost (c)	day ward assessment unit cost (d)	Admission unit cost (e)	total cost
Total cost								£2,481

Abbreviations: NYHA: New York Heart Association

a) Schweikert 2014 [871]

b) Committee expert opinion

c) NHS Schedule for Reference Costs 2015-2016[250]. "Respiratory medicine" Service code 340; weighted average of HRG codes for consultant –led outpatient follow-up visit (HRG codes WF01A, WF01C, WF02A, WF02C)

d) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average of HRG codes for Day case, "Heart failure or shock" with CC 0-3 to 14+. HRG codes EB03A, EB03B, EB03C, EB03D and EB03E.

e) NHS Schedule for Reference Costs 2015-2016[250]. Weighted average of HRG codes for elective inpatient, "Heart failure or shock" with CC 0-3 to 14+. HRG codes EB03A, EB03B, EB03C, EB03D and EB03E.

P.1.3.6.3.2 Post-thrombotic syndrome

In the case of **post-thrombotic syndrome** (PTS) we used a US-based study[153] that calculated the cost of managing PTS according to severity and year after diagnosis. This study has been used in TA157[675] and a recent UK HTA study[983]. We converted the costs to UK pounds using OECD purchasing power parity (PPP) calculator and inflated these to 2015-2016 UK pounds using the PSSRU hospital & community health services (HCHS) index.[224] Based on these estimates, the cost of managing mild/moderate PTS in the first and subsequent years are £841 and £342, respectively. The cost of managing severe PTS is the first and subsequent years are £3,824 and £1,680, respectively (see **Table 306**).

Table 306: Costs of managing post-thrombotic syndrome

	Reported cost (2000 US$)	Converted to 2000 UK£ (a)	Inflation index(b)	Inflated to 2015/16
mild-to-moderate PTS- year 1	$839	£533	1.576	£841
mild-to-moderate PTS- year 2+	$341	£217		£342
Severe PTS- years 1	$3,817	£2,427		£3,824
Severe PTS- years 2+	$1,677	£1,066		£1,680

(a) Converted using OECD purchasing power parity (PPP) calculator. [715]

(b) Source: PSSRU 2016.[224]

P.1.3.6.3.3 Disabled- post stroke

The cost of stroke management in the long term was based on the costs reported in NICE guideline CG144 "VTE management and thrombophilia testing". [668] The costs reported were adjusted for inflation using the PSSRU hospital & community health services (HCHS) index (see **Table 307**).[224] An average of the cost per patient in dependent and independent states was then used in the model. This was £17,374 in year 1 and £8,140 in subsequent years.

Table 307: Costs of managing people with haemorrhagic stroke in the first and subsequent years

	Cost (95% CI) (a)	Source
Cost of stroke per patient in the first year –dependent state	£29,776 (£22,332 to £37,220)	NICE VTE management and thrombophilia testing guideline (CG144), appendix H[668]
Cost of stroke per patient in the first year –independent state	£4,971 (£3,729 to £6,214)	NICE VTE management and thrombophilia testing guideline (CG144), appendix H[668]
Cost of stroke per patient for subsequent years – dependent state	£15,108 (£880 to £18,885)	NICE VTE management and thrombophilia testing guideline (CG144), appendix H[668]

	Cost (95% CI) (a)	Source
Cost of stroke per patient for subsequent years – independent state	£1,172 (£880 to £1,465)	NICE VTE management and thrombophilia testing guideline (CG144), appendix H[668]

a)Values from CG144 updated using an inflator index = 1.11 (from year 2010/2011 to year 2015/2016) calculated from PSSRU 2016 using the Hospital and Community Health Services Pay and Prices Index.[224]

P.1.3.6.3.4 Amputated- post HIT

The cost for individuals who were amputated post-HIT in the long term was based on the costs reported in NICE guideline CG147 "lower limb peripheral arterial disease".[667] The costs reported were adjusted for inflation using the PSSRU hospital & community health services (HCHS) index.[224] The cost per patient in year 1 was £31,259 and in subsequent years £25,987.

P.1.4 Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by cohort simulation. Time dependency was built in the long-term Markov part of the model by cross referencing the cohorts age as a respective risk factor for mortality. Baseline utility was also time dependent and was conditional on the number of years after entry to the model.

Patients start in cycle 0 in the health state corresponding to the end state of the decision tree part of the model. Patients moved to the dead health state at the end of each cycle as defined by the mortality transition probabilities from the life tables and CTEPH mortality.

Transition probabilities for DVT, PE and MB were calculated based on the results of systematic review and NMAs conducted for the guideline, detailed in appendix M of the full guideline.

PTS and CTEPH incidence rates were converted into transition probabilities for the respective cycle length (1 year in the base case) before inputting into the Markov model. These conversions were done using the following formulae:

$Selected\ rate\ (r) = \frac{-\ln(1-P)}{t}$	Where *P*=probability of event over time *t* *t*=time over which probability occurs (2 years)
$Transition\ Probability\ (P) = 1 - e^{-rt}$	Where *r*=selected rate *t*=cycle length (1 year)

Life years for the cohort were computed each cycle. To calculate QALYs for each cycle, Q(t), the time spent in states other than death in the model (1 year) was weighted by a utility value that is dependent on the time spent in the model and the utility value at the point of entry to the Markov model in Cycle 0. QALYs were then discounted to reflect time preference (discount rate 3.5%). QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs per cycle, C(t), were calculated in the same way as QALYs. Costs were discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discount formula:

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: *r*=discount rate per annum *n*=time (years)

P.1.5 Sensitivity analyses

A number of one-way sensitivity analyses were undertaken to assess the parameter uncertainty of the model. These are listed in **Table 308.**

Table 308: List of one-way sensitivity analyses

	description	Base case input value	Alternative value for sensitivity analysis
SA1	Cost effectiveness threshold	£20,000	£30,000
SA2	Discount rate for costs and QALYs	3.5%	1.5%
SA3	Prophylaxis duration	Based on the RCTs included in the DVT NMA	based on summary of product characteristics (SmPC)
SA4	Cohort starting age	eTHR: 68.7 years (a) eTKR: 69.3 years (a)	40 years
SA5	Cohort body weight	NJR cohort mean body weight(a)	Cohort body weight distribution calculated based on the NJR cohort BMI distribution (a) and average height for a UK male (1.75m) and female (1.62 m) (b)
SA6	All costs +10%	See section P.1.3.6	Costs increased by 10%
SA7	All costs -10%	See section P.1.3.6	Costs decreased by 10%
SA8	Timing of VTE and MB events	Based on committee expert opinion	Based on data from Warwick 2007[993]
SA9	Rate VTE recurrence at 90 days after : Treated DVT PE	Assumption based on committee opinion 0% 0%	Calculated based on data from TA245 and TA354 manufacturer submissions. 2.74% 0.26%
SA10	Costs of pharmacological prophylaxis	Calculated assuming no wastage	Calculated taking possible wastage into account
SA11 (c)	Risk of DVT when using LMWH (std/std) followed by aspirin for the eTHR population	Calculated using the odds ratio from the PE network 0.05%	Calculated using the odds ratio from Anderson 2013 for the outcome Proximal DVT 3.68%

Abbreviations: eTHR: elective total hip replacement; eTKR: elective total knee replacement; NMA: network meta-analysis; SA: sensitivity analysis

(a) Source: National Joint Registry[109]

(b) Source: ONS [708]

(c) Only for the eTHR population

P.1.6 Model validation

The model was developed in consultation with the Committee; model structure, inputs and results were presented to and discussed with the Committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NGC; this included systematic checking of many of the model calculations.

P.1.7 Estimation of cost-effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost-effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A

Cost-effective if:
- ICER < Threshold

When there are more than 2 comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of 2 other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Monetary\ Benefit\ (X) = \left(QALYs(X) \times \lambda\right) - Costs(X)$$

Where: λ = threshold (£20,000 per QALY gained)

Cost-effective if:
- Highest net benefit

Results are also presented graphically where total costs and total QALYs for each strategy are shown. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio.

