Decision analytic modelling to inform policy and research decisions on the use of risk assessment models to select patients at risk of venous thromboembolism for pharmacologic prophylaxis

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Abstract

Pharmacological thromboprophylaxis can be used to reduce the risk of venous thromboembolism (VTE), but it is costly and is associated with an increased risk of bleeding. Selecting higher-risk individuals for thromboprophylaxis using a risk-assessment model (RAM) has the potential to be cost-effective if the population selected has a more favourable balance of costs, benefits and harms.

This thesis discusses the use of decision-analytic modelling to assess the cost-effectiveness of RAM-based prophylaxis in several distinct populations: outpatients having lower limb immobilisation following injury, medical and surgical inpatients, and women who are pregnant or in the puerperium. In each population, RAM-based prophylaxis was compared against prophylaxis for all and prophylaxis for none. The RAMs modelled were those validated for use in each specific population. Where data allowed, the analyses compared alternative RAMs, alternative RAM cut-offs for prophylaxis and the optimal trade-off between RAM sensitivity and specificity in a given population. Cost-effectiveness was assessed by comparing lifetime costs and quality-adjusted life years from an NHS and personal social services perspective.

The cost-effectiveness of RAM-based prophylaxis varied across the populations considered due to differences in the risks of VTE and the differences in the prognostic accuracy of the available RAMs. In postpartum women, RAM-based prophylaxis was not cost-effective compared to no prophylaxis due to the very low risk of VTE and the poor specificity of the available RAMs. In people having lower limb immobilisation, a RAM would need to have a sensitivity of between 84% and 89% and a specificity of between 46% and 55% for RAM-based prophylaxis to be cost-effective. Whereas in medical and surgical inpatients, a RAM would need to have very high sensitivity for RAM-based prophylaxis to be more cost-effective than prophylaxis for all. The cost-effectiveness of RAM-based prophylaxis was most uncertain in high-risk antepartum women and obese postpartum women.

Contents

Abstract 1
Abbreviations 4
1. Introduction 6
2. Background 12
2.1 Venous thromboembolism 12
2.2 Pharmacological thromboprophylaxis 12
2.3 Risk assessment models for identifying individuals for pharmacological thromboprophylaxis. 13
2.4 Decision-analytic modelling to inform healthcare policy and research priorities 14
2.5 Aims of the research programme 16
3. Comparison of the decision problems addressed 18
3.1 Context 18
3.2 Population 18
3.3 Thromboprophylaxis strategies compared 20
3.4 Prophylaxis agent and duration of prophylaxis 22
4. Methods 23
4.1 Conceptual modelling 23
4.2 Data sources 28
4.2.1 Introduction to data sources 28
4.2.2 RAM performance 33
4.2.3 Effectiveness of prophylaxis 33
4.2.4 Baseline risks of symptomatic VTE in those not having prophylaxis 34
4.2.5 Ratio of asymptomatic to symptomatic DVT 35
4.2.6 Case-fatality rate for PE 35
4.2.7 Risk of major bleeding in those receiving or not receiving thromboprophylaxis 36
4.2.8 Risk of bleeding during anticoagulant treatment for VTE 37
4.2.9 Risks of VTE complications 37
4.2.10 Mortality 38
4.2.11 Resource use and costs 38
4.2.12 Utilities 38
5. Key findings 39
5.1 Introduction to key findings 39
5.2 Impact of thromboprophylaxis on the incidence of adverse clinical outcomes 39
5.3 Interaction between VTE risk and RAM performance 44
5.4 Decision uncertainty assessed using EVPI 45
5.5 Decision uncertainty assessed using deterministic analyses 46

5.6 Impact of using alternative pharmacological agents for prophylaxis. 47
5.7 Value of future research 48
5.8 Summary of key findings from the decision-analytic modelling 48
6. Limitations 50
6.1 Populations examined 50
6.2 Studies assessing RAM performance 50
6.3 Data availability 51
6.4 Model structure 51
7. Contribution to knowledge and implications for future research 52
7.1 Novelty of the research conducted 52
7.2 Implications for clinical practice 53
7.3 Use of research findings to inform the design of the TiLLI trial 54
7.4 Use of research findings to inform other research projects in people having LLI 55
7.5 Implications for future research in women at risk of pregnancy-related VTE 55
8. Researcher development over the programme of work 56
9. Bibliography 57
Appendix 1 – Summary of Permissions 66
Appendix 2 – Submitted work 1 67
Appendix 3 - Submitted work 2 148
Appendix 4 - Submitted work 3 216

List of Tables

Table 1: Summary of the research projects described in the submitted works 8
Table 2: Data sources used to inform different parameters across the projects. 29
Table 3: Summary cost-effectiveness results 41
Table 4: Predicted short-term and long-term clinical outcomes for prophylaxis versus no prophylaxis 42

List of Figures

Figure 1: Short-term decision-tree model 25
Figure 2: Long-term state-transition model 26

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Abbreviations

aDVT	Asymptomatic DVT
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
CG	Clinical Guideline
CRNMB	Clinically relevant non-major bleeding
CTEPH	Chronic thromboembolic pulmonary hypertension
DOACs	Direct oral anticoagulants
DVT	Deep vein thrombosis
EQ-5D	EuroQol-5 Dimensions
EThIG	Efficacy of Thromboprophylaxis as an Intervention during Gravidity
EVPI	Expected value of perfect information
EVPPI	Expected value of partial perfect information
EVSI	Expected value of sample information
GEMNet	Guidelines in Emergency Medicine Network
GI	Gastrointestinal
HTA	Health Technology Appraisal
HRQoL	Health-related quality-of-life
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial haemorrhage
ISTH	International Society for Thrombosis and Haemostasis
LLI	Lower limb immobilisation
LMWH	Low molecular weight heparin
L-TRiP(cast)	Leiden - Thrombosis Risk in Plaster (cast)
NG	NICE Guideline
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	Network meta-analysis
NMB	Net monetary benefit
PE	Pulmonary embolism
PPI	Patient and public involvement

PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PTS	Post thrombotic syndrome
QALY	Quality-adjusted life-years
RAM	Risk-assessment model
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised controlled trials
ROC	Receiver operating characteristic
RR	Relative risk
sDVT	Symptomatic DVT
SLR	Systematic Literature Review
SFOG	Swedish Society of Obstetrics and Gynaecology
TiLLI	Thromboembolism in Lower Limb Immobilisation
TRiP(cast)	Thrombosis Risk Prediction Following Cast Immobilization
UK	United Kingdom
VOI	Value of information
VTE	Venous thromboembolism
VTEAM	Venous Thromboembolism Assessment Model
VTEP	Venous Thromboembolism in Pregnancy
WTP	Willingness-to-pay

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1. Introduction

This thesis discusses the use of decision-analytic modelling to inform policy and research decisions on the use of risk assessment models (RAMs) to select individuals at risk of venous thromboembolism (VTE) for pharmacological prophylaxis.

It draws on work conducted across three research projects commissioned by the National Institute for Health and Care Research (NIHR) Health Technology Appraisal (HTA) Programme (see Table 1). All three projects used decision-analytic modelling to assess the cost-effectiveness of alternative thromboprophylaxis strategies to identify the most cost-effective strategy given the current evidence in a particular population. All of the cost-effectiveness analyses compared RAM-based prophylaxis to prophylaxis for all or prophylaxis for none, but the RAMs assessed were different for each population. The broad populations covered in each project were:

- Adult outpatients having lower limb immobilisation after injury (LLI) in the Thromboembolism in Lower Limb Immobilisation (TiLLI) project
- Hospitalised patients (excluding children, pregnant women and critical care patients) in the Venous Thromboembolism Assessment Model (VTEAM) project
- Women who are pregnant or in the puerperium (up to 6 weeks after giving birth) in the Venous Thromboembolism in Pregnancy (VTEP) project

Whilst decision-analytic modelling is commonly used to the identify the most cost-effective policy or treatment strategy given the current evidence, it can also be combined with expected value of perfect information (EVPI) analysis to identify areas of uncertainty that might be reduced by future research and expected value of sample information (EVSI) analysis to formally estimate the value of potential future research studies. Whilst EVPI was conducted to explore decision uncertainty in all three projects, the analyses for the VTEP project adopted the more formal EVSI approach to determining future research priorities.

This thesis will focus on the decision-analytic modelling conducted within each project, as this is the aspect of each project for which I was lead researcher. The decision-analytic modelling aspect of each project is described in distinct chapters within three HTA monographs, with further relevant text in the discussion and conclusion chapters of the monographs.[1-3] These chapters are the published works submitted for the purposes of this thesis (see Table 1).

However, it should be noted that in each case, the decision-analytic modelling was one aspect of a broader applied research project which included elements led by co-investigators. For example, in each project there was at least one systematic literature review (SLR) element which was used to inform some of the model inputs. These other elements of the research projects have been described in separate distinct chapters of the HTA monographs and are treated in this thesis as separate published sources used to inform the decision-analytic modelling.

The structure of the thesis is as follows. Section 2 provides background information on VTE, thromboprophylaxis and the use of RAMs for selecting individuals to receive preventative interventions, such as thromboprophylaxis, in clinical practice. It also lays out the aims of the research projects. Section 3 describes the decision problems addressed across the projects and Section 4 describes the methods, with a focus on differences and similarities across the projects. The key findings and limitations are discussed in Sections 5 and 6. Section 7 discusses the contribution to knowledge and the implications for future research. Section 8 describes my development as a researcher over the programme of work.

Table 1: Summary of the research projects described in the submitted works

Project and grant details	Personal contribution to the research	Publications
Short title: **TiLLI** Title: Thromboprophylaxis for lower limb immobilisation: An evidence synthesis Funder: NIHR Programme: HTA Funding Stream: HTA Clinical Trials & Evaluation Grant number: 15/187/06 Dates: April 2017 to March 2018 Chief Investigator: Prof. Steve Goodacre	I was the **lead for all aspects of the decision-analytic modelling and economic evaluation.** Prof. Stevenson, a more senior health economist, was a co-applicant on the funding application and provided advice relating to the health economics but his contribution was not sufficient for him to be a co-author. My specific contributions were as follows: - Contributed to writing the decision analytic modelling sections of the funding application with oversight from Prof. Stevenson. - Systematically reviewed published economic evaluations to inform the conceptual model development - Led development of the conceptual model with input from clinical and patient expert members of the research group - Designed and programmed the decision-analytic model - Identified parameters to populate the model from published literature with the exception of RAM performance data and data on effectiveness and safety of prophylaxis which came from SLRs conducted by co-investigators, and which were reported separately in Chapter 3 of the HTA monograph - Led discussions with clinical experts to obtain data inputs based on expert opinion where published data sources were lacking - Conducted iterative model verification and validation during development - Evaluated and reported model outcomes - **Led writing of the economic chapter of the HTA monograph (Chapter 4: Assessment of cost-effectiveness)** - **Contributed text** related to the economic evaluation within the Discussion and Conclusion chapters of the HTA monograph **(Chapters 5 and 6)**	**Submitted work 1:** Pandor A, Horner D, **Davis S**, Goodacre S, Stevens JW, Clowes M, *et al.* Different strategies for pharmacological thromboprophylaxis for lower-limb immobilisation after injury: systematic review and economic evaluation. *Health Technol Assess* 2019;**23**(63). [**Chapter 4:** pages 55-104; **Chapter 5**: pages 106-111; **Chapter 6**: page 113-114] doi:10.3310/hta23630 The relevant chapters are reproduced in Appendix 2.
Short title: **VTEAM** Title: The cost-effectiveness of venous thromboembolism risk assessment tools for hospital inpatients	I was the **lead for all aspects of the decision-analytic modelling and economic evaluation**. My specific contributions were as follows: - Led writing of the decision analytic modelling sections of the funding application - Led development of the conceptual model with input from clinical and patient expert members of the research group	**Submitted work 2:** Horner DE, **Davis S**, Pandor A, Shulver H, Goodacre S, Hind D, *et al.* Evaluation of venous thromboembolism risk assessment models for hospital inpatients: the VTEAM

Funder: NIHR Programme: HTA Funding Stream: HTA Commissioned Grant number: NIHR127454 Dates: July 2019 to December 2021 Chief Investigator: Prof. Steve Goodacre	- Designed and programmed the decision-analytic model - Identified parameters to populate the model from published literature with the exception of RAM performance data which came from a SLR conducted by co-investigators, and which was reported separately in Chapter 3 of the HTA monograph - Conducted iterative model verification and validation during development - Evaluated and reported model outcomes - **Led the writing of the economic chapter of the HTA monograph (Chapter 4: Workstream 1 – economic evaluation)** - **Contributed text** related to the economic evaluation within the Discussion and Conclusion chapters of the HTA monograph (**Chapters 8 and 9)** - **Led the writing of two peer-reviewed articles describing the decision-analytic modelling** The decision-analytic modelling described here fell within the evidence synthesis workstream of the VTEAM project (workstream 1). There was also a second workstream which used primary research methods to address different research objectives. I was not involved in the research conducted in workstream 2, but I did contribute to the overall conclusions reported in Chapter 9 which drew on findings across both workstreams.	evidence synthesis. *Health Technol Assess* 2024;**28**(20). [**Chapter 4**: pages 27-69; **Chapter 8**: pages 93-97; **Chapter 9**: 101-103] https://doi.org/10.3310/AWTW6200 The relevant chapters are reproduced in Appendix 3. Additional peer-reviewed articles describing research included in the submitted work: **Davis, S**.; Goodacre, S.; Horner, D, *et al.* Decision-analysis modelling of effectiveness and cost-effectiveness of pharmacological thromboprophylaxis for surgical inpatients, using variable risk assessment models or other strategies. Journal Thromb Haemost. 2023;21(6):1580-1591. doi.org/10.1016/j.jtha.2023.02.018 **Davis S**, Goodacre, S, Horner D, *et al.* Decision-analysis modelling of the effectiveness and cost-effectiveness of thromboprophylaxis for medical inpatients. BMJ Medicine 2024; 3(1): e000408. doi.org/10.1136/bmjmed-2022-000408
Short title: **VTEP** Title: Estimating the value of future research to improve guidelines on thromboprophylaxis for	I was the **Chief Investigator** which included the following contributions: - **Led writing of the funding application** with contributions from co-applicants - Chaired research team meetings - Recruited steering committee members	**Submitted work 3:** **Davis S**, Pandor A, Sampson FC, Hamilton J, Nelson-Piercy C, Hunt BJ, *et al.* Thromboprophylaxis during pregnancy and the puerperium: a systematic review and economic

women during pregnancy and after delivery Funder: NIHR Programme: HTA Funding Stream: HTA Commissioned Grant number: NIHR131021 Dates: January 2021 to March 2022 **Chief Investigator: Ms Sarah Davis**	- Presented findings to the steering committee and fed back advice to the research team - Provided oversight of the project to ensure overall coherence across aspects being led myself and co-investigators, for example: a) ensuring the review and statistical analysis of RAM performance studies were reported in a manner that could be used to inform the decision-analytic modelling; b) contributing to the design of the stakeholder workshops and clinician surveys (described in Chapter 5) to ensure they addressed the uncertainties identified by the cost-effectiveness analysis and provided direction for the EVSI analysis - **Took overall responsibility for completion of the HTA monograph** which involved; a) leading the writing of the Abstract, Scientific Summary and the introductory Chapters (1 and 2) whilst incorporating contributions from co-investigators; b) incorporating the chapters led by co-investigators (Abdullah Pandor led writing on the SLR in Chapter 3, and Fiona Sampson led writing on the qualitative research on stakeholder perspectives in Chapter 5); c) **leading the writing of the Discussion and Conclusions** (**Chapters 7 and 8**) incorporating contributions from co-investigators: d) leading the response to peer review and editorial comments on the HTA monograph I was the **lead for all aspects of the decision-analytic modelling and economic evaluation.** My specific contributions were as follows: - Systematically reviewed published economic evaluations to inform the conceptual model development - Led development of the conceptual model with input from clinical and patient expert members of the research group - Designed and programmed the decision-analytic model - Identified parameters to populate the model from published literature with the exception of RAM performance data which came from a SLR conducted by co-investigators, and which was reported separately in Chapter 3 of the HTA monograph - Conducted iterative model verification and validation during development (an independent verification and validation of the final model was conducted by Andrew Metry in line with best practice guidance)	evaluation to estimate the value of future research *Health Technol Assess*, 2024: **28**(9). [**Chapter 4:** pages 21-65; **Chapter 6**: pages 85-88, **Chapter 7**: pages 89-94 and **Chapter 8**: pages 95-97] **https://doi.org/10.3310/DFWT3873** The relevant chapters are reproduced in Appendix 4. Additional peer-reviewed article describing research included in the submitted work: **Davis S**, Pandor A, Sampson S, *et al.* Estimating the value of future research into thromboprophylaxis for women during pregnancy and after delivery: a value of information analysis. Journal Thromb Haemost. 2024 Apr;22(4):1105-1116. doi: 10.1016/j.jtha.2023.12.035.

	- Evaluated and reported model outcomes - **Led writing of economic chapter of the HTA monograph (Chapter 4: Decision-analytic modelling)** - Conducted the informal review of NIHR funded trials to assess typical research costs for trials in women who are pregnant or have recently given birth. - **Led writing of the chapter describing the EVSI analysis (Chapter 6: Estimating the expected value of future research)** - **Led the writing of a peer reviewed article describing the decision-analytic modelling**	

Abbreviations: EVSI, expected value of sample information; HTA, Health Technology Appraisal; NIHR, National Institute for Health and Care Research; RAM, risk assessment model; SLR, systematic literature review

2. Background

2.1 Venous thromboembolism

VTE is a collective term for conditions caused by a clot forming in a vein. A deep vein thrombosis (DVT) is when a clot forms in a large vein deep within a muscle, mostly commonly in the leg. DVT may result in symptoms such as pain, swelling and redness in the leg, but it can also occur asymptomatically.[4] In some cases the blood clot can also dislodge and travel to lungs causing a blockage to a pulmonary artery, known as a pulmonary embolism (PE).[4] This may cause symptoms of breathlessness or chest pain and PE can be fatal in some people.[4]

VTE can also result in long-term complications. Post-thrombotic syndrome (PTS) may occur if a DVT has caused damage to the leg veins leading to long-term symptoms such as pain, swelling, itching, discolouration, and in some patients, venous leg ulcers.[5] People who survive a PE may go on to develop chronic thromboembolic pulmonary hypertension (CTEPH) resulting in chronic breathing difficulties and fatigue.[6]

Despite the range of anticoagulant and thrombolytic treatments available for treating VTE,[7] it is still associated with significant morbidity and mortality. For example, NHS England reported that in 2022/23 there were 15,012 deaths from VTE as recorded on death certificates.[8] A substantial proportion of these deaths (68%) were associated with recent hospital admission (i.e., hospital admission ending in the previous 90 days), but only a minority (37%) occurred in patients with a VTE related diagnosis recorded during their last admission, highlighting the risk of VTE in patients admitted to hospital for other reasons.[8] Whilst admission to hospital is a well-recognised risk factor for VTE, people with lower limb injury having outpatient immobilisation are also at increased risk.[9] Pregnancy-related VTE also remains the leading cause of maternal death, despite the absolute risk of VTE being low during pregnancy.[10]

2.2 Pharmacological thromboprophylaxis

Pharmacological prophylaxis is one of the strategies used to prevent VTE in people who are identified to be at increased risk.[9] Although various pharmacological agents are available for thromboprophylaxis, the agent recommended most broadly for the prevention of VTE is low-molecular-weight heparin (LMWH), with other agents, such as fondaparinux, unfractionated heparin, or direct oral anticoagulants (DOACs), being recommended in specific patient groups or where LMWH is contraindicated.[9,11] Mechanical forms of VTE prophylaxis, such as anti-embolism stockings or intermittent pneumatic compression devices may be used in combination with pharmacological prophylaxis, or they may be used in patients contraindicated

to pharmacological prophylaxis.[9] In this research, I examined whether pharmacological thromboprophylaxis should be offered to individuals who may or may not already be receiving mechanical prophylaxis, on the assumption that any mechanical prophylaxis being offered in a particular patient group will not be altered by the decision regarding whether the individual is also eligible for pharmacological prophylaxis.

2.3 Risk assessment models for identifying individuals for pharmacological thromboprophylaxis

In VTE prevention, there is a trade-off between the risk of VTE, the increased risk of bleeding associated with pharmacological thromboprophylaxis and the cost of offering thromboprophylaxis. Selecting individuals to receive thromboprophylaxis requires balancing these risks, benefits and costs against each other. Offering thromboprophylaxis to too broad a group of people may be inefficient from a cost perspective but will also potentially expose lower risk individuals to unnecessary harm from an increased risk of bleeding. Conversely, offering thromboprophylaxis to only the highest risk individuals may result in some lower risk individuals experiencing the adverse health consequences of a VTE, with an associated cost for VTE treatment. Using RAMs to target thromboprophylaxis at higher risk individuals therefore has the potential to be more cost-effective than a strategy of offering thromboprophylaxis to all people falling within a broad population known to be at increased risk (e.g., all hospitalised inpatients).

RAMs can be used to select higher-risk individuals to receive VTE prophylaxis based on the presence or absence of specific risk factors. In its simplest form a RAM may consist of a set of risk factors with different risk factors being used to place individuals in different risk categories. At the other end of the scale, a very quantitative approach may be taken whereby the individual's risk factors are entered into a calculation tool that provides an estimate of their absolute risk, allowing the threshold for intervention to be expressed on a continuous absolute risk scale. More commonly, a semi-quantitative approach it taken, whereby different points are scored for different risk factors, which are then summed, and the threshold is expressed as a particular combined score. Regardless of how the RAM is implemented, the cost-effectiveness of any RAM-based prophylaxis strategy will be dependent on the cut-off score used to classify people as being at sufficient risk for prophylaxis and the prognostic accuracy of the RAM at the chosen cut-off.

2.4 Decision-analytic modelling to inform healthcare policy and research priorities

Whilst randomised controlled trials (RCTs) are a methodologically rigorous approach for determining the treatment effects and safety of offering a particular pharmacological intervention to the specific population eligible for enrolment in the trial, individual clinicians are left to decide whether a particular pharmacological intervention offers an appropriate balance of risks and benefits for the person they are treating. In doing so, they often turn to clinical guidelines, such as those published by the National Institute for Health and Care Excellence (NICE), which aim to ensure that patients are offered consistent care across the National Health Service (NHS) in England, whilst making the best use of available resources.

Decision-analytic modelling is a useful tool for informing these guidelines as it allows the net costs and net health benefits of alternative policies or treatment strategies to be compared based on the evidence currently available.[12] For preventative interventions, decision-analytic modelling can be used to compare different thresholds for intervention, allowing guideline developers to consider whether different policies offer an appropriate balance of costs, benefits and harms across the population at risk. The decision as to whether to prescribe in each case will still be an individual one made between the patient and their clinician, but having evidence-based guidance on the optimal threshold for intervention should increase consistency in care and minimise the chances that resources are used inefficiently or that patients are harmed from being either overtreated or undertreated.

Decision-analytic modelling can be used to combine information from different sources to estimate the clinical outcomes expected when using a RAM to select individuals for thromboprophylaxis. This would include evidence on the prognostic accuracy of the RAM, the risk of VTE in the population of interest, and the safety and efficacy of thromboprophylaxis. Costs and health outcomes can then be attributed to those clinical outcomes to determine an overall balance of costs (or savings) for the healthcare system and health benefits (or losses) for patients. Health benefits are commonly modelled using quality-adjusted life-years (QALYs) as these capture the impact of clinical outcomes on both survival and health-related quality-of-life (HRQoL). The cost-effectiveness of one strategy compared with another is usually presented using an incremental cost-effectiveness ratio (ICER), reported as the incremental cost per QALY gained.[12] If the decision-maker's willingness-to-pay (WTP) for an additional QALY is known, then the cost-effectiveness can also be expressed as the net monetary benefit (NMB), which is the monetary value of the QALYs gained minus the costs required to achieve those gains. The optimal strategy is then the one that maximises the NMB.[12] Decision-analytic

modelling can therefore be used to identify the optimal thromboprophylaxis strategy given the current evidence available and the decision maker's WTP for an additional QALY. Guidance making bodies such as the NICE use this information to inform national guidance ensuring that resources are used efficiently across the healthcare system.[13,14]

Decision-analytic modelling is also able to incorporate information on the uncertainty in the evidence informing the model inputs. Probabilistic sensitivity analysis (PSA) can be used to propagate the uncertainty in the model inputs through the decision-analytic model to determine the uncertainty in the costs and QALYs predicted by the model for the different strategies being compared.[12] This provides an estimate of the probability that each strategy is the most cost-effective and therefore the probability that the decision maker is making an error by choosing a particular strategy. Uncertainty regarding the choice of data sources or any assumptions within the model structure are not generally captured in the PSA and instead are usually explored using deterministic scenario and sensitivity analyses.[12] Information on uncertainty regarding the optimal strategy forms part of the decision-making process used by NICE guidance developers when making recommendations and it may determine the strength of the recommendation or it may be used to inform a recommendation for further research.[13,14]

When a recommendation for further research is made, additional information is needed on the type of research that should be conducted and whether that research will provide a reasonable return on investment. Decision-analytic modelling combined with value of information (VOI) analysis provides information on which data sources are associated with the greatest decision uncertainty when trying to assess the optimal strategy.[12] VOI analysis can therefore be used to inform the design of future research studies. The global EVPI provides an estimate of the NMB that could be achieved by obtaining perfect information on all model inputs.[12] Whilst a decision-analytic model will typically estimate outcomes for a single person, the outputs can be scaled up to reflect the population likely to be affected by the decision, by considering the number of people whose care will be determined by the guidance over the period the guidance is likely to be in place before being reviewed. This population-level global EVPI provides an upper ceiling on the amount that could be justifiably spent on further research.[12] The expected value of partial perfect information (EVPPI) provides an estimate of the NMB that could be achieved by obtaining perfect information on a parameter (or set of parameters) of interest whilst obtaining no additional information on other parameters.[12] This can be used to determine which particular model inputs should be the focus of future research studies, with studies being prioritised that would reduce the uncertainty on those parameters with the highest EVPPI. The

population-level EVPPI provides an upper limit for the resources that could be spent on further research to reduce uncertainty in a particular set of parameters.[12] However, no research that can be pragmatically undertaken will provide perfect information on a particular model parameter as the size of the population studied will necessarily limit the accuracy to which the parameter can be estimated. The population-level EVSI can be used to determine the value of the information likely to be achieved by different studies of different sizes.[12] This is done by simulating the expected study findings for a particular study of a particular size. As the outcome of any future trial is uncertain, a set of predictions for the study findings are simulated to reflect that uncertainty. These estimates are then used in the decision-analytic model to determine how likely it is that the future study would change the optimal strategy and the consequences this would have in terms of expected costs and QALYs over the population affected by the decision. This EVSI estimate can then be compared to the costs of conducting the research to determine whether the study would provide value for money. The balance between the EVSI obtained and the cost of conducting the research can also be explored for studies of different sizes. In this way, decision-analytic modelling can be used not only to determine the optimal use of healthcare resources given the current evidence, but also what further research should be funded.[12]

2.5 Aims of the research programme

Each of the research projects examined a broad population of individuals who are known to be at increased risk of VTE relative to the general population and who may therefore benefit from thromboprophylaxis. The cost-effectiveness of using prophylaxis in any target population will be dependent on several factors which have the potential to vary across different populations including: the baseline risk of VTE across the target population when thromboprophylaxis is not offered; the cost of thromboprophylaxis which depends mainly on the duration; the effectiveness of thromboprophylaxis for reducing the VTE risk in the specified population; and the risks of major bleeding during both prophylaxis and VTE treatment. The potential for variation in these factors across different patient groups means that separate analyses must be conducted for different target populations. In addition, the cost-effectiveness of RAM-based prophylaxis will depend on the prognostic accuracy of the RAMs used in the target population. As RAMs are usually developed and validated for use within a specific population, separate analyses are needed in populations addressed by a specific RAM. Therefore, although the methods used across the three projects were similar, the various populations addressed across the projects were distinct, requiring different model parameters, and in one case a modified

model structure, leading to different conclusions regarding the optimal thromboprophylaxis strategy.

The strength of the evidence base available to support the analyses also varied across the populations studied which meant that the research aims also varied. In the VTEAM project, the evidence base for thromboprophylaxis in medical and surgical inpatients was fairly well developed, and extensive evidence synthesis work had already been undertaken to inform the NICE guidelines (NG) on VTE prevention in hospitalised patients (NG89).[9] This included an assessment of the cost-effectiveness of thromboprophylaxis for all versus no thromboprophylaxis using estimates of prophylaxis effectiveness based on a systematic literature review (SLR) and network meta-analysis (NMA) that included numerous RCTs.[9] Therefore, the main research aims in this population were: to determine whether RAM-based prophylaxis was more cost-effective than universal prophylaxis; to compare the cost-effectiveness across alternative RAMs; and to explore the optimal threshold for RAM-based thromboprophylaxis.

Contrastingly, in the VTEP project, the existing Royal College of Obstetricians and Gynaecologists (RCOG) guidance was based on much weaker evidence,[11] with no large scale RCTs of thromboprophylaxis in women who are pregnant or in the puerperium identified in a recent SLR.[15] Therefore, a key aim of this project was to use EVPI to identify potential future research studies that might reduce the decision uncertainty around using thromboprophylaxis in this group and to use EVSI to provide a quantitative assessment of the value of those future studies. We were mindful that any future research studies should be acceptable to the patients and clinicians who would be involved in the research. Therefore, a survey of clinical experts and a series of stakeholder workshops were conducted to explore the acceptability of these potential future studies. Whilst this qualitative research was led by a co-investigator and is considered outside of the work presented in this thesis, the information from the qualitative research was taken into account when interpreting the EVSI findings to make research recommendations.

In the TiLLI project, there was some RCT evidence on thromboprophylaxis in LLI,[16] but there were no existing cost-effectiveness analyses and the existing evidence for RAM performance was weak. Therefore, a key aim in this project was to determine whether RAM-based thromboprophylaxis in this population had the potential to be cost-effective and what the RAM

performance would need to be for RAM-based thromboprophylaxis to be more cost-effective than thromboprophylaxis for all.

3. Comparison of the decision problems addressed

In an economic evaluation, the decision problem specifies the population of interest, the alternative healthcare interventions being compared and the relevant healthcare context. This section describes the decision problem being addressed across each of the projects, with a focus on differences and similarities across the projects.

3.1 Context

In all three projects, the economic analysis took a UK NHS and Personal Social Services (PSS) perspective and discounting was applied at 3.5% per annum to both costs and benefits. All the cost-effectiveness analyses measured health benefits using QALYs and identified the optimal thromboprophylaxis strategy at both a £20,000/QALY and £30,000/QALY threshold, reflecting the threshold range adopted by NICE at the time the research was conducted.[17] However, conducting EVPI and EVSI analyses requires a single WTP threshold to be specified. In the TiLLI and VTEAM projects, EVPI was assessed assuming a WTP of £20,000/QALY, whereas in the VTEP project I applied the higher value of £30,000/QALY. This distinction was made to reflect the fact that empirical estimates of the cost per QALY gained for existing services for maternity and neonatal care are higher than the empirical estimates for the average cost per QALY gained across all services, which could be interpreted as reflecting a higher societal WTP for services related to maternity and neonatal care.[18]

3.2 Population

In the TiLLI population I considered all people having outpatient LLI as a single population within the decision-analytic modelling as this group was considered to be sufficiently homogenous and the RAMs identified were relevant across the entire population. Immobilisation was defined as involving a splint, cast or boot that prevents movement of the knee and/or ankle and is removed when the injury in healed. Patients having removable splints that are only used during periods of activity or hinged splints or bandages that allow joint movement were considered to fall outside of the target population.

In the VTEAM project, the broad target population was hospitalised inpatients excluding children, critical care patients and women admitted to hospital for pregnancy-related reasons.

Given the diversity of patients admitted to hospital, it was important to consider whether it was necessary to separate the inpatient population into several more homogenous subgroups. We decided *a priori* to divide the population into two main categories: acutely ill medical inpatients; and surgical inpatients. The rationale for this was that the balance of risks and benefits were expected to differ between these groups and the majority of RAMs had been validated in either one group or the other. We considered whether it would be better to examine elective and emergency surgical patients separately but decided that it was better to assess whether a particular threshold for thromboprophylaxis could be identified across all surgical inpatients. This was partly because one of the more established RAMs included questions to differentiate between elective and emergency patients.[19] Although RAMs designed for use exclusively in trauma patients were identified in the SLR conducted by my co-investigators,[2,20] we decided not to look at trauma patients as a particular subgroup, because in the UK these patients tend to be managed according to their main complaint, rather than within a specific trauma service. In addition, many of the RAMs that were specifically developed for trauma patients were validated in countries where trauma is treated within a critical care environment which fell outside of our scope. We excluded patients having elective hip or knee replacement from our primary analysis for surgical inpatients because extended prophylaxis (i.e., prophylaxis beyond the duration of admission) is recommended in these patients.[9] However, separate exploratory analyses were conducted to assess if the optimal thromboprophylaxis strategy would be different in populations who require extended prophylaxis.

In the VTEP project, the population was separated *a priori* into antepartum and postpartum women to reflect the fact that VTE risk assessment is generally conducted once at the start of pregnancy to identify individuals requiring antepartum prophylaxis, who would continue prophylaxis postpartum, and again after delivery to identify those requiring postpartum prophylaxis, which will include risk factors emerging at the time of delivery.[11]

Individuals known to be at increased risk of bleeding were excluded from the population considered in the economic analysis in each project as these people are assumed not to be eligible to receive thromboprophylaxis under any strategy. Therefore, although one of the strategies compared is prophylaxis for all, this should be interpreted as applying only to individuals not known to be at elevated risk of bleeding or otherwise contraindicated to thromboprophylaxis.

3.3 Thromboprophylaxis strategies compared

In each of the projects, the strategies compared were RAM-based prophylaxis, prophylaxis for all and prophylaxis for none. If the target population has a high overall risk of VTE then the advantage of using a RAM is to identify the minority of individuals for whom either the risks or costs of prophylaxis outweigh the benefits. Conversely if the target population has a low overall risk of VTE, then the advantage of using a RAM is to identify the minority of individuals in whom the benefits from thromboprophylaxis outweigh both the risks and costs. It was therefore necessary to model both prophylaxis for all and prophylaxis for none as comparator strategies.

In each project, the choice of RAMs to compare in the decision-analytic model was informed by a SLR of published RAMs conducted by co-investigators.[1-3] These SLRs included studies that reported the performance of RAMs in an external validation cohort, i.e., a cohort that was separate from the one used to derive the RAM. However, an exception was made in the SLR conducted for VTEP, to include a study that conducted an internal validation within the same cohort used to derive the RAM, as this study used a bootstrap validation approach to capture optimism in model performance when applied to similar future patients. This was considered acceptable, as the majority of the other RAM performance studies included in the SLR reported external validation of a RAM that was not statistically derived, which means they may be subject to overfitting and optimism.[21] RAMs identified in the SLRs could only be included in the decision-analytic modelling if studies were available reporting both the sensitivity and the specificity of the RAM for predicting VTE risk.

In the TiLLI project, only the Leiden - Thrombosis Risk in Plaster (L-TRiP)(cast) tool was included in the decision-analytic modelling.[22] Although two other RAMs were identified in the SLR (Guidelines in Emergency Medicine Network [GEMNet] and Plymouth),[23,24] the sensitivity and specificity data for these tools suggested that they would be outperformed by the L-TRiP(cast) RAM, so they were not explored further in the modelling. The L-TRiP(cast) RAM provides a numeric score and data were available on the sensitivity and specificity of the RAM for different cut-off scores.[22]

In the VTEAM project, a large number of RAMs were identified in the SLR for medical inpatients.[2,20] To minimise the bias introduced by comparing RAM performance across different cohorts, my primary analysis examined a set of RAMs which had been externally validated in a single cohort.[25,26] I then conducted a secondary analysis including performance

estimates for these and other RAMs which had been externally validated in other cohorts.[27-31] For surgical inpatients, the number of externally validated RAMs was more limited, so I modelled any RAM externally validated in either a surgical cohort or a mixed medical and surgical cohort.[27,32,33]

In the VTEP project, the SLR identified two RAMs (Efficacy of Thromboprophylaxis as an Intervention during Gravidity [EThIG] and Lyon) with the necessary performance data which were validated for use in antepartum women identified as being at high risk due to either known thrombophilia or prior VTE.[34,35] Based on the availability of these RAMs, and guidance from clinical experts, I decided to conduct a specific analysis for high-risk antepartum women. The least extensive prophylaxis option considered in the EThIG and Lyon tools was 6 weeks of postpartum prophylaxis. So I assumed that these RAMs would be used to determine whether or not antepartum prophylaxis would be offered in addition to postpartum prophylaxis. For this reason, I included a strategy of postpartum prophylaxis for all as a comparator strategy in the high-risk antepartum population. This was in addition to the standard comparator strategies of no prophylaxis and prophylaxis for all (i.e., from the time of the initial antenatal appointment until 6 weeks postpartum).

Although the RCOG guideline provides recommendations on which antepartum women should be offered prophylaxis, no suitable data on the performance of RCOG in unselected antepartum women was identified. The only RAM identified with performance data for unselected antepartum women was the STRATHEGE RAM.[36] However, the available data showed this RAM to have poor sensitivity (0%) and therefore the decision-analytic modelling in unselected antepartum women was limited to exploratory analyses to determine the range of sensitivity and specificity values that a RAM would require to be cost-effective in this population.

In the postpartum population, the SLR of RAMs identified the Sultan, Caprini, RCOG, and Swedish Society of Obstetrics and Gynaecology (SFOG) RAMs for use in unselected postpartum women.[37-39] It identified the Binstock and RCOG RAMs as being validated in a post-caesarean section population and it also identified the Ellis-Kahana RAM as having been specifically developed for use in obese postpartum women.[40,41] Therefore the three postpartum populations considered based on the RAM evidence available were: unselected postpartum women, women post-caesarean section, and obese postpartum women.

In addition to assessing the RAM cut-off for thromboprophylaxis that optimises cost-effectiveness for the existing RAMs available, an additional research question was to identify

the optimal trade-off between sensitivity and specific for future RAMs that may be developed. I examined this explicitly in both the TiLLI and VTEAM projects. In the TiLLI project, I used a linear regression on the logit scale fitted to points on the receiver operating characteristic (ROC) curve for L-TRiP(cast). I then identified the point on the ROC curve that optimised cost-effectiveness when applying a cost-effectiveness threshold of either £20,000/QALY or £30,000/QALY. This analysis was of interest because the SLR identified very few RAMs that had been externally validated, and the RAM performance estimates were uncertain due to high or unclear risk of bias in these studies.[3] I also explored whether the optimal strategy would be different if RAM performance was lower by using a theoretical ROC curve with a lower area under the curve (AUC). In the VTEAM project there appeared to be some consistency in RAM performance for the set of RAMs which had been validated in a single cohort of medical inpatients. I therefore explored the optimal trade-off between sensitivity and specificity for a typical RAM in medical inpatients with a performance similar to existing RAMs by fitting a trend line across the ROC curve including data from this set of RAMs.[25,26] The SLR also identified a single RAM (Padua) that had been developed for medical inpatients, but which had been validated in a mixed cohort of medical and surgical inpatients, and which had performed better in this particular study.[27] RAM performance data from this study were explored in scenario analysis to examine whether the optimal thromboprophylaxis strategy would differ, in either medical or surgical inpatients, if a RAM with higher performance could be identified.

3.4 Prophylaxis agent and duration of prophylaxis

In all three projects, we assumed that LMWH would be the thromboprophylaxis agent of choice in the base-case analysis and it was assumed that the LMWH preparation with the lowest cost for the required dose would be prescribed. In the TiLLI project, LMWH was considered the most relevant agent for the primary analysis because there were no RCTs on the effectiveness of DOACs and only 2 studies for fondaparinux.[2] For hospitalised patients, LMWH is the most commonly recommended prophylaxis agent within NG89 and this was therefore presumed to be the agent of choice across the majority of medical and surgical inpatients.[9] However, prophylaxis regimens involving DOACs or aspirin are recommended as alternatives in those specific orthopaedic populations who require extended prophylaxis.[9] Therefore, these were also explored in the scenario analyses for those specific populations. In women who are pregnant or in the puerperium, LMWH is clearly described in the RCOG guideline as the thromboprophylaxis agent of choice and no alternatives agents were examined.[11]

Hospitalisation, outpatient LLI and pregnancy are all time limited risk factors for VTE and when prophylaxis is offered, it is usually offered for the duration of time the person continues to be exposed to that risk factor. In the TiLLI population, we assumed that thromboprophylaxis would be offered for the duration of immobilisation, which we assumed would last 6 weeks on average. In the VTEAM project, the primary analysis assumed that thromboprophylaxis would consist of LMWH administered for the duration of hospitalisation (an average of 5 days), to reflect current UK clinical practice. However, scenario analyses were examined exploring whether the conclusions were similar if LMWH was offered for a minimum of 7 days, as specified in NG89.[9] Exploratory analyses were also conducted for specific populations requiring extended prophylaxis using the treatments durations recommended in NG89.[9]

In women who are pregnant or in the puerperium, data show an increased risk relative to the general population that persists for the duration of pregnancy and up to 6 weeks after delivery.[42,43] In VTEP, we assumed that the initial risk assessment would occur at the initial antenatal booking appointment, which typically occurs around 10 weeks gestation. Therefore, women assessed as requiring antepartum prophylaxis are assumed to receive LMWH from 10 weeks gestation to delivery (i.e., ~30 weeks) and then for a further 6 weeks postpartum.

Although the risk of VTE is known to persist for up to 6 weeks after delivery,[42] the highest risk is recognised to be in the immediate few weeks.[11] I assumed that the duration of LMWH offered to postpartum women would be 10 days as this is the duration recommended by RCOG in women having 2 or more risk factors, which will be the most common reason women qualify for prophylaxis; postpartum prophylaxis lasting 6 weeks is mainly offered to women having antepartum prophylaxis and some women who have multiple or persistent risk factors.[11]

4. Methods

This section provides a broad overview of the methods employed in the decision-analytic modelling across the three projects with a focus on exploring the differences and similarities in the methods used. For a detailed description of the methods for each project, please refer to the published works (see Table 1).

4.1 Conceptual modelling

I developed the conceptual model for each project by examining published cost-effectiveness analyses addressing similar decision problems and discussing relevant clinical events for

inclusion in the model with patient and clinical experts. The decision-analytic models used across the three projects were based on a core model that was first developed for the TiLLI project and which was later adapted to address the decision problems in the VTEAM and VTEP projects. Here I describe features of the decision-analytic modelling that were consistent across the three models, followed by a discussion of the features that differed between the models.

Each decision-analytic model comprises a short-term decision tree model, designed to capture the period over which the individual is at risk of VTE and the 3-month period required for VTE treatment. This is followed by a state-transition (Markov) model to extrapolate outcomes over the individual's lifetime. Relevant events included in the short-term model were symptomatic and asymptomatic DVT (separated into proximal and distal DVT), fatal and non-fatal PE, fatal major bleeding, non-fatal intracranial haemorrhage (ICH) and non-fatal non-ICH major bleeding (see Figure 1). The subsequent state-transition model captures long-term complications arising after VTE, such as PTS and CTEPH (separated into medically and surgically managed) and ongoing morbidity from non-fatal PE or non-fatal ICH (see Figure 2).

Key assumptions that were common across the models included the assumption that in people experiencing VTE associated with a provoking factor (i.e., LLI, hospitalisation or pregnancy), any subsequent VTE recurrence would most likely be due to an underlying risk factor that is ongoing. Therefore, the risk of VTE recurrence is not likely to be affected by whether or not prophylaxis was provided during the period of increased risk associated with the provoking factor. For this reason, I did not include VTE recurrence within the model. Based on clinical advice, I assumed that the likelihood of VTE and the likelihood of bleeding during treatment for VTE would be independent of whether the person had major bleeding during prophylaxis. I also assumed that future costs and QALYs in those having a non-fatal ICH are primarily determined by morbidity related to their post-ICH status and therefore no further VTE-related outcomes were modelled in these individuals.