P.1.8 Interpreting Results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[676] sets out the principles that Committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost-effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As we have several interventions, we use the NMB to rank the strategies on the basis of their relative cost-effectiveness. The highest NMB identifies the optimal strategy at a willingness to pay of £20,000 per QALY gained.

P.2 Results

P.2.1 eTHR

P.2.1.1 Base case

The results of the probabilistic base case analysis for the eTHR population are presented in **Table 309** and in the cost-effectiveness plane in **Figure 848.** These show that the most effective option, with the highest mean gain in QALYs over lifetime per person, was the combined prophylaxis with LMWH (standard dose, standard duration) for 10 days followed by aspirin 100 mg for 28 days (10.293 discounted QALYs gained; 95% CI: 8.02 to 12.00). It was followed closely by LMWH (std,extd)+ AEs (10.288; 95% CI: 8.02 to 12.00). The most costly option was aspirin (standard duration), with mean discounted cost of £1,687 (95% CI: £157 to £4,039) per person. The least costly prophylaxis strategy was AES with mean discounted cost per person of £299 (95% CI: £102 to £793) followed by LMWH (standard, std) +aspirin (extd) with mean discounted cost of £311 (95% CI: £148 to £1437).

Based on these results, the most cost-effective prophylaxis strategy, with the highest NMB, was LMWH (std,std) + aspirin (extd) with mean INMB vs LMWH (stand, std)+AEs of £530 (95% CI: -£784 to £1,103). It also had the highest probability of being the most cost effective option (72%). Other interventions which have a positive mean INMB when compared with LMWH (std, std)+AEs are: LMWH (std,extd)+ AEs (mean £36; 95% CI: -£745 to £484) and AES (mean £5; 95% CI: -£2,106 to £781). However, compared to no prophylaxis, all interventions except aspirin (standard duration), foot pump and AES (above knee) have positive INMB.

Among the mechanical prophylaxis interventions; AEs seemed to be more cost effective compared to IPCD and foot pumps, ranking 3rd (95% CI: 1 to 14) when length was unspecified. However, above knee AES had negative INMB compared to no prophylaxis and ranked in the 14th place.

The DOACs (Rivaroxaban, apixaban and dabigatran) were dominant compared to no prophylaxis but were dominated by the model comparator (LMWH [standard dose, standard duration] +AES). Of the three DOACs, rivaroxaban was cost-effective compared to apixaban with an ICER of £12,242 per QALY gained both rivaroxaban and apixaban were dominant (more effective and less costly) compared to dabigatran. The probability of being the most cost-effective was higher for apixaban (2.24%) compared to rivaroxaban (0.2%). However; there was more uncertainty around the ranking of apixaban, with a probability of being the least cost effective of 0.16% compared to 0.08% for rivaroxaban..

The disaggregated costs and health outcomes presented in **Table 310** and **Table 311** show that the strategies that resulted in the lowest number of VTE events are LMWH (std,std)+aspirin (extd) and LMWH (std,extd) + AES (8 [95%: 0 to 55] and 34 [95% CI: 5 to 116] per 1000 persons; respectively). The highest number of VTE events was seen with the no prophylaxis strategy (491 per 1000 (95% CI: 146 to 953).

The number of surgical site bleeding events was highest for fondaparinux+ AES (51 per 1000 [95% CI: 8 to 187]) followed by dabigatran with 44 per 1000 [95% CI: 6 to 160] (see **Table 310**). Aspirin (std duration) was associated with the highest number of PE, PTS and CTEPH events (373, 60 and 11 per 1000 respectively).

The breakdown of costs for all prophylaxis strategies is presented in **Table 311** and is in line with the results for health outcomes. The cost of the prophylaxis itself was highest for LMWH (std,extd)+ AEs (£419 per person); driven by the high administration and monitoring costs for an extended duration.

P.2.1.2 Sensitivity analyses

The one-way sensitivity analyses (SAs) were all run deterministically. The results of the SAs show that the most cost-effective option remained the same in all except when the mean age of the cohort was reduced to 40 years; where it dropped to the second rank and LMWH (std,std) + AES became the most cost effective.

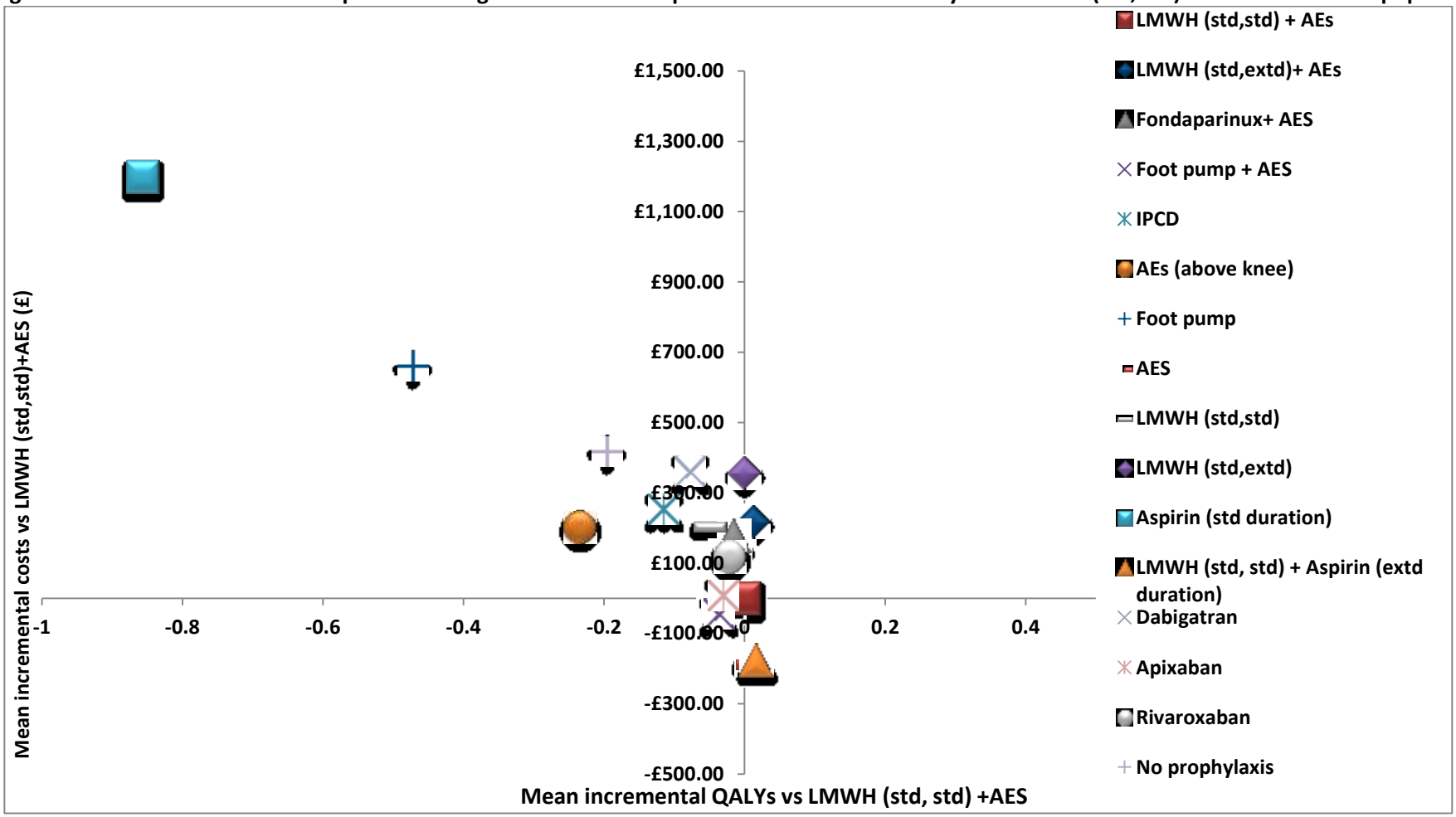
Table 309: Results of the base case probabilistic analysis for the eTHR population

Intervention	Mean discounted QALYs (95% CI)	Mean Discounted Costs (95% CI)	Incremental QALYs vs LMWH+ AEs (95% CI)	Incremental costs vs LMWH+ AEs (95% CI)	Mean INMB at £20K (95% CI)	Probability most CE option (a)	Rank (95% CI) (b)
LMWH (std,std) + AEs	**10.28** (8.01 to 11.98)	**£489** (£350 to £832)	**0.000** (0.000 to 0.000)	**£0** (£0 to £0)	**£0** (£0 to £0)	0.1%	**4** (3, 11)
LMWH (std,extd)+ AEs	**10.29** (8.02 to 12.00)	**£706** (£509 to £1,376)	**0.013** (-0.004 to 0.030)	**£217** (-£42 to £694)	**£36** (-£745 to £484)	0.6%	**2** (2, 12)
Fondaparinux+ AES	**10.26** (7.98 to 11.96)	**£665** (£336 to £1,563)	**-0.015** (-0.112 to 0.013)	**£176** (-£92 to £800)	**-£478** (-£2,618 to £278)	0.2%	**6** (3, 15)
Foot pump + AES	**10.24** (7.99 to 11.94)	**£445** (£209 to £926)	**-0.036** (-0.182 to 0.012)	**-£44** (-£329 to £398)	**-£684** (-£3,930 to £478)	0.6%	**9** (2, 15)
IPCD	**10.16** (7.86 to 11.91)	**£742** (£255 to £1,968)	**-0.115** (-0.681 to 0.011)	**£253** (-£246 to £1,455)	**-£2,550** (-£14,733 to £396)	0.1%	**12** (4, 15)
AEs (above knee)	**10.04** (7.35 to 11.93)	**£691** (£119 to £3,765)	**-0.234** (-2.197 to 0.027)	**£202** (-£424 to £3,310)	**-£4,873** (-£46,725 to £861)	13.2%	**14** (1, 16)
Foot pump	**9.80** (6.96 to 11.77)	**£1,150** (£161 to £4,054)	**-0.472** (-2.681 to 0.015)	**£661** (-£344 to £3,578)	**-£10,104** (-£57,043 to £590)	1.4%	**15** (2, 16)
AES	**10.27** (8.01 to 11.97)	**£299** (£102 to £793)	**-0.009** (-0.103 to 0.022)	**-£189** (-£460 to £261)	**£5** (-£2,106 to £781)	8.4%	**3** (1, 14)
LMWH (std,std)	**10.23** (7.95 to 11.94)	**£691** (£375 to £1,413)	**-0.048** (-0.283 to 0.009)	**£202** (-£44 to £767)	**-£1,162** (-£6,266 to £197)	0.0%	**10** (6, 13)
LMWH (std,extd)	**10.27** (7.98 to 11.98)	**£844** (£528 to £1,582)	**0.000** (-0.070 to 0.025)	**£356** (£24 to £954)	**-£361** (-£2,042 to £349)	0.1%	**5** (4, 13)
Aspirin (std duration)	**9.42** (6.50 to 11.59)	**£1,687** (£157 to £4,039)	**-0.856** (-3.179 to 0.009)	**£1,198** (-£390 to £3,610)	**-£18,312** (-£66,988 to £479)	0.7%	**16** (2, 16)
LMWH (std, std) + Aspirin (extd duration)	**10.29** (8.02 to 12.00)	**£311** (£148 to £1437)	**0.018** (0.003 to 0.036)	**-£178** (-£548 to £781)	**£530** (-£784 to £1,103)	72.0%	**1** (1, 11)
Dabigatran	**10.20** (7.93 to 11.94)	**£849** (£319 to £1,957)	**-0.077** (-0.465 to 0.010)	**£360** (-£122 to £1,331)	**-£1,903** (-£10,144 to £254)	0.0%	**11** (5, 15)
Apixaban	**10.25** (7.96 to 11.97)	**£497** (£163 to £1,588)	**-0.030** (-0.270 to 0.022)	**£8** (-£302 to £895)	**-£598** (-£6,089 to £632)	2.2%	**8** (2, 14)
Rivaroxaban	**10.25** (7.97 to 11.97)	**£606** (£227 to £1,452)	**-0.021** (-0.190 to 0.019)	**£117** (-£234 to £814)	**-£529** (-£4,385 to £514)	0.4%	**7** (2, 13)
No prophylaxis	**10.08** (7.80 to 11.82)	**£908** (£297 to £2,185)	**-0.196** (-0.885 to -0.008)	**£419** (-£195 to £1,677)	**-£4,336** (-£19,297 to -£95)	0.0%	**13** (10, 16)

Abbreviations: AEs: anti-embolism stockings; CE: cost effective; CI: confidence interval; eTHR: elective total hip replacement; extd: extended; IPCD: intermittent pneumatic compression devices; INMB: incremental net monetary benefit; LMWH: low molecular weight heparin; QALYs: quality-adjusted life-years; std: standard

(a) *Calculated at cost effectiveness threshold of £20,000 per QALY gained. (b) The rank is calculated based on the INMB. The intervention with the highest INMB is ranked first, The 95% CI has been calculated probabilistically*

Figure 848: Cost-effectiveness plane showing the results of the probabilistic base case analysis vs LMWH (std, std) + AES for the eTHR population



Abbreviations: AEs: anti-embolism stockings; eTHR: elective total hip replacement; extd: extended; IPCD: intermittent pneumatic compression devices; INMB: incremental net monetary benefit; LMWH: low molecular weight heparin; QALYs: quality-adjusted life-years; std: standard

Table 310: Health outcomes per 1000 for each prophylaxis strategy - eTHR population

Intervention	Short-term health outcomes (n [95% CI])							Long-term health outcomes (n [95% CI])	
	Symptomatic DVTs	Sympt Proximal DVT	Asymptomatic DVTs	PEs	Total VTEs	Surgical site bleeding	Total Deaths	PTS	CTEPH
LMWH (std,std) + AEs	**9** (8 to 11)	**8** (6 to 9)	**46** (44 to 48)	**7** (6 to 7)	**62** (61 to 64)	**28** (7 to 83)	**1** (1 to 3)	**7** (6 to 8)	**0** (0 to 0)
LMWH (std,extd)+ AEs	**6** (1 to 19)	**5** (1 to 16)	**27** (4 to 96)	**1** (0 to 9)	**34** (5 to 116)	**29** (2 to 131)	**0** (0 to 2)	**4** (1 to 13)	**0** (0 to 0)
Fondaparinux+ AES	**20** (7 to 42)	**17** (6 to 35)	**98** (36 to 204)	**12** (1 to 52)	**130** (52 to 263)	**51** (8 to 187)	**2** (0 to 11)	**14** (6 to 30)	**0** (0 to 2)
Foot pump + AES	**25** (3 to 81)	**21** (3 to 68)	**122** (16 to 388)	**22** (3 to 87)	**169** (35 to 486)	**13** (2 to 49)	**5** (0 to 19)	**19** (4 to 54)	**1** (0 to 3)
IPCD	**56** (10 to 134)	**47** (8 to 111)	**275** (49 to 634)	**53** (2 to 299)	**383** (79 to 858)	**13** (2 to 49)	**11** (0 to 62)	**43** (9 to 99)	b (0 to 9)
AEs (above knee)	**16** (2 to 58)	**14** (1 to 48)	**80** (8 to 278)	**106** (0 to 909)	**203** (16 to 996)	**13** (2 to 49)	**23** (0 to 202)	**26** (2 to 138)	**3** (0 to 26)
Foot pump	**17** (1 to 73)	**14** (1 to 61)	**84** (5 to 363)	**213** (1 to 980)	**314** (20 to 1078)	**13** (2 to 49)	**44** (0 to 243)	**41** (2 to 152)	**6** (0 to 30)
AES	**20** (1 to 91)	**16** (1 to 76)	**97** (4 to 440)	**11** (1 to 49)	**127** (11 to 539)	**13** (2 to 49)	**2** (0 to 11)	**14** (1 to 58)	**0** (0 to 2)
LMWH (std,std)	**34** (6 to 93)	**28** (5 to 78)	**168** (29 to 451)	**25** (2 to 128)	**227** (48 to 573)	**28** (7 to 83)	**5** (0 to 27)	**26** (6 to 65)	**1** (0 to 4)
LMWH (std,extd)	**32** (3 to 100)	**27** (3 to 83)	**158** (17 to 482)	**4** (0 to 32)	**194** (22 to 589)	**29** (2 to 131)	**1** (0 to 6)	**21** (2 to 65)	**0** (0 to 1)
Aspirin (std duration)	**10** (2 to 32)	**8** (1 to 26)	**49** (8 to 156)	**373** (3 to 995)	**433** (34 to 1066)	**10** (8 to 12)	**79** (1 to 288)	**60** (4 to 155)	**11** (0 to 31)
LMWH (std, std) + Aspirin	**1** (0 to 8)	**1** (0 to 7)	**6** (0 to 42)	**1** (0 to 6)	**8** (0 to 55)	**22** (0 to 190)	**0** (0 to 1)	**1** (0 to 6)	**0** (0 to 0)
Dabigatran	**48** (4 to 136)	**40** (4 to 113)	**233** (21 to 649)	**37** (1 to 204)	**317** (42 to 830)	**44** (6 to 160)	**8** (0 to 43)	**36** (5 to 93)	**1** (0 to 6)
Apixaban	**7** (0 to 30)	**6** (0 to 26)	**33** (2 to 145)	**21** (0 to 131)	**61** (6 to 252)	**42** (4 to 173)	**4** (0 to 28)	**7** (1 to 32)	**1** (0 to 4)
Rivaroxaban	**35**	**29**	**171**	**13**	**219**	**36**	**3**	**24**	**0**