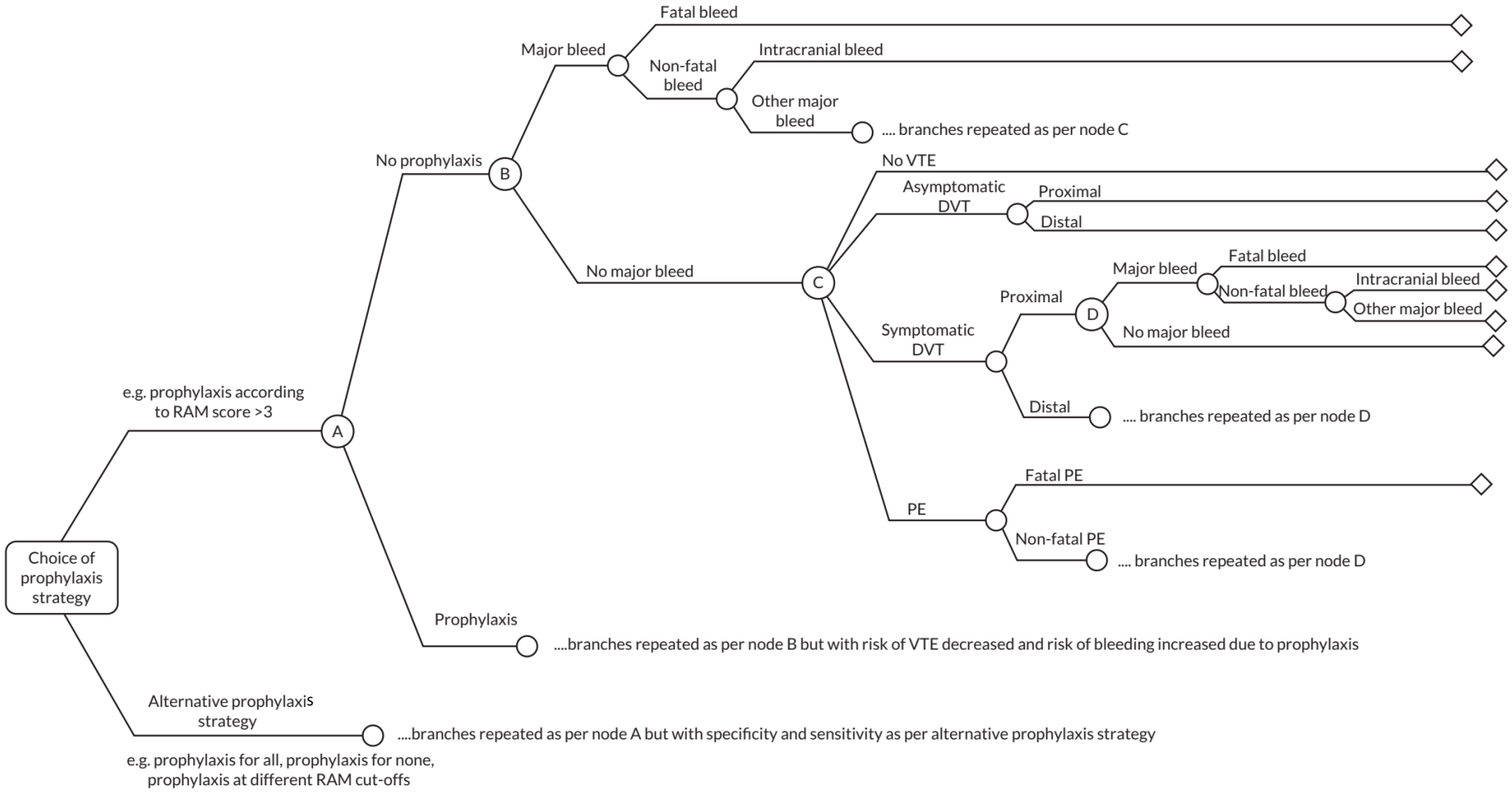

Figure 1: Short-term decision-tree model

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; RAM, risk-assessment model; VTE, venous thromboembolism

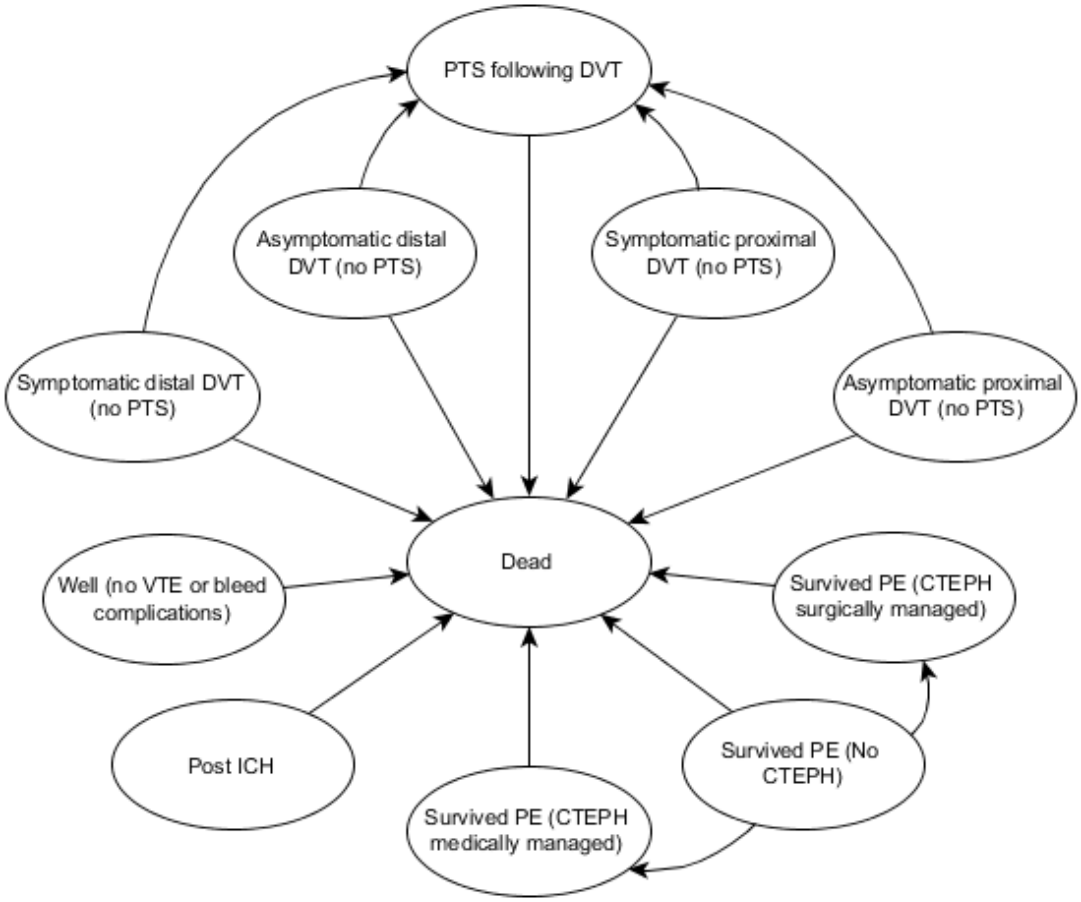

Figure 2: Long-term state-transition model

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism

Across all the models, I incorporated fatal bleeds and fatal PEs directly in the decision-tree and I applied state-specific mortality risks to those having ICH or CTEPH. In the TiLLI and VTEP models, I applied all-cause mortality risks for the general population to the remaining population. However, people who have been hospitalised tend to be older and frailer and have more comorbidities than the general population. Therefore, in VTEAM I included an increased risk of mortality relative to the general population in the time after discharge even in those not having either ICH or CTEPH.

Following advice from the patient and public involvement (PPI) representatives that the model should capture the discomfort and inconvenience of LMWH requiring daily injections, I applied utility decrements for people receiving prophylaxis.[44] I also applied a utility decrement to those having warfarin as VTE treatment to account for regular blood tests being needed.

In both the TiLLI and VTEAM projects, the time period covered by the decision-tree model was six months. However, there were some key differences. In TiLLI, immobilisation is the provoking factor for VTE and the duration of immobilisation was assumed to define both the duration of prophylaxis and the period of increased risk for VTE. Whereas, in VTEAM, patients are offered prophylaxis for the duration of hospitalisation, as this is the provoking factor for VTE, but patients are known to remain at risk of hospital-associated VTE for up to 90 days after discharge, so the risks of VTE in the model were applied over this longer period.

The decision-tree model phase in the VTEP project was more complex due to the fact that women should be risk-assessed both at the start of pregnancy, to assess the need for antepartum prophylaxis, and after delivery to assess the need for postpartum prophylaxis.[11] Given these two distinct opportunities for risk assessment and initiation of prophylaxis, the VTEP model needed to capture both the antepartum and the postpartum period. This was achieved by having two linked decision-tree models, one covering the period from antepartum risk assessment to delivery (the antepartum model) and the other covering the period after delivery (the postpartum model). The antepartum model was assumed to cover the 30-week period from 10 weeks gestation to delivery. The postpartum model covers the next 155 days, giving a total time for the decision-tree analysis of 1 year. The postpartum decision tree was therefore shorter than the 6 months assumed in the TiLLI and VTEAM projects, but was still sufficient to capture the 6 weeks at risk of postpartum VTE and the 3-month treatment period. When assessing postpartum risk assessment in women not offered antepartum prophylaxis, the antepartum phase of the decision-tree analysis was skipped so that only the second postpartum decision-tree was implemented. When assessing antepartum prophylaxis strategies, only women who have experienced no VTE and no ICH or fatal bleeding during the antepartum model progress to the postpartum decision-tree. The incidence of asymptomatic VTE was set to zero in the antepartum model to ensure these women remain at risk of symptomatic VTE in the postpartum model. Women who have experienced a symptomatic VTE, non-fatal ICH or any fatal event in the antepartum model were assumed to remain in the same health states until the start of the state-transition model. The state-transition phase of the VTEP model was identical in structure to that employed in the TiLLI and VTEAM projects.

Whilst major bleeding was included in all the models, the consideration of clinically relevant non-major bleeding (CRNMB) and wound outcomes varied slightly across the three projects. In the VTEAM and TiLLI projects CRNMB was considered only within scenario analyses. Whereas in the VTEP project, wound haematomas for people having caesarean section

deliveries were included in the model as a form of CRNMB in the base-case analysis. In the TiLLI project, there was concern from clinical peer reviewers that the model did not include any increased risk of infections or wound breakdown at wounds sites for patients having open fracture or surgical repair of injuries. However, we considered that exclusion of such events was reasonable as participants having surgery were a minority in the RCTs and it was unclear whether thromboprophylaxis influences wound healing. Wound outcomes were also of interest in the surgical population in the VTEAM project. However, clinical advice was that the majority of major bleeding occurs distant to the surgical site and any bleeding that occurred at the surgical site requiring return to theatre would be captured in the International Society for Thrombosis and Haemostasis (ISTH) definition for major bleeding.

4.2 Data sources

4.2.1 Introduction to data sources

In each project I endeavoured to identify data sources that were specific to the population being modelled. Where these were not available, I used data from indirect populations, such as other populations at risk of VTE, with the appropriateness of this approach being checked with clinical experts. Where SLRs were conducted by co-investigators as part of the project (e.g., RAM performance in all three projects and prophylaxis effectiveness in TiLLI), I used these to inform the model. However, it was not feasible to conduct SLRs to inform all parameters included within the model. In general, I relied on existing published SLRs, or where these were lacking, data sources identified in published economic evaluations. When I was unable to identify suitable data from the literature, I presented what data there were available to the clinical experts and used clinical expert opinion to populate the model. However, a formal expert elicitation approach was not used to generate any of the model parameters.

The data sources used across the three projects are summarised in Table 2, with later discussion in Sections 4.2.2 to 4.2.12 focusing on areas where there was a challenge identifying appropriate data including: when the available data were sparse, uncertain or unavailable; when it was necessary and appropriate to use indirect data; and when I relied on assumptions or clinical opinion.

Table 2: Data sources used to inform different parameters across the projects.

Parameter type	TiLLI	VTEAM	VTEP
RAM performance	SLR conducted by co-investigators[3]	SLR conducted by co-investigators[2,20]	SLR conducted by co-investigators[1,45]
Efficacy of thromboprophylaxis	SLR and NMA conducted by co-investigators[3,16]	Published SLRs that included NMAs of RCTs comparing prophylaxis to no prophylaxis[9,46]	Pilot RCT identified from a published SLR[15]
Baseline risk of symptomatic VTE in those not having prophylaxis	Event rates pooled across the RCTs included in the SLR of thromboprophylaxis efficacy[3,16]	Cohort studies identified in the SLR of RAM performance[33,47]	Retrospective cohort study for high-risk antepartum women;[48] large longitudinal cohort using routine healthcare data for postpartum women[37]
Ratio of asymptomatic to symptomatic VTE	Event rates pooled across the RCTs included in the SLR of thromboprophylaxis efficacy[3,16]	Pooled estimate across multiple RCTs included in the SLRs for CG92[49]	Pooled estimate across multiple cohort studies identified from a SLR[50]
Case-fatality for PE	Outpatient subgroup of RIETE registry [51]	Pooled across RCTs included in the SLRs for medical and surgical inpatients conducted for CG92[49]	SLR reporting case-fatality rates in people having pregnancy associated VTE[52]
Risk of major bleeding in those receiving prophylaxis	RR of major bleeding from published SLR for an indirect population (inpatients),[49] applied to estimates of absolute risks of bleeding without prophylaxis[53]	Event rates from prophylaxis arms of RCTs comparing prophylaxis to no prophylaxis identified from a SLR[9]	Cohort studies reporting major bleeding in women having antepartum or postpartum LMWH[54-56]

Parameter type	TiLLI	VTEAM	VTEP
Risks of major bleeding in those not receiving prophylaxis	Incidence of ICH and gastrointestinal (GI) bleeding based on general population sample using routine healthcare data[53]	Risk of bleeding with prophylaxis divided by RR from SLR of RCTs comparing prophylaxis with no prophylaxis[9]	Risk of bleeding with prophylaxis divided by RR from SLR of RCTs comparing prophylaxis with no prophylaxis in indirect population (medical inpatients)[9]
Methods used to apportion major bleeds into fatal, non-fatal ICH and other	ICH incidence estimated separately from other major bleeds and case-fatality rate applied to ICH [53,57,58]	Registry data used to determine proportion of major bleeds in each category[59,60]	Incidence of fatal bleeds and non-fatal ICH estimated separately from other major bleeds[61,62]
Risk of bleeding during anticoagulant treatment for VTE	Prospective cohort for rate and RIETE registry for bleeding type[63,64]	Same as TiLLI	Registry data for subgroup having pregnancy-related VTE [65,66]
Risk of PTS	Prospective registry study of patients with DVT[67]	Same as TiLLI	Case-control study for PTS risk after pregnancy-related VTE[68]
Risk of CTEPH in non-fatal PE	Published SLR[69]	Same as TiLLI	Same as TiLLI
All-cause mortality	General population mortality from life-tables[70]	General population mortality inflated by SMR for hospitalised patients[71-73]	General population mortality from life-tables[73]
Standardised mortality risk of ICH	Retrospective population-based cohort study[74]	Same as TiLLI	Same as TiLLI
Survival curve for CTEPH	Prospective registry study[75,76]	Same as TiLLI	Same as TiLLI
Cost for administering RAM	Clinical opinion on resources use; published NHS unit costs for staff time[77]	Same as TiLLI	Same as TiLLI

Parameter type	TiLLI	VTEAM	VTEP
Cost for administering thromboprophylaxis	Published estimate for outpatient thromboprophylaxis[78]	Clinical opinion on resources use for inpatient administration; published NHS unit costs for staff time[77]	Same as TiLLI
Cost for VTE	Resource use from clinical expert opinion informed by estimates from other models; unit costs from NHS reference costs[79] and NHS Drug Tariff [80]	Same as TiLLI	Estimates of resource use from TiLLI were adjusted to reflect clinical expert expectation of higher resource use in pregnancy
Costs for PTS and CTEPH	Resource use based on published models;[81] unit costs from NHS reference costs[77,79]	Same as TiLLI	Same as TiLLI
Costs of managing fatal bleeds and non-fatal ICH	Prospective study of stroke patients[82]	Same as TiLLI	Same as TiLLI
Cost of major bleeding (non-fatal, non-ICH)	NHS reference cost for GI bleeding[79]	Same as TiLLI	Same as TiLLI
Utility for VTE	Registry study reporting EQ-5D in patients having VTE[83]	Updated estimate from same registry study[84,85]	Same as VTEAM
Utility for major bleeding	Assumption of similar disutility to PE at 1 month	Same as TiLLI	Same as TiLLI but disutility also applied for 1 week for wound haematoma as a form of CRNMB
Utility for non-fatal ICH, PTS and CTEPH	Published sources identified from review of published models[49,76,86-88]	Same as TiLLI	Same as TiLLI

Parameter type	TiLLI	VTEAM	VTEP
Direct treatment disutility associated with LMWH prophylaxis or VTE treatment with warfarin	Published estimate using a time-trade-off approach[44]	Same as TiLLI	Same as TiLLI
General population utility	Published estimates[89]	Same as TiLLI	Same as TiLLI

Abbreviations: CG92, Clinical Guideline 92; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; EQ-5D, EuroQoL 5-Dimensions; GI, gastrointestinal; ICH, intracranial haemorrhage; LMWH, low molecular weight heparin; NMA, network meta-analysis, PE, pulmonary embolism; PTS, post-thrombotic syndrome; RAM, risk assessment model; RCT, randomised controlled trial; RIETE, The Computerized Registry of Patients with Venous Thromboembolism; SLR, systematic literature review; VTE, venous thromboembolism

4.2.2 RAM performance

In each project, co-investigators conducted a SLR of RAM performance and I used estimates from these reviews to inform the economic analysis.[1,3,20,45] The analyses possible were restricted by the RAM performance data available in each population. In the TiLLI and VTEAM populations, data were available on the performance of RAMs when using different cut-off scores, which allowed an exploration of the cut-off score that provides the optimal balance of sensitivity and specificity. Studies reporting the performance of the same RAM across multiple cohorts, which could be used to conduct sensitivity analyses on RAM performance, were limited to the unselected postpartum population, and the medical inpatient population. However, data for the Padua RAM from a mixed cohort of surgical and medical inpatients were explored in scenario analyses for both the medical and surgical inpatient populations.[27]

4.2.3 Effectiveness of prophylaxis

In TiLLI, a SLR and NMA of RCTs comparing LMWH to no prophylaxis, and alternative prophylaxis agents, was conducted by co-investigators and I applied the effectiveness estimates from the NMA in the model.[3,16] As a new review of clinical effectiveness for thromboprophylaxis was not part of the research programme for VTEAM, I relied on estimates provided in published SLRs.[9,46] In the VTEP project, a published SLR identified that there was a paucity of evidence on the effectiveness of thromboprophylaxis given during pregnancy or in the puerperium.[15]

A key aim of the VTEP project was to determine the value of potential future research studies in women at risk of pregnancy-related VTE. It was therefore important that the model accurately reflected the best current estimate of thromboprophylaxis effectiveness in this population and the uncertainty surrounding that estimate in order to accurately determine the value of future studies that might reduce that uncertainty. Using evidence from indirect populations, such as medical or surgical inpatients, would have been counterproductive in this case, as it would have overestimated the certainty in the effectiveness of LMWH in this population and could have led to the finding that this was not an area for future research despite the lack of RCTs specifically conducted in this population. I therefore identified studies comparing LMWH to no prophylaxis from the published SLR,[15] and used clinical expert opinion to identify, from the data available, the most suitable estimate for quantifying uncertainty around the effectiveness of LMWH in both the antepartum and postpartum populations. This resulted in a small pilot RCT in antepartum women being used to reflect the

effectiveness of LMWH in both antepartum and postpartum populations.[90] Whilst this provided a point estimate that was reasonably consistent with the range of effectiveness estimates seen in other populations, the confidence interval (CI) was broader reflecting greater uncertainty.

In the antepartum population, prophylaxis is given for the entire period over which women are considered to be at increased of VTE, whereas in the postpartum population I was assuming that postpartum prophylaxis is only given for 10 days, but women remain at risk of VTE for up to 6 weeks. This made the application of efficacy data from the antepartum population to the postpartum population problematic, as it was unclear whether the relative risk (RR) should be applied for the duration of prophylaxis (10 days) or whether there would be some ongoing efficacy over the 6-week period that women remain at increased risk of VTE. Clinical advice was that the reduced risk of clots may extend beyond the duration of LMWH because clots that occur in the early postpartum period may not present symptomatically until after 10 days. I therefore assumed a 3-week period of treatment efficacy in the base case but explored this additional uncertainty in sensitivity analyses.

4.2.4 Baseline risks of symptomatic VTE in those not having prophylaxis

In the VTEAM model, I decided not to use the RCTs included in the SLR of prophylaxis effectiveness as the source of VTE incidence. This was due to specific concerns raised by the clinical experts that many of the RCTs were historical and would not reflect the risk of VTE in contemporary clinical practice due to changes in care such as the increased emphasis on early mobilisation to prevent VTE. In addition, there were concerns that the restrictive inclusion and exclusion criteria for RCTs may mean that the risk in the trial cohort does not reflect the VTE risk in clinical practice. Instead I applied data on the risk of VTE from the cohort studies used to validate the RAMs.[33,47] A limitation of this approach was that a proportion of patients in these cohorts received prophylaxis. Where possible I used the risk in those not receiving prophylaxis, but I also acknowledged that this subgroup of the cohort may be biased towards lower risk patients. Due to these uncertainties, I explored a range of values for the risk of VTE in sensitivity analysis.

In the TiLLI project, the trials were more recent and were considered by the clinical experts more likely to reflect contemporary care. Therefore, I used the pooled event rates in the RCTs included in the SLR of clinical effectiveness studies directly to estimate the absolute risk of VTE in patients not having thromboprophylaxis.[3,16]

In the VTEP project, the RCT data were too sparse to be used to estimate the baseline risk of VTE, and instead I used data from observational cohorts.[37,48]

4.2.5 Ratio of asymptomatic to symptomatic DVT

An asymptomatic DVT (aDVT) is one that has no symptoms or symptoms too minor for the person to seek medical care, but which can be identified when screening people for DVT using an ultrasound. I included aDVTs in the cost-effectiveness model because individuals having aDVT are still at risk of experiencing PTS. However, quantifying the risk of aDVT requires studies in which people are proactively screened for DVT, meaning data were more limited for this outcome.

In the TiLLI project, the majority of the studies included in the SLR reported both symptomatic DVT (sDVT) and aDVT, allowing me to calculate the incidence of aDVT directly from the RCTs.[3,16] However, in the VTEAM and VTEP projects, I estimated the ratio of aDVT to sDVT using data reported in published SLRs. In VTEAM, the ratio was based on outcomes reported across multiple RCTs included in the SLR for NICE's previous Clinical Guideline (CG) on venous thromboembolism (CG92), meaning that it was informed by a relatively high number of events (604:40).[49] In contrast in VTEP, a total of 4 aDVTs and 1 sDVT were reported in a pooled cohort of 717 participants across 6 studies.[50] This meant that the ratio was particularly uncertain in the VTEP project. To limit the possibility of unrealistically high ratio samples being generated within the PSA, I inflated the number of events by an arbitrary factor of 10 in the beta distribution used to represent the uncertainty in this parameter. There was also concern from the clinical experts regarding the clinical significance of aDVT and the associated PTS risk. I explored these uncertainties in sensitivity analyses examining the impact of removing PTS following aDVT from the model.

4.2.6 Case-fatality rate for PE

In the TiLLI project, no fatal PEs were recorded in the clinical trials included in the SLR of prophylaxis efficacy,[3] therefore I sought estimates of the case-fatality rate for PE from registry data. I selected an outpatient specific estimate as clinical advice was that the case-fatality rate for PEs would be lower in patients having PE after LLI than in patients having PE provoked by other factors such as hospitalisation.[51]

In the VTEAM project, I used the case-fatality rates for PE reported in CG92, which had been estimated by pooling RCTs of thromboprophylaxis treatments separately for medical and surgical inpatients.[49] These were considered preferable to registry-based estimates owing to the

greater risk of fatal PE in hospitalised patients who may not survive long-enough to be recruited to a registry.

In VTEP, I applied a case-fatality rate for PE from a SLR that presented a meta-analysis across 4 studies examining pregnancy-related VTE in population-based samples or registries.[52]

4.2.7 Risk of major bleeding in those receiving or not receiving thromboprophylaxis

The amount of evidence available from which to estimate the absolute risk of major bleeding with and without prophylaxis varied considerably across the projects, meaning that in some cases it was necessary to use data from indirect populations.

In the VTEAM project, data on the absolute risks of major bleeding were available from the RCTs included in the SLRs conducted to inform NG89.[9] However, in the TiLLI and VTEP projects the RCT data identified in the relevant SLRs were too sparse to be used for this purpose.[3,15,16] In the TiLLI project, the absolute risk of upper GI bleeding or ICH in those not having prophylaxis was taken from a cohort study reporting outcomes for the general population using a large primary care database.[53] In the VTEP project, I identified cohort studies reporting the risk of major bleeding for women having LMWH either during pregnancy or the puerperium.[54-56] However, there were some issues around identifying events that met the ISTH criteria for major bleeding, meaning that event rates for major bleeding were explored extensively in sensitivity analysis

In the VTEAM project, the SLRs of RCTs conducted to inform NG89 were sufficient to estimate the RR of bleeding for prophylaxis versus no prophylaxis, for both the medical and surgical inpatient populations.[9] However, in both the TiLLI and the VTEP projects, the RCT evidence available was too sparse to estimate this parameter directly from the RCTs identified in relevant SLRs.[3,15,16] Therefore, in these projects I applied the RR of bleeding associated with prophylaxis in medical inpatients as an indirect estimate.[9,49] This use of indirect data was considered reasonable as the clinical experts advised that although the absolute risks of bleeding are likely to vary between populations, the RR of bleeding due to LMWH is likely to be similar for people having a similar dose of LMWH.

In the VTEAM project, I used registry data to estimate the proportion of major bleeds that are fatal, non-fatal ICH and other major bleeds. Population specific registry estimates were available for medical inpatients;[59] however, for surgical inpatients the only registry data available were for patients having major orthopaedic surgery.[60] Although these data were considered indirect, as these patients were excluded in the main analysis for surgical inpatients,

the clinical experts advised that the proportion of major bleeds that are fatal or ICHs is likely to be transferable from the orthopaedic population to the non-orthopaedic population.

4.2.8 Risk of bleeding during anticoagulant treatment for VTE

In the TiLLI and VTEAM projects, I applied risks of bleeding during anticoagulation treatment from a cohort study that reported the risks for people classified at low risk of bleeding, to align with the modelled population.[63] In the VTEP project, I updated the model to use data from registry studies that reported outcomes for a subgroup having pregnancy-related VTE.[65,66]

4.2.9 Risks of VTE complications

One of the challenges I experienced was estimating the risk of PTS for untreated aDVTs, as any study proactively scanning participants to identify aDVTs would be likely to offer treatment for ethical reasons. In the VTEAM and TiLLI projects, I based the 3-year incidence of PTS risk for sDVT (15.6% for distal and 32.4% for proximal) on a prospective registry study.[67] I inflated the risk of PTS for proximal aDVT to reflect the fact that aDVT would be untreated. For this I used a study that reported the odds ratio for PTS in patients having inadequate versus adequate anticoagulation.[91] However, this was an area of considerable uncertainty, as it is unclear if the risk would be even higher for those receiving no anticoagulation, or whether it would be lower because aDVTs may be less extensive than sDVTs. I therefore explored the impact of assuming no increased risk of PTS for asymptomatic versus symptomatic proximal DVTs in sensitivity analysis.

In the TiLLI project, the clinical experts were concerned that the PTS risk associated with DVT may be lower in the TiLLI population compared to those having DVT after other provoking factors, such as major surgery or acute illness requiring hospitalisation. However, I identified a study in patients having Achilles tendon repair that reported an 8% risk of PTS following aDVT, despite patients receiving 3 months of anticoagulation and the DVTs being predominantly distal DVTs (3 proximal and 35 distal).[92] Given the risk would be expected to be higher for untreated DVTs, this provided some reassurance that a 15.6% PTS risk following distal aDVT was reasonable. However, as there was uncertainty about the risk of PTS, and indeed the relevance of PTS as an outcome in distal aDVT, I also conducted sensitivity analyses in which I set the PTS risk in this group to zero.

The clinical experts considered that the estimates of PTS risk following DVT applied in the TiLLI and VTEAM projects were unlikely to be applicable to the VTEP population due to the fact that mechanical compression of venous flow is a unique risk factor for antenatal

thrombosis. Instead, I obtained data from a study on PTS risk associated with pregnancy-related DVT.[68] It was interesting that in this study proximal DVT was found to increase the PTS risk relative to distal DVT, but only in postpartum women.

I applied data on the CTEPH risk in patients having non-fatal PE, obtained from an SLR, consistently across all three models.[69]

4.2.10 Mortality

The methods for incorporating mortality into the model were generally consistent across the projects. A key exception was that for hospitalised inpatients, I adjusted the general population mortality risks to reflect a higher mortality risk in people who have been admitted to hospital in the previous year.[71,72]

4.2.11 Resource use and costs

I estimated resource use associated with diagnosing and managing VTE based on clinical expert opinion. The clinical experts advised that the resource use estimates from TiLLI could be considered applicable to the VTEAM population, as the majority of VTEs experienced following hospital admission would occur after discharge. However, in the VTEP project, I adjusted the estimates to reflect the clinical expert advice that pregnancy-associated VTE is more likely to result in admission to hospital or require management in critical care.

In all three projects, I assumed that the costs of major bleeding (excluding fatal bleeds and ICH) would be similar to the costs of managing a non-fatal GI bleed. This approach was considered reasonable for surgical inpatients as clinical advice was that the majority of major bleeds in surgical inpatients were distant from the surgical site and were managed without a return to theatre. In the VTEP project, I was unable to identify relevant data on the costs for major bleeding in the pregnant or postpartum populations. Information on the additional length of stay for postpartum haemorrhage suggested that the cost of GI bleeding could be used as a reasonable proxy. However, as this was an area of uncertainty in the VTEP project, I explored major bleeding costs in the sensitivity analyses.

4.2.12 Utilities

I used the PREFER-VTE registry to obtain utility estimates for people who have experienced symptomatic VTE. The values used in the TiLLI project were based on an early analysis of the PREFER-VTE data reported in an abstract,[83] whereas in VTEAM, I used updated values reported in a later full-text article.[84,85] The latter were also applied in VTEP due to a lack of pregnancy-specific utility estimates.

In all three projects, I made the assumption that the utility decrement in the month after a major bleed, would be similar to the utility decrement in the month after a PE based on a study reporting similar utility values for these health states when using a time trade-off approach.[93] I estimated utility values for the other health states included in the model and the disutility for prophylaxis from the literature and applied these consistently across the models.

5. Key findings

5.1 Introduction to key findings

In each of the projects, I assessed the optimal strategy for prophylaxis by identifying the strategy that maximised NMB at a specified threshold (£20,000/QALY for TiLLI and VTEAM; £30,000/QALY for VTEP), using mean costs and QALYs simulated within the PSA (presented in Table 3). Using this approach, the optimal strategies were:

- RAM-based prophylaxis in people having LLI,
- Prophylaxis for all in medical inpatients and surgical inpatients,
- Postpartum prophylaxis for all (i.e., no antepartum prophylaxis) in high-risk antepartum women,
- No prophylaxis in each of the postpartum populations modelled (unselected, obese, and post-caesarean section).

As the more detailed findings of each analysis are already presented and discussed in the published works, these will not be repeated here in detail on a study-by-study basis, although a summary is provided in Section 5.8. Instead, this section focuses on discussing differences and similarities in the key findings across the projects to draw out broader conclusions that can be made about the cost-effectiveness of alternative thromboprophylaxis strategies across the different populations. A summary of these common findings across the projects is also provided in Section 5.8.

5.2 Impact of thromboprophylaxis on the incidence of adverse clinical outcomes

Much of the policy development around the use of thromboprophylaxis in hospitalised patients followed from a 2005 House of Commons Health Committee report,[94] which described PE as being the most common preventable cause of death in hospitalised patients.[95] Given this historical context, thromboprophylaxis is often presented as a patient safety issue, with a focus on the need to prevent avoidable deaths.[96,97] However, in the analyses conducted across the

various projects, the absolute incidence of severe adverse consequences, including fatal PE, fatal bleeding and non-fatal ICH, varied very little between people having prophylaxis or no prophylaxis (see Table 4). The two populations with the greatest change in the incidence of severe adverse consequences were the surgical and medical inpatient populations, although the absolute difference was small in both cases; an increase from 0.7 per 1000 to 1.1 per 1000 and a decrease from 5.3 per 1000 to 4.2 per 1000, respectively.

In all of the populations modelled, the most frequently occurring benefit of prophylaxis was the avoidance of PTS in individuals who would have experienced PTS following an aDVT (see Table 4). This finding was unexpected when it was first observed in the TiLLI analysis, but the finding was later reproduced in the VTEAM and VTEP analyses (see Table 4). This contrasts with the historical focus on VTE prevention as a patient safety issue.

Table 3: Summary cost-effectiveness results

Project	Population	Baseline risk of VTE	Baseline risk of major bleeding	ICER for prophylaxis for all versus prophylaxis for none	Optimal strategy [a]	Probability of decision error from selecting optimal strategy [a]	EVPI per person
TiLLI	People having LLI	1.34%	0.04%	£13,524	RAM-based prophylaxis	23%	£4.12
VTEAM	Medical inpatients	3.40%	0.67%	Prophylaxis for all is dominant	Prophylaxis for all	<1%	£0.06
	Surgical inpatients	1.40%	1.24%	£1,364	Prophylaxis for all	30%	£16.35
VTEP	High risk antepartum women (e.g., prior VTE)	12.3%	3.15%	£10,796 [b]	Postpartum prophylaxis only	64%	£1,453.87
	Unselected postpartum women	0.07%	3.00%	Prophylaxis for none is dominant	Prophylaxis for none	11%	£0.68
	Obese postpartum women	0.15%	3.00%	Prophylaxis for none is dominant	Prophylaxis for none	64%	£22.35
	Postpartum women following c-section	0.14%	3.00%	Prophylaxis for none is dominant	Prophylaxis for none	7%	£2.06

Abbreviations: EVPI, expected value of perfect information; ICER, incremental cost-effectiveness ratio; LLI, lower limb immobilisation; RAM, risk assessment model; VTE, venous thromboembolism;

[a] the optimal strategy was defined as the one that maximises net monetary benefit (NMB) estimated using mean costs and QALYs across the PSA simulations; when estimating NMB a £30,000/QALY WTP threshold was applied for pregnant and postpartum women and a £20,000/QALY WTP threshold was applied for all other populations

[b] for high-risk antepartum women prophylaxis for all means both antepartum and postpartum prophylaxis for all

Table 4: Predicted short-term and long-term clinical outcomes for prophylaxis versus no prophylaxis

Project	Population	Prophylaxis strategy	Outcomes at 6 months per 100,000 individuals							Outcomes at 5 years per 100,000 individuals				
			Fatal PE	Fatal bleed	Non-fatal ICH	Other major bleed[a]	Non-fatal PE	sDVT	aDVT	PTS	PE with CTEPH	PE without CTEPH	ICH survivor	Dead (any cause)
TiLLI	People having LLI following injury	No prophylaxis	12	9	5	26	415	907	7052	1859	11	397	5	1133
		Prophylaxis	7	12	8	35	225	492	3820	1007	6	215	7	1129
VTEAM	Medical inpatients	No prophylaxis	370	103	58	529	1006	2009	30410	7871	23	832	46	14981
		Prophylaxis	181	150	87	792	492	983	14889	3854	11	407	70	14860
	Surgical inpatients [b]	No prophylaxis	37	14	24	1216	582	781	12604	3675	14	544	22	3526
		Prophylaxis	11	35	68	3603	169	226	3654	1065	4	158	64	3519
VTEP	High-risk antepartum women	No prophylaxis	59	7	5	3423	2890	9300	19593	10824	74	2790	5	321
		Prophylaxis [c]	20	4	4	5400	974	3136	6733	3696	25	941	4	266
	Unselected postpartum women	No prophylaxis	0	1	1	2996	17	55	219	101	0	16	1	238
		Prophylaxis [d]	0	1	2	4582	9	29	116	53	0	9	2	238
	Obese postpartum women	No prophylaxis	1	1	1	2996	36	116	465	215	1	35	1	238
		Prophylaxis [d]	0	1	2	4582	19	62	246	114	0	18	2	238

	Postpartum women following caesarean section	No prophylaxis	1	1	1	2996	32	104	415	192	1	31	1	238
		Prophylaxis [d]	0	1	2	4582	17	55	219	101	0	16	2	238

Abbreviations: aDVT, asymptomatic deep vein thrombosis; CTEPH, chronic thromboembolic pulmonary hypertension; ICH, intracranial haemorrhage; LLI, lower limb immobilisation; PE, pulmonary embolism; PTS, post-thrombotic syndrome; sDVT, symptomatic deep vein thrombosis.

[a] Patients having other major bleeds could also have a DVT or non-fatal PE; [b] Surgical population includes patients having elective and emergency surgical procedures but excludes day cases and those having elective hip or knee replacement; [c] antepartum prophylaxis and 6 weeks of postpartum prophylaxis; [d] 10 days of postpartum prophylaxis

5.3 Interaction between VTE risk and RAM performance

One of the key findings across the projects was the observation that the cost-effectiveness of RAM-based prophylaxis is dependent on the interaction between the absolute risk of VTE and the performance of the RAM. In populations where the risk of VTE is sufficiently high for prophylaxis for all to be cost-effective compared to prophylaxis for none (e.g., hospital inpatients), the purpose of a RAM is to identify individuals within these populations in whom the risk of VTE is low enough for prophylaxis to be safely avoided. Therefore, a RAM would need to have high sensitivity to be more cost-effective than prophylaxis for all in these higher risk populations. Contrastingly, in populations with a much lower risk of VTE (e.g., postpartum women), the purpose of a RAM is to identify the small minority of people who would benefit from prophylaxis and therefore a RAM with high specificity is required. Therefore, in both high-risk and low-risk populations, RAM-based prophylaxis has the potential to be cost-effective, compared to strategies of either prophylaxis for all or prophylaxis for none, respectively, but only if the RAM provides good prognostic accuracy and a suitable balance of sensitivity and specificity for the target population. This conclusion is demonstrated by comparing the optimal strategy when varying RAM performance in the different populations.

In both medical inpatients and the surgical inpatients, the optimal strategy in the base case analysis was prophylaxis for all. However, in both inpatient cohorts, RAM-based prophylaxis was found to be the optimal strategy when using more optimistic RAM performance data,[27] although the level of sensitivity required was very high (99.9%).

In the TiLLI population, I found that RAM-based prophylaxis would be the optimal strategy if the RAM used performed similarly to the L-TRiP(cast) RAM, with cost-effectiveness being optimised for a sensitivity of 84-89% combined with a specificity of 46-55%. However, a scenario analysis examining lower RAM performance (AUC for the ROC of 0.62 instead of 0.76), found that prophylaxis for all would be the optimal strategy.

In unselected postpartum women, RAM-based prophylaxis was not the optimal strategy due to the very low risk of VTE (0.07%). However, RAM-based prophylaxis had an ICER under £30,000/QALY in the deterministic scenario analysis applying alternative RAM performance data for the SFOG RAM (sensitivity and specificity of 49% and 95% versus base case values 21% and 94%). Therefore, even in this very low risk cohort, a RAM with moderate sensitivity combined with high specificity has the potential to be cost-effective.

In the post-caesarean section population, the optimal strategy was prophylaxis for none, due to the two population-specific RAMs available having low specificity (8% for Binstock and 6% for RCOG) meaning that over 90% of women would be offered prophylaxis after risk assessment. I explored whether RAM-based prophylaxis had the potential to be cost-effective in this population if a better performing RAM was available, and found that a high specificity would be needed (95%).

The absolute risks of VTE in the obese postpartum population (0.15%) was similar to the post-caesarean section population (0.14%), but the availability of a RAM with higher specificity (88%) and moderate sensitivity (58%) meant that RAM-based prophylaxis had an ICER under £30,000/QALY versus no prophylaxis in the deterministic analysis. Although no prophylaxis was still the optimal strategy in the PSA, the optimal strategy was highly uncertain. This further reinforces the conclusion that RAM-based prophylaxis has the potential to be cost-effective in groups with a low absolute VTE risk (~0.15%) provided the RAM used has high specificity and moderate sensitivity.

In high-risk antepartum women, postpartum prophylaxis for all was the optimal strategy, despite the very high risk of symptomatic VTE and the availability of an antepartum RAM with 100% sensitivity. This is due to the risk of symptomatic VTE being fairly evenly split between the antepartum and postpartum periods but the cost of antepartum prophylaxis being much higher than the cost of postpartum prophylaxis, due to the longer duration. Therefore, the purpose of a RAM in this cohort is to limit the numbers receiving antepartum prophylaxis and a RAM that prioritises high specificity for predicting antepartum VTE is needed. However, both the available RAMs had low specificity for predicting antepartum VTE (28% for EThiG, 35% for Lyon ≥3).

5.4 Decision uncertainty assessed using EVPI

The decision uncertainty, as assessed by the global EVPI per person, varied a great deal across the different populations (see Table 3). In general, these differences reflected the weaker evidence base for thromboprophylaxis in pregnant and postpartum women, the greater consequences of selecting the wrong strategy in populations with a higher baseline VTE risk, and the impact of RAM performance on decision uncertainty.

The probability of a decision error when selecting the optimal strategy, based on mean costs and QALY across the PSA samples, was highest in the high-risk antepartum population and the obese postpartum population (see Table 3). In both cases, the uncertainty around the RR of

VTE (RR of 0.33: 95% CI 0.02 to 7.14) led to a broad spread of incremental QALYs on the cost-effectiveness plane, with the ratio of EVPPI to global EVPI attributable to this individual parameter being 0.94 for the high-risk antepartum population and 0.99 in the obese postpartum population. However, the global EVPI per person was much higher in the high-risk antepartum population (£1453.87 versus £22.35) as the consequences of selecting the wrong prophylaxis strategy are much greater in the high-risk antepartum population due to the higher VTE risk (12.3% versus 0.15%).

In contrast, in the other postpartum populations, the EVPI was much lower, despite there being the same uncertainty regarding prophylaxis efficacy. This was due to a low risk of VTE being combined with a lack of RAMs with adequate specificity. Scenario analyses exploring the impact of assuming that a better performing RAM was available, conducted in both the post-caesarean section and medical inpatient populations, found that the EVPI increased in both cases (from £2.06 to £7.74 and from £0.06 to £2.42, respectively). This demonstrates that the decision uncertainty associated with whether to offer RAM-based prophylaxis is also dependent on the availability of an adequately performing RAM.

The EVPI per person was higher in the surgical inpatient population compared to the medical inpatient population (£16.35 versus £0.06). The lower EVPI in the medical inpatient population reflects the fact that prophylaxis for all resulted in both cost savings and QALY gains in this population.

Although the VTE risk for the TiLLI population was similar to that of the surgical population, and the probability of decision error was broadly similar (23% versus 30%), the global EVPI was lower, at £4.12 per person. This is because in the TiLLI population, the two strategies with the highest probability of being optimal both involved RAM-based prophylaxis and differed only in the RAM cut-off applied, meaning they had similar costs and QALYs.

5.5 Decision uncertainty assessed using deterministic analyses

Whilst the PSA and EVPI analysis consider parameter uncertainty for the parameter estimates chosen to inform the model, they do not capture uncertainty associated with the choice of data source or other model assumptions. Instead, I explored these using deterministic scenario analyses.

A common finding in the scenario analyses conducted across all three projects was that the utility decrement for PTS and the risk of PTS in aDVT were important areas of uncertainty. This is because a large proportion of the QALY gains associated with prophylaxis are coming

from reducing the risk of long-term morbidity from PTS, the majority of which is associated with aDVT. However, parameters associated with PTS were more important in some populations than others. For example, the optimal strategy was much more sensitive to these parameters in the surgical inpatients compared with the medical inpatients. This may be because surgical inpatients are younger on average than medical inpatients, and therefore they have a longer life expectancy over which to accrue benefits from avoiding long-term complications such as PTS.

5.6 Impact of using alternative pharmacological agents for prophylaxis.

In both TiLLI and VTEAM, I explored the use of alternative pharmacological agents for thromboprophylaxis to determine if the optimal prophylaxis strategy would differ in patients requiring extended prophylaxis. In these analyses, I assumed that DOACs would be clinically equivalent to LMWH in terms of their impact on the risks of VTE and major bleeding, and due to their oral formulation, they would avoid the direct treatment-related disutility associated with subcutaneous administration of LMWH. The general finding across the analyses conducted for the TiLLI and VTEAM populations was that alternative prophylaxis agents such as DOACs may allow a broader use of thromboprophylaxis within the current cost-effectiveness thresholds, due to their lower drug acquisition cost.

In the TiLLI population, I found that RAM-based prophylaxis could be offered at a lower threshold (L-TRiP(cast) score of 8 instead of 9), if assuming equivalent VTE and bleeding risks between DOACs and LMWH, due to the lower drug costs.

In the VTEAM population, the analysis identified that for elective hip replacement patients, the optimal strategy was dependent on the prophylaxis agent used, with RAM-based prophylaxis being optimal when assuming LMWH is offered for 28 days but prophylaxis for all being optimal when assuming DOACs can be used with equivalent effectiveness but lower cost.

Whilst these analyses suggest that DOACs may allow a broader use of thromboprophylaxis within current cost-effectiveness thresholds for patients requiring extended prophylaxis, these analyses should only be considered as exploratory as they rely on the assumption of clinical equivalence to LMWH. For the elective hip and knee replacement populations, this assumption is broadly supported by the evidence reviews produced for NG89, which reported wide overlapping CIs for the outcomes of DVT, PE and bleeding, for a broad range of prophylaxis strategies involving LMWH, DOACs and aspirin.[9] In contrast, the SLR conducted for TiLLI

identified no studies examining DOACs in people having LLI.[3,16] We therefore concluded that further research should be conducted to assess non-inferiority between DOACs and LMWH in people having LLI and this research is now ongoing (see Section 7.3).

5.7 Value of future research

Although each of the projects involved estimating the global EVPI per person as a measure of decision uncertainty, only the VTEP project involved using EVSI analysis to formally quantify the potential value of future research studies. In the VTEP population, the evidence-base for prophylaxis was known *a priori* to be limited, and therefore an EVSI analysis to direct future research was the primary aim of the research project. In contrast, the research protocols for VTEAM and TiLLI proposed conducting EVSI only if the EVPI analysis suggested that further research on specific parameters may be valuable, and this further research was not prioritised in either case.

In the VTEP project, we recommended that future research should focus on estimating the effectiveness of thromboprophylaxis in obese postpartum women who have not had a previous VTE but who have additional risk factors. This was based on the EVSI analysis which estimated that an RCT in obese postpartum women with 300 participants per arm would have a value of £2.8 million if used to inform future thromboprophylaxis decisions for obese postpartum women over 5 years of births across England and Wales. Whilst the population-level EVSI for a similar sized trial in high-risk antepartum was much higher, this did not lead to a research recommendation for an RCT in this population, because the stakeholder work identified that such a trial would not be acceptable to either the women who would be asked to participate or the recruiting clinicians.

5.8 Summary of key findings from the decision-analytic modelling

Key findings specific to individual populations modelled:

- A RAM would need to have a sensitivity of between 84% and 89% and a specificity of between 46% and 55% for RAM-based prophylaxis to be cost-effective in people having LLI.
- In medical and surgical inpatients, offering prophylaxis to all eligible patients is more cost-effective than RAM-based prophylaxis
- In postpartum women, RAM-based prophylaxis is unlikely to be cost-effective compared to prophylaxis for none, due to the very low risk of VTE, but the optimal

strategy is more uncertain in obese postpartum women due to a better performing RAM being available.

- Six weeks of postpartum prophylaxis is cost-effective for high-risk antepartum women, but the cost-effectiveness of offering additional RAM-based antepartum prophylaxis is uncertain due to its high cost and the low specificity of available RAMs.
- Future research to inform thromboprophylaxis in women who are pregnant or in the puerperium should focus on estimating the effectiveness of LMWH to prevent VTE in postpartum women who have not had a prior VTE but who have other VTE risk factors, such as obesity.

Key findings that were common across multiple populations:

- The cost-effectiveness of RAM-based prophylaxis is dependent on there being a RAM available with an appropriate balance of sensitivity and specificity, with high sensitivity being a priority in high-risk cohorts and high specificity being a priority in low-risk cohorts.
- The risk of PTS following aDVT, and the utility decrement associated with this outcome were identified as key areas of uncertainty, due to this being the clinical outcome most likely to be avoided by offering prophylaxis in all populations modelled.
- Although VTE prophylaxis has often been presented as primarily a patient safety issue, the difference in severe adverse consequences (fatal PE, non-fatal ICH and fatal bleeds) between prophylaxis and no prophylaxis is small in absolute terms (<1.2 per 1000 individuals across all populations modelled).
- Decision uncertainty was highest when high uncertainty regarding the effectiveness of LMWH to prevent VTE is combined with a population at high risk of VTE
- Decision uncertainty was lowest when the risk of VTE was very low or when RAM performance was too poor for RAM-based prophylaxis to have the potential to be cost-effective.
- Exploratory analyses suggest that it may be cost-effective to offer extended prophylaxis at a lower RAM threshold if DOACs are used as prophylaxis instead of LMWH, provided DOACs can be assumed to be clinically equivalent to LMWH.

6. Limitations

Given the similarities across the three projects, many of the limitations were common across the projects and these are the focus of discussion in this section. Limitations that were specific only to individual projects are not discussed here but can be found in the discussion chapters of the published works.

6.1 Populations examined

Each of the analyses addressed a specific population at risk of VTE and the conclusions should not be extrapolated to other groups. For example, any conclusions about the balance of risk and benefits or the cost-effectiveness of prophylaxis should not be extrapolated to individuals with a known increased bleeding risk, as these individuals were excluded from the populations modelled.

6.2 Studies assessing RAM performance

The evidence on RAM performance was identified to be at high-risk of bias in many of the studies used to inform the economic analysis. In the TiLLI project in particular, the estimates of RAM performance for L-TRiP(cast) were based on a case-control study, and the optimal strategy was sensitive to uncertainty in the RAM performance estimates. This supported our conclusion that an implementation study of RAM-based prophylaxis would provide useful information.

The EVSI analysis that identified obese postpartum women as a potential target population for a future trial, was informed by the Ellis-Kahana RAM which had not been externally validated. One of the reasons that the EVSI was higher in obese postpartum women compared to the other postpartum populations modelled was the better performance of this RAM relative to the RAMs validated in other postpartum populations. Therefore, further research to validate the Ellis-Kahana RAM in an external cohort would be worthwhile.

A key limitation of the analyses in the VTEAM and VTEP projects was a lack of available performance data for RAMs commonly used in the UK. In VTEAM, I was unable to include the Department of Health tool for hospitalised inpatients in the analysis despite this being the most widely used tool in UK hospitals.[98] In VTEP, I was unable to assess the cost-effectiveness of offering antepartum thromboprophylaxis according to the RCOG recommendations.

6.3 Data availability

A common challenge across the three projects was identifying data that were specific to the population being modelled, as previously discussed in Section 4.2. Where possible, these uncertainties were explored using scenario analyses considering alternative data sources or sensitivity analyses testing the impact of varying a particular parameter. For example, in the VTEP population, the RR of major bleeding from medical inpatients was applied as an indirect estimate, as the only study reporting major bleeding in antepartum women used a higher dose of LMWH than is recommended for prophylaxis, and the only study available in postpartum women was a small pilot study which gave an estimate with a very wide CI. However, the optimal strategies in the four populations modelled for VTEP were unchanged in scenario analyses using the estimates from these alternative sources.

Another common limitation was uncertainty in the risk of PTS for people having an aDVT that remains undetected and untreated. This is due to it being unethical to screen patients for aDVT and then not offer treatment when a DVT is identified. The findings of the sensitivity analyses suggest that this uncertainty is particularly important in surgical inpatients, where RAM-based prophylaxis becomes the optimal strategy when lowering the PTS risk.

The use of estimates of VTE risk from cohort studies where a proportion of patients received prophylaxis is a key limitation of the analysis as this may underestimate VTE risk in the target population when no prophylaxis is offered. This was a particular issue in the VTEAM project, as risk-based thromboprophylaxis for hospitalised inpatients is standard practice in many countries.[98-101] However, if the VTE risk in hospitalised inpatients was in fact higher than modelled, this would only strengthen our conclusion that prophylaxis for all is the optimal strategy. The estimates of RAM performance may also be impacted by the use of prophylaxis within the cohort, however Elias *et al*. reported similar estimates of RAM performance in patients who did and did not receive thromboprophylaxis in a mixed cohort of medical and surgical inpatients.[27]

6.4 Model structure

The decision to use a cohort-level model meant that I was not able to capture the fact that the individuals who would be identified as being at higher risk by the RAM would be likely to have different characteristics than those identified as being at lower risk. For example, if age is used as a risk factor, then the average age would be expected to be higher in the group identified as requiring thromboprophylaxis. Whereas the cohort-level modelling approach

assumes that everyone in the model has the same age, based on the average age in the whole cohort receiving risk assessment. However, the sensitivity analyses found that age was not a strongly predictive factor, with the optimal prophylaxis strategy not varying with baseline age in the majority of the populations modelled. Therefore, the use of a cohort-level modelling approach was considered to be a reasonable approximation.

A similar issue arose in the VTEP project, where the dosing of LMWH in pregnant and postpartum women is dependent on weight, and body mass index (BMI) is also a risk factor for prophylaxis. I found that the optimal prophylaxis strategy was sensitive to the body weight used to calculate the prophylaxis dose, but only in high-risk antepartum women, who require prophylaxis for longer than postpartum women. However, the average BMI in the EThIG RAM study was reported to be similar across the different risk classifications suggesting that application of the EThIG RAM would not preferentially select those with higher BMI for antepartum thromboprophylaxis. Therefore, applying a cost based on the dose for a woman with average BMI is still likely to be a reasonable approximation.

7. Contribution to knowledge and implications for future research

7.1 Novelty of the research conducted

The research findings outlined in Section 5 are novel because whilst there have been many published studies reporting the cost-effectiveness of thromboprophylaxis compared to no thromboprophylaxis or different thromboprophylaxis agents, few studies have evaluated the cost-effectiveness of using a validated RAM to direct pharmacological thromboprophylaxis. Some researchers have reported the absolute VTE risk at which prophylaxis becomes cost-effective, but have not modelled the use of a validated RAM to identify individuals meeting that absolute risk threshold.[102-104] Others have examined the cost-effectiveness of prophylaxis in subgroups of patients stratified into risk categories,[105-109] with a subset of these studies using a validated RAM to define the risk categories.[105,106,108] However, none of these analyses assessed the cost-effectiveness of RAM-based prophylaxis across the whole cohort being risk assessed. One single-centre study compared outcomes before and after the implementation of a thromboprophylaxis protocol for surgical inpatients, however, RAM-based pharmacological prophylaxis was only one element of the protocol implemented making it difficult to isolate its impact.[110] Furthermore, none of the above studies compared alternative RAMs or explored the optimal balance of sensitivity and specificity required for RAM-based prophylaxis to be cost-

effective. In addition, although EVPI analyses are becoming more commonplace in the literature, applied EVSI analyses conducted with the intention of informing future research decisions, such as the one presented for VTEP, are much less common.[111-113]

7.2 Implications for clinical practice

Each of these projects provides novel information on the cost-effectiveness of using RAMs to select individuals for thromboprophylaxis (see Section 5.8), that could be used to inform clinical practice including future updates to national guidance on VTE prevention.

The most recent NICE guideline (NG89), which was finalised before my findings were published, recommended offering thromboprophylaxis to people having LLI, *"whose risk of VTE outweighs their risk of bleeding,*" but did not recommend a specific RAM or RAM-threshold for prophylaxis.[9] A 2022 national survey of emergency departments has since identified that whilst risk assessment for people having LLI is almost universal (≥ 95% of sites), it most commonly done using a 'locally developed tool' or the Department of Health tool, with only 16% of sites reporting using a RAM with published external validation studies.[114] This variation in practice suggests that further guidance is needed to ensure that the RAM used has an appropriate balance of sensitivity and specificity. Therefore, our findings from TiLLI could be used in future updates of NG89 to make more specific recommendations on the RAMs to be used and the threshold to be adopted to ensure prophylaxis is cost-effective. This would include identifying an appropriate threshold for the newly developed Thrombosis Risk Prediction Following Cast Immobilisation [TRiP(cast)] score, which is a modified version of L-TRiP(cast).[115]

In the VTEAM project I found that thromboprophylaxis for all eligible medical and surgical inpatients (i.e., those without contraindications or known to be at increased risk of bleeding) is more cost-effective than RAM-based prophylaxis, which is currently recommended in NG89.[9] We concluded that this could be used to justify a move in clinical practice towards an 'opt-out' rather than an 'opt-in' approach to thromboprophylaxis in hospital patients. These findings have the potential to be used to inform the next update of NG89, and the NICE surveillance team has confirmed that they are aware of our research findings (personal communication, Paul Jacklin, April 2025).

In the VTEP population my findings suggest that the current level of thromboprophylaxis offered to postpartum women is likely to be too high. I found that a RAM would need to have high specificity, resulting in around 5% of women being offered prophylaxis, to be cost-

effective in either unselected postpartum women or women who have had a caesarean section delivery. In comparison, Sultan *et al.* estimated that 35% of the postpartum population who do not have a prior VTE are offered thromboprophylaxis under current RCOG guidance,[37] and O'Shaughnessey *et al.* estimated that 85% of women having a caesarean section would currently qualify for prophylaxis when using RCOG.[116] I have presented these findings to the committee currently undertaking the update of the RCOG guideline on thromboprophylaxis in pregnancy. Although the update is still ongoing, my findings were cited in a recent commentary article, authored by the clinician leading the guideline update, which describes the need for a significant change in thromboprophylaxis for pregnant and postpartum women in UK clinical practice.[117]

7.3 Use of research findings to inform the design of the TiLLI trial

I am a co-investigator on an ongoing research project recruiting people having LLI (referred to hereafter as the TiLLI trial). The TiLLI trial is a multicentre study comprising two linked open-label RCTs (referred to as TiLLI-High and TiLLI-Low). TiLLI-High is comparing LMWH to DOACs in higher-risk patients and TiLLI-Low is comparing LMWH, DOACs and no prophylaxis in lower-risk patients. The design the TiLLI trial was informed by the findings described in this thesis in several ways.

Firstly, the scenario analysis examining the potential cost-effectiveness of DOACs identified the need for a non-inferiority study comparing DOACs and LMWH. The potential benefits to patients of being able to offer an oral DOAC treatment to replace subcutaneous LMWH, was highlighted in the PPI meetings conducted as part of the broader TiLLI project. There was also evidence that DOACs were already being used off-label in this indication,[114] despite no studies having been identified on their clinical effectiveness in this population.[16] My exploratory analysis found that prophylaxis could potentially be cost-effectively offered to a broader range of patients, if using DOACs instead of LMWH, but this was based on an assumption of clinical equivalence. We therefore concluded that research was needed on the effectiveness of DOACs in this indication and a trial comparing DOACs and LMWH would provide the information required.

Secondly, my finding that RAM-based prophylaxis was cost-effective compared to prophylaxis for all in the TiLLI population supported the rationale to conduct two linked trials, with recruitment stratified by the individual's VTE risk, and including a comparator of no prophylaxis in the lower risk group. The decision to use a TRiP(cast) score of ≥ 6, to stratify

patients into TiLLI-High and TiLLI-Low, which provides a sensitivity of 85.7%,[115] was informed by my finding that a RAM with a sensitivity of 84-89% would be optimal. It should be noted that this led to a cut-off score being applied in the TiLLI trial that is different to the high-risk score specified by the developers of TRiP(cast) (≥ 7), as this would have only provided a sensitivity of 76.1%.[115]

Finally, my research findings across the three projects highlighted the importance of PTS as a potential driver for cost-effectiveness. This finding led to the study team deciding to request consent within the TiLLI trial for 5-year follow up via routine electronic health records, as any PTS events would not be captured within the primary outcome measured at 90 days.

7.4 Use of research findings to inform other research projects in people having LLI

There have also been a number of other studies examining either RAM performance or RAM-based prophylaxis in people having LLI, which have made reference to my findings within their study protocols. These include the ongoing RIVACAST RCT which is comparing rivaroxaban to LMWH in patients with a TRiP(cast) score of 7 or more,[118,119] and the completed CASTING study, which compared offering prophylaxis according to current practice with offering RAM-based prophylaxis.[120,121] This demonstrates that whilst the use of RAMs to direct prophylaxis in people having LLI is still an active area of research, the cost-effectiveness analysis conducted within the TiLLI project has contributed to the justification of ongoing and completed research projects.

7.5 Implications for future research in women at risk of pregnancy-related VTE

A key finding from the VTEP project was that the decision uncertainty was primarily due to the lack of RCTs quantifying the effectiveness of LMWH in this group. This evidence gap has led to large disparities in recommendations under different international guidelines, with the proportion eligible for thromboprophylaxis following caesarean section varying from 0.2% to 73.4%.[122] The EVSI identified that due to the very limited data currently available, even a small trial (e.g., 300 participants per arm) comparing LMWH to no prophylaxis would be useful in narrowing the current uncertainty regarding the effectiveness of LMWH in women who are pregnant or in the puerperium. However, we note that the size of trial required to meet traditional frequentist hypothesis-testing requirements is likely to be much larger than the size of trial required for the benefits of research to outweigh the research costs. Therefore, those designing and funding any future trial would need to decide whether the trial would need to be larger in order to be considered acceptable to those using the evidence to inform future clinical

practice or guidelines. Although recruitment of postpartum women to thromboprophylaxis studies has been problematic historically,[90,123,124] two pilot RCTs have recently published findings supporting the feasibility of large-scale RCTs examining postpartum thromboprophylaxis.[125,126]

8. Researcher development over the programme of work

These three projects demonstrate a period of growth and development within my research career. Firstly, my use of VOI analysis methods increased in terms of the level of complexity and specialist skills required across the projects. In the TiLLI and VTEAM projects although EVPPI was conducted, it was assessed only for individual parameters and uncertainty related to the RAM performance estimates was not incorporated in the PSA. Whereas in the VTEP project, the EVPPI analysis considered groups of parameters, and RAM sensitivity and specific was included in the PSA by assuming that these were normally distributed on the logit scale. Furthermore, as the VOI analysis to inform future research was the main focus of the VTEP project, an EVSI analysis was undertaken to estimate the potential value of a future RCT, which is a technique I had not previously used in my research practice. These projects have also established me as an expert in the health economics of thromboprophylaxis as demonstrated by my involvement in ongoing research projects.

The VTEP project was my first experience of taking a project through from grant application to delivery as the NIHR Chief Investigator. This gave me several new experiences including: leading the writing and submission of a grant application, managing a research budget, working with a steering committee. I chaired the monthly research team meetings, which were an opportunity to discuss progress and methodological challenges with the research team including patient and clinical experts. I was also responsible for ensuring that the various researchers worked together to produce a final report that was coherent and that built on the contribution of each specialist. Specific examples included collaborating with the reviewer and statistician to ensure that the RAM performance data were presented and analysed in the manner needed to inform the model, and informing the design of the clinician survey to ensure that the clinical scenarios reflected the different populations that would be selected by the different RAMs included in the modelling. Although I had previously led research projects for the NIHR, these projects formed part of a larger programme grant on which I was a co-investigator, and VTEP was my first opportunity to experience all aspects of being a Chief Investigator.

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Horner DE, Davis S, Pandor A, Shulver H, Goodacre S, Hind D, *et al.* Evaluation of venous thromboembolism risk assessment models for hospital inpatients: the VTEAM evidence synthesis. *Health Technol Assess* 2024;**28**(20). https://doi.org/10.3310/AWTW6200	Copyright © 2024 Horner *et al.* This work was produced by Horner *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This is an Open Access publication distributed under the terms of the Creative Commons Attribution CC BY 4.0 licence, **which permits unrestricted use, distribution, reproduction and adaptation in any medium and for any purpose provided that it is properly attributed**. See: https://creativecommons.org/licenses/by/4.0/. For attribution the title, original author(s), the publication source – NIHR Journals Library, and the DOI of the publication must be cited.	Horner, D.E. Pandor, A. Shulver, H. Goodacre, S. Hind, D. Rex, Saleema. Gillet, M. Bursnall, M. Griffin, X. Holland, M. Hunt, B.J. de Wit, K. Bennet, S. Pierce-Williams, R.
Davis S, Pandor A, Sampson FC, Hamilton J, Nelson-Piercy C, Hunt BJ, et al. Thromboprophylaxis during pregnancy and the puerperium: a systematic review and economic evaluation to estimate the value of future research *Health Technol Assess*, 2024:**28**(9). https://doi.org/10.3310/DFWT3873	Copyright © 2024 Davis *et al.* This work was produced by Davis *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This is an Open Access publication distributed under the terms of the Creative Commons Attribution CC BY 4.0 licence**, which permits unrestricted use, distribution, reproduction and adaptation in any medium and for any purpose provided that it is properly attributed.** See: https://creativecommons.org/licenses/by/4.0/. For attribution the title, original author(s), the publication source – NIHR Journals Library, and the DOI of the publication must be cited.	Pandor, A. Sampson, F. Hamilton, J. Nelson-Piercy, C. Hunt, B.J. Daru, J. Goodacre, S. Carser, R. Rooney, G. Clowes, M.

Appendix 2 – Submitted work 1

Published source is acknowledged as:

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The submitted work is described in Chapters 4, 5 and 6 of the published source, and therefore only these Chapters are reproduced below. The full published source can be accessed here:

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Chapter 4 Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

A systematic review was undertaken to identify any existing studies on the cost-effectiveness of thromboprophylaxis for lower-limb immobilisation due to injury.

Methods of reviewing cost-effectiveness

Identification of studies

Studies were identified by searching the following electronic databases and research registers:

- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, MEDLINE and Versions(R) (via OvidSP), 1946 to October 2017.
- EMBASE (via OvidSP), 1974 to October 2017.
- Cochrane Database of Systematic Reviews (via Wiley Online Library), 1996 to October 2017.
- Database of Abstracts of Review of Effects (via Wiley Online Library), 1995 to March 2015.
- HTA database (via Wiley Online), 1995 to October 2017.
- NHS EED (via Wiley Online Library), 1995 to March 2015.

For the MEDLINE and EMBASE searches, the aim was to maximise the specificity of the search in these databases that do not target economic evaluations. In these searches, the keyword strategies developed in the review of clinical effectiveness (see *Chapter 3*, *Objective*), which combined terms related to VTE with terms related to lower-limb immobilisation, were used with sensitive economic evaluation, quality of life and cost search filters[91–93] aimed at restricting search results to economic and cost-related studies. For the searches of HTA and NHS EED, terms for lower-limb immobilisation were not included, in order to maximise sensitivity and find all economic evaluations relating to VTE. All resources were searched initially from inception to October 2017 (or, in the case of discontinued sources such as NHS EED, the date at which coverage ceased). Further details on the search strategy can be found in *Appendix 9*.

All identified citations from the electronic searches and other resources were imported into and managed using EndNote bibliographic software.

Inclusion and exclusion criteria

The inclusion of potentially relevant articles was undertaken using a two-step process by a single reviewer. During the screening stage, all titles were examined for inclusion by the health economist and any citations that clearly did not meet the inclusion criteria (e.g. non-human, unrelated to VTE) were excluded. During the screening stage, abstracts were also examined if the paper could not be excluded based on the title alone. During the eligibility stage, all full-text articles that could not be excluded based on title and abstract were examined.

Studies were selected for inclusion on the basis of pre-determined inclusion and exclusion criteria. The population, interventions and comparators were defined as per the clinical effectiveness review of pharmacological thromboprophylaxis for preventing VTE (see *Chapter 3, Inclusion and exclusion criteria*). In addition, the study population was restricted to patients treated in the UK NHS because estimates of resource use and costs may not be transferable between different health-care settings. Criteria for the study design and outcomes were specified to identify studies meeting the NICE reference case.[94] In terms of study design, the review was restricted to cost-effectiveness studies, thereby excluding cost-minimisation studies. In terms of outcomes, the review was restricted to studies that measured benefits using QALYs because the QALY has been defined by NICE as the reference case measure for benefit for UK cost-effectiveness

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studies[94] and the NICE methods guide[94] provides guidance on the range of cost-per-QALY values that can be considered to represent good value for money within the UK NHS. Studies reporting alternative outcomes, such as cost per VTE avoided, were therefore excluded. Cost-consequence studies and other studies that reported data on costs, resource use or utility values in relevant populations were excluded from the cost-effectiveness review but were examined for relevant data that might inform the modelled estimates of cost-effectiveness (described in *Independent economic assessment methods*).

Results of cost-effectiveness review

The literature searches identified 1299 citations. Of these, no relevant published cost-effectiveness studies were identified. A flow chart describing the process of identifying relevant literature can be found in *Figure 8*. A total of three full-text articles were excluded as they did not meet all the prespecified inclusion criteria.[95–97] The articles were excluded for the following reasons: inappropriate study design (not a cost-effectiveness analysis)[96] and wrong target population (not isolated lower-limb injury requiring temporary immobilisation).[95,97] A full list of excluded studies with reasons for exclusion is presented in *Appendix 10*. One study was identified that examined the costs of providing thromboprophylaxis following lower-limb injuries but benefits were not assessed. This study was retained as a potential source of cost inputs for the analysis described in *Independent economic assessment methods*.

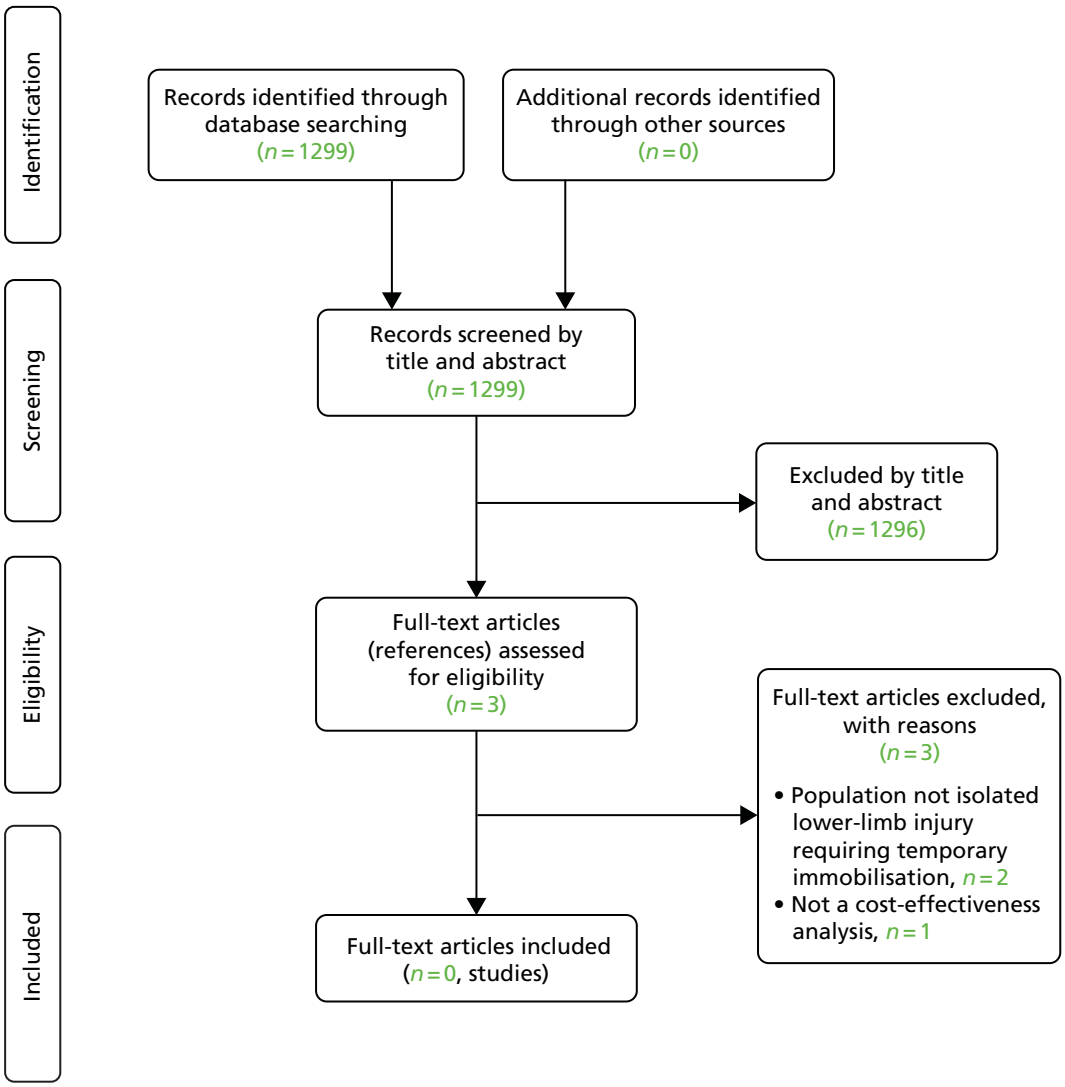

FIGURE 8 Study flow chart (adapted):[37] cost-effectiveness review of pharmacological thromboprophylaxis for preventing VTE in patients having lower-limb immobilisation due to injury. © 2009 Moher *et al.* This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Given the lack of published analyses in directly relevant populations, it was decided to retain papers describing cost-effectiveness analyses in related populations for the purpose of identifying suitable model inputs. Based on clinical advice, only those studies examining the cost-effectiveness of thromboprophylaxis in patients having elective knee surgery were retained, as these patients are more likely to be generally fit and well prior to surgery, do not have long periods of hospitalisation, will have some degree of reduced mobility in the lower limb during their recovery from surgery and the impact of surgery may mimic, to some extent, the trauma of lower-limb injury. Although two papers[98,99] were identified that reported the cost-effectiveness for thromboprophylaxis in patients having elective knee surgery, both corresponded to the same study, namely main analysis[99] and subgroup analysis[98] of patients aged > 75 years or with moderate renal impairment. Given that the parameter sources of interest did not vary between these two citations, only the paper reporting the main analysis was retained.[99] The parameters identified from this paper are described in the next section.

Independent economic assessment methods

Given the lack of published analyses examining the cost-effectiveness of thromboprophylaxis in patients having lower-limb immobilisation due to injury (see *Systematic review of existing cost-effectiveness evidence*), a de novo economic evaluation was conducted using decision-analytic modelling.

Decision problem

The aim of the decision-analytic model was to estimate the incremental cost-effectiveness of different strategies for thromboprophylaxis in patients with lower-limb injury requiring immobilisation. The thromboprophylaxis strategies examined were based on treating all patients or treating patients in accordance with the application of the RAMs identified in the review of RAMs described in *Chapter 3*, *Review of risk assessment models for predicting venous thromboembolic risk*. Based on the estimates of sensitivity and specificity identified in the review, it was decided to examine the L-TRiP(cast) tool, published by Nemeth *et al.*,[32] using cut-off scores ranging from 6 to 10. The Plymouth tool, published by Keenan *et al.*,[31] and the GEMNet tool, published by Roberts *et al.*,[17] were not included in the economic analysis. The only available estimates of the sensitivity and specificity for these RAMs, from an evaluation by Watson *et al.*,[82] suggested that both of these tools would be outperformed by the L-TRiP(cast) tool. The comparator considered in the economic analysis was no thromboprophylaxis. The base-case economic analysis assumes that prophylaxis consists of LMWH being given for the duration of lower-limb immobilisation (e.g. duration of casting or splinting).

Context

The model estimates lifetime costs and QALYs for the different thromboprophylaxis strategies and the comparator of no thromboprophylaxis under a NHS and Personal Social Services perspective. Future costs and benefits are discounted from their net present value at a rate of 3.5% per annum in accordance with the NICE *Guide to the Methods of Technology Appraisal*.[94] Costs are reported in Great British pounds, based on 2017 prices. To achieve this, historical prices used as model inputs were inflated using the hospital and community health services pay and prices index.[100]

Conceptual model

The clinical events that are expected to be affected by whether or not thromboprophylaxis is given to patients with lower-limb immobilisation due to injury are as follows:

- bleeding events during the period of prophylaxis, including fatal bleeds, non-fatal intracranial bleeds, other major bleeds and clinically relevant non-major bleeds
- VTE events, which includes distal and proximal DVT, both of which may be either symptomatic or asymptomatic, and PE, which may be either fatal or non-fatal
- bleeding events during the treatment of symptomatic VTE with anticoagulants
- long-term complications of VTE, such as PTS and CTEPH
- long-term complications of bleeds, such as disability following non-fatal intracranial bleeds.

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It should be noted that, within the modelling framework, symptomatic DVTs include any DVTs causing symptoms that result in the patient seeking medical care and any DVTs categorised as asymptomatic would include those with minor symptoms that are not sufficient for the patient to seek medical care. In the context of lower-limb injury and immobilisation, some DVTs may be categorised as asymptomatic in this analysis despite symptoms being present if these symptoms are attributed to the injury and do not prompt the patient to seek medical care.

Model structure

The model structure consists of a decision tree followed by a Markov model. The decision tree captures outcomes related to prophylaxis and VTE events in the first 6 months. The Markov model is used to extrapolate the QALY losses from fatal events and the costs and QALY losses from long-term complications that develop or persist beyond 6 months. The model estimates outcomes for a cohort of identical patients with average characteristics.

The decision tree captures the impact of alternative strategies on thromboprophylaxis rates, the impact of thromboprophylaxis on VTE events (e.g. symptomatic/asymptomatic DVT and PE) and bleeding complications related to either the initial thromboprophylaxis or anticoagulants used in the management of VTE in symptomatic patients. Bleeding complications are split into fatal bleeds, non-fatal intracranial haemorrhage (ICH) and other (i.e. non-fatal non-intracranial) major bleeds. The decision tree captures the first 6 months after lower-limb injury as this is considered a sufficient time frame to capture both 6–8 weeks of thromboprophylaxis during lower-limb immobilisation and 3 months of anticoagulant treatment for any VTEs arising during lower-limb immobilisation. All costs and health effects related to major bleeds that are non-fatal and non-intracranial are assumed to resolve within the 6-month timeframe of the decision tree model. Any chronic complications of VTE are assumed not to be diagnosed until after the completion of VTE treatment as it is difficult to distinguish PTS and CTEPH from acute symptoms during the first 3 months after VTE. Therefore, PTS and CTEPH are assumed not to occur during the decision tree phase of the model. The decision tree structure is shown in *Figure 9*. The key model assumptions were as follows:

- Bleeding events during immobilisation are possible in both those having thromboprophylaxis and those having no thromboprophylaxis.
- Bleeds associated with thromboprophylaxis are assumed to occur before VTE associated with immobilisation and both are assumed to occur within 12 weeks of the start of lower-limb immobilisation.
- Patients who have major bleeding will stop thromboprophylaxis immediately, but the treatment effect of thromboprophylaxis is assumed to be the same as for those who completed treatment, as patients who bleed are assumed to be adequately anticoagulated.
- The risk of VTE is the same whether or not prophylaxis caused bleeding.
- All patients with symptomatic DVT receive accurate diagnosis and initiate treatment with anticoagulants (3 months of either DOACs or phased anticoagulation).
- Asymptomatic DVTs are not detected and are not treated.
- All PEs are symptomatic and lead to detection and treatment with anticoagulants in all cases.
- Patients treated for symptomatic DVT and PE have a bleed risk associated with treatment, which is assumed to occur during the 3-month treatment period (i.e. within 6 months of the start of lower-limb immobilisation).
- Chronic complications of VTE (e.g. CTEPH following PE and PTS following DVT) are assumed to be diagnosed at least 3 months after VTE and, therefore, occur after any bleeds associated with VTE treatment.
- Deaths caused by PE occur before any bleeding associated with the treatment of PE.
- Risk of bleeding during treatment of VTE is independent of whether or not the patient bled during prophylaxis.
- Risk of VTE, risk of bleeding and risk of PTS/CTEPH are not dependent on patient characteristics.

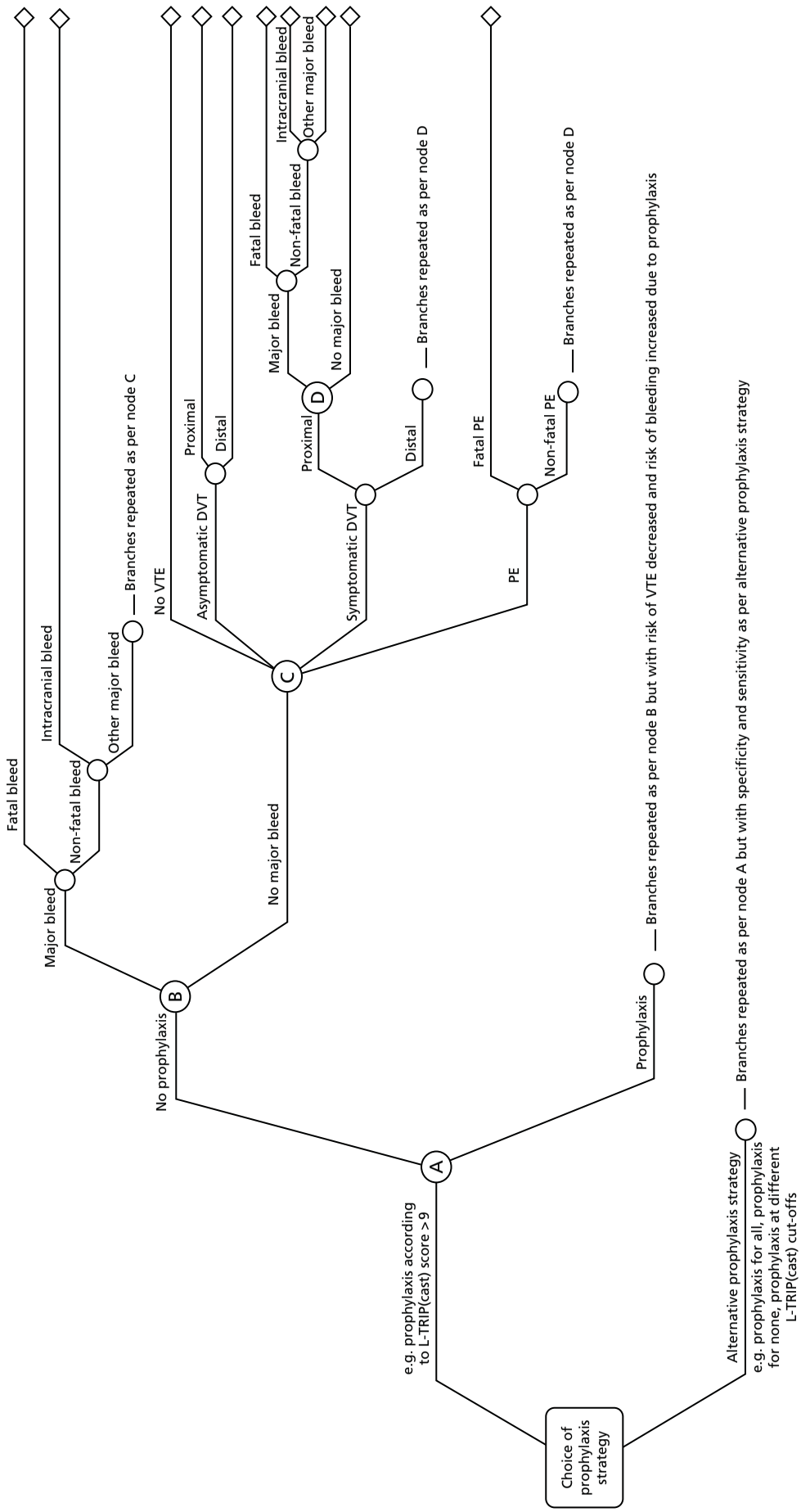

FIGURE 9 Decision tree structure.

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A key structural assumption within the model is the use of a cohort modelling approach that assumes that all patients have identical characteristics based on the average characteristics of those having lower-limb immobilisation due to injury. Depending on the RAMs used, the likelihood of receiving prophylaxis may be dependent on patient characteristics, leading to the treated and untreated populations having different characteristics, which is not captured in a cohort model. Based on clinical advice, it was expected that age would be the only relevant patient characteristic that would predict different outcomes. A scenario analysis was conducted to explore whether or not patient heterogeneity would affect the conclusions by varying the age of the cohort. Based on this, it was concluded that the cohort-level modelling approach was adequate and would not introduce significant bias.

Clinically relevant non-major bleeding (CRNMB), which is any non-major bleeding that results in contact with a health-care professional, was not expected to be a significant driver of cost-effectiveness. It was therefore excluded from the base-case analysis, but the impact of this assumption was explored in a scenario analysis. As CRNMB has no long-term implications, it was not modelled using a separate branch in the decision tree. Instead, it was included in a scenario analysis by applying a simple one-off cost for consultation to a proportion of the population having thromboprophylaxis.

Outcomes related specifically to surgical site wounds, such as wound infection and wound breakdown, were excluded from the model as there is substantial uncertainty as to whether or not thromboprophylaxis influences wound healing. Furthermore, only a small proportion of the lower-limb immobilisation population would have surgical intervention or open fractures. This is supported by data from the largest RCT to date,[59] in which only 12% of participants across both arms had surgery and the rate of infections was similar across arms (12/719 for treatment vs. 14/716 for control).

The aim of the Markov model is to capture QALY losses due to fatal PEs or fatal bleeds and the costs and QALY losses associated with chronic complications following VTE events (e.g. PTS or CTEPH) or bleeds (e.g. disability following ICH). At 6 months, patients enter one of eight Markov states: (1) well, (2) dead, (3) post-ICH, (4) asymptomatic proximal DVT, (5) asymptomatic distal DVT, (6) symptomatic proximal DVT, (7) symptomatic distal DVT or (8) PE. The Markov model is then used to estimate the number of patients from the DVT and PE states who develop either PTS or CTEPH, respectively, and the long-term survival in each health state. Separate DVT states were required to capture differences in PTS risk depending on whether the DVT was proximal or distal and whether it was symptomatic and treated or was asymptomatic and, therefore, remained undiagnosed and untreated. The prevalence of PTS and CTEPH is captured by having separate health states for patients with these long-term complications. All patients with PTS are combined in a single health state, as costs, utilities and survival are not expected to be affected by whether or not PTS occurred following proximal or distal DVT. The PTS state is not split into different severity levels as the utility estimates are based on the average across severity levels and the costs are not expected to differ by severity. Separate Markov states were required for medically and surgically managed CTEPH as the type of management affects life expectancy, costs and utilities in patients with CTEPH. The health states are shown in *Figure 10*.

The Markov model has one 6-month cycle, to extrapolate the decision tree outcomes to the end of the first year, followed by annual cycles thereafter. All-cause mortality during the first year is assumed to occur at 6 months (i.e. between the end of the decision tree and the start of the Markov model) and then mid-way through each annual cycle thereafter. The CTEPH and post-ICH health states have state-specific mortality risks, whereas the other states experience general population mortality rates. Average costs and QALYs across each model cycle were calculated by applying a half-cycle correction.

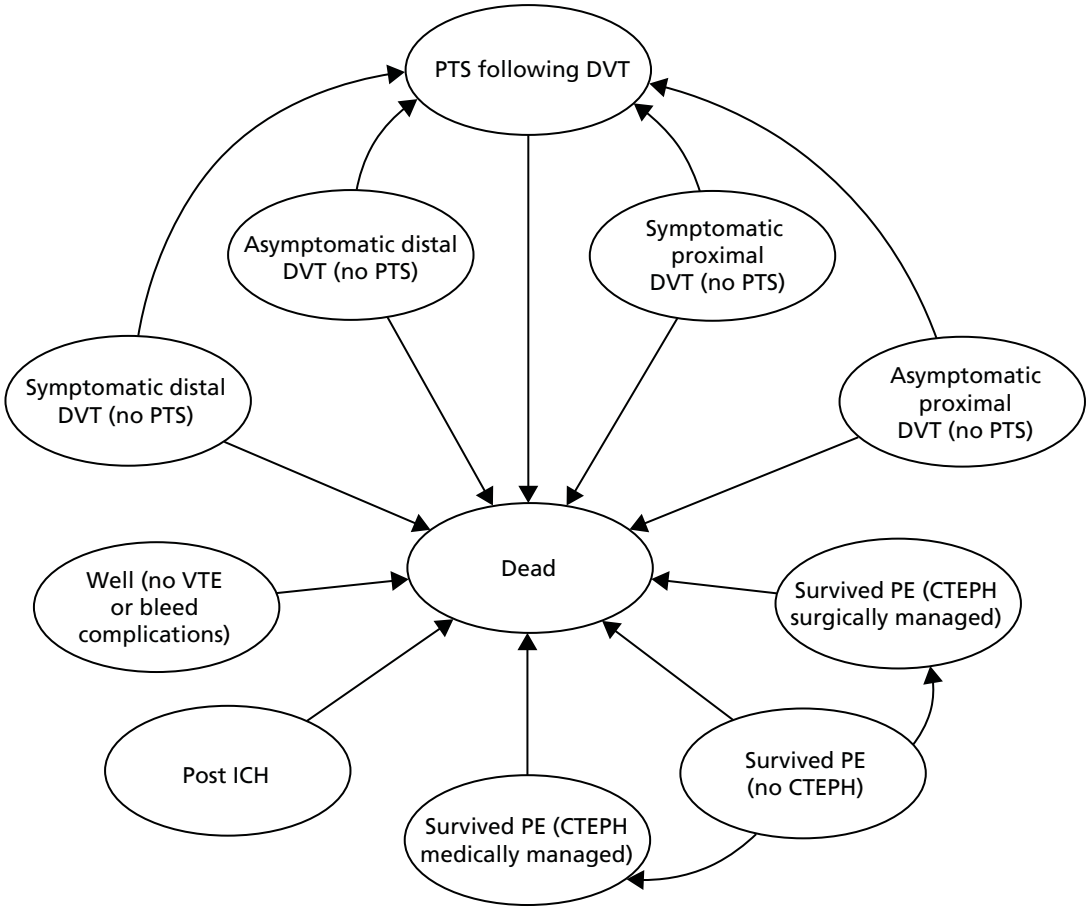

FIGURE 10 Markov model structure.