Intervention	Short-term health outcomes (n [95% CI])							Long-term health outcomes (n [95% CI])	
	Symptomatic DVTs	Sympt Proximal DVT	Asymptomatic DVTs	PEs	Total VTEs	Surgical site bleeding	Total Deaths	PTS	CTEPH
	(4 to 110)	(3 to 92)	(19 to 527)	(0 to 88)	(28 to 651)	(4 to 138)	(0 to 18)	(3 to 73)	(0 to 3)
No prophylaxis	**68** (16 to 139)	**57** (13 to 115)	**335** (80 to 669)	**88** (8 to 384)	**491** (146 to 953)	**13** (2 to 49)	**18** (1 to 82)	**56** (16 to 112)	**3** (0 to 12)

Abbreviations: AEs: anti-embolism stockings; CTEPH: chronic thromboembolic pulmonary hypertension; DVT: deep vein thrombosis; eTHR: elective total hip replacement; extd: extended; IPCD: intermittent pneumatic compression devices; LMWH: low molecular weight heparin; PE: pulmonary embolism; PTS: post thrombotic syndrome; std: standard; VTE: venous thromboembolism.

Table 311: Cost breakdown for each prophylaxis strategy per person - eTHR population

Intervention	Prophylaxis costs	VTE costs (95% CI)	All Bleeding costs (95% CI)	CTEPH costs (95% CI)	PTS costs (95% CI)	Post-amputation Costs (95% CI)	Total costs (a) (95% CI)
LMWH (std,std) + AEs	**£169**	**£11** (£10 to £11)	**£210** (£72.8 to £554)	**£19** (£15.4 to £23)	**£60** (£52 to £69)	**£20** (£13 to £27)	**£489** (£350 to £833)
LMWH (std,extd)+ AEs	**£419**	**£4** (£5.1 to £13)	**£217** (£39 to £847)	**£4.2** (£3 to £26)	**£32** (£5 to £107)	**£28** (£18 to £39)	**£706** (£509 to £1,376)
Fondaparinux+ AES	**£115**	**£20** (£5.8 to £59)	**£375** (£92 to £1,248)	**£32** (£2 to £144.5)	**£124** (£49 to £254)	**£0.00** (£0.00 to £0.00)	**£665** (£336 to £1,563)
Foot pump + AES	**£91**	**£32** (£7.3 to £103)	**£99** (£23 to £334)	**£60** (£7 to £228)	**£163** (£34 to £456)	**£0.00** (£0.00 to £0.00)	**£445** (£209 to £926)
IPCD	**£68**	**£75** (£11.3 to £327)	**£99** (£23 to £334)	**£129** (£4 to £654.5)	**£371** (£78 to £847)	**£0.00** (£0.00 to £0.00)	**£742** (£255 to £1,968)
AEs (above knee)	**£50**	**£112** (£1.6 to £908)	**£99** (£23 to £334)	**£211** (£36 to £1,502)	**£219** (£15 to £1,183)	**£0.00** (£0.00 to £0.00)	**£691** (£119 to £3,765)
Foot pump	**£60**	**£218** (£4.7 to £978)	**£99** (£23 to £334)	**£420** (£3.5 to £1,632)	**£354** (£19 to £1,300)	**£0.00** (£0.00 to £0.00)	**£1,150** (£161 to £4,054)
AES	**£31**	**£19** (£2.5 to £61.7)	**£99** (£23 to £334)	**£30** (£2 to £136)	**£121** (£11 to £498)	**£0.00** (£0.00 to £0.00)	**£299** (£102 to £793)
LMWH (std,std)	**£138**	**£39** (£7.6 to £140)	**£210** (£72.8 to £554)	**£66** (£5 to £311)	**£218** (£47 to £555)	**£20** (£13 to £27)	**£691** (£375 to £1,413)
LMWH (std,extd)	**£387**	**£17** (£2.4 to £54.7)	**£217** (£39 to £847)	**£12** (£0.1 to £87)	**£181** (£21 to £551)	**£28** (£18 to £39)	**£845** (£528 to £1,582)
Aspirin (std duration)	**£0.24**	**£374** (£7.2 to £989)	**£98** (£82 to £119)	**£702** (£8 to £1,687)	**£512** (£34 to £1,322)	**£000** (£000 to £000)	**£1,687** (£157 to £4,034)
LMWH (std, std) + Aspirin	**£115**	**£1.4** (£2 to £9)	**£163** (£11 to £1,225)	**£3** (£0 to £18)	**£7.5** (£0.01 to £54)	**£20** (£13 to £27)	**£311** (£148 to £1,437)
Dabigatran	**£80**	**£55.6** (£7.5 to £227)	**£316** (£75.5 to £1,048)	**£93** (£4 to £487)	**£305** (£42 to £795)	**£0.00** (£0.00 to £0.00)	**£849** (£319 to £1,957)
Apixaban	**£59**	**£23.5** (£1.5 to £132.6)	**£298** (£56.5 to £1,139)	**£53** (£1 to £321)	**£63** (£6.5 to £270)	**£0.00** (£0.00 to £0.00)	**£497** (£163 to £1,588)
Rivaroxaban	**£74**	**£27** (£3.4 to £105)	**£265** (£58.6 to £907)	**£34** (£0.4 to £225)	**£206** (£28 to £629)	**£0.00** (£0.00 to £0.00)	**£606** (£227 to £1,452)
No prophylaxis	**£0**	**£115** (£26 to £416)	**£99** (£23 to £334)	**£213** (£24 to £810)	**£481** (£140 to £957)	**£0.00** (£0.00 to £0.00)	**£908** (£297 to £2,185)

Abbreviations: AEs: anti-embolism stockings; CI: confidence interval; eTHR: elective total hip replacement; extd: extended; IPCD: intermittent pneumatic compression devices; LMWH: low molecular weight heparin; std: standard; VTE: venous thromboembolism; CTEPH: chronic thromboembolic pulmonary hypertension; PTS: post thrombotic syndrome.

1. May not exactly equal the sum of the components due to rounding.

P.2.2 eTKR

P.2.2.1 Base case

The results of the probabilistic base case analysis for the eTKR population are presented in **Table 312** and on the cost-effectiveness plane in **Figure 849**. These showed that the most effective option, with the highest mean gain in QALYs over lifetime per person, was foot pump (9.814 [95% CI: 7.86 to 11.58] discounted QALYs gained). This was followed closely by aspirin with a mean of 9.809 (95% CI: 7.86 to 11.58) and LMWH (std,std)+AES with a mean of 9.807 (95% CI: 7.86 to 11.58). The most costly option was fondaparinux+ AES, with mean discounted costs £904 (95% CI: £358 to £3,016). The least costly prophylaxis strategy was aspirin, with mean discounted costs of £187 (95% CI: £118 to £304).