Assumptions related to the Markov phase of the model are as follows:

- All symptomatic DVTs are associated with a risk of PTS but the rate is allowed to differ depending on whether the DVT is distal or proximal and whether it is symptomatic and treated or asymptomatic and untreated.
- There is no risk of PTS for PE.
- CTEPH is possible only after PE.
- Further outcomes (i.e. VTE, CTEPH and PTS) are not modelled for those who experience ICH, as lifetime cost and QALYs will be determined predominantly by disability related to the ICH.
- All-cause mortality is applied to all Markov states with state-specific mortality rates possible for patients who have experienced ICH or who have CTEPH that is either medically or surgically managed.
- Recurrent VTE is not modelled as it is not likely to be related to the initial provoked VTE and, therefore, would occur equally regardless of whether or not thromboprophylaxis was given during immobilisation.

Data sources

Identification of data sources

A summary of the model parameters and data sources used to populate the model are provided in *Table 15*, with the exception of utility values, which are provided in *Treatment-related utility decrement*. The number of patients receiving thromboprophylaxis under the various treatment strategies is estimated by combining data on sensitivity and specificity, from the systematic review of RAMs (see *Chapter 3*, *Review of risk assessment models for predicting venous thromboembolic risk*), with data on the risk in untreated patients, from the review of RCTs comparing thromboprophylaxis with no thromboprophylaxis (see *Chapter 3*, *Review of pharmacological thromboprophylaxis for preventing venous thromboembolism*). Parameters relating to the

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TABLE 15 Summary of clinical and cost parameters

Parameter description	Mean value	95% CI[a]	Source	Notes
Clinical parameters				
Sensitivity of decision tools			See *Chapter 3*, *Narrative data synthesis*	
L-TRiP(cast) score of				
≥ 6	98.4%	Assumed fixed		
≥ 7	95.3%	Assumed fixed		
≥ 8	92.6%	Assumed fixed		
≥ 9	80.8%	Assumed fixed		
≥ 10	65.1%	Assumed fixed		
Specificity of decision tools			See *Chapter 3*, *Narrative data synthesis*	
L-TRiP(cast) score of				
≥ 6	14.2%	Assumed fixed		
≥ 7	26.2%	Assumed fixed		
≥ 8	39.7%	Assumed fixed		
≥ 9	60.8%	Assumed fixed		
≥ 10	72.2%	Assumed fixed		
Probabilities of VTE in patients having lower-limb immobilisation without thromboprophylaxis			Systematic review of thromboprophylaxis effectiveness	Average proportion across 12 RCTs (see *Table 16*)
PE	0.4%	0.2% to 0.7%		
Symptomatic DVT	0.9%	0.5% to 1.3%		
Asymptomatic DVT	7.1%	6.0% to 8.1%		
Proportion of asymptomatic DVTs that are distal	83.9%	73.3% to 92.2%	Systematic review of thromboprophylaxis effectiveness	Average proportion across six RCTs (see *Table 16*)
Proportion of symptomatic DVTs that are distal	50%	26.5% to 73.4%	Systematic review of thromboprophylaxis effectiveness	Based on a single RCT that focused exclusively on symptomatic DVTs (see *Table 16*)

Parameter description	Mean value	95% CI[a]	Source	Notes
Effectiveness of prophylaxis: OR for VTE	0.52	0.37 to 0.71	Systematic review of decision tools for identifying patients at risk of VTE	OR for LMWH vs. placebo for all VTE based on random-effects Bayesian NMA
Risk of major bleed with no prophylaxis	1.89 per 1000 person-years	1.86 to 1.92 per 1000 patient years	Hippisley-Cox and Coupland[101]	Age-standardised incidence across whole cohort used to derive the QBleed[101] risk score: • 1.34 per 1000 person-years for GI bleed • 0.55 per 1000 person-years for ICH
Bleed risk for prophylaxis vs. no prophylaxis: HR	1.64	0.98 to 2.75	Pooled analysis of bleed risks across all VTE prophylaxis studies in NICE CG92[24]	Data presented in CG92 reanalysed on log-odds scale using random-effects Bayesian meta-analysis
Proportion of major bleeds during lower-limb immobilisation that are fatal (with and without prophylaxis)	21.0%	17.0% to 25.0%	• Case fatality rate of ICH bleeds taken from Fang *et al.*[102] • Case fatality rate of GI bleeds taken from Button *et al.*[103] • Proportion of bleeds that are GI and ICH are based on Hippisley-Cox and Coupland[101]	Average fatality across GI and ICH bleeds with case fatality rates of 10% (95% CI 9.7% to 10.4%) and 49% (95%CI 37% to 60%), respectively
Proportion of non-fatal major bleeds during lower-limb immobilisation that are ICH (with and without prophylaxis)	19.0%	15.4% to 22.2%	Fang *et al.*,[102] Button *et al.*[103] and Hippisley-Cox and Coupland[101]	Estimated based on incidence and case fatality rates for GI and ICH bleeds
Risk of bleeding during 3-month anticoagulant treatment for VTE	0.9%	0.2% to 2.0%	Kooiman *et al.*[104]	6-month incidence pooled across patients with HAS-BLED score of 0 or 1
Proportion of major bleeds during VTE treatment that are fatal	25.0%	21.0% to 28.0%	Nieto *et al.*[105]	Based on case fatality rates for major bleeds within RIETE (Nieto *et al.*)[105]
Proportion of non-fatal major bleeds during VTE treatment that are ICH	9.0%	6.5% to 11.9%	Nieto *et al.*[105]	Based on proportion of major non-fatal bleeds within RIETE that were ICH (Nieto *et al.*)[105]
All-cause (non-VTE-related) mortality	Varies by age	N/A	ONS lifetables[106]	Risk applied each year is based on current age and is not adjusted to account for contribution of VTE to population mortality

continued

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TABLE 15 Summary of clinical and cost parameters (*continued*)

Parameter description	Mean value	95% CI[a]	Source	Notes
SMR for patients surviving ICH, compared with general population		Ranges for SMRs not stated so ± 20% on the logged scale is assumed	Fogelholm *et al.*[107]	Assumed no increased mortality risk after 6 years
Year 1 after ICH	4.5			
Years 2 to 6 after ICH	2.2			
Probability of PE being fatal	2.9%	2.5% to 3.3%	Maestre *et al.*[108]	• Data from RIETE • Case fatality rate of clinically overt PE in outpatients
Cumulative risk of PTS for treated symptomatic DVT at 3 years			Hach-Wunderle *et al.*[109] (TULIPA PLUS registry)	Cumulative incidence at 3 years based on the TULIPA PLUS registry. Distribution of risk across years 1 to 3 based on van Dongen *et al.*[110] Zero risk assumed from year 4 onwards
Proximal	32.4%	22.1% to 43.6%		
Distal	15.6%	7.9% to 25.3%		
Cumulative risk of PTS for untreated asymptomatic DVT at 3 years			Hach-Wunderle *et al.*[109] and van Dongen *et al.*[110]	• For proximal DVT, the data for symptomatic DVT were uplifted using the OR from van Dongen *et al.*[110] for the impact of inadequate anticoagulation on PTS risk: OR 2.71 (95% CI 1.44 to 5.1) • Assumed no increased risk for asymptomatic distal DVT
Proximal	56.5%	29.0% to 79.8%		
Distal	15.6%	Fixed relative to symptomatic		
Risk of CTEPH per annum applied in the first 2 years after PE	1.6%	1.0% to 2.2%	Ende-Verhaar *et al.*[111]	• 3.2% (95% CI 2.0% to 4.4%) at 2 years based on the incidence in those surviving the initial treatment period of 3–6 months • Assumed no risk beyond 2 years, based on Pengo *et al.*[112]

Parameter description	Mean value	95% CI[a]	Source	Notes
Proportion of CTEPH treated surgically	59.5%	55.8% to 63.2%	Delcroix *et al.*[113]	
Mortality for CTEPH				
Medically treated	Exponential survival curve with mean hazard of 0.1168	SE of mean hazard 0.0123	Original data from Delcroix *et al.*[113] but curves taken from Goodacre *et al.*[114]	• Medically treated patients have a death risk of 11% per annum (fixed over time) • If the death hazard falls below general population values, then general population values apply
Surgically treated	Log-normal survival curve with mean 5.081 and SD of 3.343	• SE of mean 0.574 • SE of SD 0.399	Original data from Delcroix *et al.*[113] but curves taken from Goodacre *et al.*[114]	• Surgically treated patients have a risk that declines over time (6% in year 1 declining to 1.5% at year 5, 1% at year 10 and 0.8% at year 15) • If the death hazard falls below general population values, then general population values apply
Cost parameters				
Application of RAM to patient	£8.83	Fixed	Curtis and Burns[100]	Cost for 5 minutes of hospital consultant time
Prophylaxis: 6 weeks of LMWH (dalteparin), including costs of initiating treatment and district nurse administration for 4% of patients	£224.64	£197 to £267	• Administration costs based on Menakaya *et al.*[115] • Drug costs based on Drug Tariff[21]	• Costs from Menakaya *et al.*[115] updated to current prices using inflation indices from Curtis and Burns[100] • Dalteparin is the lowest-cost formulation of LMWH based on 2018 Drug Tariff prices[21] • See *Table 18* for a more detailed costing breakdown
Treatment of symptomatic proximal DVT	£687.69	£660 to £715	NHS reference costs[116] Drug Tariff[21]	Clinical expert discussion regarding the likelihood of resource use, combined with NHS reference cost data[116] for health-care contacts and Drug Tariff[21] costs for treatments (see *Table 19* for a more detailed costing breakdown)

continued

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TABLE 15 Summary of clinical and cost parameters (*continued*)

Parameter description	Mean value	95% CI[a]	Source	Notes
Treatment of symptomatic distal DVT	£559.62	£536 to £584	NHS reference costs[116] Drug Tariff[21]	Clinical expert discussion regarding the likelihood of resource use, combined with NHS reference cost data[116] for health-care contacts and Drug Tariff[21] costs for treatments (see *Table 19* for more detailed costing breakdown)
Treatment of non-fatal PE	£1788.44	£1995 to £2168	NHS reference costs[116] Drug Tariff[21]	Clinical expert discussion regarding the likelihood of resource use, combined with NHS reference cost data[116] for health-care contacts and Drug Tariff[21] costs for treatments (see *Table 19* for more detailed costing breakdown)
Fatal PE	£1498.14	£1430 to £1571	NHS reference costs[116]	As per non-fatal bleed, minus drug therapy for PE
Fatal bleed	£1802.48	£322 to £3283	Luengo-Fernandez *et al.*[117]	• Costs of fatal haemorrhagic stroke from OXVASC subgroup with atrial fibrillation • Updated to current prices using inflation indices[100]
Non-fatal, non-ICH bleed	£1197.88	£1118 to £1288	NHS reference costs 2015/16[116]	Weighted average of reference costs for GI bleed (HRG codes FZ38G – FZ38P)
Post non-fatal ICH: first 90 days	£21,255.00	£16,814 to £26,217	Luengo-Fernandez *et al.*[117]	Weighted average of costs for non-fatal haemorrhagic strokes Uplifted to current prices using inflation indices[100]
Post non-fatal ICH: post acute (beyond 90 days) costs per annum	£8013.00	£5300 to £11,271	Luengo-Fernandez *et al.*[117]	• Average costs across all stroke types (haemorrhagic not reported separately) • Includes GP and ED costs and long-term care cost • Updated to current prices using inflation indices[100]

Parameter description	Mean value	95% CI[a]	Source	Notes
PTS cost per annum: year 1 (mild/moderate/severe)	£308 in year 1	£294 to £323	NHS reference costs 2015/16[116]	One first and one follow-up vascular surgery outpatient appointment Weighted average of consultant-led and non-consultant-led outpatient appointments for non-admitted face-to-face first attendance (WF01B) and follow-up (WF01A) for vascular surgery (service code 107)
PTS cost per annum: year 2 (mild/moderate/severe)	£74 in each subsequent year	Fixed	Curtis and Burns[100]	Two GP surgery consultations with qualification costs including direct-care staff costs at £37 per appointment
CTEPH cost per annum				
Medically managed	£17,942 each year	Fixed	NICE CG92[24]	• Cost in CG92 was £1219 per 4 weeks in 2008/09 prices.[24] This was updated to 2016/17 prices using inflation indices[100] • Assume treatment is lifelong
Surgically managed	£9890 in year 1 and zero in year 2 onwards	£9471 to £10,370	NHS reference costs 2015/16[116]	• Average of DZ02H, DZ02J and DZ02K 'complex thoracic procedures' relating to procedure code L041 • 'Pulmonary thromboendodartectomy' for elective inpatients including excess bed-days • In addition, 29% of surgically treated patients require medical bridging therapy for 4.6 months (average cost £1992)

CG, clinical guideline; GI, gastrointestinal; GP, general practitioner; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly, Drugs/alcohol concomitantly; HR, hazard ratio; HRG, Healthcare Resource Group; N/A, not applicable; ONS, Office for National Statistics; OXVASC, Oxford Vascular Study; RIETE, Computerized Registry of Patients with Venous Thromboembolism; SE, standard error; SMR, standardised mortality ratio; TULIPA PLUS, Thrombosis and Pulmonary Embolism in Out-Patients – plus; VKA, vitamin K antagonist.
a Except where stated otherwise (e.g. SD or SE).

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relative risk (RR) of VTE events in patients receiving thromboprophylaxis compared with those not receiving thromboprophylaxis have been taken from the review of clinical effectiveness of thromboprophylaxis to prevent VTE in lower-limb immobilisation. For all other parameters, data were obtained by reviewing the data sources used in published cost-effectiveness analyses and other published sources. As no relevant models were identified that were specific to the population having lower-limb immobilisation, the search for parameter sources was broadened to models in related populations or indications. This search focused, first, on models used to inform NICE guidance on anticoagulants to prevent and treat VTE as the models used to inform any existing NICE guidance were considered highly likely to contain data relevant to the UK context and the NICE reference case, and have been critically scrutinised by independent academic groups. Second, the additional studies identified in the literature review for the related population of patients having elective knee surgery were used (as discussed in *Results of cost-effectiveness review*). Finally, ad hoc searches were conducted using the reference lists of recently published reviews to identify any relevant sources not identified during the review of published models and clinical experts were consulted to see if any key data sources known to them had been missed. This included any sources used in relevant models known to the authors. The published cost-effectiveness analyses identified as potential sources of model inputs are summarised in *Appendix 11*.

Characteristics of population having lower-limb immobilisation

The Prevention of Thrombosis after Lower Leg Plaster Cast (POT-CAST) trial by van Adrichem *et al.*[59] was selected as being representative of the population having lower-limb immobilisation due to injury who are at risk of thrombosis. This was selected as it is a recent, large RCT conducted exclusively in Europe (the Netherlands) and the inclusion and exclusion criteria were not too restrictive; patients with a prior history of VTE were excluded but those with cancer or family history of DVT were not excluded. The starting age in the model was set to be 46 years of age and 51.5% of the starting population were male.

Risk of venous thromboembolism and types of venous thromboembolism

The risk of VTE was based on data taken from the systematic review of clinical effectiveness for LMWH versus control (see *Chapter 3*, *Review of pharmacological thromboprophylaxis for preventing venous thromboembolism*). The rate of any form of VTE (i.e. PE, symptomatic DVT or asymptomatic DVT) was 8.39% across the 12 studies[23,49–56,58–60] reporting data for control (i.e. placebo, aspirin, no thromboprophylaxis). The risk of PE, including those that experienced PE with DVT, was 0.43%. Therefore, the risk of DVT without PE was 7.96%. Only nine studies[23,49–52,54,56,58,60] reported outcomes for both symptomatic and asymptomatic DVT. From these studies, it was estimated that 11.4% of DVT are symptomatic (16/140), giving an absolute incidence of 0.91% for symptomatic DVT and 7.05% for asymptomatic DVT in patients having lower-limb immobilisation without thromboprophylaxis. These are slightly higher than the raw figures (*Table 16*) as three studies[53,55,59] did not report outcome data for both symptomatic and asymptomatic DVT but did report data for all VTE and PE. These estimates effectively assume the same split of symptomatic and asymptomatic DVT for the three studies with missing data to achieve the total VTE rate observed across all 12 studies. For asymptomatic DVT, only six studies[23,50–52,58,60] reported outcomes for both distal and proximal asymptomatic DVT. From these six studies, it was estimated that 16% (9/56) of asymptomatic DVTs are proximal (and, therefore, 84% are distal). The data on the location of symptomatic DVTs (distal or proximal) were very sparse, with only 46 events reported across all trial arms and many studies not reporting the location. It was possible to extract data on the location of symptomatic DVTs for four studies[54,57–59] included in the review, covering a total of 34 events across all trials arms. The proportion of symptomatic DVTs that were proximal varied from 14% to 100% across these four studies, with a median estimate of 36%. The POT-CAST trial[59] was the only one of these four studies that focused exclusively on symptomatic VTE. The other three studies[54,57,58] screened patients for asymptomatic DVTs as well as recording the number of DVTs that were symptomatic. There is a risk that the process of screening patients for asymptomatic DVTs may lead to patients attributing symptoms to screening-detected DVTs that may otherwise not have been sufficiently symptomatic to result in the patient presenting with symptoms in routine care. For this reason, it was decided to use the POT-CAST trial[59] as the single source of estimates for the proportion of symptomatic DVTs that are proximal, as no routine screening was used in this trial to detect asymptomatic DVTs. As this single study provided a low number of events, it was decided to pool the data across trial arms. This resulted

TABLE 16 Data from the systematic review on clinical effectiveness used to inform VTE event rates

Event type	*n* with event	*N* at risk	Rate based on studies (%)	Number of studies	Data applied in model (%)
Any VTE	196	2336	8.39	12[23,49–56,58–60]	8.39
PE risk	10	2336	0.43	12[23,49–56,58–60]	0.43
DVT without PE[a]	186	2336	7.96	12[23,49–56,58–60]	
Asymptomatic DVT	124	1466	8.58	9[23,49–52,54,56,58,60]	7.05[b]
Symptomatic DVT	16	1466	1.11	9[23,49–52,54,56,58,60]	0.91[b]
Asymptomatic proximal DVT	9	1055	0.85	6[23,50–52,58,60]	1.13[c]
Asymptomatic distal DVT	47	1055	4.45	6[23,50–52,58,60]	5.59[c]
Symptomatic proximal DVT	8	1435	0.56	1[59]	0.45[d]
Symptomatic distal DVT	8	1435	0.56	1[59]	0.45[d]

a Based on the difference between the two rows above.
b Estimated using the total rate of DVT without PE from 12 studies and proportion that are symptomatic from six studies.
c Estimated using the total that are asymptomatic from nine studies and proportion that are proximal from six studies.
d Estimated from the total that are symptomatic from nine studies and proportion that are symptomatic from the POT-CAST trial[59] (50%) that focused exclusively on symptomatic VTE events.

in 50% of the 16 symptomatic DVTs being proximal. Given that these data were based on a single study and a small number of events, two extreme scenarios were examined, assuming that either 0% or 100% of symptomatic DVTs are proximal, to see if the overall conclusions were sensitive to uncertainty around this parameter.

All-cause mortality

It was not considered necessary to model males and females separately as the risks of VTE during lower-limb immobilisation were not expected to vary according to sex. However, life-expectancy is dependent on sex and, consequently, any QALY gains from deaths prevented would be dependent on sex. For this reason, a weighted mortality risk was applied, based on the proportion of males (51.5%) in the POT-CAST trial,[59] using data on the risk of death for males and females by age obtained from lifetables. The weighting across males and females was allowed to vary over the course of the model to allow for the fact that lower mortality risks in females leads to a slight increase in the proportion of people alive who are female over time.

Case fatality rate for pulmonary embolism

None of the studies included in the review of clinical effectiveness reported any fatal PEs. Given that 14 PEs were reported within the 13 studies[23,49–60] included in the review, this suggests that the rate of fatality due to PE is < 7% in the population having lower-limb immobilisation due to injury. The research team looked for alternative data sources on the case fatality rate of PE. Data were identified from the Computerized Registry of Patients with Venous Thromboembolism (RIETE) (an extensive data registry of consecutive patients with VTE), which found that the rate of all-cause mortality at 30 days had fallen over time from 6.6% in 2001–05 to 4.9% in 2010–13 (reported by Jiménez *et al.*[118]). However, some of this mortality may not be related to PE. When looking at only PE-related mortality, the rate at 30 days was 1.8%. Another analysis of RIETE, by Maestre *et al.*,[108] found that rates of fatal PE at 90 days were lower for outpatients than inpatients. They found that of 7591 outpatients with clinically overt PE, 219 (2.9%) had fatal PE at 90 days; this was lower than the 4.1% (119/2870) rate with clinically overt PE having a fatal PE in the inpatient population. Given that patients having lower-limb immobilisation due to injury would generally be managed as outpatients, this suggests that a lower risk may be seen in this population.

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The Emergency Medicine Pulmonary Embolism in the Real World Registry (EMPEROR) cohort study (reported by Pollack *et al.*[119]), which recruited patients with PE from EDs in the USA, reported a 30-day all-cause mortality rate of 5.4% for patients with confirmed PE, but the rate of mortality was only 1.1% when restricted to PE-related in-hospital mortality. These data seem reasonably consistent with the 30-day data from RIETE.

It was decided to apply the case fatality rate for outpatients from the RIETE study (2.9%) in the model, as patients having lower-limb immobilisation would be managed as outpatients and there was a slight increase from 30 days to 90 days, which is captured in the analysis by Maestre *et al.*[108] but not in the other two analyses, which were limited to 30 days.

Combining the incidence and case fatality rate for PE, it is estimated that one fatal PE per 8097 patients having lower-limb immobilisation without thromboprophylaxis would be expected, which is consistent with there being no fatal PEs observed in the studies included in the systematic review for treatment effectiveness.

Effectiveness of thromboprophylaxis on prevention of venous thromboembolism during lower-limb immobilisation

We applied the OR for LMWH versus control for the outcome of any VTE estimated from the NMA to all forms of VTE within the model. Although the NMA provides estimates of clinical effect that are specific to different types of VTE (i.e. symptomatic DVT, asymptomatic DVT and PE) the estimates for these specific VTE types are more uncertain as they are based on fewer events. The pooled effect for the OR (0.52, 95% CrI 0.37 to 0.71) was converted to a RR and applied to the baseline risk within the model.

For the sensitivity analyses examining thromboprophylaxis using alternative drug classes, it was assumed that DOACs would have the same effectiveness as LMWH, as no studies examining the effectiveness of DOACs in this population were included in the systematic review. For the analysis assuming that fondaparinux is used, the OR for fondaparinux versus control from the NMA was applied (0.13, 95% CrI 0.05 to 0.30). In both cases, the same adverse effects profile for LMWH, DOACs and fondaparinux were implicitly assumed, as the only adverse event included in the model was bleeding and it was assumed that all prophylaxis had the same impact on bleeding rates.

Risk of bleeding during lower-limb immobilisation

There is a risk of major bleeding within the general population regardless of whether or not they receive treatment with anticoagulants. A cohort study (reported by Hippisley-Cox and Coupland[101]), conducted in a large primary care population using data from 4.4 million patients with 16.4 million person-years of follow-up, estimated an age-standardised incidence rate of 1.34 (95% CI 1.32 to 1.36) per 1000 person-years for upper GI bleeding and 0.55 (95% CI 0.54 to 0.56) per 1000 person-years for intracranial bleeds for patients not taking anticoagulants. Given that the study cohort was patients aged 21–99 years registered with a general practice and that the only relevant exclusion criteria appears to be existing anticoagulated patients, this study was considered to be reflective of the risk of GI bleeds and ICH in the general population at risk of lower-limb injury who are not currently taking anticoagulants. The baseline characteristics of patients not taking anticoagulants in the study by Hippisley-Cox and Coupland[101] were compared with the characteristics of those in the comparator arm of the POT-CAST trial[59] (*Table 17*). Although Hippisley-Cox and Coupland[101] did not present a mean age, a weighted mean age was calculated using the distribution across age bands and the mid-point ages for each band: this was found to be 40 years (with a range of 36–45 years when using the lower and upper limits of the age bands), which is lower than the mean age of 46 years from the POT-CAST trial.[59] The proportion of non-smokers was slightly lower in the POT-CAST trial and the proportion of patients with previous cancer was slightly higher.

TABLE 17 Comparison of baseline characteristics reported by both QBleed (reported by Hippisley-Cox and Coupland[101]) and the POT-CAST trial (reported by van Adrichem *et al.*[59])

Characteristic	QBleed (no anticoagulation)[101]	POT-CAST[59]
Male (%)	48.9	51.5
Age (years), mean (SD)	NR[a]	46 (16)
Age group (years) (%)		
21–24	54.6	NR
45–64	29.0	NR
65–74	8.5	NR
75–84	5.4	NR
≥ 85	2.5	NR
BMI (kg/m^2), mean (SD)	26 (4.8)	26 (4.4)
Smoking status (%)		
Non-smoker	55.9	46.5
Former smoker	18.7	26.8
Current smoker	21.7	26.8
Previous cancer (%)	2.7	4.3

NR, not reported.
a The mean age of 40 years was estimated using the mid-point ages for each age band and age 85 years for the '≥ 80 years' band (range of mean 36–45 years, using upper and lower limits of age bands).

To see if the rates of major bleeding in the RCTs included in the clinical effectiveness review were similar, data on the rates of major bleeding (see *Appendix 3*) were combined with data on the number of person-years people were at risk of bleeding within each study. It was assumed that the period at risk was the period of cast immobilisation, unless the study explicitly reported a longer duration of follow-up. The number of person-years at risk could be estimated for only 11 of the 13 studies.[23,49–56,59,60] One study used an active control group,[57] whereas another did not explicitly report the duration of follow-up.[23] There was only one episode of major bleeding across 447 person-years, giving an incidence of major bleeding of two per 1000 person-years. This appears to be relatively consistent with the estimates for ICH and GI bleeds combined from the cohort reported by Hippisley-Cox and Coupland.[101] Therefore, it was decided to use the age-standardised estimates from the cohort reported by Hippisley-Cox and Coupland[101] within the model.

Thromboprophylaxis would be expected to increase the risk of a major bleed but the very small number of major bleeding events in the systematic review meant that the estimate of the risk of major bleeding due to thromboprophylaxis in people with lower-limb immobilisation was very uncertain (OR 1.45, 95% CrI 0.08 to 32.17). Although the baseline risk of bleeding will vary between patient groups, there is no strong reason to believe that the relative effect of thromboprophylaxis will vary. Therefore, data from the NICE clinical guideline (CG) on reducing the risk of VTE (NICE CG92)[24] was used, which pooled all indications into a single meta-analysis.[24] These data were reanalysed to use a random-effects approach. In this meta-analysis, the median OR was found to be 1.643 (95% CrI 0.90 to 2.53). The OR was converted to a RR and applied to the baseline risk within the model.

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The significance of major bleeding depends primarily on whether or not it is fatal; for non-fatal bleeds, the significance depends on whether or not it is intracranial, as ICH has the potential to result in long-term disability. Fang *et al.*[102] examined death and disability following bleeds associated with warfarin (Coumadin®, Bristol-Myers Squibb Company, New York City, NY, USA). These data were used to estimate the proportion of major bleeding episodes that were fatal. Fang *et al.*[102] found that 48.6% of patients having ICH died within 30 days, whereas only 5.1% of patients having non-intracranial bleeds died within 30 days.[102] Although it is acknowledged that bleeds associated with warfarin use may be more likely to result in fatalities than bleeds in patients not having anticoagulation,[120] it seemed reasonable to apply the case fatality rates from bleeds associated with warfarin use in the model as these would be directly applicable to the additional cases of bleeding associated with thromboprophylaxis. Any overestimation of mortality in those having bleeds not related to anticoagulant use would be similar across arms and, therefore, would affect estimates of absolute QALYs for each thromboprophylaxis strategy but not the incremental QALY gains when comparing thromboprophylaxis strategies.

The case fatality rate for non-intracranial bleeds reported by Fang *et al.*[102] was lower than the case fatality rates observed for GI bleeds by Rockall *et al.*[121] and Button *et al.*,[103] but this may be because GI bleeds have a greater mortality risk than other non-ICHs. Although Button *et al.*[103] found that the case fatality rate had fallen over time, the case fatality rate of 10% estimated by Button *et al.*[103] appears to be consistent with a 2015 report[122] from the National Confidential Enquiry into Patient Outcome and Death, based on data collected in 2013. As the data from QBleed[101] related only to the incidence of ICH and GI bleeds, the 10% risk of mortality from Button *et al.*[103] was used instead of the 5% for extracranial bleeds from Fang *et al.*[102]

In addition to the risk of ICH being fatal at the time of the bleed itself, there is an increased risk of death in patients having ICH compared with population norms. Fogelholm *et al.*[107] found that patients with primary ICH who survived to 28 days had a standardised mortality rate that was 4.5-fold higher in the first year and 2.2-fold higher in years 2–6 than that of age- and sex-matched controls. These figures were applied as RRs to the all-cause mortality rates to increase the risk of mortality in those patients who survived ICH. Although Fogelholm *et al.*[107] reported a 10% reduction in mortality compared with general population norms in years 7–16, no increased or decreased risk beyond 6 years was assumed as there was doubt over the clinical plausibility of a reduced risk of death following ICH.

Risk of bleeding during anticoagulation treatment of venous thromboembolism

Several sources of data on bleeding risks during treatment of VTE were identified. These included the RIETE[105] and Prevention of thromboembolic events – European registry in venous thromboembolism (PREFER-VTE)[123] studies and a systematic review of RCTs and cohort studies by Carrier *et al.*[124] In the review by Carrier *et al.*,[124] 56 of the 69 studies included were RCTs, which the authors say are not generalisable to all patients with VTE because those with additional comorbid conditions are often excluded from clinical trials. Carrier *et al.*[124] reported a rate of major bleeding for any VTE of 1.6% (95% CI 1.3% to 2.0%) at 3 months and a rate of fatal bleeding of 0.2% (95% CI 0.1% to 0.3%). The case fatality rate for bleeding following any VTE was 11.3%. RIETE reports a rate of major bleeding of 2.24% (95% CI 2.05% to 2.42%) at 3 months and a rate of fatal major bleeding of 0.55% (95% CI 0.46% to 0.65%) giving a case fatality rate equivalent to 24.7%.[105] This higher case fatality rate may be because of a higher rate of comorbidities in an unselected cohort. In the PREFER-VTE cohort, the rate of major bleeds was 1.5% at 12 months but the rate of fatal bleeds was not reported.[123] In addition, the timing of the bleeds was not reported so it is unclear what the rate of bleeding would have been during the treatment period. The data from PREFER-VTE were considered to be more applicable to current UK practice than the data from RIETE as PREFER-VTE included only European sites, included UK patients and recruited patients after the introduction of DOACs. However, it was noted that only 56.7% of patients in the PREFER-VTE cohort had a low risk of bleeding at baseline [a HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly, Drugs/alcohol concomitantly) score of 0 or 1].[123] As thromboprophylaxis for lower-limb

injury is likely to be limited to those with a low risk of bleeding, the research team looked for alternative data sources. A study by Kooiman *et al.*[104] estimated the incidence of major bleeding at 6 months for patients having treatment for VTE stratified by HAS-BLED score. The combined incidence for patients with a HAS-BLED score of 0 or 1 was 0.9% (3/335). Kooiman *et al.*[104] did not report risks separately for PE and DVT but Cohen *et al.*[123] reported that, in PREFER-VTE, the rates of major bleeds were not significantly different after PE and DVT, so the same rate of 0.9% has been applied to both DVT and PE. This seems reasonable given that the same treatment is assumed in both groups.

Owing to the greater detail reported by RIETE, the breakdown of major bleeding events into fatal events, non-fatal ICH and other non-fatal major bleeds was based on the event rates from RIETE.[105] The analysis of RIETE also found that symptomatic PE was not a significant predictor of whether a fatal bleed occurred and the site of DVT was not a significant predictor unless the DVT was distal when the OR was 0.39 (95% CI 0.16 to 0.95). This lower rate may be as a result of less aggressive anticoagulation therapy or another confounding factor not accounted for in the analysis. It was decided to apply the same rates of fatal bleeding in all patients treated for VTE regardless of the VTE event type.

Clinically relevant non-major bleeding during prophylaxis

Clinically relevant non-major bleeding was not included in the base-case analysis as it has a low impact on quality of life and would be likely to incur a relatively small cost compared with major bleeding. However, to test whether or not the model was sensitive to this structural assumption, the cost of one ED attendance was applied to those experiencing CRNMB. To estimate the rate of CRNMB, the ratio of CRNMB to major bleeding (2.05) from Cohen *et al.*[123] (PREFER-VTE) was applied to the rate of major bleeding for those having prophylaxis to estimate the proportion of patients having CRNMB during prophylaxis. Owing to the low rate of bleeding during prophylaxis, the cost of CRNMB was only £0.19 for each patient receiving prophylaxis. Therefore, the exclusion of this cost from the base-case analysis is not expected to have significantly biased the base-case results.

Risk of chronic thromboembolic pulmonary hypertension

The incidence of CTEPH following PE was based on a systematic review by Ende-Verhaar *et al.*,[111] which reported an overall incidence of CTEPH of 2.3% (95% CI 1.5% to 3.1%). The review[111] also reported the incidence separately for all patients with PE (0.56%, 95% CI 0.13% to 0.98%) and for those who survived the initial 3- to 6-month treatment period for PE (3.2%, 95% CI 2.0% to 4.4%). The follow-up period in the studies included in the review varied from 3 months to 8 years, with most reporting follow-up of ≈2 years. One study, by Pengo *et al.*,[112] which followed patients prospectively for 10 years, found that no cases occurred beyond 2 years, despite a median follow-up of 94 months. It is therefore assumed in the model that all cases are diagnosed between 6 months and 2 years after PE. The rate of CTEPH for those surviving the initial 3- to 6-month treatment period (3.2%) was considered to be the most relevant estimate for the model as no diagnoses of CTEPH are assumed until patients complete their anticoagulant treatment, and deaths during VTE and during anticoagulation are already accounted for in the decision tree part of the model.

Mortality risks in patients with CTEPH were based on data from an international prospective registry reported by Delcroix *et al.*[113] A recent HTA report by Goodacre *et al.*[114] used data from this registry to estimate survival curves for patients having medical or surgical management of CTEPH. The same survival curves were used in this model to estimate the hazard of death over time for patients diagnosed with CTEPH. The proportion having surgical management in the registry was 60% and this was applied in the model. Given that deaths related to PE occurring within 6 months of PE are already accounted for in the model, all-cause mortality has been applied to those with PE in the first year regardless of whether or not CTEPH occurs and the rate of mortality for those with CTEPH is applied from year 2 onwards. To ensure that the risk of death in the CTEPH group was not artificially low compared with the risk of death in the general population, general population mortality risks were applied whenever these were higher than the risk in the CTEPH population, based on the survival curves.

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Risk of post-thrombotic syndromes

A review of epidemiological studies by Galanaud *et al.*[125] describes how the incidence of PTS is dependent on the scoring system used to diagnose PTS, the location and extent of the DVT (e.g. proximal vs. distal), and the duration of time since DVT. Galanaud *et al.*[125] also discuss how pre-existing chronic venous insufficiency and the symptomatic versus asymptomatic nature of the DVT may also affect the risk of PTS.

The risk of PTS in patients with symptomatic DVT in the model was estimated from a prospective registry [Thrombosis and Pulmonary Embolism in Out-Patients – plus (TULIPA-PLUS)], reported by Hach-Wunderle *et al.*[109] This source was chosen as the study design excluded patients with previous DVT or signs of PTS prior to the index DVT. The incidence is reported separately for proximal and distal DVT and is stratified into mild, moderate and severe PTS using a validated scoring system (Villalta scale), which is the scale preferred by the International Society on Thrombosis and Haemostasis.[126] The prevalence of symptomatic PTS at 3 years was 24.4% for all DVTs, 32.4% for proximal DVT and 15.6% for distal DVT, with 70% being mild, 24% being moderate and 6% being severe (average across both proximal and distal).[109]

One applicability issue related to this study was that patients received anticoagulation for a whole year, which is longer than the period of anticoagulation assumed in the model. Therefore, the rates of PTS may be underestimated if longer anticoagulation is protective of PTS. However, as it was not known if longer anticoagulation was protective, and the risk of PTS in this study may reasonably be lower than other estimates as a result of careful exclusion of PTS symptoms at the time of the index DVT, it was decided that it was reasonable to apply the incidence from Hach-Wunderle *et al.*[109] in the model given that the incidence was in the range generally reported (20–50%).[125]

There are only limited data on the incidence of PTS in patients with asymptomatic DVT because these patients are less likely to be followed up for a PTS diagnosis as their DVT is less likely to be diagnosed outside a research setting. However, a study by Persson *et al.*[127] examining PTS incidence in 83 patients operated on for Achilles tendon rupture, which prospectively identified DVT using colour duplex scanning 3 and 6 weeks after surgery and assessed PTS (assessors were blinded to DVT diagnosis) 5 years post operatively, reported a low rate of a PTS diagnosis (Villalta score of ≥ 5) of 8% (3/38) in the DVT group and 4% (2/45) in the no-DVT group. All of the diagnosed cases had a Villalta score of < 15 and were therefore of mild to moderate severity. However, it should be noted that most of those patients with asymptomatic DVT diagnosed post operatively received warfarin for 3 months and were advised to wear compression stockings for 1 year. As a result, the rate of PTS in asymptomatic, undiagnosed and, therefore, untreated DVT is unknown but is likely to be at least 8%. Furthermore, only three of the 38 DVTs were proximal, making it difficult to estimate the rate of PTS in patients with asymptomatic proximal DVTs from this study.[127]

A study by Schindler and Dalziel[128] in a related population (those having total hip or knee arthroplasty) found that four of 34 (11%) with asymptomatic distal DVT and three of eight (32.5%) with asymptomatic proximal DVT developed PTS 15 to 24 months after surgery. In the knee arthroplasty subgroup (which is considered to be more clinically relevant to those having lower-limb immobilisation), 28 patients had distal DVT with one of these having clot propagation leading to proximal DVT. Four of these 28 patients (14.3%) with DVT developed PTS, with one of these being the patient who had clot propagation. However, PTS was also diagnosed in 5.3% of those patients without DVT. In this study,[128] all those with proximal DVT were treated with anticoagulants (i.e. 3 months of warfarin), whereas those with distal DVT received 3 months of aspirin. Therefore, the rate of PTS in untreated asymptomatic DVT following hip and knee surgery remains unknown.

van Dongen *et al.*[110] studied the relationship between inadequate anticoagulation with vitamin K antagonist (VKA) and the risk of PTS with symptomatic proximal DVT and found that patients who spend $> 50\%$ of their time beneath the international normalised ratio (INR) level of 2.0 are at a higher risk for PTS (OR 2.71,

95% CI 1.44 to 5.10). Based on this, one would expect a higher risk of PTS in patients with asymptomatic proximal DVT that is untreated than in those with treated asymptomatic proximal DVT. Although van Dongen *et al.*[110] did not include untreated patients in their study, they reported a fourfold increase (OR 3.69, 95% CI 1.29 to 10.53) for those patients spending > 90% of their time outside the target INR range, which suggests that the risks may be higher still in those patients not offered any anticoagulation.

The rate of PTS in patients with asymptomatic proximal DVTs reported by Schindler *et al.*[128] (32.5%) was similar to that reported in symptomatic proximal DVT by Hach-Wunderle *et al.*[109] (32.4%). This suggests that the risk of PTS is similar regardless of whether or not the proximal DVT is symptomatic, provided that it is treated with anticoagulants. However, given that patients who are asymptomatic in the model will not receive any anticoagulant treatment as they are not being proactively screened for asymptomatic DVT, a higher rate for asymptomatic proximal DVT was applied using the OR reported by van Dongen *et al.*[110] for good versus poor anticoagulation (OR 2.71 for those patients spending > 50% of their time outside the target INR). This gave a rate of PTS of 56.5% for untreated asymptomatic proximal DVT. It is recognised that the rate of PTS may be higher still for those receiving no anticoagulation at all, as discussed in the previous paragraph, but this may be partially offset by asymptomatic DVTs being less extensive and, therefore, less likely to cause PTS.

The rate of PTS in asymptomatic untreated distal DVT was set as equal to that for treated symptomatic distal DVT, namely 15.6% as reported by Hach-Wunderle *et al.*[109] Inflating this risk further by applying the OR from van Dongen *et al.*[110] did not seem appropriate, given that this would give a risk of 33.4% and the clinical experts believed that the rate for untreated distal DVT should be lower than for treated proximal DVT. Furthermore, it is noted that the rate from Hach-Wunderle *et al.*[109] of 15.6% is nearly twice the rate reported for treated asymptomatic distal DVT by Persson *et al.*,[127] which would support not inflating the rate further.

The timing of PTS within the model has been based on data reported by van Dongen *et al.*,[110] who reported the incidence of PTS at 0.5, 1, 2 and 4 years (*Figure 11*). The shape of the curve for incidence over time was compared with that reported by Prandoni *et al.*[129] and was found to be similar, although the magnitude better matched the upper 95% CI of the estimates of incidence reported by Prandoni *et al.*[129] The hazards based on the incidence reported by van Dongen *et al.*[110] were scaled to match the rate reported at 3 years by Hach-Wunderle *et al.*[109] for symptomatic proximal and distal DVT. As van Dongen *et al.*[110] reported no further incidence beyond 4 years, no new incidence of PTS from 4 years was assumed. The prevalence of PTS over time incorporated within the model is shown in *Figure 12*.

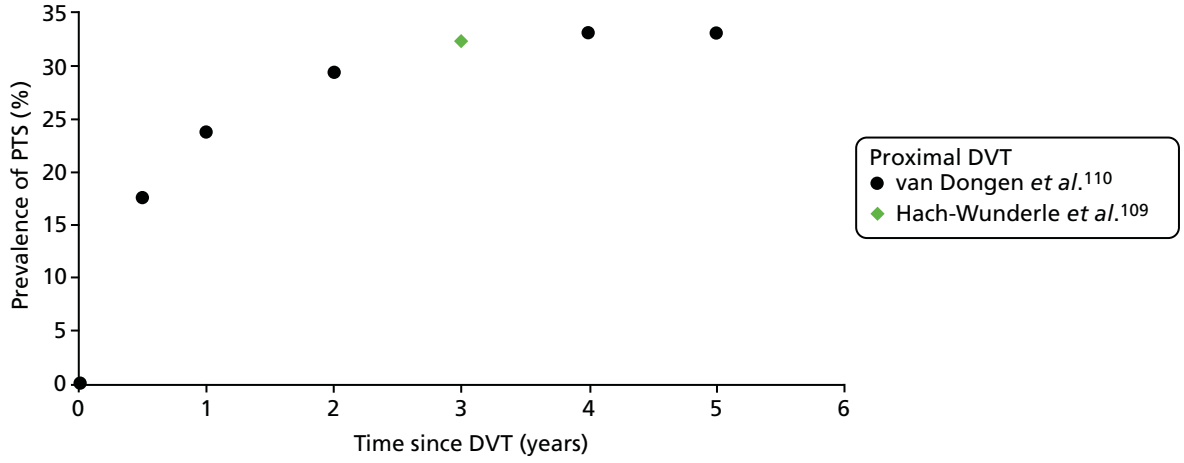

FIGURE 11 Prevalence of PTS in years following proximal DVT from studies.

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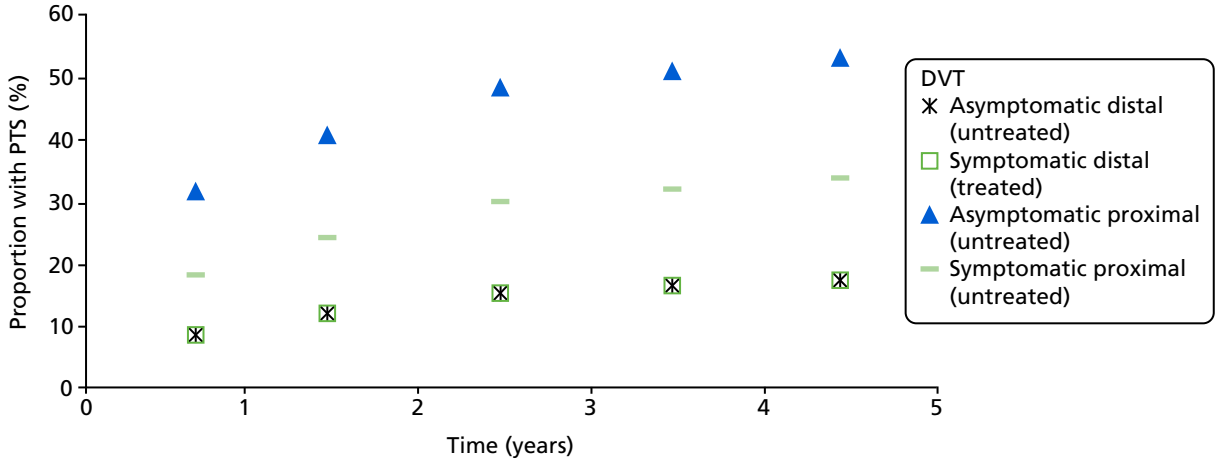

FIGURE 12 Prevalence of PTS in the model for treated symptomatic and untreated asymptomatic DVTs.

Costs of prophylaxis

For thromboprophylaxis during lower-limb immobilisation, it was assumed that patients receive 6 weeks of treatment using LMWH at the dose recommended for long-term treatment after hip or knee replacement. In the base-case analysis, it was assumed that the lowest-cost formulation of LMWH would be used (dalteparin), but the impact of treatment with either fondaparinux or dabigatran was explored in sensitivity analyses as these represented the highest- and lowest-cost alternatives to LMWH. The dosages and drug costs are summarised in *Table 18*.

Menakaya *et al.*[115] estimated the costs of outpatient VTE prophylaxis for patients having lower-limb injuries based on 388 patients receiving prophylaxis who were recruited from 7048 patients attending a fracture clinic in England. The total cost for an average of 46 days of anticoagulant treatment was £107.54 for the self-administration of LMWH, with £46 of this being the drug cost (the authors assumed £1 per day). Therefore, the total cost of administration was £61.54. This covered clinical time for counselling and taking blood samples (including a 5-day platelet count), pharmacy dispensing and initial administration. For patients requiring district nurse administration (£23 per home visit), the average cost of administration across the treatment course was £1096.54 but this was required in only 4% of cases, giving an average cost of £102.94 across the cohort. Adjusting the number of doses from 46 to 42, which affects only the district nurse administration costs, and updating this from 2011/12 to 2016/17 prices (Curtis and Burns[100]), gives a total administration cost of £105.13. The total cost for the 6-week course of dalteparin, including administration costs, was £223.70.

For the sensitivity analysis on fondaparinux, the same administration costs as those required for LMWH were assumed. Patients initiating treatment with a DOAC were assumed to require one nurse-led telephone consultation at 10 days. The range tested in sensitivity analysis for the whole course of treatment was £84.23 for dabigatran to £355.66 for fondaparinux.

When assessing the cost-effectiveness of using RAMs to determine thromboprophylaxis, it is necessary to include the cost of the time spent by the clinician to determine the individual's risk score. It was assumed that this would require 5 minutes of time by a hospital consultant, which was estimated to be £8.83 based on an hourly cost of £106.[100] This was applied to all patients in the RAM-based thromboprophylaxis strategies but to none of the patients in the treat-all and treat-none strategies.

TABLE 18 Drug costs for pharmacological prophylaxis of VTE in patients having lower-limb immobilisation

Drug	Dosing and delivery[21]	Product and cost[21]	Cost per day (£)	Cost per course (assuming 42 days treatment) (£)	Administration cost per course (£)	Total cost per course (£)
Dalteparin	5000 units every 24 hours by subcutaneous injection for 4–6 weeks	Dalteparin sodium 5000 units/0.2 ml solution for injection: £28.23 for 10 pre-filled syringes	2.82	118.57	105.13	223.70
Exonaparin	40 mg every 24 hours by subcutaneous injection for 4–6 weeks	Enoxaparin sodium 40 mg/0.4 ml: £30.27 for 10 pre-filled syringes	3.03	127.13	105.13	232.26
Tinzaparin	4500 units every 24 hours by subcutaneous injection for 4–6 weeks	Tinzaparin sodium 4500 units/0.45 ml solution for injection: £35.63 for 10 pre-filled syringes	3.56	149.65	105.13	254.78
Fondaparinux	2.5 mg every 24 hours by subcutaneous injection for 4–6 weeks	• Arixtra 2.5 mg/0.5 ml solution for injection: £62.79 for 10 pre-filled syringes • Fondaparinux 2.5 mg/0.5 ml solution for injection: £59.65 for 10 pre-filled syringes [Dr Reddy's Laboratories (UK) Ltd, Beverley, UK]	5.97 (assuming that the lowest-cost formulation was prescribed)	250.53	105.13	355.66
Apixaban	2.5 mg orally twice daily	Eliquis 2.5 mg tablets	1.90	79.80	12.83	92.63
Dabigatran	220 mg orally daily	Pradaxa 110 mg capsules: £51.00 for 60 capsules (same cost per capsule for 10)	1.70	71.40	12.83	84.23
Rivaroxaban	10 mg orally daily	Xarelto 10 mg tablets: £54.00 for 30 tablets (same cost per tablet for 10)	1.80	75.60	12.83	88.43

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Cost of treatment

Patients who have lower-limb immobilisation may later present with symptomatic DVT or PE, requiring diagnosis and treatment. The costs of VTE have been estimated for three broad categories of costs: health-care contacts, diagnostic costs and drug treatment costs. It was assumed that all patients presenting with symptomatic VTE would require an ED assessment, but that a proportion would present first to a general practitioner (GP) before attending an ED, and that only a proportion of those attending an ED would require admission. It was assumed that those patients requiring admission would also be likely to require ambulance transfer to the ED. The proportion of patients attending GPs prior to ED attendance and the proportion requiring admission (*Table 19*) were based on clinical expert opinion. Discussions with clinical experts were informed by the assumptions used in the model described in the 2017 draft update to the NICE guideline on managing VTE[130] and the assumptions used in relevant NICE single technology appraisals (STAs).[131–139]

Diagnostic tests that occur during the ED episode of care, such as electrocardiography monitoring and chest radiography, are not costed separately. However, scans occurring later as outpatient activity were costed separately as these diagnostic tests are 'unbundled' within the NHS reference cost data.[116] Assumptions regarding the use of diagnostic tests to assess patients with suspected DVT and PE were based on clinical expert opinion. The main costs not covered within the ED episode of care are assumed to be leg vein ultrasonography for patients with a suspected DVT and computerised tomography pulmonary angiography (CTPA) or ventilation/perfusion scans for patients with a suspected PE. A minority of patients (20%) with suspected PE are also assumed to require echocardiography. The diagnostic tests are summarised in *Table 19*. It was assumed that all patients presenting with PE or symptomatic DVT (proximal or distal) would be treated with anticoagulants.

Treatment for VTE was assumed to consist of 3 months of either a VKA (warfarin) or a DOAC. Patients being treated with a VKA would also require initial anticoagulation with LMWH until adequate oral anticoagulation is established. The proportion receiving DOACs versus VKA was informed by data from the PREFER-VTE study,[123] which found that 40% of patients in countries where DOACs had been launched were receiving a DOAC as their initial treatment following DVT. The split between drugs in the LMWH class was informed by assumptions used in a previous appraisal.[140] The costs of administering treatment with LMWH are based on the costs estimated by Menakaya *et al.*[115] for initiating prophylaxis using LMWH but with a reduction in district nurse administration based on the shorter duration of treatment (7 vs. 42 days). Patients receiving VKA are assumed to require nine visits to an anticoagulation service in 3 months to monitor their INR. Patients initiating treatment with a DOAC are assumed to require one nurse-led telephone consultation at 10 days. All patients are assumed to require a consultant-led face-to-face visit at 3 months to assess the need for ongoing treatment. The overall cost, including monitoring, when averaged across the treatment strategies was £290.24 (*Table 20*).

The total cost for non-fatal PE was estimated to be £1788, which includes health-care contacts, diagnostic costs and 3 months of drug treatment for VTE. Fatal PE was assumed to incur the same costs for health-care contacts and diagnostics, but without the cost of VTE treatment, giving a cost of £1498. Symptomatic proximal and distal DVTs had a total cost of £688 and £560, respectively, with the higher cost of proximal DVTs driven by a greater likelihood of admission.

Cost of bleeding complications

A paper by Luengo-Fernandez *et al.*[117] on the acute and long-term costs of care after stroke in patients with atrial fibrillation (AF) was identified as a source of costs in those having ICH from the NICE appraisal of edoxaban tosylate (Lixiana®; Daiichi Sankyo UK Ltd, Gerrards Cross, UK) for the treatment and secondary prevention of DVT and/or PE.[140] The paper[117] provides estimates of acute (up to 90-day) and long-term costs (average annual costs up to 5 years post stroke) using data from the Oxford Vascular Study (OXVASC), which was a prospective study of 91,000 UK patients registered with general practices in Oxfordshire. The paper by Luengo-Fernandez *et al.*[117] reports costs for the subset of patients who experienced a stroke during the study and who had a history of AF prior to that index stroke (n = 153). The mean age of patients in this subset was 80 years, with 26% of patients having previous stroke and 20% of patients having pre-morbid warfarin use.

TABLE 19 Resource use and costs for patients presenting with PE and symptomatic DVT

Resource item	Proportion using resource (%)			Unit cost per patient using this resource (£)	Description
	Non-fatal PE	Symptomatic proximal DVT	Symptomatic distal DVT		
Health-care contacts/admission					
GP visit	20	50	50	37	Curtis and Burns,[100] GP cost per surgery consultation with qualification costs, including direct care staff costs
Ambulance transfer to ED	60	10	0	236	NHS Schedule of Reference Costs 2015–16.[116] 'See and treat and convey', code ASS02
ED visit leading to admission	60	10	0	228	NHS Schedule of Reference Costs 2015–16.[116] VB05Z type 01 admitted (category 2 investigation with category 3 treatment)
ED visit without admission	40	90	100	196	NHS Schedule of Reference Costs 2015–16.[116] VB05Z type 01 non-admitted (category 2 investigation with category 3 treatment)
Short stay admission for PE	60	0	0	1498	NHS Schedule of Reference Costs 2015–16.[116] Weighted average cost of non-elective inpatient (short and long stay with excess bed-days) for 'pulmonary embolus with interventions', codes DZ09 J to DZ09 N and DZ09P and DZ09Q
Short stay admission for DVT	0	10	0	1012	NHS Schedule of Reference Costs 2015–16.[116] Weighted average cost of non-elective inpatient (short and long stay with excess bed-days) for 'deep-vein thrombosis', CC score 0 to ≥ 12, codes YQ51 A to YQ51E
Critical care unit stay	10	0	0	1012	NHS Schedule of Reference Costs 2015–16.[116] Weighted average cost of adult critical care, 0 to 6 or more organs supported, codes XC01Z to XC01Z
Subtotal for health-care contacts (£)	1365	342	214		

continued

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TABLE 19 Resource use and costs for patients presenting with PE and symptomatic DVT (*continued*)

Resource item	Proportion using resource (%)			Unit cost per patient using this resource (£)	Description
	Non-fatal PE	Symptomatic proximal DVT	Symptomatic distal DVT		
Diagnostic costs					
Risk assessment tool (Wells score)	Included in an ED episode of care so not costed separately				
D-dimer	Included in an ED episode of care so not costed separately				
ECG	Included in an ED episode of care so not costed separately				
Chest radiography					
Proximal leg vein ultrasonography	0	100	100	55	RD40Z, outpatient ultrasound scan (duration of < 20 minutes), without contrast, cost £55 [RD47Z may be more relevant for the diagnosis of distal DVTs, but cost is similar (£58)][116]
CTPA	90	0	0	102	RD21A, outpatient computerised tomography scan of one area, with post contrast only, patients aged ≥ 19 years[116]
V/Q SPECT	5	0	0	261	RN08A, outpatient SPECT, patients aged ≥ 19 years[116]
V/Q planar	5	0	0	274	RN18A, outpatient lung ventilation or perfusion scan, patients aged ≥ 19 years[116]
Echocardiography	20	0	0	72	RD51A, outpatient simple echocardiography[116]
Subtotal for unbundled diagnostics (£)	133	55	55		
Subtotal for drug treatment (£)	290	290	290		See *Table 20*
Total (£)	1788[a]	688	560		

CC, complication or comorbidity; ECG, electrocardiography; SPECT, single-photon emission computed tomography; V/Q, ventilation/perfusion.
a Fatal PEs are assumed to incur diagnostic and inpatient costs but not VTE treatment costs (i.e. total cost of £1498).

TABLE 20 Drug costs for treating DVT and PE

Drug	Dosing and delivery	Product and cost	Cost (£)		Percentage using treatment
			Drug, per course	Monitoring/ administration	
Apixaban	Initially, 10 mg twice daily for 7 days, orally, followed by 5 mg twice daily, orally, for the remainder of the 3-month (91-day) treatment period	Apixaban, 5 mg: £53.20 for 56 tablets (cost per tablet is the same for the 28-tablet pack size)	186.20	50.00[a]	20% (half of the 40% using DOACs)
Rivaroxaban	Initially, 15 mg twice daily for 21 days, to be taken orally with food. This is followed by 20 mg once daily, to be taken orally with food for the remainder of the 3-month (91-day) treatment period	Rivaroxaban, 20 mg: £50.40 for 28 tablets (cost per tablet is the same for 15 mg tablets and larger and smaller pack sizes)	201.60	50.00[a]	20% (half of the 40% using DOACs)
Enoxaparin	1.5 mg/kg every 24 hours by subcutaneous injection until adequate oral anticoagulation established (7 days) (i.e. 120 mg of enoxaparin if assuming weight of 80 kg)	• Clexane Forte, 120 mg/0.8 ml solution: £87.93 for 10 pre-filled syringes, prescription-only medicine • Assumed for other drugs	61.55	70.26[b]	30% (45% of heparin use)
Dalteparin	15,000 units (assuming body weight of 80 kg) once daily until adequate oral anticoagulation established (7 days)	Dalteparin sodium, 15,000 units/ 0.6 ml solution: £42.34 for five pre-filled syringes	59.28	70.26[b]	18% (35% of heparin use)
Tinzaparin	175 units/kg once daily until adequate oral anticoagulation established (7 days) (i.e. 14,000 units if assuming body weight of 80 kg)	Innohep, 14,000 units/0.7 ml solution: £83.30 for 10 pre-filled syringes	58.31	70.26[b]	6% (20% of heparin use)
Warfarin	5 mg twice daily orally for 3 months (91 days)	Warfarin sodium, 5 mg (various suppliers): £0.70 for 28 tablets	4.55	186.27[c]	60%
Average across those using DOACs and those using LMWH/VKA			116.35	173.89	Total: £290.24

HRG, Healthcare Resource Group.

a Based on one nurse-led telephone follow-up (WF01C) at 10 days and one consultant-led follow-up (WF01A) at 3 months to assess the need for ongoing treatment.[116]

b Based on the costs estimated by Menakaya *et al.*,[115] with the number of district nurse administrations reduced to reflect the shorter duration of treatment (7 days vs. 6 weeks).

c Based on HRG costs for nine face-to-face visits at a non-consultant-led anticoagulation service over 3 months (WF01B for first attendance and WF01A for follow-up) plus a consultant-led follow-up at 3 months to assess the need for ongoing treatment.[116]

Note

Costing assumes that packs of syringes and packets of tablets can be split between patients by the dispensing pharmacy.

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The costs were reported separately on the basis of disability level and whether the type of stroke was ischaemic, haemorrhagic or not known. Only 17 of the 191 strokes experienced by the 153 patients were haemorrhagic. The mean acute cost of fatal haemorrhagic strokes was £1592 (SD £1886; *n* = 8). This mean cost was substantially lower than the average for all haemorrhagic strokes, which was £10,683 (SD £12,885; *n* = 17). Given that these estimates were based on a small number of patients, the estimates for all stroke types were also considered. The cost of fatal strokes across all types was also lower, at £2680 (SD £2661; *n* = 40), than the average for all strokes (mean £10,413, SD £15,105; *n* = 191), suggesting that fatal strokes do incur a lower acute cost than non-fatal strokes. The cost of fatal haemorrhagic strokes was used in the base-case analysis for fatal intracranial bleeds. The cost was updated from 2008/9 prices to 2016/17 prices (using Curtis and Burns[100]), giving an acute cost of £1802 over 3 months.

The paper by Luengo-Fernandez *et al.*[117] also provided relevant data on the cost of non-fatal ICHs. The cost of a non-fatal haemorrhagic stroke was estimated to range from £3401 to £24,234, depending on the level of disability following the stroke. A weighted average cost for non-fatal haemorrhagic strokes of £18,764 was calculated across the non-disabling, moderately disabling and totally disabling haemorrhagic strokes. However, it was noted that these estimates were based on only nine non-fatal haemorrhagic strokes. The equivalent average across all non-fatal strokes was £12,461. The higher cost for haemorrhagic non-fatal strokes appeared reasonable given that haemorrhagic strokes appeared to result in higher than average costs across all categories except fatal strokes. This is supported by data presented by Fernando *et al.*,[141] which show that patients with haemorrhagic stroke who are admitted to an intensive care unit (ICU) incur higher costs than matched patients (matched for age, sex and comorbidity) admitted to an ICU for other (non-ICH) reasons. Furthermore, ICHs associated with oral anticoagulant use were also found to be significantly more costly than those not associated with oral anticoagulant use.[141] The weighted average cost for non-fatal haemorrhagic stroke from Luengo-Fernandez *et al.*[117] was used in the base-case analysis for the acute cost of non-fatal ICH. This cost was updated from 2008/9 prices to 2016/17 prices (using Curtis and Burns[100]), giving non-fatal ICH a cost of £21,245 over 3 months.

It was noted that this cost for non-fatal ICH is significantly higher than the weighted average cost of stroke based on NHS reference costs for non-elective long- and short-stay inpatients (including excess bed-days), which was £3290 [average of reference costs[116] for Healthcare Resource Group (HRG) codes AA35A to AA35F]. However, the average NHS reference cost is similar to the cost reported by Luengo-Fernandez *et al.*[117] for non-disabling stroke costs. This may reflect the fact that rehabilitation costs are reported separately in NHS reference costs and these costs are between £332 and £402 per day for admitted rehabilitation. These rehabilitation costs would have been included in the hospitalisation costs reported by Luengo-Fernandez *et al.*[117] and would be much higher for moderately and totally disabling strokes, which may explain the higher costs in these groups than the NHS reference cost for admitted care in stroke patients, which excludes rehabilitation.

The model also required post-acute costs (post 90 days) for patients having non-fatal ICH. Luengo-Fernandez *et al.*[117] estimated the post-acute costs per annum relative to the year before stroke (baseline). The total post-acute costs were found to be non-significantly higher versus baseline costs at £804 (95% CI –£832 to £2440). However, the GP and emergency care components were significantly higher at £98 (95% CI £27 to £169) and £99 (95% CI £56 to £141), respectively. In addition, the paper separately reported long-term residential care costs for patients not previously admitted to residential care. They reported that 18% of strokes resulted in a new admission to long-term care (i.e. warden housing, residential care or nursing home care), with an average annual cost of £6880 across all patients surviving the acute period (90 days). Post-acute and long-term costs were not reported separately by stroke type (haemorrhagic vs. other) by Luengo-Fernandez *et al.*[117] The total costs of GP, emergency care and long-term care were averaged across all stroke types and uplifted to current prices (using inflation indices from Curtis and Burns[100]) to give a total cost per year for non-fatal ICH patients of £8013 in the post-acute (beyond 90 days) period. This was applied in the Markov phase of the model to patients in the non-fatal ICH health state. It was also applied pro rata to patients having non-fatal ICH more than 90 days before the end of the decision tree model.

The cost of non-fatal extracranial bleeds was estimated using average inpatient costs for GI bleeds, based on the approach taken in the NICE Technology Appraisal (TA) 354.[140] A weighted average was taken across bleeds requiring single, multiple or no intervention and across short- and long-stay non-elective inpatients (including excess bed-days). This gave an average cost of £1198 based on 2015/16 reference costs (HRG codes FZ38G to FZ38P).[116]

Cost of post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension

Several reviews of studies relating to PTS were examined to identify any cost papers cited.[125,142–145] None of the cost papers identified were specific to the UK NHS. Three examined costs from a US perspective (Caprini *et al.*,[146] MacDougall *et al.*[147] and Olin *et al.*[148]), one examined costs from a Brazilian perspective (Ramacciotti *et al.*[149]), one examined costs from a Swedish perspective (Bergqvist *et al.*[150]) and one examined costs from a Canadian perspective (Guanella *et al.*[151]). Although the paper by Bergqvist *et al.*[150] was from a European country, the data related to patients diagnosed between 1970 and 1985.

Several of the NICE STAs identified in *Appendix 11* cited cost assumptions from Goodacre *et al.*[152] One cited the US study by Caprini *et al.*[146] and another cited costs from a 2001 abstract by Cohen *et al.*[153]

It was assumed in the model that management of PTS would involve one first and one follow-up vascular surgery outpatient appointment in the first year after diagnosis and two follow-up GP appointments every year thereafter. This was based on clinical expert advice regarding current management of PTS in the UK and is consistent with the assumptions made by Goodacre *et al.*,[152] which have been applied in several previous NICE STAs.[131,132,140,154]

A review by Grosse *et al.*[143] on the costs attributable to VTE in the USA identified one paper[155] on the cost burden of CTEPH. Kirson *et al.*[155] compared costs for patients with CTEPH with those for controls (matched for age, sex, employee status and geographical region) in a cohort of privately insured US patients. They found that costs per month were US$2368 ($p < 0.0001$) higher in patients with CTEPH than in matched controls, but they also found higher rates of comorbidities, suggesting that some of the differences may not be directly attributable to CTEPH. Grosse *et al.*[143] commented that CTEPH patients are far more likely to have chronic heart failure or chronic pulmonary disease, and no risk-adjusted treatment cost estimates were identified in their review.

The cost of CTEPH was based on the approach taken in technology appraisal (TA) number 354 (i.e. TA354)[140] in which pulmonary endarterectomy costs were applied based on reference costs for complex thoracic procedures. Updating this estimate by using current reference costs[116] gave a cost of £7898. The Evidence Review Group's preferred assumption for TA354[140] was to use the cost of drugs from CG92,[24] which estimated a cost of £1219 per 4 weeks, giving a cost of £17,942 per annum when uplifted to 2016/17 prices (using inflation indices from Curtis and Burns[100]). Data from Delcroix *et al.*[113] were used to estimate the proportion having surgical management and the proportion receiving medical management. The fact that some surgical patients receive bridging therapy, as reported by Delcroix *et al.*,[113] was taken into account by allowing them 4.6 months of medical therapy based on the average time to surgery for these patients. This increased the costs in the first year for patients having surgical management to £9890. It was assumed that no further costs are incurred in year 2 and beyond for those having surgical management.

Summary of methods used to identify studies reporting utility values relevant to the model

The searches for the systematic review of published cost-effectiveness studies included a filter to identify health-related quality of life (HRQoL) data. While sifting these studies, one study[156] reporting HRQoL data in patients with lower-limb immobilisation was identified; this study by Arverud *et al.*,[156] reported EuroQol-5 Dimensions (EQ-5D)[157] scores in patients who had an Achilles tendon rupture. The study reported mean EQ-5D scores at 1 year for patients who did and patients who did not experience DVT following surgical repair and immobilisation. The average EQ-5D score was lower in patients with DVT but the difference was

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not statistically significant ($p = 0.6$). A second study[158] identified in the search reported the validation of a disease-specific HRQoL measure, Deep Venous Thrombosis Quality of Life (DVTQoL), in patients with DVT but this study reported only the correlation between the EQ-5D and the domains of the DVTQoL; utility values based on EQ-5D scores could not be extracted. No other studies reporting preference-based measures of utility in patients with lower-limb immobilisation were identified from the searches conducted for the economic review.

One published study by Wolowacz *et al.*[99] was identified from the literature review that examined the cost-effectiveness of thromboprophylaxis for a similar, but not directly relevant, population (elective knee replacement) as described in *Results of cost-effectiveness review*. This was supplemented by searches of the NICE website to identify models developed to inform NICE TAs and CGs, as these models would be expected to have a relevant setting and methodological approach and would not always be identified through database searches. The cost-effectiveness analyses identified are summarised in *Appendix 11*.

In addition, ad hoc searches for systematic reviews of utilities for relevant model states (e.g. PTS) were conducted using the Google Scholar search engine (Google Inc., Mountain View, CA, USA). This identified a published systematic review of HRQoL studies for VTE and related complications by Lubberts *et al.*[159] This review focused on studies with a minimum follow-up of 1 year in order to capture the long-term impact of complications such as PTS and CTEPH. Only two of the studies included by Lubberts *et al.*[159] reported a generic preference-based utility measure (EQ-5D). One of the two studies reporting EQ-5D was conducted in patients with subclavian DVT and is therefore less applicable to this population. The other study, by Haig *et al.*,[160] reported EQ-5D scores for patients with and without PTS following DVT.

In addition, the systematic review by Lubberts *et al.*[159] reports outcomes for 15 studies that used either the Short Form questionnaire-36 items (SF-36)[161] or the Short Form questionnaire-12 items (SF-12). Data from these studies were meta-analysed to assess the difference in HRQoL between patients and members of the general population matched by country, age and sex. Lubberts *et al.*[159] report the meta-analysed decrement in SF-36/SF-12 mental component summary (MCS) and physical component summary (PCS) scores compared with general population norms (matched by country, age and sex) using the standardised mean difference (SMD) as a common currency across studies. These meta-analyses by Lubberts *et al.*[159] do not provide a preference-based utility measure that can be used directly in the model, but their outcomes are summarised below as they provide evidence as to whether or not each VTE-related outcome has an important impact on long-term HRQoL based on more than a single study. They are therefore useful in interpreting the utility estimates from individual studies identified from existing cost-effectiveness models.

Although Lubberts *et al.*[159] included only studies reporting outcomes more than 1 year after VTE, they also listed nine studies[158,162–169] that were excluded for reporting outcomes at shorter follow-up points. Of these, one study by Hogg *et al.*[163] reported useful data (see *Appendix 12*); the remaining eight studies did not report utility values for relevant health states.[158,162,164–169]

One additional HRQoL study[170] was identified from ad hoc searches; Roberts *et al.*[170] examined the predictors of HRQoL for patients following DVT using the SF-36. This is also discussed below as it provides useful additional information on PTS as a determinant of HRQoL.

The sources of utility data identified from both the published models listed in *Appendix 11* and the systematic review by Lubberts *et al.*[159] are summarised in *Appendix 12*.

Utility values in pulmonary embolism

Lubberts *et al.*[159] report that PE is associated with a significant reduction in SF-36 PCS score (SMD –0.30, 95% CI –0.45 to –0.14) but not SF-36 MCS score (SMD 0.14, 95% CI –0.01 to 0.30), relative to general population norms at time periods of > 1 year based on an analysis of two studies.[171,172] This suggests that PE has an important long-term impact on patients. Three studies[173–175] reported EQ-5D outcomes for patients with PE, although two of these studies[173,174] were published only in abstract form and the other

study[175] used Danish rather than UK population norms. One study used an alternative generic preference-based measure, the Short Form questionnaire-6 Dimensions (SF-6D).[163] In addition, two studies[176,177] reported utility values for PE measured directly using either standard gamble or time trade-off (TTO). Data from the study abstract by Cohen *et al.*[173] were reported in additional detail in the company submission for TA354[140,178] (*Figure 13*).

The data from Cohen *et al.*[153] were selected for use in the model because these were measured using the EQ-5D, were sourced from a large registry database (PREFER-VTE) including patients recruited in the UK and the paper included estimates of the change in utility over time (see *Figure 13*). The data reported by Cohen *et al.*[173] demonstrated that utility values varied depending on the time since PE, with utility values appearing to stabilise at between 3 and 6 months. The average utility in patients with PE during the 6 months following PE was calculated using the data from Cohen *et al.*[173] This was compared with the utility value at 6 months in patients with DVT (who do not have a long-term utility decrement according to the review Lubberts *et al.*[159]) to calculate the utility multiplier for PE, which was then applied to the age appropriate utility for patients without PE. A linear change in utility between the points measured was assumed, giving an average utility of 0.775 over the 6 months after PE, which is a 9% decrement relative to utility at 6 months post DVT. Given that there was some evidence of a reduction in HRQoL for patients with PE found by Lubberts *et al.*[159] at 1 year, it was decided to use the 6-month utility decrement for PE relative to DVT, when no long-term reduction was found, to estimate the long-term utility reduction for patients following PE. This gave a 5% reduction in utility beyond 6 months for a patient surviving PE beyond 6 months. Tavoly *et al.*[175] reported mean EQ-5D values of 0.8 in patients post PE versus 0.86 in age- and sex-matched general population controls, suggesting a 7% reduction in utility despite a median time since diagnosis of 3.8 years. This supports the assumption that there are some ongoing post-PE symptoms beyond 6 months.

Utility values in deep-vein thrombosis

The data sources for utility values in DVT were similar to those identified for PE, except that the study by Tavoly *et al.*[175] was not relevant because it examined only patients with PE. However, a similar study by Utne *et al.*[179] examining DVT outcomes from the same hospital registry was identified instead. One additional study by Arverud *et al.*[156] examining DVT versus no DVT after lower-limb immobilisation due to injury was also identified. This study found that DVT identified by screening (colour duplex sonography) 2 weeks post operatively was a non-statistically significant predictor of worse EQ-5D scores (0.918 vs. 0.906; $p = 0.604$). This may be expected given that the DVTs were detected by screening and, therefore, may have been asymptomatic. Utne *et al.*[179] found that EQ-5D score was statistically significantly lower for patients with DVT compared with age- and sex-matched buddy controls. However, these patients were recruited any time after DVT, and a significant proportion had PTS, so the reduction compared with controls may have been partly due to PTS symptoms, which are likely to be persistent beyond 6 months.

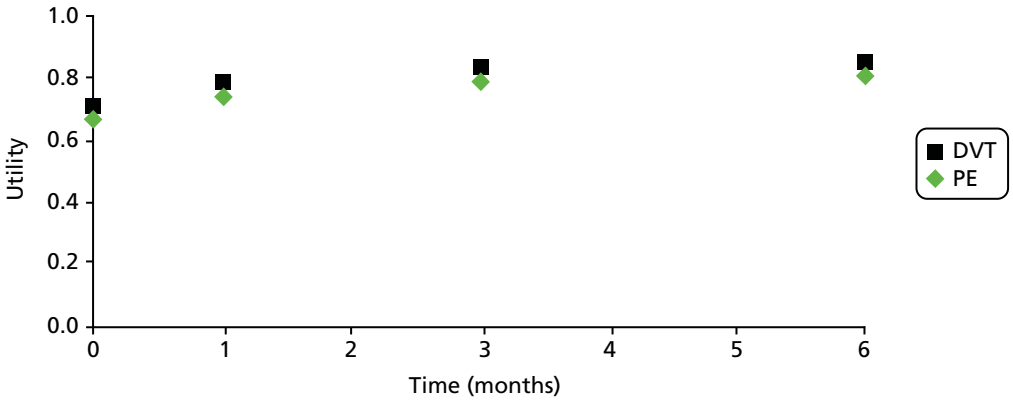

FIGURE 13 Data from Cohen *et al.*,[173] as reported in the company submission for TA354.[140,178]

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In the first 6 months of the model, the data from Cohen *et al.*[173] were used to estimate the average utility, which was compared with the utility at 6 months. This gave a utility decrement of 4%, on average, during the first 6 months after DVT. Beyond 6 months, no utility decrement for patients without PTS was assumed, as the systematic review by Lubberts *et al.*[159] reported that there was no statistically significant difference in SF-36 PCS and MCS scores for DVT at time periods of > 1 year based on an analysis of nine studies.[172,180–187] Utne *et al.*[179] did not find a statistically significant difference in the odds of having impaired HRQoL, measured by EQ-5D, depending on whether the DVT was proximal or distal. In the absence of any other data on the difference in HRQoL impact of proximal versus distal DVT, the same utility loss was assumed during the first 6 months for symptomatic proximal DVT and symptomatic distal DVT.

Utility values in post-thrombotic syndrome

Lubberts *et al.*[159] reported that patients with PTS had significantly lower MCS and PCS scores than matched population norms (SMD for MCS score –0.27, 95% CI –0.43 to –0.11; SMD for PCS score –0.89, 95% CI –1.21 to –0.57), based on an analysis of seven studies.[180–182,184–186,188] Five studies reported utility values for patients with PTS,[160,177,189–191] with two studies[160,189] reporting EQ-5D scores and three studies[177,190,191] using direct measures of utility such as standard gamble or TTO. The data reported by Haig *et al.*[160] and Enden *et al.*[189] were the 2-year and 5-year follow-up points from the catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (CaVenT) study that compared catheter-directed thrombolysis (with 24 months of compression stockings) against standard treatment (6 months of anticoagulant and 24 months of compression stockings) for patients with high proximal DVT. The CaVenT study[189] found no difference in EQ-5D scores between treatment arms at 6 months, 2 years or 5 years, but did find a statistically significant difference in HRQoL between those with PTS ($n = 92$) and those without PTS ($n = 97$) at 24 months and 5 years. At 6 months, the mean EQ-5D scores were lower for those with PTS but the difference was not statistically significant ($p = 0.062$).

The decrement measured at 2 years in the CaVenT study[189] was applied to all patients with PTS in the Markov phase of the model. It was decided not to model a change in HRQoL for patients with PTS over time as some HRQoL decrement is likely to be present from the time of diagnosis of PTS (i.e. 6 months after DVT) and the HRQoL impact of PTS appears to remain apparent at 5 years. Therefore, a 10% decrement was applied based on the 24-month data from Enden *et al.*[189]

Supportive evidence is provided in the study by Roberts *et al.*,[170] which reported that patients without PTS recovered their SF-36 PCS scores from below population norms by 6 months, whereas those with mild or moderate/severe PTS did not experience a similar recovery. This study[170] also reported that the location of DVT (i.e. proximal or distal) was not an independent predictor of HRQoL, with only sex, comorbidities and PTS being significant predictors in the multivariate analysis.

As the CaVenT study[189] reported the average utility decrement across all PTS, without stratifying by PTS severity, this value was applied in the model for all patients with PTS. This may overestimate the utility decrement if patients in the CaVenT study had more severe PTS than would be seen in the modelled population and severity was a predictor of utility decrement. However, in the study by Roberts *et al.*,[170] the coefficients for mild versus no PTS and for moderate/severe versus no PTS were similar in the regressions for SF-36 PCS and MCS scores, suggesting that both mild and moderate/severe PTS had similar implications for HRQoL. Furthermore, the review by Lubberts *et al.*[159] shows that the 5-year estimates from the CaVenT study reported by Haig *et al.*[160] are fairly consistent with the average across the 10 studies[160,180–182,184–186,188,192,193] that reported outcomes for the disease-specific measure of HRQoL Venous Insufficiency Epidemiological and Economic Study – Quality of life (VEINES-QoL). A sensitivity analysis was conducted to see if halving the utility decrement for PTS had a significant impact on the model results. A sensitivity analysis was also conducted using the data from Lenert and Soetikno[190] and estimating a weighted average utility across severe and mild/moderate PTS using the data from Hach-Wunderle *et al.*[109] to estimate the proportion of PTS that is severe (6%). This gave an average utility decrement of 2% rather than the 10% assumed in the base-case analysis.

Utility values in chronic thromboembolic pulmonary hypertension

Only one study included in the review by Lubberts *et al.*[159] reported outcomes for CTEPH, and this reported statistically significantly lower MCS (SMD –0.31, 95% CI –0.54 to –0.08) and PCS scores (SMD –1.72, 95% CI –1.95 to –1.48) than matched population norms. Six studies were identified as providing information on preference-based measures of HRQoL in patients with CTEPH. Three of these studies reported data based on the EQ-5D,[194–196] a fourth reported data from an alternative generic preference-based measure, the SF-6D[197] and a fifth reported data from a condition-specific preference-based measure, the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).[198] Finally, one study reported values based on a standard gamble.[199] Only one of the papers reported values specifically for patients with CTEPH[195] but this paper was restricted to those with resistant/recurrent or inoperable CTEPH (i.e. those in whom pulmonary endarterectomy had failed or was not possible). The paper by Ara and Brazier[194] reported data for 'other heart problems' (i.e. not heart attack/angina). The study by Keogh *et al.*[197] only included patients with idiopathic pulmonary arterial hypertension (PAH) or PAH related to connective tissue disease. Two studies, by Olschewski *et al.*[196] and Meads *et al.*,[198] included patients with CTEPH and other forms of PAH but Meads *et al.*[198] reported utility outcomes separately for those with CTEPH. Meads *et al.*[198] also reported a statistically significant difference in utility between CTEPH and those with PAH associated with connective tissue disorder. There was some inconsistency in the estimates provided by Ghofrani *et al.*[195] and Meads *et al.*,[198] with higher baseline scores in the population with inoperable/recurrent resistant CTEPH (0.66 for placebo arm) in Ghofrani *et al.*[195] than in the CTEPH subgroup reported by Meads *et al.*[198] (0.56). This may be because patients accepted into trials have slightly better general health than those receiving treatment in general practice. It was decided to use the data from Meads *et al.*[198] in the model; this was calculated based on the difference between the average utility for patients with CTEPH (0.56) and the average utility for those with New York Heart Association (NYHA) class 1 (0.89), who would be expected to have minimal HRQoL impact. This gave a multiplier of 0.63 or, equivalently, a 37% decrement relative to patients who are well. The decrement was applied for a patient's lifetime for those who were medically managed but only applied for the first year for those being surgically managed, who had the decrement for PE applied thereafter.

Utility values following intracranial haemorrhage

Of the 10 studies[177,190,194,200–206] reporting utility values for stroke patients, six studies [194,200–204] measured utility using the EQ-5D. Another four studies[177,190,205,206] reported utility values using a direct standard gamble or TTO measure, but these were disregarded as generic measures of HRQoL are preferred by NICE.[94] The values based on the EQ-5D ranged from 0.31 (as reported by Pickard *et al.*)[203] to 0.70 (as reported by Lunde *et al.*).[202] Luengo-Fernandez *et al.*[201] reported that the decrement ranged from 0.22 at 1 month to 0.09 at 5 years. Studies that reported multiple time points found that the absolute utility value increased and the decrement versus controls decreased over time. The study with the longest follow-up[201] found that utility values were relatively stable from 6 months to 5 years post stroke. The data from the 5-year follow-up of the OXVASC study[201] were chosen for application in the model as this was the largest sample of stroke patients, the population was selected from the UK, the duration of follow-up allowed time since stroke to be accounted for, and a comparison was made against general population norms. A decrement of 0.22 was assumed in the decision tree part of the model where time since stroke was < 6 months and a decrement of 0.09 was assumed in the long-term part of the model.

Utility values for major non-intracranial haemorrhage bleeds

For major non-ICH bleeds, no studies were identified that measured utility using the EQ-5D or another generic preference-based measure. Two studies[176,206] reported values using the standard gamble and a third used TTO.[177] Two of the studies that recruited at least some patients with VTE reported a utility value of 0.65,[176,177] whereas the study in patients with AF reported a much higher value of 0.841.[206] The study by Locadia *et al.*[177] (median 0.65, interquartile range 0.49 to 0.86) was considered to be the most relevant as it used TTO, which is the same method used to generate utility vales for the EQ-5D, and it explicitly included patients with experience of major bleeding episodes during VKA treatment in addition to some patients with VTE. However, using the data from Locadia *et al.*[177] directly would have resulted in a lower utility value for non-ICH bleeds than for ICH, which would not have had face validity. As the study by

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Locadia *et al.*[177] showed similar valuations for the PE and GI bleed health states, and these states were ranked as equivalent, it was decided to use the data for PE from Cohen *et al.*[173] in the model as the longer-term data provided by Cohen *et al.*[173] allows the utility multiplier to be calculated relative to a patient who has recovered from VTE (i.e. relative to a patient 6 months after a DVT). The utility multiplier was, therefore, estimated to be 0.80 (0.68/0.84). As major non-ICH bleeds are not expected to lead to long-term disability, the utility multiplier for major bleeding was applied for 28 days.

Treatment-related utility decrement

Given that thromboprophylaxis involves giving patients treatment even though they may not go on to experience a VTE event without treatment, it is important to include in the model the possibility that treatment itself is associated with harm.

Several sources of data were identified for the decrement associated with prophylaxis and treatment of VTE. Six studies reported the utility decrement for warfarin or other VKAs. Four of these studies[177,205–207] used a direct measure of utility (e.g. TTO or standard gamble) and two of these studies[173,208] measured utility using the EQ-5D. The study by Monz *et al.*[208] examined HRQoL in a subset of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, which was a randomised comparison of dabigatran and warfarin in patients with AF. Therefore, it was unable to measure the utility impact of warfarin alone. However, it did report that there was no statistically significant difference in HRQoL based on treatment type (DOAC vs. warfarin) and the utility scores observed were similar to age-comparable population norms. Cohen *et al.*[173] reported EQ-5D data by treatment type (heparin only, heparin/VKA, DOAC) from the PREFER-VTE registry. However, it was not clear whether or not patients receiving heparin alone in the PREFER-VTE registry would have different characteristics from those receiving other forms of treatment for VTE, in which case the difference in utility between heparin and other VTE treatments may have been confounded by patient characteristics and their influence on clinicians' choice of anticoagulant.

Only two studies[173,207] provided data on the disutility associated with heparin. Given the potential bias described above for Cohen *et al.*,[173] it was decided to use the data provided by Marchetti *et al.*;[207] in this study, a TTO exercise was used in 48 patients attending an anticoagulation clinic who had experience of LMWH. The trade-off was based on clinical vignettes for hypothetical patients receiving LMWH. The average number of days they were willing to trade was 2.7 days over a 1-year time frame. Therefore, a mean decrement of 0.007 was applied during thromboprophylaxis.

Four studies provided directly elicited measures of utility for warfarin therapy. Two were in patients with AF.[205,206] Marchetti *et al.*[207] was the only study conducted exclusively in patients with a history of VTE. Half of the patients recruited by Marchetti *et al.*[207] had previous experience of receiving warfarin. All of the patients in the study reported by Locadia *et al.*[177] had been treated previously with a VKA, but not all had previous VTE. The utility decrement for VKA versus no VKA was 4% for Locadia *et al.*[177] (0.92 vs. 0.96) based on median estimates of utility for both states, whereas it was 1% for Marchetti *et al.*[207] based on a willingness to trade 4 of 365 days of full health to avoid warfarin. The estimate from Marchetti *et al.*[207] is similar to the estimates from Gage *et al.*[205] in patients with AF, whereas the estimate from Locadia *et al.*[177] is close to the estimate from Robinson *et al.*[206] It was decided to use the data from Marchetti *et al.*[207] to provide an estimate consistent with the methodology used to estimate the utility decrement for LMWH.

In the sensitivity values exploring the use of DOACs as prophylaxis, no utility decrement has been assumed, as DOACs are taken orally and do not require frequent blood tests to monitor INR levels. In the sensitivity analysis exploring the use of fondaparinux as prophylaxis, the same utility decrement as for LMWH was assumed as both treatments are given by subcutaneous injection.