Based on these results, the most cost-effective prophylaxis strategy, with the highest NMB, was foot pump with mean INMB vs LMWH (stand, std)+AEs of £353 (95% CI: -£101 to £665) followed by aspirin with mean INMB of £281 (95% CI: -£195 to £703). However, the results show considerable uncertainty where the most cost-effective option (foot pump) rank having a 95% CI of 1 to 10 and a probability of being the most cost-effective of only 18%. The only interventions with positive INMB when compared with LMWH (std, std)+AEs were foot pump, aspirin and combination of foot pump + AES. Compared to no prophylaxis, though, all interventions had a positive INMB except dabigatran.

Of the DOACs included in the model; rivaroxaban dominated both apixaban and dabigatran. However, the model comparator (LMWH [standard dose, standard duration]+AES) was cost effective compared to rivaroxaban (ICER: £7,686). The probability of being the most cost-effective was higher for apixaban (44%) compared to rivaroxaban (18%). However; there was more uncertainty around the ranking of apixaban, with a 5% probability of being the least cost effective compared to 0% for rivaroxaban.

The disaggregated health outcomes and costs for all prophylaxis strategies are presented in **Table 313** and **Table 314.** These show that rivaroxaban had the lowest number of VTE events (60 per 1000 persons [95% CI: 14 to 211]). The number of surgical site bleeding events was highest for fondaparinux+ AES (79 per 1000 [95% CI: 2 to 411]) followed by rivaroxaban (16 per 1000 [95% CI: 1 to 67]). The “no prophylaxis” strategy was associated with the highest number of PTS events (23 per 1000 [7 to 81]), Dabigatran had the highest number of PE events (51 per 1000 [0 to 644]).

The disaggregate costs were in line with the results for health outcomes. The cost of the prophylaxis itself was highest for LMWH (std,extd) at £356 per person.

P.2.2.2 Sensitivity analyses

One-way SAs were run deterministically. The optimal strategy (foot pump) remained the same in all SAs. Dabigatran was the least cost effective option in all SAs.

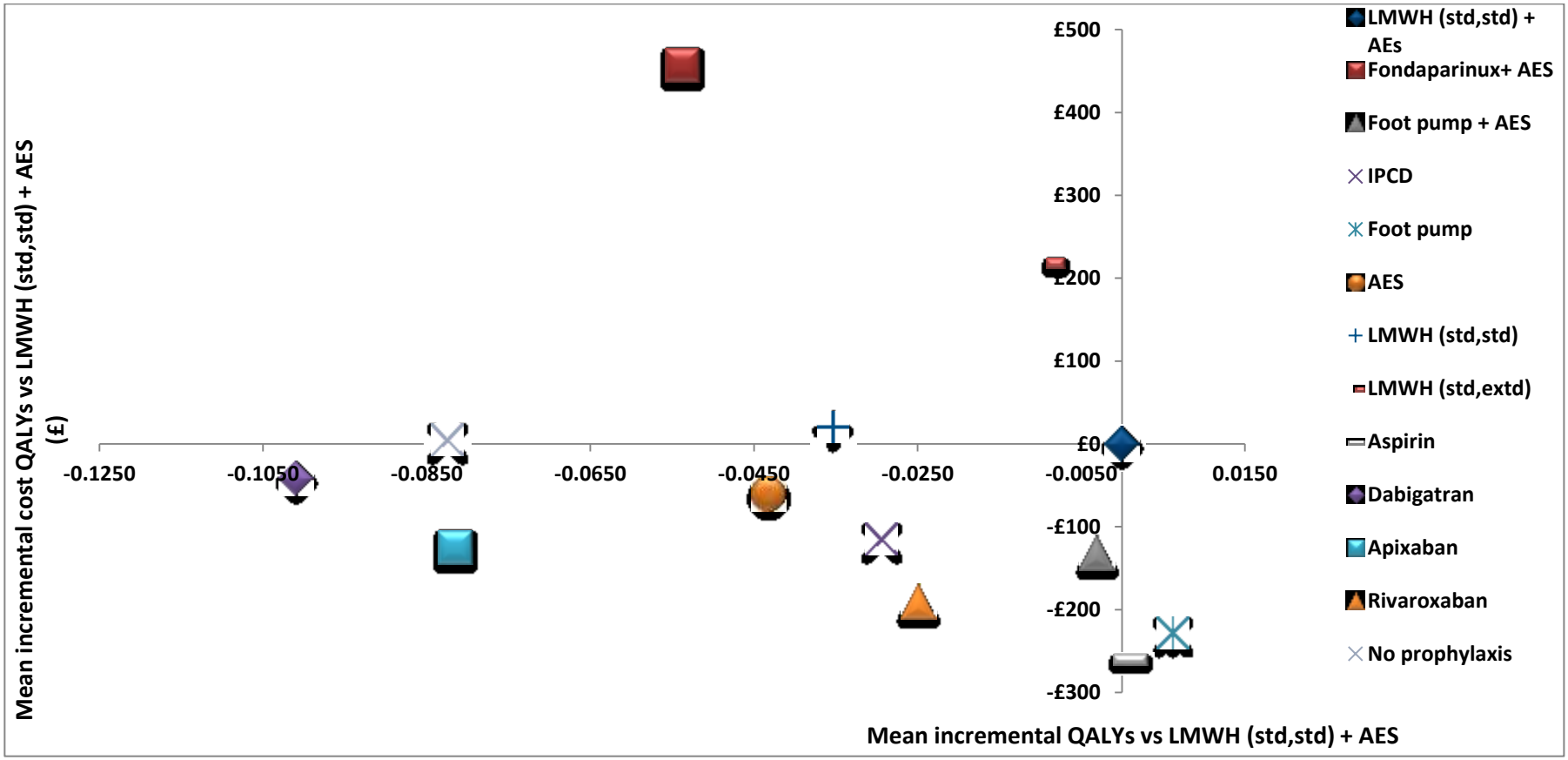
Table 312: Results of the base case probabilistic analysis vs LMWH (std, std)+AES for the eTKR population

Intervention	Mean discounted QALYs (95% CI)	Mean Discounted Costs (95% CI)	Incremental QALYs vs LMWH+ AEs (95% CI)	Incremental costs vs LMWH+ AEs (95% CI)	Mean INMB at £20K (95% CI)	Probability most CE option (95% CI) (a)	Rank (95% CI)
LMWH (std,std) + AEs	**9.81** (7.86 to 11.58)	**£448** (£364 to £613)	**0.000** (0.000 to 0.000)	**£0** (£0 to £0)	**£0** (£0 to £0)	0.1%	**4** (4, 12)
Fondaparinux+ AES	**9.75** (7.83 to 11.52)	**£904** (£358 to £3016)	**-0.054** (-0.183 to -0.009)	**£457** (-£53 to £2466)	**-£1,532** (-£6,183 to -£176)	0.0%	**11** (6, 13)
Foot pump + AES	**9.80** (7.86 to 11.58)	**£315** (£208 to £590)	**-0.003** (-0.020 to 0.006)	**-£132** (-£234 to £32)	**£72** (-£379 to £343)	0.1%	**3** (3, 12)
IPCD	**9.78** (7.82 to 11.56)	**£332** (£133 to £1246)	**-0.029** (-0.367 to 0.019)	**-£115** (-£304 to £698)	**-£473** (-£8,223 to £635)	5.8%	**7** (1, 13)
Foot pump	**9.81** (7.86 to 11.58)	**£219** (£119 to £473)	**0.006** (-0.011 to 0.018)	**-£228** (-£332 to -£65)	**£353** (-£101 to £665)	18.1%	**1** (1, 10)
AES	**9.76** (7.77 to 11.57)	**£387** (£167 to £1397)	**-0.043** (-0.420 to 0.014)	**-£60** (-£271 to £876)	**-£803** (-£9,251 to £520)	0.2%	**9** (3, 13)
LMWH (std,std)	**9.77** (7.79 to 11.55)	**£468** (£287 to £1563)	**-0.035** (-0.441 to 0.018)	**£21** (-£105 to £989)	**-£728** (-£10,057 to £445)	0.0%	**8** (4, 11)
LMWH (std,extd)	**9.80** (7.85 to 11.58)	**£666** (£508 to £1302)	**-0.009** (-0.111 to 0.023)	**£218** (£34 to £832)	**-£398** (-£3,013 to £397)	0.1%	**6** (3, 12)
Aspirin	**9.81** (7.86 to 11.58)	**£187** (£118 to £304)	**0.001** (-0.018 to 0.014)	**-£260** (-£436 to -£125)	**£281** (-£195 to £703)	9.0%	**2** (1, 12)
Dabigatran	**9.71** (7.53 to 11.56)	**£406** (£100 to £2987)	**-0.101** (-1.308 to 0.020)	**-£42** (-£343 to £2524)	**-£1,977** (-£28,720 to £707)	3.6%	**13** (1, 13)
Apixaban	**9.73** (7.62 to 11.54)	**£322** (£69 to £2624)	**-0.081** (-1.178 to 0.023)	**-£125** (-£392 to £2166)	**-£1,504** (-£25,838 to £802)	42.8%	**10** (1, 13)
Rivaroxaban	**9.78** (7.79 to 11.57)	**£256** (£82 to £1205)	**-0.025** (-0.333 to 0.021)	**-£191** (-£360 to £634)	**-£306** (-£6,975 to £747)	19.7%	**5** (1, 11)
No prophylaxis	**9.73** (7.68 to 11.53)	**£453** (£137 to £2281)	**-0.082** (-0.894 to 0.014)	**£6** (-£298 to £1,715)	**-£1,655** (-£20,058 to £540)	0.4%	**12** (3, 13)