The utility values applied in the model are summarised in *Tables 21* and *22*.

TABLE 21 Utility values included in the decision tree model

Health state value	Absolute utility value	Range	Source	Notes
Well/asymptomatic DVT without prophylaxis	0.879	0.878 to 0.882	Ara and Brazier[194]	Population mean utility values based on person (average for male and females) with starting age of 46 years
Symptomatic proximal or distal DVT	0.848	0.846 to 0.850	Cohen *et al.*[173] (using additional detail reported in TA354,[140] Daiichi Sankyo company submission, table B78[178])	5% reduction relative to well patients based on comparison of average utility over 6 months for DVT (0.819) vs. utility at 6 months (0.850) for patients with DVT
Non-fatal PE	0.80	0.780 to 0.825	Cohen *et al.*[173] (using additional detail reported in TA354,[140] Daiichi Sankyo company submission, table B78[178])	9% reduction relative to well patients based on comparison of average utility over 6 months (0.775) for PE vs. utility at 6 months (0.850) for patients with DVT
Non-fatal ICH	0.66	0.616 to 0.701	Luengo-Fernandez 2013[201]	Absolute decrement of 0.22 measured at 1 month
Non-fatal non-ICH bleed	0.69	0.652 to 0.688	Cohen *et al.*[173]	• Assumed same utility decrement for PE and GI bleeds at 1 month • 21% reduction based on utility for PE at 1 month (0.67) versus utility for DVT at 6 months (0.85) from Cohen *et al.*[173]
Prophylaxis: absolute decrement applied to utility values of well/ asymptomatic DVT	0.007	0.000 to 0.050	Marchetti *et al.*[207]	Patients willing to trade average of 2.7 days per year to avoid treatment with LMWH
Treatment: absolute decrement applied to utility values for non-fatal PE or symptomatic DVT	0.011	0.000 to 0.081	Marchetti *et al.*[207]	Patients willing to trade average of 4 days per year to avoid treatment with warfarin
Fatal PE	0	NA	Assumption	

Timing and duration of utility decrements applied in the decision tree

To calculate the QALYs gained by patients having different paths through the decision tree, it is necessary to make some assumptions regarding the timing of events, as these are not explicitly modelled in a decision tree. The following assumptions were made when estimating QALYs in the decision tree:

- Baseline utilities using general population utility values for the starting age are applied to those not having treatment and not having any clinical events (e.g. VTE, bleeds).
- Bleeds during lower-limb immobilisation are assumed to occur halfway through the immobilisation period, which is assumed to last 8 weeks (56 days), namely bleeds occur at 28 days.
- VTEs occurring during lower-limb immobilisation are assumed to be diagnosed at the end of immobilisation (i.e. at 56 days) and utility decrements for PE and DVT are applied from diagnosis until the end of the decision tree period.
- Bleeds occurring during treatment for VTE are assumed to occur at 13, 32 and 12 days post diagnosis of VTE for fatal, ICH and other major bleeds, respectively (based on data from RIETE, reported by Nieto *et al.*[105]).

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- Disutilities for ICH are applied lifelong, but separate disutilties are applied in decision tree and Markov phases of the model (i.e. before and after 6 months post lower-limb immobilisation).
- Disutility of GI bleeding is assumed to last a maximum of 28 days.
- Disutility of prophylaxis applies for the duration of prophylaxis (6 weeks) and is therefore less in those stopping early because of major bleeding.
- Disutility of treatment for VTE applies for the duration of treatment (3 months) and is therefore less in those stopping early because of major bleeding.

The following assumptions were made when estimating QALYs in the Markov model:

- Utility values for patents without any long-term sequelae (e.g. ICH, CTEPH, PTS) are taken from general population values and decrease as patients age in the model.
- All other utility values are applied as multipliers, such that the absolute utility value decreases for all patients as a result of ageing.
- Utility decrements continue in the Markov model for the remainder of a patient's lifetime for PE but not for DVT, for which patients are assumed to return to general population utility values at 6 months.
- Patients with CTEPH who are treated medically have a lifelong utility decrement, whereas those treated surgically return after 1 year to the same utility as those surviving PE without CTEPH.
- Patients with PTS have the same utility decrement from diagnosis to death.
- Patients with ICH have the same utility decrement from 6 months (i.e. the start of Markov model) to death.

TABLE 22 Utility multipliers applied in the Markov model to the absolute utility value for well patients

Health state(s)	Utility multiplier relative to well	Range	Source	Notes
PE survivor without CTEPH and PE survivor > 1 year after surgery for CTEPH	0.95	0.927 to 0.978	Cohen *et al.*[173]	5% reduction relative to well patients based on comparison of average utility at 6 months for patients with PE (0.81) vs. utility at 6 months (0.85) for patients with DVT
Any DVT without PTS	1	N/A	Assumption	Supported by Lubberts *et al.*'s[159] systematic review finding no significant HRQoL decrement in nine long-term studies based on SF-36 outcomes
Non-fatal ICH	0.89	0.810 to 0.955	Luengo-Fernandez *et al.*[201]	Multiplier calculated based on absolute decrement of 0.09 at 5 years (utility values stable from 6 months to 5 years) relative to absolute utility for well state of 0.88 from general population values
PTS	0.90	0.855 to 0.944	Enden *et al.*[189]	Multiplier calculated based on absolute decrement of 0.09 relative to absolute utility for well state of 0.86
CTEPH: first year for surgically managed and every year for medically managed	0.63	0.579 to 0.690	Meads *et al.*[198]	Multiplier calculated based on comparison of utility for CTEPH (0.56) vs. utility for NYHA class I (0.89)
Dead	0		Assumption	

N/A, not applicable; NYHA, New York Heart Association.

Methods used to quantify decision uncertainty

A probabilistic sensitivity analysis (PSA) was used to estimate the impact of parameter uncertainty on the estimates of costs and QALYs. For each input parameter, a probability distribution was assigned that reflected the degree of uncertainty surrounding the mid-point parameter estimate and we sampled from the distribution 10,000 times. This number of runs was deemed sufficient because it ensured that the coefficient of variation was < 2% for both incremental costs and incremental QALYs. In general, utility values, which must be < 1, and probabilities, which are bounded by 0 and 1, were sampled from beta distributions, and costs, which must be > £0, were sampled from gamma distributions. Uncertainty surrounding the ORs for efficacy (all VTE events) and adverse events (major bleeds) were captured using the convergence diagnostics and output analysis (CODA) samples from the NMA. When parameters were calculated from regression equations, multivariate normal sampling was used to incorporate the covariance between the regression parameters. The estimates of sensitivity and specificity were fixed within the PSA as the uncertainty around these parameters was not reported by Nemeth *et al.*[32] *Table 39* in *Appendix 13* presents the distributions for each parameter included in the PSA. For each of the 10,000 sets of parameter inputs, the costs and QALYs of each thromboprophylaxis strategy were re-estimated.

The 10,000 PSA estimates of costs and QALYs were used to estimate the mean costs and QALYs for each thromboprophylaxis strategy. From this, the incremental net monetary benefit (INMB) was estimated when using a willingness-to-pay threshold of £20,000 or £30,000 per QALY, which is the range of thresholds used by NICE when assessing value for money in the context of the UK NHS.[94] The strategy with the maximum INMB at a given threshold is considered to have the optimal cost-effectiveness. The INMB was used to calculate the optimal thromboprophylaxis strategy at both of these thresholds and the proportion of times, within the 10,000 PSA samples, that each strategy is optimal across a range of thresholds was estimated in order to generate the cost-effectiveness acceptability curve (CEAC).

The global expected value of perfect information (EVPI) was estimated, which tells a decision-maker the value of reducing all current decision uncertainty associated with the parameters included in the PSA. This was estimated across all the complete set of possible thromboprophylaxis strategies. The parameter EVPI analysis was also used to assess the importance of each individual parameter in generating uncertainty around the optimal strategy. The Sheffield Accelerated Value of Information (SAVI) tool was used to calculate parameter EVPI.[209]

It should be noted that a PSA and an EVPI analysis can capture only uncertainty related to parameters included in the PSA and will not capture any uncertainty associated with structural assumptions or the choice of data inputs used to estimate parameter uncertainty. These uncertainties are quantified instead using deterministic sensitivity analyses, in which a range of alternative parameter inputs and assumptions are explored within the model to see whether or not the conclusions are robust under these changes.

Results of the de novo economic evaluation

Clinical outcomes predicted by the model

The symptomatic adverse clinical outcomes predicted by the model at 6 months (based on mid-point parameter values) are summarised in *Figures 14* and *15*. As patients may have more than one adverse outcome during the 6-month time period of the decision tree model, patients are summarised on the basis of the worst outcome experienced, such that those recorded as having non-fatal PE or symptomatic DVT are those who did not also have fatal bleed, fatal PE or ICH. In *Figure 14* it can be seen that prophylaxis for all is the strategy that minimises the total number of symptomatic adverse outcomes at 6 months. The numbers of the most serious adverse clinical outcomes (e.g. fatal bleeds, fatal PEs or ICHs) are similar across the prophylaxis strategies and the differences are too small to see based on *Figure 14*. *Figure 15* focuses solely on these serious adverse clinical outcomes and shows that giving prophylaxis based on a L-TRiP(cast) score of ≥ 9 minimises the total number of these outcomes, although the rate is very low (≈1 in 4000) and shows little variation between strategies.

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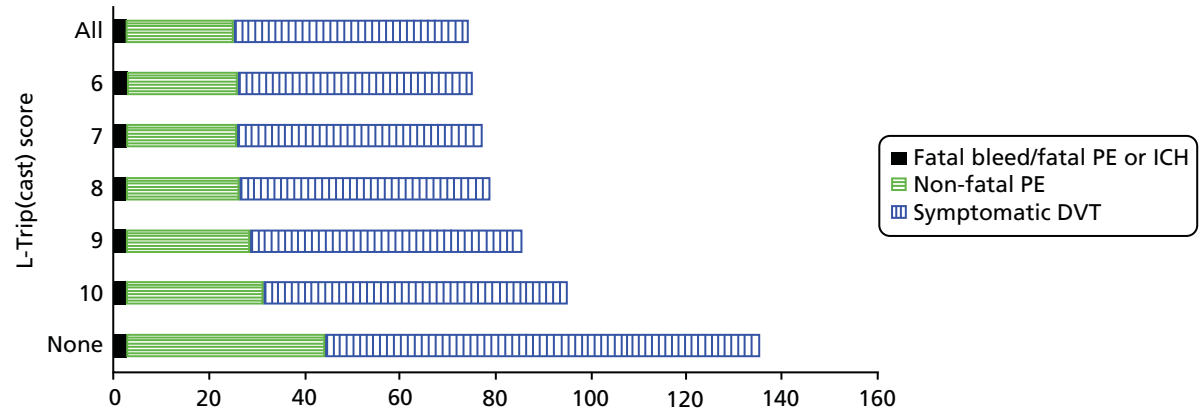

FIGURE 14 Symptomatic clinical outcomes predicted at 6 months for 10,000 patients having lower-limb immobilisation due to injury.

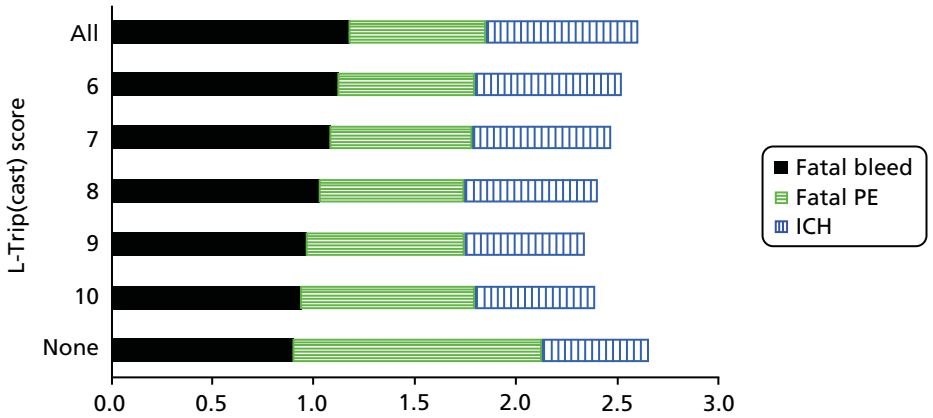

FIGURE 15 Serious adverse clinical outcomes predicted at 6 months for 10,000 patients having lower-limb immobilisation due to injury.

It should be noted that major bleeds that are non-fatal and not ICHs are assumed to resolve within 6 months and are, therefore, not included in *Figure 14*. The number of major bleeding outcomes is summarised in *Figure 16*, which shows that the total number of major bleeds, including fatal and non-fatal ICHs, increased from 4.03 per 10,000 having lower-limb immobilisation when no prophylaxis is given to 5.38 per 10,000 when prophylaxis is given to all. Giving prophylaxis to all patients with lower-limb immobilisation, therefore, results in fewer than two additional cases of major bleeding per 10,000 patients receiving prophylaxis. The increase in major bleeding is smaller than would be expected based solely on the RR of 1.64 for bleeding with prophylaxis versus bleeding without prophylaxis, because prophylaxis prevents VTE, thereby lowering the rate of bleeding experienced during VTE treatment.

The adverse clinical outcomes predicted by the model at 5 years (based on mid-point parameter values) are summarised in *Figure 17*. Only those outcomes resulting in long-term morbidity are included; therefore, patients who experience DVTs without any subsequent PTS are not included in the adverse clinical outcomes shown. It can be seen that the number of people surviving to 5 years is fairly similar across all the thromboprophylaxis strategies. The strategy of thromboprophylaxis for all results in the smallest number of people surviving with CTEPH, PTS or ongoing morbidity due to previous ICH or PE. The numbers surviving with either ongoing morbidity due to ICH or CTEPH following PE are relatively small, at ≈1 per 10,000 patients for each outcome.

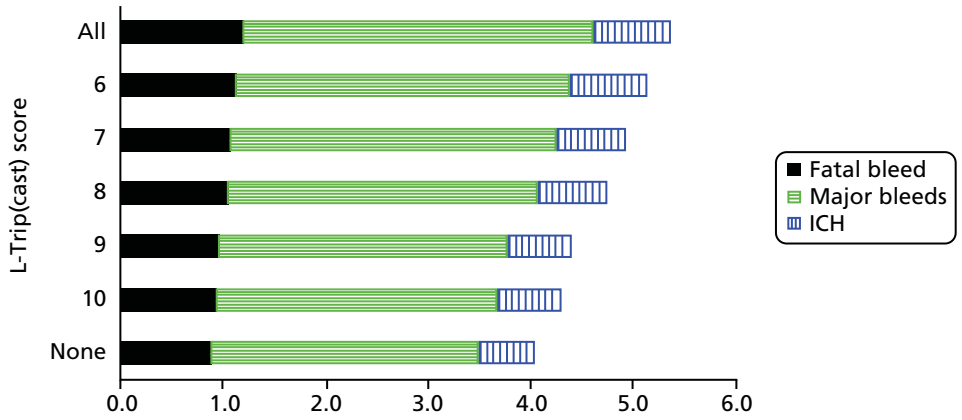

FIGURE 16 Major bleeding predicted at 6 months for 10,000 patients having lower-limb immobilisation due to injury.

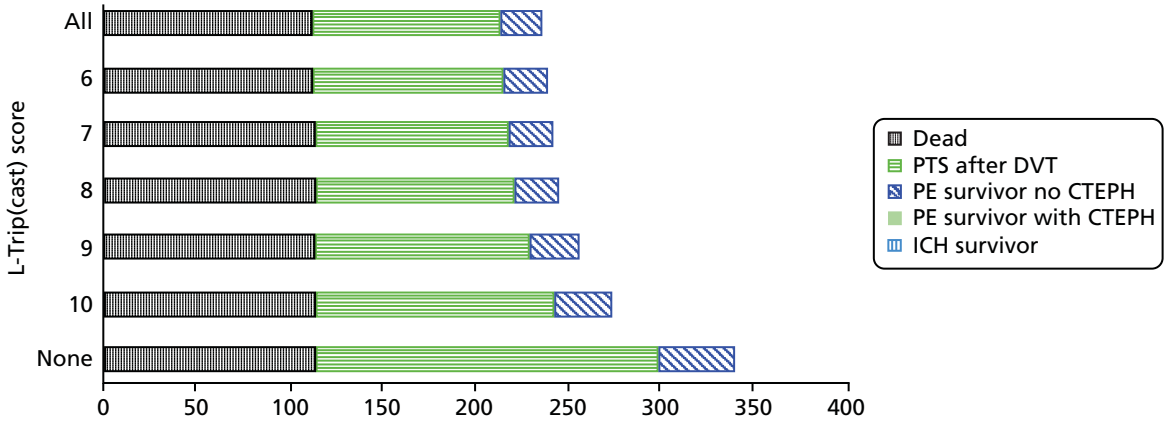

FIGURE 17 Adverse clinical outcomes predicted at 5 years for 10,000 patients having lower-limb immobilisation due to injury.

Cost-effectiveness of thromboprophylaxis for all compared with thromboprophylaxis for none

Figure 18 shows the estimates of incremental costs and QALYs for the comparison of thromboprophylaxis for all with thromboprophylaxis for none for 10,000 PSA samples. The mean incremental costs and QALYs from the 10,000 PSA samples are shown as an × on the cost-effectiveness plane. The mean QALY gain is 0.015, but it can be seen that there is a wide spread of incremental QALY estimates, with 95% of the incremental QALYs falling in the range of 0.004 to 0.029 but with some PSA samples (0.53%) having a negative QALY gain. The mean incremental cost is £203 with 95% of the PSA estimates falling in the range £172–245. The incremental cost-effectiveness ratio (ICER) for thromboprophylaxis for all compared with thromboprophylaxis for none based on the mean costs and QALYs is £13,524. Therefore, if a decision-maker is willing to pay £20,000 per QALY, it would be cost-effective to give thromboprophylaxis to all patients with lower-limb immobilisation due to injury if this was the only alternative to giving thromboprophylaxis to none. However, it can be seen that a significant proportion of the PSA estimates fall above the £20,000 per QALY threshold; therefore, there is a 24% probability that thromboprophylaxis for all is not cost-effective.

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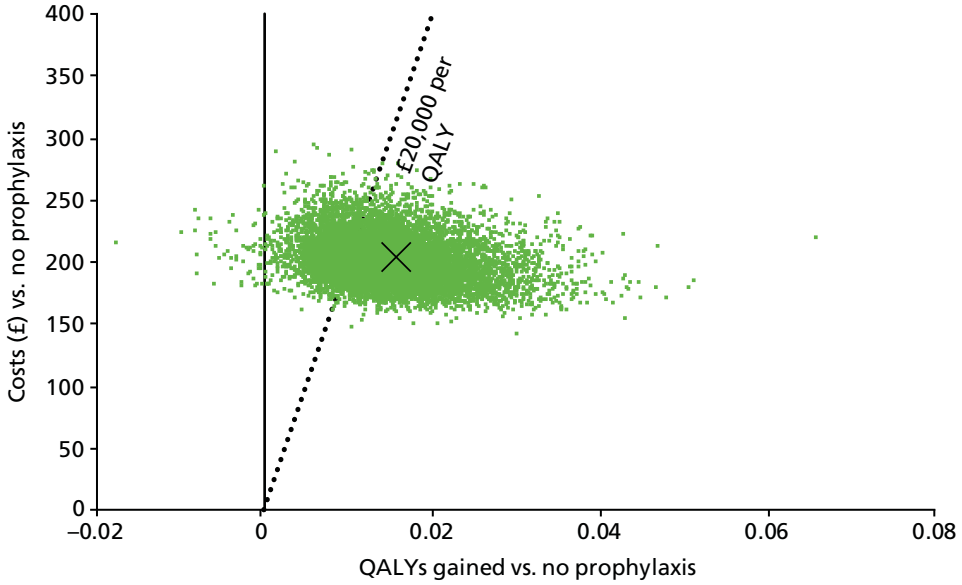

FIGURE 18 Cost-effectiveness plane for the comparison of thromboprophylaxis for all vs. thromboprophylaxis for none.

Cost-effectiveness of using a risk assessment model to determine thromboprophylaxis

The results of all of the thromboprophylaxis strategies considered in the model (based on the mean outputs of the PSA for 10,000 samples) are summarised in *Table 23* and *Figure 19*. It can be seen in *Figure 19* that, generally, the QALYs increase as the proportion receiving prophylaxis increases across the decision tools, with the QALY gains becoming more marginal as the proportion receiving prophylaxis increases. Furthermore, it can be seen in *Figure 19* that L-TRiP(cast)-7 is extendedly dominated, as the ICER to move from L-TRiP(cast)-8 to L-TRiP(cast)-6 would be lower than the ICER to move from L-TRiP(cast)-8 to L-TRiP(cast)-7, but more QALYs are gained by L-TRiP(cast)-6. However, it should be noted that the point for L-TRiP(cast)-7 is close to falling on the cost-effectiveness frontier [i.e. on the line between L-TRiP(cast)-8 and L-TRiP(cast)-6]. The incremental analysis for the remaining non-dominated strategies is shown in *Table 24*. The optimal strategy would be L-TRiP(cast)-9 if the decision-maker values QALYs at £20,000 and L-TRiP(cast)-8 if the decision-maker values QALYs at £30,000.

Optimal balance of sensitivity and specificity for a risk assessment model

From the base-case results, it can be seen that as we move from higher to lower thresholds of the L-TRiP(cast) score, the QALYs gained increase as the sensitivity of the risk assessment tool increases but the cost increases as the specificity decreases. The ROC curve for the L-TRiP(cast) score provided by Nemeth *et al.*[32] allows us to explore where the optimal balance of sensitivity and specificity lies when assuming that it lies somewhere on the ROC curve provided by L-TRiP(cast). To do this, a linear regression on the logit scale was fitted to the points on the ROC plane from L-TRiP(cast)-6 to L-TRiP(cast)-10 (intercept = –1.5256, gradient = 0.8098, R^2 = 0.9926). The sensitivity and specificity values were then varied between the L-TRiP(cast)-9 and L-TRiP(cast)-8 points of the curve to maximise the INMB using the deterministic model that uses mid-point parameter estimates. It was identified that, when valuing a QALY at £20,000, the INMB is maximised for a sensitivity of 84% and a specificity of 55%, resulting in 48% of patients being treated. When valuing a QALY at £30,000, the INMB is maximised for a sensitivity of 89% and a specificity of 46%, resulting in 57% of patients being treated. Therefore, even when using an optimised balance between sensitivity and specificity on the ROC curve predicted by the data from Nemeth *et al.*,[32] between 43% and 52% of patients would not receive thromboprophylaxis. The incremental costs and QALYs for these optimal points are shown in *Figure 20*. It can be seen from this that the optimal points on the ROC curve are actually extendedly dominated by the points for LTRiP(cast)-9 and LTRiP(cast)-8. This is because the ROC curve predicted by the linear regression on the logit scale passes below the data points for LTRiP(cast) scores of 9 and 8.

TABLE 23 Base-case results (mean from 10,000 PSA samples) in order of the percentage receiving prophylaxis

Prophylaxis strategy	% receiving prophylaxis	Sensitivity	Specificity	Absolute costs (£)	Absolute QALYs	Cost vs. no prophylaxis (£)	QALYs vs. no prophylaxis	ICER vs. prophylaxis for none (£)	INMB vs. prophylaxis for none, at £20,000 per QALY (£)[a]	INMB vs. prophylaxis for none, at £30,000 per QALY (£)[a]
Prophylaxis for none	0	0	1	65.37	16.6198	N/A	N/A	N/A	N/A	N/A
L-TRiP(cast)-10	31	0.651	0.722	128.11	16.6301	62.73	0.0103	6085	143.44	246.53
L-TRiP(cast)-9	43	0.808	0.608	150.96	16.6326	85.58	0.0127	6724	**168.96**	296.23
L-TRiP(cast)-8	63	0.926	0.397	194.41	16.6342	129.04	0.0144	8984	158.24	**301.88**
L-TRiP(cast)-7	76	0.953	0.262	222.55	16.6345	157.17	0.0146	10,755	135.10	281.23
L-TRiP(cast)-6	87	0.984	0.142	247.51	16.6348	182.14	0.0150	12,183	116.87	266.38
Prophylaxis for all	100	1	0	268.35	16.6348	202.98	0.0150	13,524	97.20	247.29

N/A, not applicable.

a INMB at £20,000 per QALY and INMB at £30,000 per QALY are the INMBs when valuing a QALY at £20,000 and £30,000 per QALY, respectively.

Note

Bold text indicates the optimal strategy.

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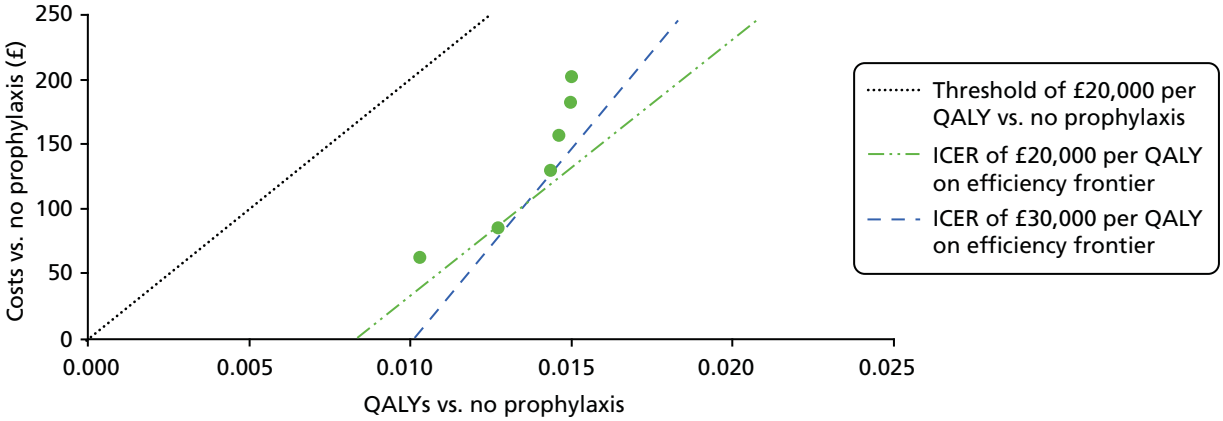

FIGURE 19 Base-case results on CE plane (mean from 10,000 PSA samples).

TABLE 24 Incremental analysis for interventions sitting on the cost-effectiveness frontier[a]

	Absolute costs (£)	Absolute QALYs	Cost vs. previous row (£)	QALY vs. previous row	ICER vs. previous row (£)
No prophylaxis	65.37	16.6198	N/A	N/A	N/A
L-TRiP(cast)-10	128.11	16.6301	62.73	0.01031	6085
L-TRiP(cast)-9	150.96	16.6326	22.85	0.00242	9448
L-TRiP(cast)-8	194.41	16.6342	43.46	0.00164	26,550
L-TRiP(cast)-6	247.51	16.6348	53.09	0.00059	90,554
Prophylaxis for all	268.35	16.6348	20.84	0.00006	357,026

N/A, not applicable.
a L-TRiP(cast)-7 does not fall on the cost-effectiveness frontier as it is extendedly dominated.

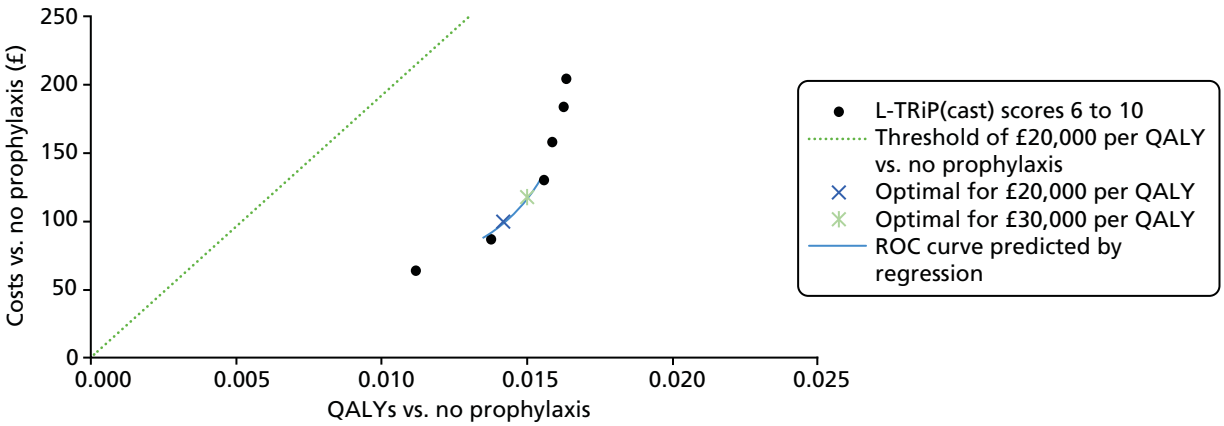

FIGURE 20 Cost-effectiveness plane showing optimal points on the ROC curve when valuing a QALY at either £20,000 or £30,000 (generated using mid-point parameter values).

Uncertainty surrounding base-case results

Figure 21 shows the cost-effectiveness plane for L-TRiP(cast)-9 (the optimal strategy when valuing QALYs at £20,000) versus no prophylaxis. It can be seen that there is considerable uncertainty in the size of the QALY gain but there is a low chance of the optimal strategy resulting in QALY losses, compared with no prophylaxis, with 95% of the incremental QALYs falling in the range of 0.005 to 0.024. In terms of costs savings, 95% of the incremental costs fell in the range of £69 to £107, suggesting that the optimal strategy is unlikely to result in cost savings compared with no prophylaxis. This is expected, as prophylaxis results in definite costs to those receiving it but the benefits of preventing VTE are small and uncertain when averaged over the whole population receiving prophylaxis. Similar distributions of incremental costs and QALYs were seen for the other L-TRiP(cast) cut-off scores, with all predicting additional costs and additional QALYs and a mean ICER of < £20,000 relative to a strategy of no prophylaxis.

Figure 22 is the CEAC, which shows the probability that each strategy is optimal when varying the amount that the decision-maker is willing to pay for a QALY. It can be seen that L-TRiP(cast)-9 has the highest probability (66.8%) of being optimal when valuing a QALY at £20,000, which is consistent with the results in

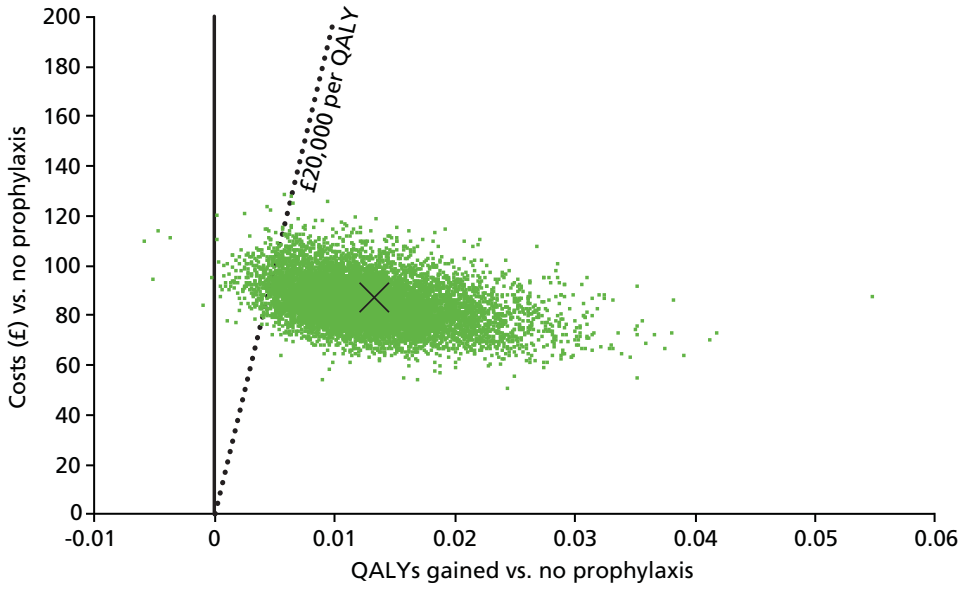

FIGURE 21 Cost-effectiveness plane for L-TRiP(cast)-9 showing incremental costs and QALYs relative to no prophylaxis.

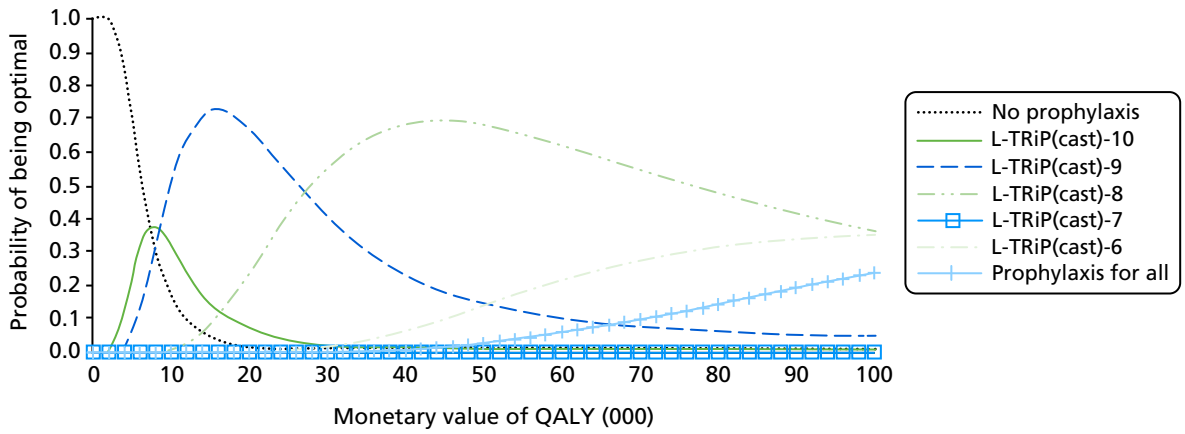

FIGURE 22 Cost-effectiveness acceptability curve.

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Table 24. L-TRiP(cast)-8 has a slightly higher probability of being optimal when valuing a QALY at £30,000, but there is also a high probability of L-TRiP(cast)-9 remaining optimal. This makes sense given that the ICER for L-TRiP(cast)-8 versus L-TRiP(cast)-9 is only just under £30,000 per QALY. It can also be seen that L-TRiP(cast)-7 always has a low probability of being optimal regardless of what the decision-maker is willing to pay and that the decision-maker would need to be willing to pay more than £100,000 per QALY before prophylaxis for all is the optimal strategy. This is interesting because if the risk-stratifying decision tools had not been included in the analysis, then prophylaxis for all would have been cost-effective compared with prophylaxis for none. This demonstrates the potential value of using decision tools to target prophylaxis in a cost-effective manner instead of focusing on evaluating all or nothing prophylaxis options.

To demonstrate the impact of different strategies on a health service, L-TRiP(cast)-9 can be compared with a strategy of using prophylaxis for all across the English NHS. In *Chapter 1*, *Description of the health problem*, it was estimated that 70,000 people per year across the English NHS experience temporary lower-limb immobilisation due to injury as an outpatient. Using the mean outputs from the PSA, it is found that prophylaxis for all would result in an additional 0.0023 QALYs per person, but for an additional cost of £117.40 per person when compared with L-TRiP(cast)-9. Applied to the 70,000 annual population for the English NHS, the cost saving that could be achieved by giving prophylaxis to only those with a L-TRiP(cast) score of ≥ 9 would be £8.2M pounds and the QALYs lost would be 160. Conversely, if the impact of giving prophylaxis to patients at a L-TRiP(cast) score of 9 compared with treatment for none is considered, it is found that the additional cost to the NHS is £6.0M, with QALY gains of 891 for a population of 70,000 patients having lower-limb immobilisation. One-tenth of this additional cost to the NHS is the upfront cost of performing risk assessment in all patients with lower-limb immobilisation following injury to identify those requiring prophylaxis.

Value to the decision maker of reducing uncertainty in the estimates of cost-effectiveness

The global EVPI was estimated, which tells a decision-maker the value of reducing all current decision uncertainty associated with the PSA parameters. It was found that the overall EVPI was £4.12 per patient treated, suggesting that although treating patients at the L-TRiP(cast)-9 cut-off score would be expected to achieve an INMB of £168.96 per patient compared with no prophylaxis, based on current information, only 2.4% more INMB could be achieved with perfect information. This suggests that the value of reducing the decision uncertainty further is low on a per-patient basis. However, if the EVPI is estimated over 5 years, assuming that 70,000 patients have lower-limb immobilisation due to injury every year, then the overall discounted population EVPI is £1.3M.

Parameter EVPI analysis was also used to assess the importance of each individual parameter in generating uncertainty around the optimal strategy. Based on this, the most important parameters for decision uncertainty were the utility value for PTS, the efficacy of thromboprophylaxis in reducing VTE, the probability of PTS for patients with distal DVT and the utility decrement associated with taking prophylaxis. This suggests that the main factors driving uncertainty in the model are the efficacy and disutility of receiving prophylaxis, and the long-term complications of PTS. The incidence of PTS in patients with distal DVT is particularly important probably because asymptomatic DVT is more common than symptomatic DVT and the majority of asymptomatic DVTs are expected to be distal in this population. However, the magnitude of the overall EVPI suggests that a large-scale RCT comparing thromboprophylaxis with no thromboprophylaxis would be unlikely to be cost-effective.

It should be noted that EVPI analysis can capture only uncertainty related to parameters included in the PSA and will not capture any uncertainty associated with structural assumptions or the choice of data inputs used to estimate parameter uncertainty. These uncertainties are quantified instead using deterministic sensitivity analyses.

Important factors driving the cost-effectiveness estimates identified during model validation were:

- incidence, long-term costs and utility decrement for PTS
- baseline risks of VTE and the proportion of DVTs that are distal
- costs and efficacy of prophylaxis and prophylaxis-related disutility.

These have been explored in deterministic sensitivity analyses by examining changes in the outputs of the deterministic model (the values produced when assuming mid-point parameter inputs) when changing one or more selected parameter inputs.

Scenario analyses and threshold analyses

The results of the individual scenario analyses are summarised in *Table 25* by reporting the optimal thromboprophylaxis strategy when valuing a QALY at £20,000 and £30,000 for each scenario.

Whether or not the age of the cohort being offered prophylaxis would alter the conclusions was examined, as it is likely that those receiving prophylaxis under the various decision tools would be older than the mean age of the whole group who have lower-limb immobilisation due to injury. It was found that increasing the mean starting age of the whole cohort to 70 years increased the ICERs but L-TRiP(cast)-9 remained optimal at £20,000 and L-TRiP(cast)-8 remained optimal at £30,000 with an ICER of £29,555 versus L-TRiP(cast)-9. This suggests that the decision to use a cohort approach based on average age is unlikely to have over- or underestimated prophylaxis benefits sufficiently to alter the key conclusions regarding the optimal strategy.

A threshold analysis was conducted to see how much the mid-point estimates of efficacy for LMWH in preventing VTE would need to change to alter the optimal prophylaxis strategies. It was found that a decrease in the hazard ratio (HR) (improvement in efficacy) from 0.54 to 0.44 would make L-TRiP(cast)-8 the optimal strategy at both £20,000 and £30,000 per QALY, whereas an increase in the HR (decrease in efficacy) to 0.60 would make L-TRiP(cast)-9 optimal at both £20,000 and £30,000 per QALY. An increase in the HR to 0.76 would be required for L-TRiP(cast)-9 to no longer be optimal at £20,000 per QALY. An increase in the HR to 0.84 would be required for treatment for none to be the optimal strategy at £20,000 per QALY.

It was examined whether or not the conclusions would differ if all patients were assumed to receive either fondaparinux or DOACs instead of LMWH for prophylaxis. For this, no difference in adverse event rates was assumed across the different prophylaxis options. Costs were assumed to vary in each case as per the costing analysis in *Table 18*. For DOACs, equivalent efficacy to LMWH was assumed and no utility decrement for DOACs was assumed because they are taken orally. For fondaparinux, the efficacy estimates from the NMA for fondaparinux versus control (OR 0.1, 95% predictive interval 0.05 to 0.3, from the random effects analysis) were used and the same utility decrement as applied for LMWH was assumed because both drugs are given by subcutaneous injection. Using DOACs shifted the optimal strategy when valuing a QALY at £20,000 from L-TRiP(cast)-9 to L-TRiP(cast)-8 and shifted the optimal strategy when valuing a QALY at £30,000 to treat all. Using fondaparinux resulted in the ICER for L-TRiP(cast)-8 versus L-TRiP(cast)-9 falling under £20,000 per QALY but L-TRiP(cast)-8 remained optimal when valuing a QALY at £30,000. It should be noted that these two scenarios are fairly crude and do not fully explore differences between the different drug classes in terms of adverse events. Furthermore, in the case of DOACs the analysis is based on an assumption of equivalent efficacy. The intention here was to explore whether or not the optimal cut-off point for providing thromboprophylaxis would differ when using a different drug class, rather than determining the optimal drug class to use for thromboprophylaxis.

In addition to a lack of precision in the estimates of utility decrement associated with PTS, there were differences in the estimates provided by different papers. The data from Lenert and Soetikno[190] were used, which had lower decrements for PTS and showed that the optimal strategy when willing to pay £20,000 per QALY became L-TRiP(cast)-10, with L-TRiP(cast)-9 having an ICER of just under £30,000 in this scenario. This suggests that there is considerable decision uncertainty associated with the choice of utility data for PTS.

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TABLE 25 Deterministic sensitivity analyses

Scenario description	Base-case parameter value	Alternative parameter value	Optimal strategy when valuing a QALY at £20,000	Optimal strategy when valuing a QALY at £30,000
Base case	N/A	N/A	L-TRiP(cast)-9	L-TRiP(cast)-8
High starting age	46 years	70 years	L-TRiP(cast)-9	L-TRiP(cast)-8
Low starting age	46 years	20 years	L-TRiP(cast)-9	L-TRiP(cast)-8
DOACS used for prophylaxis	LMWH with cost of £223.70 and utility decrement of 0.007 and an OR for preventing VTE of 0.52	DOACs with cost of £84.23 and no utility decrement and an OR for preventing VTE of 0.52	L-TRiP(cast)-8	Prophylaxis for all
Fondaparinux used for prophylaxis	LMWH with cost of £223.70 and utility decrement of 0.007, and an OR for preventing VTE of 0.52	Fondaparinux with cost of £355.66 and utility decrement of 0.007 and an OR for preventing VTE of 0.13	L-TRiP(cast)-8	L-TRiP(cast)-8
Double utility decrement for LMWH	Utility decrement of 0.007	Utility decrement of 0.015	L-TRiP(cast)-9	L-TRiP(cast)-8
Cost of patients with CRNMB attending ED	£0 (costs of CRNMB excluded in base-case analysis)	£196 per patient having CRNMB	L-TRiP(cast)-9	L-TRiP(cast)-8
Discounting	3.5% costs and 3.5% QALYs	1.5% costs and 1.5% QALYs	L-TRiP(cast)-8	L-TRiP(cast)-8
Discounting	3.5% costs and 3.5% QALYs	3.5% cost and 1.5% QALYs	L-TRiP(cast)-8	L-TRiP(cast)-8
Utility decrement of PTS based on data from Lenert and Soetikno[190]	10% utility decrement for PTS vs. no PTS	2% utility decrement for PTS vs. no PTS	L-TRiP(cast)-10	L-TRiP(cast)-9
Costs of PTS based on US estimates by Caprini *et al.*[146]	• Year 1: £308 • Year 2: £74	• Year 1: £1022 • Year 2: £423	L-TRiP(cast)-9	L-TRiP(cast)-8
Time to complete risk assessment scoring tool	5 minutes of consultant time	20 minutes of consultant time	L-TRiP(cast)-9	L-TRiP(cast)-8
Risk of PTS in patients with asymptomatic distal DVT	15.6% at 3 years	None	L-TRiP(cast)-9	L-TRiP(cast)-9
Risk of PTS in patients with asymptomatic proximal DVT	56.4% at 3 years (inflated vs. symptomatic as untreated)	Same as symptomatic proximal DVT: 32.4% at 3 years	L-TRiP(cast)-9	L-TRiP(cast)-8
Higher risk of bleeding without prophylaxis	0.03% in 8 weeks	Five times base-case value, namely 0.15% in 8 weeks	L-TRiP(cast)-9	L-TRiP(cast)-8
Higher risk of bleeding without prophylaxis	0.03% in 8 weeks	10 times base-case value, namely 0.29% in 8 weeks	L-TRiP(cast)-9	L-TRiP(cast)-9

Scenario description	Base-case parameter value	Alternative parameter value	Optimal strategy when valuing a QALY at £20,000	Optimal strategy when valuing a QALY at £30,000
Proportion of symptomatic DVTs that are distal	50% distal	0% distal (all proximal)	L-TRiP(cast)-9	L-TRiP(cast)-8
Proportion of symptomatic DVTs that are distal	50% distal	100% distal (none proximal)	L-TRiP(cast)-9	L-TRiP(cast)-8
Proportion of asymptomatic DVTs that are distal	84% distal	0% distal (all proximal)	L-TRiP(cast)-8	L-TRiP(cast)-8
Proportion of asymptomatic DVTs that are distal	84% distal	100% distal (none proximal)	L-TRiP(cast)-9	L-TRiP(cast)-9
Increased VTE baseline risk	8.39% total VTE with 1.34% symptomatic DVT or PE	Three times baseline, namely 25% total VTE with 4.01% symptomatic DVT or PE	L-TRiP(cast)-6	Prophylaxis for all
Decreased VTE baseline risk	8.39% total VTE with 1.34% symptomatic DVT or PE	One-third of baseline, namely 2.8% total VTE risk with 0.45% symptomatic DVT or PE	Prophylaxis for none	L-TRiP(cast)-10

N/A, not applicable.

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An assumption was made regarding the resource use associated with management of PTS based on clinical expert advice. A costing study from the USA[146] reported higher costs, possibly related to more aggressive management of PTS. Whether or not using these higher cost estimates changed the conclusions was tested; it was found that the optimal strategies did not change, suggesting that the costs of managing PTS are not an important source of decision uncertainty.

It should also be noted that the PSA does not incorporate any uncertainty related to the estimates of sensitivity and specificity. Therefore, a scenario analysis was conducted in which, for each strategy, the specificity was fixed and the sensitivity was reduced so that it fell half-way between the observed value and the line on the ROC curve, which represents a tool that is no better than random selection. The alternative points are shown in *Figure 23*. The approximate AUC for the alternative points is 0.62, which is in the lower range of the CI for the AUC for the L-TRiP(cast) score is the plaster cast subgroup of the derivation cohort (AUC mean 0.76, 95% CI 0.66 to 0.86).[32] A similar AUC was achieved when L-TRiP(cast) score was validated in a subgroup of patients having plaster cast in the THE-VTE study (0.77, 95% CI 0.58 to 0.96) but a much better AUC was achieved when it was validated in the Milan study (0.95, 95% CI 0.91 to 0.99).[32] It can be seen in *Figure 24* that, in this scenario assuming a lower AUC, the ICER for moving from each L-TRiP(cast) cut-off score to the next is fairly constant, such that the gains in QALYs when increasing the numbers treated are fairly proportional to the gains in cost across all L-TRiP(cast) cut-off scores. In this scenario, treatment for all is the optimal strategy when valuing a QALY at either £20,000 or £30,000. This tells us that the shape of the ROC curve is important in determining whether or not risk assessment tools can be used to target treatments more cost-effectively. If the tool used is less efficient at identifying the patients at risk, as indicated by a lower AUC, then a strategy of treating all patients would be most cost-effective. It was examined how much the sensitivity and specificity values could change before the RAM based thromboprophylaxis became

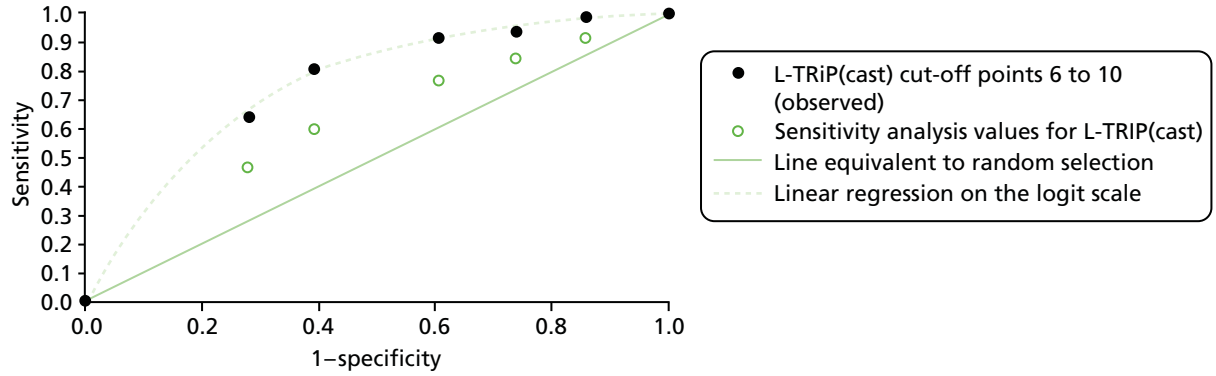

FIGURE 23 The ROC curve for the observed sensitivity and specificity values for L-TRiP(cast)-6 to L-TRiP(cast)-10 and the alternative values used in the sensitivity analysis.

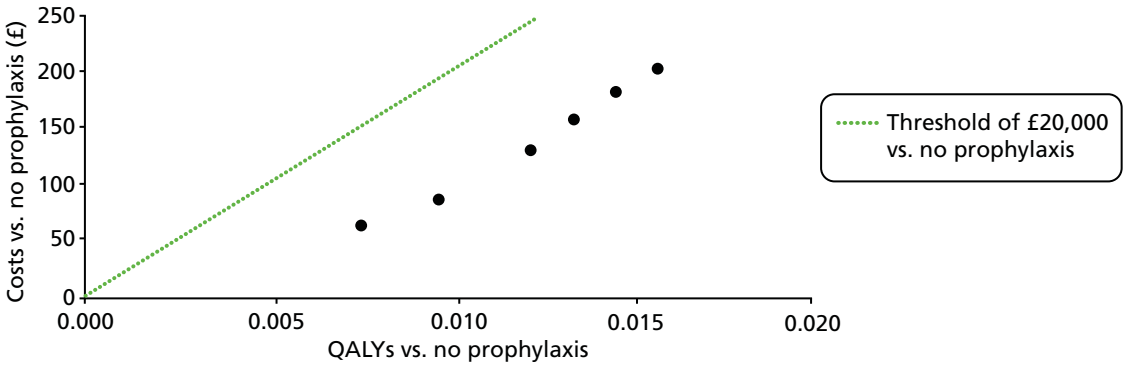

FIGURE 24 Cost-effectiveness plane when assuming that L-TRiP(cast) performs less well than observed by Nemeth *et al.*[32] (AUC of 0.62 instead).

extendedly dominated by treatment for all (i.e. when the ICER vs. no treatment was the same for both). It was found that for a specificity of 55%, the sensitivity would need to fall to 49% before thromboprophylaxis using a RAM became extendedly dominated by thromboprophylaxis for all. However, the absolute QALY gains would be 42% lower than the optimal point on the ROC curve and the costs would be only 16% lower.

Given that the use of a decision tool would result in clinical time being spent for every patient who has lower-limb immobilisation, it was important to evaluate whether or not the assumption regarding the time taken for risk assessment was associated with significant decision uncertainty. The time taken was changed from 5 minutes to 20 minutes and it was found that this had an impact on the ICER only for L-TRiP(cast)-10 versus no prophylaxis; as this remained < £20,000, L-TRiP(cast)-9 remained optimal.

Whether or not the exclusion of costs related to CRNMB had an important impact on the model conclusions was examined and it was found that the optimal strategies did not change when assuming that all patients with CRNMB attended ED for assessment.

It was initially planned to have a zero rate of PTS in patients with asymptomatic distal DVT based on clinical expectations that the rate of PTS would be low in this group. Given that we had identified that PTS following distal DVT was an important driver of uncertainty in the model, a scenario analysis was conducted with a zero rate of PTS for asymptomatic distal DVT. Under this assumption, L-TRiP(cast)-9 was still the optimal strategy when willing to pay £20,000 per QALY but L-TRiP(cast)-8 had an ICER of > £50,000 compared with L-TRiP(cast)-9. In addition, under this scenario, prophylaxis for all had an ICER of £26,962 versus prophylaxis for none. This is because the marginal gains of preventing VTE are smaller when PTS risk is limited to the minority with proximal DVTs or symptomatic distal DVTs.

There was some uncertainty regarding the rate of PTS in asymptomatic proximal DVT that remains undetected and untreated, as most of the studies that identified asymptomatic proximal DVT treated patients. It was examined whether or not the conclusions varied if assuming the same rate of PTS as observed in symptomatic proximal DVT but it was found that the optimal strategies were unchanged.

The estimates of the proportion of symptomatic DVTs that are proximal were based on 16 DVTs reported in a single study.[59] To determine if this factor was an important driver of cost-effectiveness, the proportion was varied from 0% to 100%; it was found that this had no impact on the optimal strategy when valuing a QALY at either £20,000 or £30,000.

Similarly, as the estimates of the proportion of asymptomatic DVTs that are distal was based on a small number of events, an extreme analysis was conducted to see if varying the proportion from 0% to 100% had a large impact on the conclusions. It was found that, when assuming that all asymptomatic DVTs are distal, the optimal strategy was L-TRiP(cast)-9 when valuing a QALY at either £20,000 or £30,000. Conversely, when assuming that all asymptomatic DVTs are proximal, the optimal strategy was L-TRiP(cast)-8 when using a willing-to-pay threshold of either £20,000 or £30,000 per QALY.

Given that the major risk of adverse effects to patients is the risk of a bleed following prophylaxis, a threshold analysis was conducted to see how much higher the bleed risk in the general population would need to be to change the optimal strategy. It was found that L-TRiP(cast)-9 was optimal at £20,000 per QALY until the bleed risk reached 30 times that assumed in the base-case analysis. However, a sixfold increase in bleed risk in the population was required to make L-TRiP(cast)-8 have an ICER of > £30,000 per QALY. Furthermore, when the bleed risk is 15-fold higher than assumed in the base-case analysis, the treat-all strategy is no longer cost-effective relative to the treat-none strategy at a threshold of £20,000 per QALY.

The risk of VTE without prophylaxis was increased and decreased threefold; it was found that this had a significant impact on the optimal strategy, with a threefold increase resulting in treating all being the optimal strategy when valuing a QALY at £30,000, and a threefold decrease resulting in treat none being optimal when valuing a QALY at £20,000. For a strategy of treat all to result in fewer QALYs gained than

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lost, namely for there to be a net harm to patients, the VTE risk would need to be < 9% of its base-case value, suggesting that baseline risks would need to be substantially lower than thought before prophylaxis would be at risk of doing more harm than good to a patient's health. However, at this level of risk, none of the prophylaxis strategies would be cost-effective.

Summary of key findings

- The benefits of thromboprophylaxis in terms of reducing VTE outweigh the harms in terms of increased bleeding risk in the modelled population.
- Thromboprophylaxis for all has an ICER of £13,524 compared with thromboprophylaxis for none.
- When considering whether or not the cost-effectiveness of thromboprophylaxis can be improved by using a RAM to target thromboprophylaxis, the optimal strategy would be to use the L-TRiP(cast) score with a threshold score of 9 if the £20,000-per-QALY threshold is used and with a threshold score of 8 if the £30,000-per-QALY threshold is used.
- An optimal RAM would be expected to operate with a sensitivity of 84–89% and specificity of 46–55%, assuming the ROC curve for the L-TRiP(cast) score reflects the typical trade-off between sensitivity and specificity in risk assessment.

Chapter 5 Discussion

Statement of principal findings

Clinical effectiveness reviews

Pharmacological thromboprophylaxis for preventing venous thromboembolism

In the meta-analysis, it was found that thromboprophylaxis with LMWH reduced any VTE (OR 0.52, 95% CrI 0.37 to 0.71), clinically detected DVT (OR 0.40, 95% CrI 0.12 to 0.99) and PE (OR 0.17, 95% CrI 0.01 to 0.88) compared with no thromboprophylaxis. The effect of LMWH thromboprophylaxis varied between different VTE outcomes but all estimates were consistent with an approximate halving of risk. The number of deaths and bleeding events were too small to draw reliable conclusions. Thromboprophylaxis with fondaparinux also reduced any VTE (OR 0.13, 95% CrI 0.05 to 0.30) and clinically detected DVT (OR 0.10, 95% CrI 0.01 to 0.94) compared with no thromboprophylaxis, but the effect on PE was inconclusive (OR 0.47, 95% CrI 0.01 to 9.54). Event rates for symptomatic DVT and PE were generally low across the studies, so an approximate halving of risk may result in a small absolute risk reduction. Network meta-regression did not identify evidence of effect modification associated with population characteristics, type of injury, type of immobilisation or duration of treatment. There was evidence of difference in the effect of different types of LMWH used, with certoparin having the highest probability of the greatest effect on any VTE, but this was based on findings from one study.[52]

Individual risk factors associated with venous thromboembolism risk

In the systematic review, it was found that only older age was consistently associated with increased risk of VTE across the included studies. Four studies[53,60,70,71] showed that higher BMI was associated with increased risk and six studies[11,50,52,53,69,70] show associations between injury type and risk of VTE. All studies were deemed to be at moderate[23,50,52,53,60,68,71] or serious[9,11,64–67,69,70] risk of bias overall following structured quality assessment. The use of individual risk factors to predict VTE risk in people with lower-limb immobilisation due to injury is, therefore, based on limited and weak evidence.

Risk assessment models for prediction of venous thromboembolism risk

The systematic review identified a number of RAMs but only two studies[32,82] (both case–control design) provided estimates of sensitivity and specificity for three of the RAMs. The L-TRiP(cast) score[32] using a threshold score of 8 (sensitivity 92.6%, specificity 39.7%) or 9 (sensitivity 80.8%, specificity 60.8%) may have appropriate accuracy for use in practice but these estimates are subject to considerable uncertainty.

Expert consensus study

The Delphi study resulted in agreement that the following were potentially useful predictors of VTE in lower-limb immobilisation due to injury: age, BMI of > 30 kg/m^2, active cancer, pregnancy/puerperium, thrombophilia, prior VTE, surgery in the previous 3 months, exogenous oestrogen, lower-limb paralysis, superficial thrombophlebitis, Achilles tendon rupture, above-knee plaster cast and rigid immobilisation in a cast (as opposed to removable immobilisation). Most of the predictors agreed by the experts were not supported by evidence in the systematic review. Therefore, it appears that experts are willing to draw on evidence from other patient groups, pathophysiological knowledge and their clinical experience to identify predictors of VTE.

Most of the agreed predictors were included in one or more of the RAMs, presumably reflecting the role of clinical expertise in developing most of the RAMs. However, the expert group were unable to reach consensus on many potential predictors, including many variables that were included in one or more RAMs. The differences between RAMs are likely to reflect differences in expert opinion, which may, in turn, reflect the lack of available evidence for VTE predictors in lower-limb immobilisation due to injury.

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Economic evaluation

Decision-analytic modelling compared thromboprophylaxis for all people with lower-limb immobilisation due to injury with thromboprophylaxis for none and risk-based approaches [i.e. the L-TRIP(cast) score was used to select higher-risk patients for thromboprophylaxis]. Effectiveness analysis suggested that the rate of serious adverse outcomes (ICH or death from VTE or bleeding) would be very low regardless of the approach used (around 1 in 4000). Rates of symptomatic DVT and non-fatal PE would be higher (around 22 to 41 per 10,000 and 49 to 91 per 10,000, respectively) and varied across the strategies. The total number of major bleeds, including fatal and non-fatal ICHs, ranged from 4.03 per 10,000 with no thromboprophylaxis (reflecting baseline population rates and bleeding as a result of treatment of subsequent VTE) to 5.38 per 10,000 when thromboprophylaxis is given to all. The higher rates of VTE events compared with bleeding events meant that overall quality-adjusted life expectancy increased in accordance with the proportion of the population receiving thromboprophylaxis with each strategy. It therefore appears that the benefits of thromboprophylaxis in terms of reducing VTE outweigh the harms in terms of increased bleeding risk in the modelled population.

Cost-effectiveness analysis comparing thromboprophylaxis for all with thromboprophylaxis for none showed that thromboprophylaxis for all gained a mean of 0.0147 QALYs at a mean cost of £204 per patient, with an ICER of £13,524. This suggests that, if no acceptable RAM is available, then thromboprophylaxis for all would be cost-effective according to NICE thresholds, but there was some uncertainty in this estimate, with a 24% probability that thromboprophylaxis for all is not cost-effective at the £20,000-per-QALY threshold.

Cost-effectiveness analysis comparing thromboprophylaxis for all, thromboprophylaxis according to varying thresholds of the L-TRiP(cast) score and thromboprophylaxis for none showed that the optimal strategy would use the L-TRiP(cast) score with a threshold of 9 if the £20,000-per-QALY threshold is used and with a threshold of 8 if the £30,000-per-QALY threshold is used. Analyses to determine the optimal trade-off between sensitivity and specificity suggested that INMB is maximised when sensitivity is 84% and specificity is 55% when the £20,000-per-QALY threshold is used, or when sensitivity is 89% and specificity is 46% when the £30,000-per-QALY threshold is used. An optimal RAM would therefore be expected to operate with a sensitivity of 84–89% and a specificity of 46–55%, assuming that the ROC curve of the L-TRiP(cast) score is typical of RAMs.

The EVPI analysis suggested that the most important parameters for decision uncertainty were the utility value for PTS, the effectiveness of thromboprophylaxis in reducing VTE, the probability of PTS for patients with distal DVT and the utility decrement associated with taking thromboprophylaxis. The value of reducing the decision uncertainty further was low on a per-patient basis. However, the uncertainty surrounding estimates of RAM accuracy in the PSA could not be appropriately reflected. As noted in the review of RAMs, these estimates are based on very weak and limited data, and are therefore likely to be subject to substantial uncertainty.

Strengths and limitations of the assessment

Clinical effectiveness review

Pharmacological thromboprophylaxis for preventing venous thromboembolism

The meta-analysis synthesised data from 6857 participants in 13 randomised trials that were judged to have a low risk of bias or some concerns only for most quality criteria. This represents a large, methodological robust data set across a variety of settings that allows us to draw generalisable conclusions. Reasonably precise estimates of the effect of thromboprophylaxis compared with control could be produced for most outcomes. Statistical power was more limited for uncommon outcomes, such as PE, but even here it was possible to generate an estimate that suggested a statistically significant effect. It was also possible to undertake a NMA to compare across three alternatives: (1) LMWH, (2) fondaparinux and (3) no thromboprophylaxis.

A recent Cochrane meta-analysis by Zee *et al.*[18] reported data from eight trials,[49,51–56,59] including 3680 participants, that compared thromboprophylaxis with no treatment or placebo. They found that LMWH was associated with a significantly reduced risk of any DVT (OR 0.45, 95% CI 0.33 to 0.61) and symptomatic VTE (OR 0.40, 95% CI 0.21 to 0.76) but not PE (OR 0.50, 95% CI 0.17 to 1.47). Zee *et al.*[18] excluded four trials that were included in this analysis (Goel *et al.*,[50] Selby *et al.*,[58] Gehling *et al.*[23] and Samama *et al.*[57]), and one additional trial was published after their updated meta-analysis (Zheng *et al.*[60]). Two of the trials were excluded because they focused on operatively treated fractures rather than immobilisation (Goel *et al.*[50] and Selby *et al.*[58]), one because the comparator was aspirin (Gehling *et al.*[23]) and one because the intervention was fondaparinux rather than LMWH (Samama *et al.*[57]). The inclusion of these trials has ensured that this analysis is more comprehensive and provides more precise estimates of effectiveness, but at the expense of greater heterogeneity.

This analysis was inevitably limited by the primary data. The variety of settings and patient groups may be a strength in terms of increasing generalisability; there was evidence of heterogeneity of effect for many of the outcomes, suggesting that effects may differ between populations. Three trials[23,52,53] were judged as having a high risk of bias on the basis of outcome ascertainment being potentially subject to bias in an open-label trial. One trial that administered aspirin to the control group was included on the basis that NICE guidelines on VTE[1,24] do not consider aspirin or other antiplatelet agents to be appropriate for VTE prophylaxis and aspirin is not indicated as a treatment for VTE prophylaxis in lower-limb immobilisation.[21,25,26] If aspirin has a significant prophylactic effect, then this trial may underestimate the effect of thromboprophylaxis.

The primary studies had a number of selection criteria that limit the ability to apply the findings to certain populations. Patients at a high risk of VTE (such as those with active cancer, thrombophilia, previous VTE or pregnancy/puerperium) and those with an increased risk of bleeding were often excluded. The studies generally included patients with rigid immobilisation rather than those with a degree of movement or a removable cast or splint, so the findings may be applicable only to those with full immobilisation.

The analysis included a substantial number of participants but the event rates for some outcomes were very low. As a consequence, it was not possible to produce reliable estimates of the effect of thromboprophylaxis on major bleeding or death. The low rate of bleeding provides some reassurance that thromboprophylaxis is not causing a clinically important rate of serious adverse outcome in this population but this may not be applicable to patients at a higher risk of bleeding.

Individual risk factors associated with venous thromboembolism risk

This is the first systematic review conducted to look directly at individual risk factors increasing the risk of VTE in patients with lower-limb injury immobilised in plaster, discharged to an outpatient setting. This is an important distinction, as the population of interest differs markedly from generic thrombosis data sets; patients with lower-limb injury tend to be younger, more active and devoid of comorbidity than those presenting with unprovoked or cancer-associated thrombosis. Previous work has attempted to address a similar issue in patients undergoing elective foot and ankle surgery.[72,73,81] We consider this to be a different population because of the absence of acute blunt trauma causing local vessel/endothelial injury, expert postoperative immobilisation and often bespoke immobilisation regimes.

The review was undertaken in accordance with guidelines published by the Centre for Reviews and Dissemination[75] and the protocol was registered with the PROSPERO register.[38] Clinical experts were involved throughout as checkers and to assess the validity and applicability of research during the project. Descriptive statistics were reported to provide plain insight into the limited evidence base applicable to the subject matter and the scientific concerns regarding validity of the data.

The review was limited by a lack of studies specifically examining risk prediction in lower-limb immobilisation due to injury. Therefore, studies, such as RCTs, that were designed for another purpose but reported risk predictors in their analyses were included. The studies of risk prediction were a combination of prospective cohorts and retrospective health database registries. Both have significant limitations. Retrospective studies

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of health database registries may have large numbers but may be limited by poor data quality and failure to accurately ascertain outcomes. Prospective cohorts may have better-quality data but lack statistical power because of smaller numbers. The included studies demonstrated high levels of heterogeneity, so a meta-analysis could not be undertaken.

Several studies included patients receiving operative intervention and short inpatient stays. Following the introduction of NICE guidance on thromboprophylaxis to reduce the risk of hospital-acquired thrombosis, it is reasonable to assume that, in a modern health-care environment, all these patients would receive some form of routine thromboprophylaxis.[24] For this reason, inclusion of these patients could lead to false reassurance regarding low incidence of VTE. However, patients with a short inpatient stay (< 5 days) were considered to fit within the scope of interest; these patients often remain temporarily immobilised for a period of 4–8 weeks in total, and debate persists about the role of thromboprophylaxis that is similar to debate around patients discharged directly from the ED.

All the studies within the review were classed as being at moderate or severe risk of bias. Therefore, any conclusions regarding the influence of risk factors on the subsequent development of VTE drawn are based on weak evidence and have the potential to be inaccurate.

Risk assessment models for prediction of venous thromboembolism risk

This review had strengths of following recognised guidance, prospective registration, a clear protocol and drawing on appropriate clinical and reviewing expertise. It was anticipated that the data would not allow meta-analysis; therefore, descriptive analyses only were planned.

A previous review by Watson *et al.*[82] identified two of the RAMS included in this review (Keenan *et al.*[31] and Roberts *et al.*[17]), along with three generic RAMs that could be applied to people with lower-limb immobilisation due to injury.[210–212] Watson *et al.*'s[82] review then undertook primary analysis of these two RAMs to estimate sensitivity and specificity for predicting VTE. This review included these data and a number of other studies[32,78–81] but only the study of Nemeth *et al.*[32] provided estimates of sensitivity and specificity.

The review is, therefore, limited by the paucity of data. Furthermore, case–control designs are known to be associated with a risk of bias,[213] so sensitivity and specificity may have been overestimated. The study by Watson *et al.*[82] was relatively small (21 cases and 21 controls), so estimates of sensitivity and specificity are imprecise. The study by Nemeth *et al.*[32] involved validation using two data sets but each only contained a small number of patients with lower-limb immobilisation (32 cases, 7 controls, and 143 cases, 8 controls, respectively).

Expert consensus study

The Delphi study involved a wide range of experts from emergency medicine, orthopaedics and haematology, and used recognised techniques to attempt to achieve consensus without supressing divergent views. There were acceptable levels of participation and the experts seemed to understand and engage with the process.

Expert consensus is considered to represent weak evidence and is usually sought only when (as in the case of VTE risk prediction in lower-limb immobilisation) other forms of evidence are weak or absent. It is hoped that experts will draw on weak evidence appropriately and combine it with clinical experience and pathophysiological understanding. However, experts may be subject to a number of cognitive biases that may influence their judgement. For example, the availability heuristic may lead experts to place undue emphasis on a risk predictor if they have seen a case in which a patient with that characteristic developed VTE after lower-limb immobilisation.

The Delphi process achieved consensus on 13 predictors but failed to achieve consensus on many more. This is perhaps unsurprising in the light of the limited evidence base relevant to the population of interest.

It could be argued that achieving consensus on 13 predictors reflects undue certainty in the light of the limited evidence to support these judgements.

Economic evaluation

A key strength of the de novo economic analysis is that it is able to synthesise the evidence on both benefits and harms to assess the overall impact of different thromboprophylaxis strategies in people having lower-limb immobilisation. Therefore, it was possible to explore the trade-off between preventing VTE and the adverse effects associated with prophylaxis, including the direct impact of subcutaneous injections of anticoagulants on patient quality of life. The estimates of clinical effectiveness were based on the systematic review and meta-analysis and the decision uncertainty associated with the uncertainty in the estimates of clinical effectiveness was captured in the model. The availability of the ROC curve for the L-TRiP(cast) score allowed us to explore what the optimal sensitivity and specificity might be for a tool to identify patients needing thromboprophylaxis when assuming that any future tool would have similar characteristics to L-TRiP(cast).

The main limitation of the economic analysis was that it was not possible to incorporate the uncertainty in the sensitivity and specificity estimates for the RAMs within the PSA as these were not reported. A scenario analysis was conducted, which suggested that the cost-effectiveness of using a RAM to guide thromboprophylaxis is dependent on the performance characteristics of the RAM, but it was not possible to quantify the decision uncertainty associated with the RAMs currently available.

Another potential limitation of the economic analysis is that a cohort modelling approach was used, which estimates outcomes based on average patient characteristics and, therefore, does not allow for heterogeneity in patient outcomes on the basis of patient characteristics. However, whether or not variation in outcomes on the basis of age would significantly alter the conclusions of the model was explored; it was found that the optimal thromboprophylaxis strategy was not sensitive to variations in age.

The estimate of the incidence of major bleeds during thromboprophylaxis was based solely on the incidence of GI bleeds and ICHs; therefore, this may have underestimated the impact on costs and QALYs of major bleeds at other sites. In addition, CRNMBs were excluded from the model. However, the sensitivity analyses suggest that neither of these factors is likely to have significantly biased the results, as incorporating costs for CRNMBs and increasing the risk of bleeding during thromboprophylaxis fivefold did not alter the main conclusions.

Another potential limitation is that many of the data sources quantifying the impact of VTE on patients, such as the incidence and quality-of-life impact of post-thrombotic syndrome following DVT, were not specific to patients having lower-limb immobilisation. Therefore, the benefits of thromboprophylaxis in this population may have been overestimated if the risks of complications following DVT are lower in patients having lower-limb immobilisation than in other groups at risk of VTE.

Uncertainties

The main uncertainty identified in the analysis related to the prognostic accuracy of RAMs. The estimates were based on very weak data but suggested that L-TRiP(cast) score, using a threshold score of 8 or 9, would be an optimal strategy. However, this conclusion holds only if the prognostic accuracy of L-TRiP(cast) is confirmed. More precise and accurate estimates of the prognostic accuracy of RAMs are required but this may be difficult to achieve if higher-risk patients receive thromboprophylaxis as standard care.

Most of the effectiveness data for thromboprophylaxis relate to LMWH, with a smaller number relating to fondaparinux. LMWH is administered by injection, thereby incurring additional costs and inconvenience for patients. DOACs are taken orally and, therefore, do not incur these additional costs and inconvenience. However, no studies evaluating the effectiveness of DOACs as thromboprophylaxis for lower-limb

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immobilisation were found. DOACs have been used for thromboprophylaxis in other conditions and have been shown to be generally as safe and effective as LMWH.[214–216] On this basis, a secondary economic analysis was undertaken, assuming that DOACs were as effective as LMWH and could be delivered at lower cost and with less inconvenience. This suggested that at the £30,000-per-QALY threshold, DOACs would be cost-effective in a thromboprophylaxis-for-all strategy, even compared with an optimal RAM. The obvious uncertainty affecting this conclusion is whether or not it can be assumed that DOACs are at least as effective and safe as LMWH.

The value-of-information analysis showed that the most important parameters for decision uncertainty were the utility value for PTS, the effectiveness of thromboprophylaxis in reducing VTE, the probability of PTS for patients with distal DVT and the utility decrement associated with taking prophylaxis. The importance of uncertainty around PTS is consistent with the observation from the modelling that the benefit of thromboprophylaxis lies in avoiding long-term complications rather than avoiding short-term adverse outcomes. The utility decrement associated with taking prophylaxis is relevant to the potential role of DOACs discussed in the paragraph above, because most of the decreased utility is assumed to be as a result of the need to administer LMWH by injection.

The primary studies for the review of effectiveness, and, by implication, the economic model, excluded a number of important patient groups. Patients at a high risk of VTE, because of active cancer, previous VTE, pregnancy/puerperium or thrombophilia, were excluded but, as they have a higher risk of VTE, these patients are even more likely to benefit from thromboprophylaxis. Patients with an increased risk of bleeding were also excluded; these represent a more difficult group with regard to guiding recommendations. The model assumed a low risk of bleeding so, clearly, the findings of modelling analysis cannot be applied to this group. It may be possible to develop the model to provide estimates of overall effectiveness if bleeding risk is higher, but increased bleeding risk is often associated with conditions that also increase the risk of VTE. It is, therefore, unlikely that general recommendations can be made for those with an increased risk of bleeding and decisions will have to be made on an individual case-by-case basis.

The primary studies for the review of effectiveness were also generally limited to patients with full, rigid immobilisation and did not include those with more limited immobilisation, such as splints that allow a degree of movement and removable splints or casts. There are pathophysiological reasons for expecting the VTE risk to be lower for these patients and the benefit of thromboprophylaxis to be consequently lower or even negligible. However, current evidence is insufficient to determine whether or not this is the case and what, if any, role there may be for thromboprophylaxis.

Patient and public involvement

The patient and public involvement (PPI) representatives were involved in a number of elements of the study and met regularly with the project team to discuss the interpretation and implications of the emerging findings. The PPI representatives identified the following issues at these meetings:

- The risks and benefits of thromboprophylaxis need to be explained to patients in clear and comprehensible terms so that they can participate in decision-making. It would be helpful to provide this information in written form, along with information about the symptoms of VTE and what to do if they have concerns.
- It was considered acceptable to provide thromboprophylaxis in accordance with the patient's risk of VTE. It may be acceptable for patients to be involved in assessing their risk of VTE but this should be done in consultation with a health professional.
- If a risk-based approach was used and a patient was assessed as not requiring thromboprophylaxis on the basis of lack of cost-effectiveness when the risk is low, then they should be informed of the possible benefit of thromboprophylaxis in case they wish to arrange their own treatment.

- Use of LMWH for thromboprophylaxis has clear disadvantages related to the inconvenience and discomfort of injections. Oral treatment would be much more acceptable but the risks of DOACs need to be explained to patients, specifically the lack of a means of reversing DOACs in the event of bleeding. The lack of research into the use of DOACs as thromboprophylaxis for lower-limb immobilisation was also a concern.
- If the risk of adverse outcome is low (i.e. < 1 in 100), then patients may not think the benefit of thromboprophylaxis is worth the inconvenience and discomfort of LMWH.
- An implementation study of risk-based thromboprophylaxis, potentially involving comparison of different approaches, would be acceptable provided it was justified on the basis of current practice being variable and the need to identify best practice.

Assessment of factors relevant to the NHS and other parties

Current NICE guidance[1] recommends that clinicians consider pharmacological VTE prophylaxis with LMWH or fondaparinux for people with lower-limb immobilisation whose risk of VTE outweighs their risk of bleeding. This analysis suggests that the risk of VTE outweighs the risk of bleeding for any patient who does not have risk factors for bleeding. The review for the NICE guidance[1] did not identify any relevant economic evidence and only considered the unit costs for different agents (LMWH and fondaparinux). This economic analysis showed that thromboprophylaxis with LMWH is cost-effective compared with no thromboprophylaxis and a risk-based strategy is potentially optimal, when valuing a QALY at £20,000 to £30,000. The NICE guidance[1] also recommends that clinicians assess all patients to identify the risk of VTE and bleeding, but does not identify or recommend any specific RAM for lower-limb immobilisation. This analysis suggests that the L-TRiP(cast) score with a threshold score of 8 or 9 could have appropriate prognostic accuracy for cost-effective risk stratification in lower-limb immobilisation but the available estimates of prognostic accuracy are very uncertain.

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Chapter 6 Conclusions

Implications for service provision

The meta-analysis of effectiveness suggested that thromboprophylaxis in lower-limb immobilisation due to injury approximately halves the risk of any VTE and is associated with reductions in the risks of symptomatic DVT and PE. However, the evidence is limited to LMWH and fondaparinux, so it is unclear whether or not the findings can be extrapolated to DOACs. This in an important consideration as the absolute risks of clinically relevant VTE are low and patients may not be willing to submit to the inconvenience of parenteral treatment to reduce a relatively small risk.

The economic analysis suggested that thromboprophylaxis is effective and cost-effective compared with no thromboprophylaxis, so it would be reasonable to offer thromboprophylaxis to patients undergoing lower-limb immobilisation due to injury. This is based on the potential for thromboprophylaxis to reduce the risk of DVT and PE, with their long-term sequelae, rather than any meaningful reduction in the risk of mortality. The economic analysis also suggested that risk-based thromboprophylaxis using a RAM with a sensitivity of 84–89% and specificity of 46–55% is, potentially, the most cost-effective approach. This is similar to the prognostic accuracy of the L-TRiP(cast) score using a threshold score of 8 or 9, although estimates of sensitivity and specificity are very uncertain.

The cost-effectiveness of using an appropriate RAM is based on (1) reducing the number of people requiring thromboprophylaxis (and thus costs) compared with thromboprophylaxis for all, with only a small reduction in effectiveness and (2) increasing the number of VTE events prevented (and this effectiveness) compared with no thromboprophylaxis, with only a small increase in costs. Assuming universal acceptance by patients, a risk-based strategy, as outlined in the previous paragraph, would cost the English NHS £6M per year and gain 891 QALYs compared with no thromboprophylaxis. Compared with this, providing thromboprophylaxis for all would cost an additional £8.2M per year and gain an additional 160 QALYs. These estimates are not intended to be precise figures, as strategies are unlikely to be implemented perfectly and patients may decline treatment, but they provide an indication of the potential implications of different strategies for service provision.

The PPI representatives highlighted the importance of patient involvement in decision-making and the need for clear and comprehensible information to be provided. This has important implications for service provision. To participate in shared decision-making, patients need to understand that the risk of clinically important VTE is relatively low but that it can be reduced by thromboprophylaxis. The effectiveness of thromboprophylaxis relies on the benefits of reducing DVT and PE (and their sequelae), outweighing a small increase in the risk of bleeding, but VTE events may still occur despite thromboprophylaxis. The risks of death from VTE or bleeding after immobilisation due to injury are very small regardless of the treatment strategy, and thromboprophylaxis is unlikely to have any significant impact on the risk of death.

Suggested research priorities

This analysis suggested that risk-based thromboprophylaxis using a RAM with sensitivity of 84–89% and specificity of 46–55% would be the most cost-effective strategy. However, the current evidence base for RAMs is very limited and estimates of sensitivity and specificity are subject to substantial uncertainty. Improving the evidence base for RAMs is therefore a key priority.

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Ideally, a large prognostic cohort study of people experiencing lower-limb immobilisation due to injury would be undertaken to estimate the prognostic accuracy of existing RAMs for VTE and possibly derive a new RAM. However, the evidence of effectiveness and cost-effectiveness provided by this analysis suggests that thromboprophylaxis should be offered to patients in this cohort, or at least those considered as being at a higher risk. Administration of thromboprophylaxis would be expected to reduce the risk of VTE and thus lead to underestimation of the prognostic accuracy of RAMs. Furthermore, the VTE events that were prevented by thromboprophylaxis would be precisely those that we would want a RAM to predict.

A large cohort study could still provide useful information if it is used to evaluate implementation rather than accuracy. It could determine the proportion of the cohort receiving thromboprophylaxis with different RAMs or different thresholds for treatment. It could be used to determine whether or not the low rate of bleeding events is confirmed in practice and, if risk-based thromboprophylaxis were provided, it could be used to determine whether or not the low rate of VTE events is confirmed in low-risk patients who do not receive treatment.

Direct oral anticoagulants could provide the benefits of thromboprophylaxis without the costs, inconvenience and discomfort of injections, which the PPI representatives identified as a potential barrier to patient acceptance. However, all the evidence of effectiveness in this review related to LMWH or fondaparinux. Ideally, an appropriately powered RCT comparing thromboprophylaxis of DOACs with LMWH would provide evidence of equivalent effectiveness, but such a trial may be prohibitively expensive, especially if it were felt that evidence of effectiveness of DOAC for other indications could be reasonably extrapolated to lower-limb immobilisation.

The most important parameters for decision uncertainty in the value-of-information analysis were related to the efficacy and disutility of receiving prophylaxis, and the long-term complications of PTS, so estimating these parameters should be a priority for future research. The disutility of receiving LMWH injections or oral DOACs could be investigated as part of a cohort study or trial of different types of thromboprophylaxis. The uncertainty around the long-terms effects of PTS mainly relate to subclinical DVT rather than clinically detected and treated DVT, so research to reduce uncertainty around the incidence and disutility of PTS would need to involve long-term follow-up or a retrospective observational study of people following lower-limb immobilisation due to injury.

It is currently unclear whether or not people with limited lower-limb immobilisation (such as splints that allow some movement or removable splints or casts) carry similar risks of VTE to those with full immobilisation. A cohort study of this population, perhaps undertaken alongside a cohort study evaluating risk-based thromboprophylaxis, could determine the risk of VTE and identify risk predictors.

All of these research suggestions would require large numbers of participants to generate meaningful results. There are plenty of eligible participants presenting to the NHS but an efficient research design would be required, using standardised collection of predictor variables and routine data sources for outcomes, to ensure that any study was not prohibitively expensive.

Finally, the PPI representatives identified the need for patients to receive clear and comprehensible communication of the risks and benefits of thromboprophylaxis, including written materials. Research is required to develop information for patients and ways of communicating benefits and risks.

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Appendix 3 - Submitted work 2

Published source is acknowledged as:

Horner DE, Davis S, Pandor A, Shulver H, Goodacre S, Hind D, *et al.* Evaluation of venous thromboembolism risk assessment models for hospital inpatients: the VTEAM evidence synthesis. *Health Technol Assess* 2024;**28**(20). https://doi.org/10.3310/AWTW6200

The submitted work is described in Chapters 4, 8 and 9 of the published source, and therefore only these Chapters are reproduced below. The full published source can be accessed here:

https://www.journalslibrary.nihr.ac.uk/hta/AWTW6200

The decision-analytic modelling described in submitted work 2 has also been published in two shorter-form peer-reviewed journal articles. To avoid duplication, these articles have not been included as separate submitted works, and they are not reproduced in this thesis. However, they are listed here as supportive evidence which demonstrates that the quantity of research in the submitted work is equivalent to two peer-reviewed first-authored journal articles.

Davis, S.; Goodacre, S.; Horner, D, et al. Decision-analysis modelling of effectiveness and cost-effectiveness of pharmacological thromboprophylaxis for surgical inpatients, using variable risk assessment models or other strategies. Journal Thromb Haemost. 2023;21(6):1580-1591. doi.org/10.1016/j.jtha.2023.02.018

https://www.jthjournal.org/article/S1538-7836(23)00166-6/fulltext

Davis S, Goodacre, S, Horner D, et al. Decision-analysis modelling of the effectiveness and cost-effectiveness of thromboprophylaxis for medical inpatients. BMJ Medicine 2024; 3(1): e000408. doi.org/10.1136/bmjmed-2022-000408

https://bmjmedicine.bmj.com/content/3/1/e000408

Chapter 4 Workstream 1 – economic evaluation

Decision problem

Aim

The aim of the independent economic evaluation is to assess the cost-effectiveness of different strategies for selecting hospitalised patients for pharmacological thromboprophylaxis including prophylaxis for all, prophylaxis for none and prophylaxis based on a VTE RAM. Sections of this chapter have been reproduced from Pandor *et al.* under licence CC BY 4.0.[74]

Population

The target population is hospital inpatients, including medical, surgical and trauma patients but excluding critical care patients, children and women admitted to hospital for pregnancy-related reasons. In order to allow for differences in patient characteristics and risks within this very broad population, the economic analysis considered two broad groups as follows:

- acutely ill medical inpatients
- surgical inpatients including both elective and emergency surgery.

The analysis focused on those populations where NG89 (NICE Guideline 89: Venous thromboembolism in over 16s: reducing the risk of hospital-acquired DVT or PE)[8] recommends the use of thromboprophylaxis based on the balance of VTE and bleeding risks. The analysis is not expected to be applicable to very specialist patient groups, such as neurosurgical patients, where the decision whether to use prophylaxis is based on a very individualised approach and the use of a RAM designed for general hospitalised patients is unlikely to be relevant.

Patients identified to be at increased risk of bleeding, such as those identified on the Department of Health risk assessment tool, are assumed not to receive pharmacological thromboprophylaxis under any strategy and are excluded from the model. Therefore, when we refer to a strategy of 'prophylaxis for all', this does not mean offering pharmacological thromboprophylaxis to those identified as being at high risk of bleeding.

We considered whether to model elective and emergency surgical patients separately. However, one of the more established risk-scoring tools for surgical patients, Caprini, has been validated in a mixed population of elective and emergency surgical patients and includes questions that would differentiate emergency surgical patients, such as those who have had fractures, into higher-risk groups. It therefore seemed reasonable to evaluate RAMs for use across the broad category of surgical inpatients and to treat the reason for surgery as a risk factor rather than modelling separate decision-making processes in elective and emergency surgical inpatients.

Trauma patients are not modelled as an explicit subgroup as trauma patients are highly complex, often have critical site bleeding injuries and are not managed within a specific trauma speciality in the UK. Managing speciality is often determined by their main complaint, which means they usually fall under a neurosurgical, spinal, general or orthopaedic speciality and, therefore, fall within the emergency surgical population. In addition, many of the RAMs which have been developed specifically for trauma patients, have been developed and validated in countries where trauma patients are treated within a critical care environment; this cohort is excluded from project scope.

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Patients having elective hip or knee replacements are examined as a specific subset within the surgical inpatient cohort because of procedure-specific national recommendations (NG89); these patients are recommended to have a longer duration of prophylaxis than is typical in other surgical populations.

Strategies for prophylaxis

The prophylaxis interventions examined were chosen based on the recommendations in NG89 as these were selected based on cost-effectiveness modelling and, therefore, should represent the most cost-effective strategies. For most types of surgery, NG89 recommends that low-molecular-weight-heparin (LMWH) is considered if the person's VTE risk outweighs their risk of bleeding. Although the use of mechanical prophylaxis in the form of antiembolism stockings (AES) is generally recommended for surgical patients within NG89, a recent study has shown that LMWH alone is non-inferior to LMWH with AES in elective surgical patients who were assessed as being at moderate or high risk of VTE.[75] Given that it is the use of LMWH that is being driven by risk assessment and not the use of AES, the comparison of interest for the modelling is LMWH versus no LMWH. The conclusions from the modelling should apply equally to patients having mechanical prophylaxis or no mechanical prophylaxis. This is because the model estimates whether it is cost-effective to use a RAM to decide whether to add LMWH to the treatment of patients who would not otherwise receive it and that is not dependent on any underlying care being given, provided that the underlying care is not altered by the addition of LMWH. Further discussion of mechanical thromboprophylaxis was, therefore, considered to be outside the scope of the modelling.