Abbreviations: AEs: anti-embolism stockings; CE: cost effective; CI: confidence interval; eTKR: elective total knee replacement; extd: extended; IPCD: intermittent pneumatic compression devices; INMB: incremental net monetary benefit; LMWH: low molecular weight heparin; QALYs: quality-adjusted life-years; std: standard

(a) Calculated at cost effectiveness threshold of £20,000 per QALY gained. (b) The rank is calculated based on the INMB. The intervention with the highest INMB is ranked first, The 95% CI has been calculated probabilistically.

Figure 849: Cost-effectiveness plane showing the results of the probabilistic base case analysis- eTKR population



Abbreviations: AEs: anti-embolism stockings; eTKR: elective total hip replacement; extd: extended; IPCD: intermittent pneumatic compression devices; INMB: incremental net monetary benefit; LMWH: low molecular weight heparin; QALYs: quality-adjusted life-years; std: standard.

Table 313: Health outcomes breakdown per 1000 for each prophylaxis strategy - eTKR population

Intervention	Short-term health outcomes (n (95% CI))							Long-term health outcomes (n(95% CI))	
	Symptomatic DVT	Sympt Proximal DVT	Asymptomatic DVT	PE	Total VTE	Surgical site bleeding	Total Deaths	PTS	CTEPH
LMWH (std,std) + AEs	**6** (5 to 8)	**1** (0 to 2)	**134** (132 to 136)	**4** (4 to 5)	**144** (143 to 146)	**9** (1 to 32)	**1** (0 to 2)	**8** (6 to 11)	**0** (0 to 0)
Fondaparinux+ AES	**6** (2 to 13)	**1** (0 to 3)	**121** (36 to 261)	**10** (2 to 25)	**136** (46 to 284)	**79** (2 to 411)	**2** (0 to 6)	**8** (3 to 16)	**0** (0 to 1)
Foot pump + AES	**9** (4 to 15)	**2** (0 to 4)	**181** (91 to 311)	**6** (3 to 11)	**195** (101 to 333)	**12** (1 to 51)	**1** (0 to 3)	**10** (5 to 19)	**0** (0 to 0)
IPCD	**10** (3 to 19)	**2** (0 to 5)	**202** (66 to 405)	**19** (0 to 175)	**230** (71 to 495)	**12** (1 to 51)	**4** (0 to 35)	**13** (4 to 38)	**1** (0 to 5)
Foot pump	**4** (0 to 12)	**1** (0 to 3)	**79** (11 to 243)	**3** (0 to 9)	**85** (14 to 259)	**12** (1 to 51)	**1** (0 to 2)	**5** (1 to 14)	**0** (0 to 0)
AES	**13** (6 to 22)	**3** (1 to 6)	**285** (144 to 465)	**24** (0 to 203)	**323** (158 to 567)	**12** (1 to 51)	**5** (0 to 39)	**18** (8 to 48)	**1** (0 to 6)
LMWH (std,std)	**4** (1 to 9)	**1** (0 to 2)	**89** (30 to 195)	**21** (0 to 232)	**114** (33 to 337)	**9** (1 to 32)	**4** (0 to 44)	**8** (2 to 37)	**1** (0 to 7)
LMWH (std,extd)	**4** (1 to 10)	**1** (0 to 2)	**76** (18 to 204)	**8** (0 to 49)	**88** (19 to 238)	**10** (0 to 68)	**2** (0 to 10)	**5** (1 to 16)	**0** (0 to 1)
Aspirin	**7** (2 to 17)	**1** (0 to 4)	**149** (39 to 367)	**5** (1 to 12)	**160** (45 to 390)	**9** (8 to 11)	**1** (0 to 3)	**9** (2 to 20)	**0** (0 to 0)
Dabigatran	**4** (1 to 10)	**1** (0 to 2)	**88** (27 to 199)	**51** (0 to 644)	**142** (32 to 722)	**11** (1 to 45)	**11** (0 to 127)	**12** (2 to 98)	**2** (0 to 19)
Apixaban	**2** (1 to 6)	**0** (0 to 1)	**51** (15 to 121)	**44** (0 to 568)	**97** (18 to 606)	**8** (0 to 35)	**9** (0 to 102)	**9** (1 to 85)	**1** (0 to 16)
Rivaroxaban	**2** (1 to 5)	**0** (0 to 1)	**42** (11 to 104)	**16** (0 to 163)	**60** (14 to 211)	**16** (1 to 67)	**3** (0 to 34)	**4** (1 to 24)	**0** (0 to 5)
No prophylaxis	**15** (6 to 27)	**3** (1 to 7)	**328** (132 to 565)	**41** (0 to 429)	**385** (151 to 781)	**12** (1 to 51)	**8** (0 to 87)	**23** (7 to 81)	**1** (0 to 13)

Abbreviations: AEs: anti-embolism stockings; CTEPH: chronic thromboembolic pulmonary hypertension; DVT: deep vein thrombosis; eTKR: elective total knee replacement; extd: extended; IPCD: intermittent pneumatic compression devices; LMWH: low molecular weight heparin; PE: pulmonary embolism; PTS: post thrombotic syndrome; std: standard; VTE: venous thromboembolism.

Table 314: Cost breakdown for each prophylaxis strategy per person - eTKR population

Intervention	Prophylaxis costs	VTE costs (95% CI)	All Bleeding costs (95% CI)	CTEPH costs (95% CI)	PTS costs (95% CI)	Post-amputation costs (95% CI)	Total costs (a) (95% CI)
LMWH (std,std) + AEs	**£142**	**£6** (£5 to £6)	**£93** (£32 to £260)	**£13** (£10 to £15)	**£67** (£52 to £99)	**£101** (£69 to £142)	**£448** (£364 to £613)
Fondaparinux+ AES	**£128**	**£11** (£3 to £26)	**£671** (£140 to £2,769)	**£27** (£7 to £72)	**£67** (£25 to £139)	**£0.00** (£0.00 to £0.00)	**£904** (£358 to £3,016)
Foot pump + AES	**£91**	**£8** (£4 to £13)	**£109** (£30 to £371)	**£17** (£8 to £33)	**£91** (£46 to £165)	**£0.00** (£0.00 to £0.00)	**£315** (£208 to £590)
IPCD	**£42**	**£21** (£0.9 to £177)	**£109** (£30 to £371)	**£45** (£0.001 to £448)	**£116** (£31 to £337)	**£0.00** (£0.00 to £0.00)	**£333** (£133to £1,246)
Foot pump	**£60**	**£4** (£0.8 to £10)	**£109** (£30 to £371)	**£8** (£1.0 to £25)	**£40** (£7 to £118)	**£0.00** (£0.00 to £0.00)	**£219** (£119 to £473)
AES	**£31**	**£27** (£2 to £203)	**£109** (£30 to £371)	**£59** (£0.2 to £485)	**£161** (£66 to £401)	**£0.00** (£0.00 to £0.00)	**£387** (£167 to £1,397)
LMWH (std,std)	**£111**	**£21** (£0.4 to £231)	**£93** (£32 to £260)	**£49** (£0.001 to £572)	**£67** (£14.5 to £328)	**£101** (£69 to £142)	**£468** (£287 to £1,563)
LMWH (std,extd)	**£356**	**£9** (£0.2 to £50)	**£107** (£21 to £511)	**£19** (£0.00 to £130)	**£46** (£8 to £137)	**£103** (£68 to £150)	**£666** (£508 to £1,302)
Aspirin	**£0.49**	**£6** (£2 to £14)	**£92** (£70 to £130)	**£14** (£3 to £36)	**£74** (£21 to £178)	**£0.00** (£0.00 to £0.00)	**£187** (£118 to £304)
Dabigatran	**£34**	**£51** (£0.4 to £640)	**£106** (£32 to £34)	**£111** (£0.002 to £1,322)	**£104** (£14 to £867)	**£0.00** (£0.00 to £0.00)	**£406** (£100 to £2,987)
Apixaban	**£23**	**£44** (£0.2 to £564)	**£80** (£23 to £254)	**£97** (£0.002 to £1,157)	**£79** (£8 to £753)	**£0.00** (£0.00 to £0.00)	**£322** (£69 to £2,624)
Rivaroxaban	**£25**	**£16** (£0.16 to £162)	**£139** (£38 to £470)	**£37** (£0.00 to £388)	**£39** (£6 to £214)	**£0.00** (£0.00 to £0.00)	**£256** (£82 to £1,206)
No prophylaxis	**£0**	**£44** (£2 to £429)	**£109** (£30 to £371)	**£97** (£0.05 to £962)	**£203** (£64 to £701)	**£0.00** (£0.00 to £0.00)	**£453** (£137 to £2,281)

Abbreviations: AEs: anti-embolism stockings; eTKR: elective total hip replacement; extd: extended; IPCD: intermittent pneumatic compression devices; LMWH: low molecular weight heparin; std: standard; VTE: venous thromboembolism; CTEPH: chronic thromboembolic pulmonary hypertension; PTS: post thrombotic syndrome.

1. May not exactly equal the sum of the components due to rounding.

P.3 Discussion

P.3.1 Summary of results

For eTHR, the most cost-effective prophylaxis strategy, with the highest NMB, was LMWH (standard dose, standard duration) + aspirin (extended duration) with mean INMB £530 (95% CI: -£784 to £1,103). It also had the highest probability of being the most cost-effective option (72%). Where parenteral options are not acceptable or contraindicated; rivaroxaban would be the most cost-effective prophylaxis option. Of the mechanical prophylaxis options considered in the analysis; AES-based strategies appeared to be the more cost effective option compared to IPCDs and foot pumps. However, it was not possible to directly compare the length of the AES (knee vs thigh length) in terms of cost effectiveness as there were no effectiveness data for the knee-length stockings to allow its inclusion in this analysis.

For eTKR, foot pump was found to be the most cost-effective option with mean INMB of £353 (95% CI: -£101 to £665) however, with 18% probability of being the most cost-effective option. It was followed by aspirin with mean INMB of £281 (95% CI: -£195 to £703). The incremental analysis vs LMWH (std, std)+AES also showed that dabigatran ranked worse than no prophylaxis. rivaroxaban dominated both apixaban and dabigatran for this population. Of the mechanical prophylaxis options; foot pump or IPCD were found to be more cost-effective than AES.

P.3.2 Comparisons with published studies

To our knowledge, this analysis is the first to include all interventions for primary prevention of VTE in eTHR and eTKR that are currently available in the NHS; including mechanical, pharmacological and combination prophylaxis. It is also the first to account for outcomes such as the consequences of HIT including amputation; consequences of major bleeding including joint infections, wound haematoma and return to theatre. The model structure represented both the acute phase in the immediate post-operative period as well as the long term phase to life-time time horizon; using a Markov model to capture long-term consequences including PTS and CTEPH. It has been based on NMAs of the three main outcomes DVT, PE and major bleeding. These NMAs combined the evidence from the randomised controlled trials (RCTs) included in our clinical systematic review to obtain coherent estimates of relative effectiveness, for all the included interventions, to be used in the economic analysis.

A recent literature review of economic models of VTE prophylaxis in THR and TKR,[131] included economic evaluations published from 2008 to 2015 that compared anticoagulants; as pharmacological prophylaxis options.[257, 272, 273, 351, 620-622, 638, 651, 797, 833, 1017, 1018, 1051] The source of efficacy data in most of the included studies was either a single trial or meta-analysis of two or more of the DOACs' phase-3 trials. The review authors concluded that, of the pharmacological options considered, the use of DOACs for primary prevention of VTE resulted in a small incremental QALY gain vs LMWH which may be too small to be clinically meaningful. They also concluded that out of the DOACs considered, rivaroxaban and apixaban were more cost effective than dabigatran. On the other hand, an earlier systematic review of economic evaluations of pharmacological prophylaxis published in 2010;[474] concluded that fondaparinux and extended duration LMWH appear to be cost-effective strategies. These two reviews, however, did not include studies that compared mechanical prophylaxis options or considered combinations of both mechanical and pharmacological prophylaxis.

Our systematic review of the published economic evidence identified 32 economic studies, in 35 publications, relating to THR and TKR. [41, 103, 104, 125, 149, 228, 234, 257, 267, 269, 352, 354, 374, 381, 587, 620-622, 638, 666, 670, 675, 677, 678, 766, 793, 797, 801, 833, 919, 921, 985, 1017, 1018, 1051] These included 3 NICE TAs, 2 evidence review group

[ERG] reports and the CG92 model for standard duration and post discharge prophylaxis. Also, 10 of these publications were previously included in CG46.[41, 103, 104, 228, 234, 267, 354, 374, 587, 793]
Overall, published economic evaluations in eTHR and eTKR that compared VTE prophylaxis to no prophylaxis concluded that prophylaxis was a cost-effective intervention.[666, 670] The choice of an optimum prophylaxis strategy, however, varied across studies and among countries. This is partly explained by the difference in the range of interventions included in each of these studies but also by the differences in acquisition costs and sources of effectiveness evidence. In accordance with Brockbank 2017 conclusion;[131] our analysis shows that the differences between the included interventions in terms of QALYs-gained is very small and the results are likely to be more sensitive to differences in costs.

The results also showed that out of the DOACs considered; rivaroxaban is the most cost-effective. In eTHR, rivaroxaban dominated dabigatran and was cost-effective compared to apixaban with an ICER of 12,242 per QALY-gained. This was in line with the results of TA170 where rivaroxaban was found to dominate dabigatran.[677] A recent analysis funded by the NIHR found that rivaroxaban dominated dabigatran and was cost-effective compared to apixaban with an ICER of £114 per QALY gained.[919] TA245 also found that dabigatran was dominated, apixaban was extendedly dominated and rivaroxaban had an ICER of £22,123 per QALY-gained compared to fondaparinux.[678] In eTKR, rivaroxaban dominated both apixaban and dabigatran. This was in line with the results of the economic models assessed as part of TA170 and TA245 and a more recent analysis funded by the NIHR.[677, 678, 919]

However; our analysis showed that LMWH in combination with AES is more cost effective than the DOACs. This is in accordance with the conclusion of another systematic review of economic evaluations of pharmacological prophylaxis published in 2010;[474] which concluded that fondaparinux and extended duration LMWH can be cost-effective strategies.

We have assumed no recurrence of VTE events following treatment. This was decided after discussion with the clinical experts in the committee as it was felt that recurrence may not be related to the provoked VTE event that happens after the surgery and may be related to previous VTE events. Additionally, prevention of VTE recurrence is a primary outcome for the effectiveness of the VTE treatments used. As we have assumed that these treatments are 100% effective in our base case analysis; risk of recurrence was assumed to be 0%. This assumption might have underestimated the cost effectiveness of the interventions that were more effective in preventing PE and DVT. So, we tested this assumption in a one-way sensitivity analysis using data on rate of recurrence from TA245 and TA354 which reported rates of recurrence following treated DVT and PE. This sensitivity analysis did not result in any change in the ranking of the interventions for either of the two populations.

Additionally, due to lack of data on either DVT or PE outcomes for some interventions, an assumption still had to be made about the equivalence of relative effectiveness on the DVT and PE outcomes for these interventions. However, we have limited this only to instances where data was available for one of these outcomes but not for the other. However; as this assumption may have affected the results; we have tested it in sensitivity analyses. This was clearly a possibility in case of the eTKR analysis; where the relative effectiveness of foot pump, aspirin and foot pump + AES in relation to the PE outcome was assumed to be the same as their relative effectiveness obtained from the DVT NMA. This has resulted in a much lower PE rate for these interventions compared to all the others. Similarly, the relative effectiveness of LMWH (std, std)+ aspirin (extd duration) in relation to the DVT outcome for the eTHR population was based on its relative effectiveness obtained from the PE NMA. This assumption may have also affected the results. However, we tested this assumption in a sensitivity analysis using data on proximal DVT from the same trial that reported the PE data for this intervention (Anderson 2013)(SA10). This sensitivity analysis did not result in a change in the model results.

P.3.3 Limitations and interpretation

Our model was an update of the CG92 model; so we attempted to address the limitations of that model which were highlighted by the orthopaedic surgeons' community in a number of publications. One limitation was the use of relative effectiveness from the DVT NMA for the PE outcomes. In our analysis, we avoided making this assumption unless absolutely necessary; where the intervention was not included in the PE network. However, we have verified this assumption with the committee and externally validated it using the observational data analysis that used NJR data;[450, 451] where the ratio of the relative effectiveness of LMWH vs aspirin for the DVT outcome was found to be approximately the same as for the PE outcome (analysis available on request), supporting the assumption of proportionality of effectiveness for these two VTE outcomes.

Another issue was the lack of differentiation between proximal and distal DVT. We have addressed this issue by differentiating between the proximal and distal DVT for both symptomatic and asymptomatic events. We also allowed for different probabilities of progressing from each of these DVT outcomes to PTS; to acknowledge the fact that progression from treated and untreated DVT to PTS would be different. We emphasised the fact that asymptomatic DVT also does not have an impact on costs and outcomes in the short term as it is not diagnosed in practice and its only consequence in the model is its future progression to PTS. There was also a concern regarding the baseline risk used in the model which was based on data from the no prophylaxis arm in the RCTs. This was not felt to be reflective of current incidence of VTE with some trials dating back to the 70s, especially as practice has changed in terms of encouraging early mobilisation as well as the difference in surgical techniques. Based on this, we have used LMWH +AES as our model comparator and obtained its baseline risk data from observational cohort studies that used the UK NJR data.[450, 451]

However, despite all our efforts; the results of this economic analysis are still highly uncertain; in particular for the TKR population. This reflects the uncertainty and imprecision of the NMA results that underpinned it due to the sparse data and small number of RCTs for each comparison in networks; particularly for the PE and MB outcomes. These imprecise estimates of cost effectiveness preclude defining a clear ranking of the included interventions in terms of their cost-effectiveness. This is a reflection of the state of the collective body of evidence in this clinical area and it is not correct to try to address this by using only direct, pairwise meta-analyses or economic evaluations as this will simply ignore the majority of the evidence available.

Another limitation of this analysis is that the relative safety of aspirin compared to LMWH was based on an observational cohort analysis based on NJR data. [450, 451] This was due to the lack of any randomised controlled trials that report major bleeding outcomes for aspirin in these populations. However, as the data for MB from trials are likely to be imprecisely estimated, due to the rarity of these events; it was felt that this would be an appropriate source of relative effectiveness for a safety outcome.

P.3.4 Generalisability to other populations or settings

The results of this analysis have been largely based on epidemiological and cost data specific to England including the cohort characteristics which were based on data from the NJR. Additionally, the interventions included in the analysis were true to current UK clinical practice. This may limit the generalisability to other populations and settings. However, the relative effectiveness estimates were based on comprehensive systematic reviews and NMAs that did not restrict the inclusion of studies to specific countries. Hence, the results relating to the health outcomes are likely to be generalisable. Additionally, this analysis has been undertaken from a UK NHS and PSS perspective; hence its results might not be generalizable beyond these settings. The population modelled also represents a cohort whose characteristics might be different from eTHR and eTKR cohorts in other countries.

P.3.5 Conclusions

In people undergoing elective total hip replacement e(THR), VTE prophylaxis appears to be cost effective compared to no prophylaxis. A strategy consisting of LMWH (standard dose) for 10 days followed by aspirin for 28 days was the most cost effective. This result was robust to changes in the model input parameters. LMWH-based strategies that use extended duration LMWH or its combination with AES are more cost-effective compared to LMWH standard duration alone or in combination with AES. Rivaroxaban was found to be the most cost-effective of the DOACs considered in this analysis.

In people undergoing elective knee replacement (eTKR), VTE prophylaxis appears to be cost effective compared to no prophylaxis. Foot pump was found to be the most cost-effective option in this population. This result was robust to changes in the model input parameters. However; this analysis is subject to considerable uncertainty. LMWH-based strategies that use standard duration are more cost-effective compared to extended duration LMWH. Rivaroxaban was found to be the most cost-effective of the DOACs considered in this analysis. These results, however, are subject to high uncertainty given the imprecise effectiveness results from the NMAs that underpinned this analysis.

Evidence statements

One original cost-utility analysis found that, in people admitted for elective total hip replacement surgery, the following interventions were cost-effective (having positive incremental net monetary benefit [INMB]) compared to LMWH (standard dose, standard duration) +AEs: LMWH (standard dose, standard duration) + aspirin (extended duration) (INMB £530); LMWH (standard dose, extended duration)+ AEs (INMB £36) and AES (INMB: £5). This analysis was assessed as directly applicable with minor limitations.

One original cost-utility analysis found that, in people admitted for elective knee replacement surgery, the following interventions were cost-effective (having positive incremental net monetary benefit [INMB]) compared to LMWH (standard dose, standard duration) +AEs: Foot pump (INMB £353), aspirin (INMB £281), foot pump+ AES (INMB £72). This analysis was assessed as directly applicable with potentially serious limitations.

P.3.6 Implications for future research

Future research need to focus on assessing the relative safety of the different prophylaxis strategies. No studies were found to report usable data on the side effects of the mechanical prophylaxis strategies. Additionally, the evidence available for the safety outcomes of the pharmacological interventions is only based on RCTs of short duration and, given the rarity of the events, the results are highly uncertain as the trials are not powered to detect differences in these secondary outcomes. Given the increased interest in the use of real world evidence (RWE) and the availability of large registry and audit data reporting these outcomes in the post-marketing phase; more research should focus on developing methodologies to assess the relative safety of the pharmacological prophylaxis interventions using these observational data.

Our results showed that aspirin is likely to be a cost effective prophylaxis strategy for eTKR. For eTHR it was not found to be cost effective. This was primarily based on a single, dated RCT that does not reflect current practice. Given that anecdotal evidence from current practice and evidence from large observational studies contradict the findings from this study and suggest that aspirin is likely to be more effective as a prophylaxis strategy in eTHR than what has been seen in that study; it would be highly informative if its relative effectiveness and safety in this population is assessed in a well-conducted and adequately powered RCT. Aspirin is a very cheap intervention that can be highly cost-effective if effectiveness and safety can be established in such an RCT.