For acutely ill medical patients, LMWH is recommended in NG89 but mechanical prophylaxis is not recommended in acutely ill medical patients. Therefore, for acutely ill medical patients we compare LMWH to no prophylaxis.

When LMWH is used, we assume that it is given for the duration of admission. Although NG89 recommends that LMWH is given for a minimum of 7 days, information from the National VTE Exemplar Centres Network suggests that a pragmatic approach has been taken to the implementation of NG89 with LMWH generally not being prescribed for post-discharge use.[76] Therefore, we assume in the base-case analysis that LMWH is given for the duration of admission, but we also explore a scenario analysis in which it is given for 7 days even if this means post-discharge administration.

In higher-risk populations, such as elective hip and knee replacement, an extended form of pharmacological prophylaxis is recommended in NG89. Therefore, we have modelled these groups as specific subsets of the surgical population in separate analyses, described in *Model inputs for the elective hip replacement and elective knee replacement scenarios*, to determine if the threshold for cost-effective intervention is different in these groups. In addition, NG89 recommends that clinicians should 'consider extending pharmacological VTE prophylaxis to 28 days postoperatively for people who have had major cancer surgery in the abdomen'. Therefore, a scenario analysis is conducted to determine if the threshold for cost-effective intervention is different in general surgical patients having 28 days of LMWH.

In summary, the main comparisons being modelled are:

- acutely ill medical inpatients – LMWH for duration of admission versus no prophylaxis
- surgical inpatients (excluding elective hip and knee replacement) – LMWH for duration of admission (without or without AES) versus no pharmacological prophylaxis (with or without AES).

Although the recommendations in NG89 were informed by modelling to determine the most cost-effective thromboprophylaxis strategy, the analysis did not explore the use of RAMs to determine which patients should be offered prophylaxis. The RAMs have been selected based on the review in the previous chapter. For medical patients, the primary analysis compares a group of several RAMs that have been externally validated within a single cohort as this minimises the risk of introducing bias from comparing tools that have been studied in populations with different characteristics. A secondary

analysis then compares the remaining tools that have been externally validated in different medical cohorts. The number of RAMs for surgical patients was more limited. Therefore, for surgical patients we have included in the primary analysis all tools externally validated in either a surgical or mixed medical and surgical population. In all analyses, the comparator strategies of LMWH for all and LMWH for none are included. The tools evaluated are summarised in *Table 4*.

Modelling methods

Context

The model estimates lifetime costs and QALYs for the different thromboprophylaxis strategies and the comparator of no thromboprophylaxis under a NHS and Personal Social Services perspective. Future costs and benefits are both discounted to their net present value at a rate of 3.5% per annum in accordance with the NICE guide to the methods of technology appraisal.[77] Costs are reported in Great British pounds based on 2020 prices. To achieve this, historical prices used as model inputs were uplifted using the hospital and community health services pay and prices index up to 2016 and the NHS cost inflation index thereafter.[78]

Conceptual model for medical inpatients

The model consists of a decision tree (see *Figure 5*) to capture short-term outcomes followed by a lifetime state transition (Markov) model (see *Figure 6*) to capture the impact of outcomes that result in death or ongoing morbidity. The model estimates outcomes for a cohort of identical patients with average characteristics. In reality, the application of RAMS may lead to treated and untreated patients having different characteristics. Based on clinical advice, age was the patient characteristic considered most likely to result in variation in outcomes within the cohort being risk assessed. We conducted a scenario analysis to explore whether incorporating patient heterogeneity into the model would affect the conclusions by varying the age of the cohort. From this we concluded that the cohort-level modelling approach was adequate and would not introduce significant bias as the optimal strategy was fairly robust to changes in the age.

The decision tree is used to estimate for each strategy: the number of patients receiving thromboprophylaxis, the impact of thromboprophylaxis on VTE outcomes (PEs and DVTs) and the incidence of major bleeds during either thromboprophylaxis or VTE treatment with anticoagulants. Major bleeds were considered to be those meeting the International Society for Thrombosis and Haemostasis (ISTH) definitions for major bleeding for surgical and non-surgical (medical) patients.[79,80] Major bleeds were divided into fatal bleeds, non-fatal intracranial haemorrhages (ICHs) and other major bleeds (referred to as non-fatal non-ICH major bleeds). Gastrointestinal (GI) bleeds were assumed to be a reasonable proxy for non-fatal non-ICH major bleeds and these were assumed to have no

TABLE 4 Risk assessment models (RAMs)

Population	Tools in primary analysis	Tools in secondary analysis
Medical	Caprini (Grant 2016)[38] Kucher (Greene 2016)[39] Padua (Greene 2016) IMPROVE (Greene 2016) Intermountain (Greene 2016)	Padua (Blondon 2018)[30] IMPROVE (Blondon 2018) Geneva (Blondon 2018) Simplified Geneva (Blondon 2019a)[29] Kucher (Woller 2011)[71] Intermountain (Woller 2011) Rothberg (Rothberg 2011)[60]
Surgical	Modified Caprini (Bahl 2010)[26] Pannucci (Pannucci 2014)[54]	
Mixed medical and surgical	Padua (Elias 2017)[36]	

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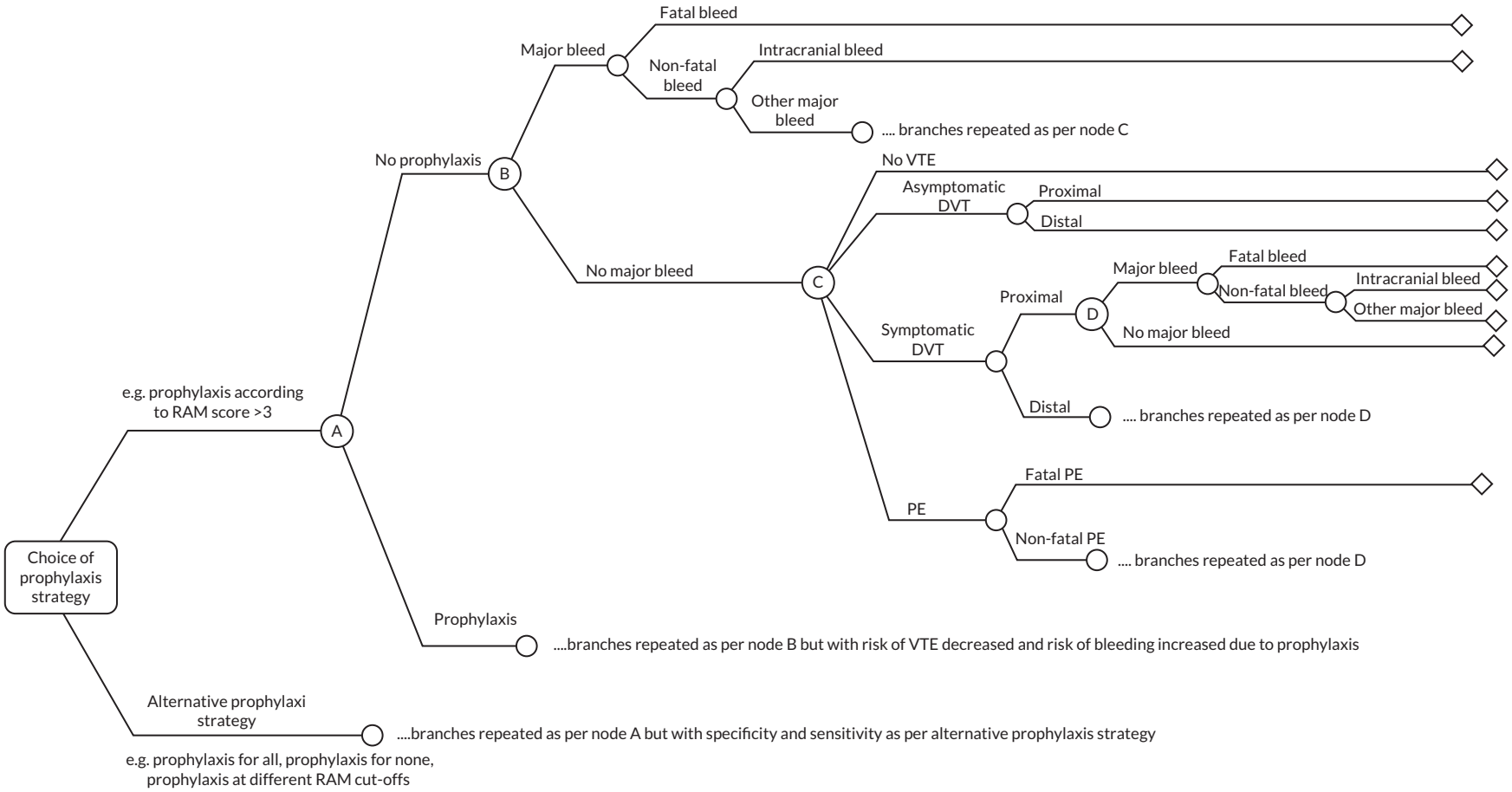

FIGURE 5 Short-term (6-month) decision tree model structure.

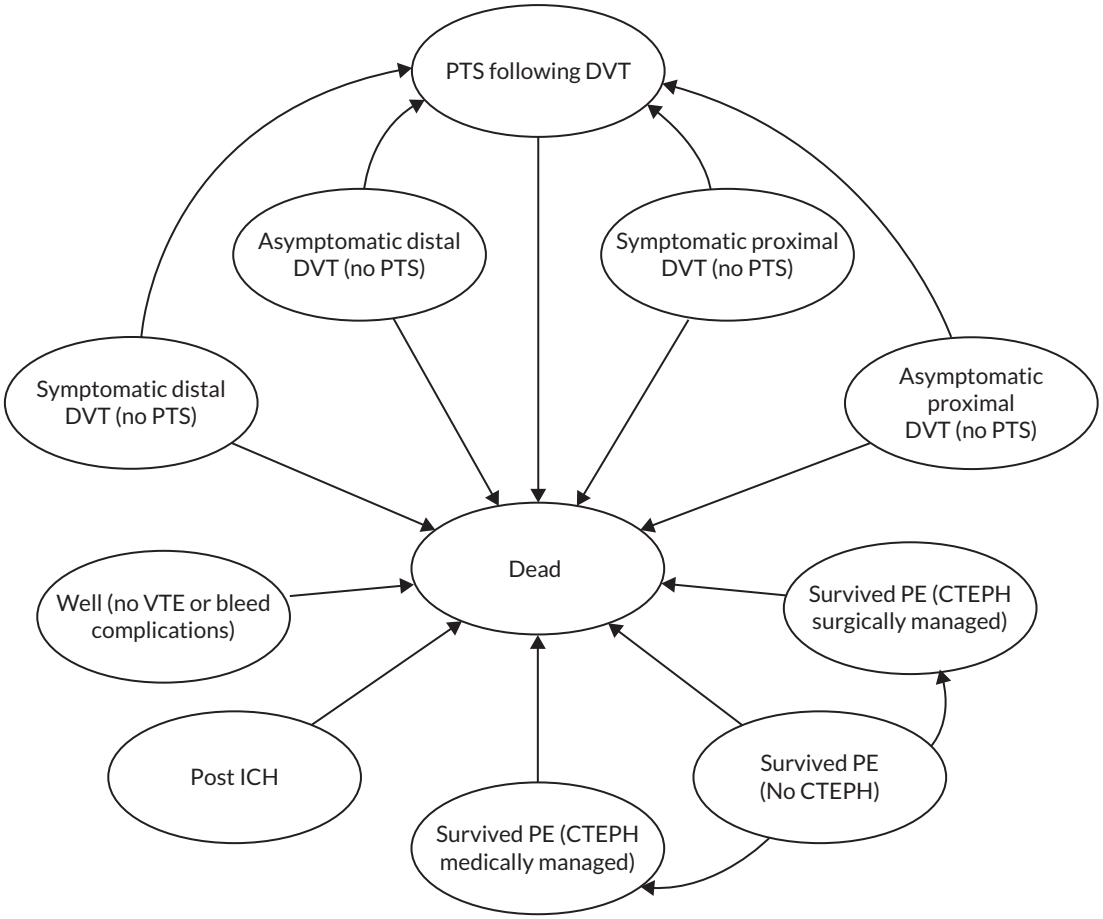

FIGURE 6 Long-term Markov model.

impact on costs or quality of life after 1 month. PEs were divided into fatal and non-fatal events. DVTs were divided first into symptomatic and asymptomatic DVTs and then into proximal and distal DVTs. Symptomatic DVTs and non-fatal PEs are assumed to result in 3 months of anticoagulant treatment. Patients having major bleeds during either prophylaxis or VTE treatment are assumed to stop their anticoagulant medication at the time of the bleed. In our previous analysis of thromboprophylaxis strategies in patients having lower limb immobilisation following injury, we found that the prevention of post-thrombotic syndrome (PTS) following asymptomatic DVT was an important driver of both cost-effectiveness and decision uncertainty due to asymptomatic DVTs being more common than symptomatic DVTs but their long-term consequences being more uncertain.[74] So while asymptomatic DVTs are assumed to remain undetected and untreated, it is important to capture these DVTs in the decision tree phase of the model in order to capture any ongoing morbidity due to PTS in the long-term state-transition model. In the decision tree, any VTE event that is related to the hospital admission is assumed to occur within 90 days of hospital admission. Therefore, a 6-month time frame was considered sufficient to capture the period of VTE risk associated with the hospital admission and the period of treatment following VTE (3 months). Diagnosis of PTS and chronic thromboembolic pulmonary hypertension (CTEPH) is assumed not to occur until the end of the decision-tree phase of the model, as it is difficult to distinguish these chronic complications from acute symptoms during the first 3 months after VTE. The decision tree allows for the possibility that patients not having anticoagulation may have a major bleed during their hospitalisation. The likelihood of VTE and the likelihood of bleeding during treatment for VTE is assumed to be independent of patient characteristics (e.g. age and sex) and independent of whether the patient had major bleeding during hospitalisation. Clinically relevant

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non-major bleeding (CRNMB) is excluded in the base-case analysis as it was considered that CRNMB occurring during hospitalisation would have a minimal impact on costs and quality of life in patients already hospitalised. Heparin-induced thrombocytopenia (HIT) was not included in the model because the most important consequence of HIT is the increased risk of VTE, but any increase in VTE related to HIT in the LMWH arms of the clinical trials would be included within the efficacy estimates for LMWH versus placebo and would, therefore, already be accounted for in the model.

The key model assumptions for the decision tree phase are as follows:

- Bleeding events following hospitalisation are possible in both those having thromboprophylaxis and those having no thromboprophylaxis.
- Bleeds associated with thromboprophylaxis are assumed to occur during prophylaxis and, therefore, before hospital discharge.
- VTE associated with hospitalisation is assumed to occur within 90 days of admission.
- Patients who have major bleeding will stop thromboprophylaxis immediately, but the treatment effect of thromboprophylaxis is assumed to be the same as for those who completed treatment, as patients who bleed are assumed to be adequately anticoagulated.
- The risk of VTE is the same whether or not thromboprophylaxis caused bleeding.
- All patients with symptomatic DVT receive accurate diagnosis and initiate treatment with anticoagulants [3 months of either direct oral anticoagulants (DOACs) or phased anticoagulation].
- Asymptomatic DVTs are not detected and are not treated.
- All PEs are symptomatic and lead to detection and treatment (3 months of either DOACs or phased anticoagulation) in all cases.
- Patients treated for symptomatic DVT and PE have a bleed risk associated with treatment which is assumed to occur during the 3-month treatment period.
- Chronic complications of VTE (CTEPH following PE and PTS following DVT) are assumed to be diagnosed at least 3 months after VTE and therefore occur after any bleeds associated with VTE treatment.
- Deaths due to PE occur before any bleeding associated with the treatment of PE.
- Risk of bleeding during treatment of VTE is independent of whether the patient bled during prophylaxis.
- Risk of VTE, risk of bleeding and risk of PTS/CTEPH are based on average patient characteristics (e.g. age and sex) for the cohort being risk assessed.

A state-transition model (see *Figure 6*) was then used to extrapolate lifetime outcomes including overall survival and ongoing morbidity related to either bleeds or VTE. The health states included within the state-transition model capture the risk of PTS following VTE and the risk of CTEPH following PE. The risk of PTS is dependent on whether the DVT is symptomatic and treated or asymptomatic and untreated, and also whether the DVT is proximal or distal. All patients with PTS are combined in a single health state as costs, utilities and survival are not expected to be affected by whether PTS occurred following proximal or distal DVT. The PTS health state is not split into different severity levels as the utility estimates are based on the average utility across severity levels and the costs are not expected to differ by severity. The CTEPH health state is divided according to whether patients receive medical or surgical management to allow for differential costs and survival between these groups. There is also a post-ICH state to capture ongoing morbidity following ICHs. Further adverse outcomes (PTS, CTEPH) are not modelled following ICH, as lifetime costs and QALYs are assumed to be predominantly determined by morbidity related to ICH. Recurrent VTEs are not modelled as it is unclear whether any recurrent VTE would be related to the VTE provoked by hospital admission or whether it is related to underlying risk factors and would therefore have occurred whether or not prophylaxis was initiated during the hospital admission. The state-transition model has one 6-month cycle to extrapolate the outcomes of the decision tree up to 1 year, followed by annual cycles thereafter. All-cause mortality during the first year is applied at exactly 6 months. Thereafter, the health state occupancy is half-cycle

corrected such that all transitions between states, including mortality, are assumed to occur mid-cycle. The key model assumptions during the state-transition phase are as follows:

- All symptomatic DVTs are associated with a risk of PTS but the rate is allowed to differ depending on whether the DVT is distal or proximal and whether it is symptomatic and treated or asymptomatic and untreated.
- There is no risk of PTS following PE and CTEPH is possible only after PE.
- Further outcomes (i.e. VTE, CTEPH and PTS) are not modelled for those who experience ICH as lifetime cost and QALYs will be determined predominantly by disability related to the ICH.
- All-cause mortality is applied to all transition states except CTEPH and post-ICH which have state-specific mortality rates.
- Recurrent VTE is not modelled.

Conceptual model for surgical patients

We considered whether it was necessary to add additional wound-related outcomes to the model for surgical patients, such as surgical site bleeding or surgical site infections associated with wound haematoma. The clinical experts advised that the vast majority of major bleeds in surgical patients are distant from the surgical site. In addition, any complications related to surgical site bleeding that require patients to return to theatre or that result in prolonged hospitalisation would fall under the ISTH definition of major bleeding in surgical patients.[79] Therefore, these would already be captured within the decision-tree model as non-fatal non-ICH major bleeds. For these reasons, the conceptual model for surgical patients was kept identical to that for medical inpatients, with the caveat that the definition of major bleeding is different for surgical patients. Extended duration thromboprophylaxis in clinical subgroups (such as surgical patients with abdominal cancer) was evaluated using the same conceptual model with a separate scenario analysis (as per *Strategies for prophylaxis*).

Data sources

The input parameters used in a previous analysis of thromboprophylaxis during lower limb immobilisation were examined to identify any that were less relevant to patients receiving prophylaxis during hospitalisation. The data related to the population characteristics (age, sex and life expectancy), the incidence of VTE, the incidence of bleeding and the costs of prophylaxis were updated to use data specific to our target population. Other data such as the incidence of chronic sequelae (PTS and CTEPH) following VTE, and the costs and utility values for patients experiencing adverse outcomes were generally based on the same sources with costs updated to reflect changes in prices. One exception is the utility data for DVT and PE which have been updated because a more detailed analysis of the study used previously is now available.

Clinical input parameters are described below in *Population characteristics* to *Mortality risks for adverse outcomes*. Those that are specific to the medical and surgical inpatient populations are summarised in *Table 5*, with full details of all clinical input parameters provided in *Appendix 2*, *Table 23*. Cost inputs are described below in *Cost of prophylaxis* to *Costs of managing PTS and CTEPH* and summarised in *Appendix 2*, *Table 24* with a detailed breakdown of drug costs for treating VTE and resource use for diagnosing and treating VTE provided in *Appendix 2*, *Tables 25* and *26*. Utility inputs are described below in *Utility values* and summarised in *Appendix 2*, *Table 27* for the decision tree phase of the model and *Appendix 2*, *Table 28* for the state-transition phase of the model. Probabilistic distributions for cost and utility inputs are summarised in *Appendix 2*, *Table 29*. The assumed timings of utility inputs are described in *Timing and duration of utility decrements applied in the decision tree*. Sensitivity and specificity data for the alternative RAMs are described in *Sensitivity and specificity of RAMs*.

Population characteristics

The cohort of patients reported in the papers by Greene *et al.* and Grant *et al.* was selected as being representative of the medical inpatient population.[38,39] This cohort was selected as it is the cohort used to estimate the sensitivity and specificity for five RAMs in the primary analysis for medical inpatients

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TABLE 5 Summary of parameters that differ between medical and surgical inpatient populations

Parameter	Medical	Surgical	Report section
Average age at admission	65.8	54.2	*Population characteristics*
% male	45%	46%	*Population characteristics*
Duration of prophylaxis (assumed to be given till discharge)	5 days	5 days	*Cost of prophylaxis*
Absolute risk of PE without prophylaxis	1.38%	0.62%	*Risk of VTE in medical inpatients* to *Risk of VTE in surgical inpatients*
Absolute risk of symptomatic DVT without prophylaxis	2.02%	0.78%	*Risk of VTE in medical inpatients* to *Risk of VTE in surgical inpatients*
Absolute risk of asymptomatic DVT without prophylaxis	30.46%	12.61%	*Risk of VTE in medical inpatients* to *Risk of VTE in surgical inpatients*
RR of VTE for prophylaxis (LMWH) vs. no prophylaxis	0.49	0.29	*Risk of VTE in medical inpatients* to *Risk of VTE in surgical inpatients*
Absolute risk of PE with prophylaxis (LMWH)	0.68%	0.18%	*Risk of VTE in medical inpatients* to *Risk of VTE in surgical inpatients*
Absolute risk of symptomatic DVT with prophylaxis (LMWH)	0.99%	0.23%	*Risk of VTE in medical inpatients* to *Risk of VTE in surgical inpatients*
Absolute risk of asymptomatic DVT with prophylaxis (LMWH)	14.93%	3.65%	*Risk of VTE in medical inpatients* to *Risk of VTE in surgical inpatients*
Absolute risk of major bleeding without prophylaxis (including fatal, ICH and other)	0.67%	1.24%	*Risk of major bleeding during prophylaxis in medical inpatients* to *Risk of major bleeding during prophylaxis for surgical inpatients*
Major bleed risk by type for patients without prophylaxis			*Risk of major bleeding during prophylaxis in medical inpatients* to *Risk of major bleeding during prophylaxis for surgical inpatients*
Fatal major bleeding	0.10%	0.01%	
ICH	0.06%	0.02%	
Other major bleeding	0.51%	1.21% (including 0.16% surgical site bleeding requiring return to theatre)	
RR of bleeding for prophylaxis (LMWH) vs. no prophylaxis	1.53	2.98	*Risk of major bleeding during prophylaxis in medical inpatients* to *Risk of major bleeding during prophylaxis for surgical inpatients*
Absolute risk of any major bleeding when receiving prophylaxis with LMWH (including fatal, ICH and other)	1.02%	3.70%	*Risk of major bleeding during prophylaxis in medical inpatients* to *Risk of major bleeding during prophylaxis for surgical inpatients*
Major bleed risk by type for patients having prophylaxis			*Risk of major bleeding during prophylaxis in medical inpatients* to *Risk of major bleeding during prophylaxis for surgical inpatients*
Fatal major bleeding	0.15%	0.03%	
ICH	0.09%	0.07%	
Other major bleeding	0.79%	3.60% (including 0.48% surgical site bleeding requiring return to theatre)	
Case-fatality rate for PE	26.8%	6%	*Mortality risks for adverse outcomes*
Standardised mortality ratio vs. general population in the year following admission	9.4	5.0	*All-cause mortality*

and the inclusion criteria were not considered to be overly restrictive compared with the target population. The starting age in the model was, therefore, set to be 65.8 years of age with 44.5% of the starting population being male.

The pooled mean age of surgical patients in the UK in 2015 was reported by Fowler *et al.* to be 54.2 years based on analysis of hospital episode statistics (HES) data.[81] This sample included both day-case procedures (45.6%) and regular inpatient admissions and did not distinguish between elective and emergency surgery. Of these 45.8% were surgical admissions in men. A cohort study examining emergency surgical admissions across six UK acute surgical units reported a mean age of 54 with 56% being female.[82] Based on these two sources we have assumed that the surgical cohort being modelled has an average age of 54 years of age and that 46% are male.

All-cause mortality

Life expectancy is known to vary between men and women of the same age, and therefore any QALY gains from deaths prevented would be dependent on sex. Rather than modelling male and female patients separately to account for their different mortality risks, we used age and sex-specific general population mortality data to calculate the average risk of mortality for the cohort as a whole based on their age at baseline and the proportion of males and females at baseline. The weighting of the mortality risk across males and females was allowed to vary over the course of the model to allow for the fact that lower mortality risks in females lead to a slight increase in the proportion alive who are female over time.

Having calculated the all-cause mortality for an age- and sex-matched cohort with general population mortality risks, it was then necessary to consider the increased risk of mortality for hospitalised patients relative to the general population. A study by Moore *et al.* reported that medical inpatients have a ninefold risk of mortality in the year following admission when compared to an age- and sex-matched general population cohort.[83] We have therefore applied relative risk (RR) of 9.4 to the estimate of general population all-cause mortality in the first year of the model. This gives a 10% absolute risk of death in the first year of the model, which is substantially lower than the absolute mortality rate observed by Moore *et al.*, which was 22.4% at 1 year. However, it is unclear whether the absolute risk of mortality reported by Moore *et al.* is representative of current practice across the UK. The 30-day risk reported by Moore *et al.* is 6.5%, which is higher than the 30-day mortality rate for non-elective inpatients reported in the Summary Hospital-level Mortality Indicator (Standard Hospital Mortality Indicator) tables for England, which was 3.4% in 2018/19.[84] We have conducted a sensitivity analysis in which an absolute mortality rate of 22.4% is applied in the first year of the model for all-cause mortality to see whether uncertainty around all-cause mortality is important in determining the optimal thromboprophylaxis strategy.

In the surgical population, the RR from Clark *et al*. for all-cause mortality in the year after hospitalisation for medical versus surgical patients (RR = 1.9, 95% CI 1.7 to 2.0) is applied to estimate the all-cause mortality in surgical patients.[85] This gives a RR for surgical patients versus the general population of 4.9 in the first year after hospitalisation. Clark *et al.* did not distinguish between emergency and elective surgery. A comparison of crude 30-day mortality rates for elective and emergency admissions, suggests that mortality is lower for elective admissions (1% vs. 3.4%)[84] but as the emergency admissions are not reported separately for medical and surgical patients it is unclear how much of this is due to the inclusion of acutely ill medical patients in the emergency admission cohort. To explore whether a lower risk of mortality in elective surgical patients could lead to different recommendations for thromboprophylaxis, we have conducted a sensitivity analysis in which we apply general population mortality rates to surgical patients.

Moore *et al.* also present information on the mortality risk over the course of the first year and this shows that the rate of mortality is high initially and then decreases over time, although they do not report whether it reaches general population levels of mortality by the end of the first year. To allow for

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the fact that the risk of all-cause mortality decreases with time since discharge, we have not included any increased risk of mortality in year 2 and beyond for hospitalised medical and surgical patients relative to the general population.

Risk of VTE in medical inpatients

The risk of VTE in medical inpatients not receiving pharmacological prophylaxis has been taken from a prospective observational study by Barbar *et al.*, which was the derivation cohort for the Padua RAM.[15] The paper reports the rate of VTEs in high- and low-risk patients according to whether or not they received prophylaxis. Therefore, it is possible to estimate the risk of VTE in those not receiving prophylaxis across both low and high-risk patients. However, a weakness of this study design is that prophylaxis is more likely to be offered to higher-risk patients. Therefore, this study does not give an estimate of the rate of VTEs in an unselected population who do not receive prophylaxis. However, only 39.7% of the higher-risk group (defined as those with a Padua score ≥ 4) received prophylaxis. Higher-risk patients not receiving prophylaxis were younger, less likely to have reduced mobility, were less likely to have heart and/or respiratory failure and were less likely to have acute infection or rheumatological disorder. Despite this the risk of VTE in higher-risk patients not receiving prophylaxis was 11.8%, which is considerably higher than the risk of 2.2% in higher-risk patients receiving prophylaxis. We cannot know what the risk would have been in the latter group had prophylaxis not been administered. However, the majority of the patients in this cohort did not receive prophylaxis, even in the higher-risk group, and this paper allows us to estimate the risks of VTE in those not receiving prophylaxis. The risks of VTE in those not receiving prophylaxis within the cohort report by Barbar *et al.* was 1.38% for PE, and 2.02% for symptomatic DVT, giving a total risk of 3.40% for symptomatic VTE.

Using data from this prospective cohort was considered preferable to using data from the placebo arms of randomised controlled trials (RCTs) for two reasons. Firstly, many of the RCTs comparing prophylaxis against placebo are old and may not be representative of the risks of VTE within current clinical practice. Secondly, many RCTs have restrictive inclusion and exclusion criteria which results in a selective population that may over or under-estimate the risk of VTE in real-world clinical practice. The rates of VTE from the subset of patients reported by Barbar *et al.* who did not receive prophylaxis were applied in the base case but scenario analyses exploring higher rates of VTE are also presented as it is unclear whether the risk of VTE would be higher in an unselected population not receiving prophylaxis.

Barbar *et al.* did not conduct any form of screening to identify asymptomatic DVT. The economic model which informed the 2009 NICE guidelines on VTE prevention in hospitalised patients (CG92) used the ratio of asymptomatic to symptomatic DVTs from those RCTs reporting both distal and proximal asymptomatic DVTs across all patient groups excluding total hip and total knee replacement.[86] This gave a ratio of 40 symptomatic DVTs to 604 asymptomatic DVTs. From this we calculated that the incidence of asymptomatic DVTs in the cohort reported by Barber *et al.* would be 30.46%. Therefore, the overall rate of VTE including asymptomatic DVTs would be 33.85%. We also needed to determine the proportion of DVTs which are proximal as distal DVTs are assumed to have different consequences, such as a lower risk of PTS. In the model that informed CG92, the ratio of distal to proximal DVTs was based on all RCTs included in their systematic review which reported the incidence of both. Based on this, the proportion of all DVTs which are proximal was estimated to be 31% and this was assumed to be constant across both symptomatic and asymptomatic DVTs.

The RR of VTE was estimated from the RCTs included in the review for NG89, which reported relevant outcomes.[8] For acutely ill medical inpatients there are 12 studies described in NG89. Of these only four compared LMWH (standard dose/standard duration) to placebo,[87–90] but one of these only reported mortality outcomes[89] (all-cause mortality and fatal-PE), leaving three studies reporting VTE outcomes. All three RCTs reported the incidence of VTE including both PE and DVT. Two of these studies[88,90] included both symptomatic DVT and asymptomatic DVT in their VTE incidence, although one included only asymptomatic proximal DVT.[88] The third study[87] did not assess patients for asymptomatic DVT and, therefore, only reported symptomatic DVT or PE. We conducted a random-effects meta-analysis

of VTE outcomes from these three studies to obtain an estimate of the RR (0.49, 95% CI 0.37 to 0.67) and applied this to all VTE outcomes within the model. Details of the numbers analysed are included in *Appendix 2*, *Figure 27*.

Risk of VTE in surgical inpatients

The risk of VTE in surgical inpatients was taken from the risk reported by Pannucci *et al.* in the derivation cohort for the Pannucci RAM.[54] This cohort was chosen as PE rates (0.62%) were reported separately in addition to the overall incidence of VTE at 90 days (1.40%). The overall incidence of VTE in the validation cohort, reported by Pannucci *et al.*, and in the validation cohort for the Caprini RAM, reported by Bahl *et al.* were similar to that reported in the derivation cohort by Pannucci *et al.* (1.40% at 90 days and 1.44% at 30 days, respectively), but details regarding the split between PE and DVTs were not provided for these validation cohorts.[26,54] The data from the Pannucci *et al.* cohort were in an exclusively non-emergent surgical population, whereas Bahl *et al.* included both elective and emergency surgical patients, but it seems reasonable to use the data from Pannucci *et al.* for all surgical patients, given that the overall rate of VTE is similar in Bahl *et al.* In both the derivation and validation cohorts reported by Pannucci *et al.*, a similar proportion of the cohort received no pharmacological prophylaxis (34% in both cases). However, the risk of VTE is not reported separately for those not receiving prophylaxis by Pannucci *et al.*, meaning that the risk of VTE in a cohort receiving no prophylaxis may have been underestimated. Bahl *et al.* did attempt to adjust for adherence to the local prophylaxis protocol, but they only reported what the VTE rate would have been for a cohort with full adherence, rather than the rate of VTE expected without any thromboprophylaxis. Therefore, the incidence from Pannucci *et al.* was applied in the model, albeit with the limitation that the use of pharmacological prophylaxis in around two-thirds of cases in this cohort may have underestimated the risk in a cohort without any pharmacological prophylaxis. Given this limitation, sensitivity analyses were conducted to explore whether the most cost-effectiveness strategy for pharmacological prophylaxis would be different if the VTE level risk was higher or lower than observed by Pannucci *et al*. The risk of asymptomatic DVT was estimated using the same assumption as applied in medical inpatients (i.e. that 6.2% of all DVTs are symptomatic), giving a risk of asymptomatic DVT of 12.6%. The same ratio of proximal to distal DVTs as applied in medical inpatients was also applied to elective surgical inpatients (i.e. 31% of all DVTs are proximal).

The RR of VTE in surgical inpatients for LMWH in combination with AES compared with AES alone was not readily available from the review reported in NG89. Separate network meta-analyses (NMA) are reported for elective hip replacement, elective knee replacement and abdominal surgery in NG89, with the latter being considered most generalisable to our target population (as discussed in *Population*). However, the NMA conducted for NG89 separated studies according to the timing and duration of LMWH, and separated studies according to the exact form of mechanical prophylaxis used meaning that the efficacy estimates for individual prophylaxis strategies are based on very few studies. As an alternative to using the data from NG89, we used data from a systematic review and economic analysis by Wade *et al.* which aimed to determine the relative effectiveness of knee versus thigh length AES when used in combination with pharmacological prophylaxis.[91] The base-case NMA conducted by Wade *et al.* made the simplifying assumption that the treatment effect for heparin with AES versus AES alone would be similar to the treatment effect of heparin versus no prophylaxis. This assumption is in part supported by the recent GAPS study, not included in the NMA but which showed no clinical benefit from adjunctive graduated compression stockings in addition to LMWH in moderate risk surgical patients.[75,92] Wade *et al.* also combined studies using LMWH, UFH and low-dose heparin within the network into a single heparin comparator. Both of these simplifying assumptions had the effect of allowing the estimate of treatment effect to draw on more studies than the approach used in NG89, which tended to split studies according to the exact prophylaxis regimen rather than lump them together. In addition, the analysis by Wade *et al.* did not distinguish between different types of surgical patients in their base case. Although scenario analyses were conducted excluding orthopaedic surgery, the economic analysis assumed that the efficacy estimates were common across all surgical patients. Wade *et al.* report that the median OR for heparin versus no heparin was 0.26 [95% credible interval (CrI) 0.09 to 0.87] in the whole surgical population for the outcome of DVT. In the economic model

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reported by Wade *et al.*, the efficacy estimates for DVT were applied to all VTE outcomes as there was no evidence of differential effects by VTE event type (i.e. DVT and PE). Similarly, we have applied this efficacy estimate for all VTE outcomes in surgical patients.

Risk of major bleeding during prophylaxis in medical inpatients

When estimating the risk of major bleeding in the model, the absolute risk in those having LMWH is likely to be estimated more precisely from empirical data sources than the absolute risk in those not having prophylaxis as it will be based on more events. We, therefore, decided to estimate the absolute risk of major bleeding in those having LMWH in the model and then use a RR to estimate the risk in those having no prophylaxis.

The current NICE guideline for preventing VTE in hospitalised patients (NG89) provides an estimate of the risk of major bleeding for patients randomised to either LMWH or placebo based on 4051 patients enrolled in three RCTs.[87,88,90] The RR of major bleeding for LMWH compared to placebo (1.53, 95% CI 0.8 to 2.92) was taken from the meta-analysis of three RCTs provided in N89 (Table 88 of NG89).

The three RCTs included in NG89 gave a risk of 1.02% for patients receiving LMWH. We considered whether it would be better to use data from a prospective cohort study such as the study by Barbar *et al.* which was used to estimate the absolute risk of VTE in those having prophylaxis.[15] However, the number of patients having prophylaxis in the Barbar *et al.* cohort was only 238, making the estimate of risk less precise than that provided by the RCTs included in NG89. In addition, the concern that patients enrolled in RCTs would be a selective group was considered less important for bleeding outcomes as inclusion/exclusion criteria for RCTs would be more likely to focus on VTE risk than bleeding risk. Therefore, we decided to use the data from NG89 based on the three RCTs to estimate bleeding risks in medical inpatients in the model.

The three RCTs used to estimate the risk of major bleeding did not provide sufficient information to determine the breakdown of major bleeding events into fatal bleeds, non-fatal ICHs and other major bleeds. For this information we used data from the IMPROVE registry, which was a multinational, observational study designed to examine VTE prophylaxis patterns and clinical outcomes in patients hospitalised with an acute medical illness.[93] Decousus *et al.* report bleeding outcomes from 10,866 patients of which 5231 (48.1%) received pharmacological prophylaxis including 4172 (38.4%) who received LMWH. The risk of major bleeding was 1.2% in the IMPROVE cohort overall. The type of bleeding is not reported according to whether or not prophylaxis was given or the type of prophylaxis used. However, the study does report data in sufficient detail to calculate the proportion of major bleeds that were fatal (14%) and the proportion of non-fatal major bleeds that were ICHs (10%). We have, therefore, assumed that these proportions are constant regardless of whether the bleeding occurred during LMWH or in patients not receiving LMWH.

Risk of major bleeding during prophylaxis for surgical inpatients

In NG89, the risk of bleeding for LMWH in surgical patients was estimated from five RCTs which compared LMWH either to placebo or to mechanical prophylaxis (which is not thought to increase the risk of bleeding) in patients having abdominal surgery.[94–98] The absolute risk of major bleeding across the 297 patients who received LMWH across the five RCTs was 3.7% (11/297). Neither of the studies reporting validation cohorts for RAMs in surgical populations reported the risk of bleeding in the population receiving prophylaxis.[26,54] Therefore, the data from NG89 for patients having abdominal surgery were used to inform the absolute risk in those receiving LMWH.

In NG89, the RR for major bleeding in patients having abdominal surgery obtained from the NMA was 2.98 (95% CI 0.88 to 14.80) for LMWH (postoperatively, standard duration, standard dose) versus placebo or mechanical prophylaxis. This RR was applied in the model for surgical patients.

The five RCTs used to estimate the absolute risk of major bleeding in surgical patients do not provide consistent information on the site of bleeding making it difficult to estimate the proportion of major

bleeds that are ICHs. The data from the IMPROVE registry, which was conducted exclusively in medical inpatients, were not considered applicable to patients having surgery due to differences in the ISTH definitions of major bleeding for surgical and non-surgical patients.[79,80]

We identified a number of registries/cohort studies that reported the rate of major bleeding in surgical patients receiving thromboprophylaxis through ad hoc searches using Google Scholar. All of the identified registry/cohort studies recruited either elective hip replacement patients,[99] elective knee replacement patients[100] or both.[101–103] As discussed in *Population*, we decided to model the use of thromboprophylaxis in patients having elective hip or knee replacement separately as the recommended duration of prophylaxis is greater in these patients than in most other surgical groups. However, we were unable to find any registry studies describing the site of major bleeding (i.e. ICH vs. non-ICH major bleeding) in non-orthopaedic populations having thromboprophylaxis. Our clinical experts advised that most major bleeds in surgical patients are distant from the surgical site and, therefore, information on the proportion of major bleeds that are fatal or ICHs is likely to be transferable from the orthopaedic population to the non-orthopaedic population.

From the registry/cohort studies identified, we chose to use the data from the XAMOS Xarelto® in the prophylaxis of post-surgical venous thromboembolism after elective major orthopedic surgery of hip or knee (XAMOS) cohort study[103] because it provided a detailed breakdown of the number of patients meeting various criteria for major bleeding, which allowed us to identify which bleeds would fall within the ISTH definition of major bleeding. We did this by taking the number meeting the EMA definition (122 for the adjusted safety population) and removing patients whose only reason for being categorised as having major bleeding was bleeding leading to treatment cessation (13 for the adjusted safety population) as this is not part of the ISTH criteria. The XAMOS study compared rivaroxaban to 'standard care', which included a variety of different thromboprophylaxis interventions, but a high proportion (81.7%) received LMWHs. Therefore, the major bleeding events in the standard-of-care arm were considered to be broadly representative of what would be expected for patients receiving LMWH. From the data reported from the XAMOX cohort, we estimated that 0.9% (1 in 109) of major bleeds meeting the ISTH definition are fatal and that 1.9% of non-fatal major bleeds are ICH (2 in 108) in patients having orthopaedic surgery. The proportion of non-fatal non-ICH major bleeds requiring reoperation is 13%. These proportions were applied in the model to the number of major bleeds for surgical patients to estimate the number of fatal bleeds and non-fatal ICHs.

Risk of major bleeding during treatment for VTE

The risk of bleeding during treatment for VTE has been taken from a paper by Kooiman *et al.* which reports the incidence of bleeding at 6 months in a cohort of patients having treatment for VTE [LMWH followed by vitamin K antagonist (VKA)] stratified by Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly, Drugs/alcohol concomitantly (HAS-BLED) score.[104] This was used to calculate the incidence in those with a HAS-BLED score of 0 to 1 which was 0.9% (3/335). The rationale for using data from a population with a low HAS-BLED score is that inpatients would be unlikely to be considered for prophylaxis if they had significant risk factors for bleeding and, therefore, the population with a low HAS-BLED score is more representative of the population being modelled than an unselected population. The risk in the whole cohort starting treatment from the same study was 2%. For comparison, the risks in other unselected cohorts were 1.5% at 6 months in the Prevention of Thromboembolic Events – European Registry in Venous Thromboembolism (PREFER-VTE) registry and 2.24% at 3 months in the Computerized Registry of Patients with Venous Thromboembolism (RIETE) registry.[105,106] The risk reported by Carrier *et al.* in a systematic review of RCTs and observational cohorts was 1.6% at 3 months.[107] Therefore, the risk in the cohort reported by Kooiman appears to be similar to other cohorts receiving VTE treatment.[104]

The proportion of major bleeds that are fatal (25%) and the proportion of non-fatal major bleeds that are ICHs (9%) was based on data from the RIETE registry, which provides a detailed breakdown of major bleeds in patients receiving treatment for VTE.

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Risk of chronic complications

The risk of CTEPH in patients having PE was taken from a systematic review by Ende-Verhaar *et al.*[108] A cumulative incidence of 3.2% (95% CI 2.0 to 4.4) over 2 years was reported in those who survived the initial 3-month period after PE and this was applied to the model giving a risk of 1.6% per annum. We assumed no risk of new CTEPH beyond 2 years based on a study with a median follow-up of 94 months which reported no new cases of CTEPH after 2 years.[109]

The risk of PTS in patients with symptomatic DVT in the model was estimated from a prospective registry [Thrombosis and Pulmonary Embolism in Out-Patients (TULIPA) PLUS], reported by Hach-Wunderler *et al.*[110] This source was chosen as the study design excluded patients with previous DVT or signs of PTS prior to the index DVT. The incidence is reported separately for proximal and distal DVT and is stratified into mild, moderate and severe PTS using a validated scoring system (Villalta scale), which is the scale preferred by the ISTH. The prevalence of symptomatic PTS at 3 years was 24.4% for all DVTs, 32.4% for proximal DVT and 15.6% for distal DVT, with 70% being mild, 24% being moderate and 6% being severe (average across both proximal and distal). Although the TULIPA registry recruited outpatients, 63.7% of the cohort were considered to have had provoked DVT, with 23.7% having had surgery in the last 12 weeks and 14.8% having had acute illness in the past 4 weeks. Given that we are assuming that DVT occurs post discharge and the majority of DVTs are managed as outpatients, it seemed reasonable to use data from this outpatient population in the current analysis.

Given that patients with asymptomatic DVT will remain undiagnosed and untreated, the incidence for asymptomatic proximal DVT was inflated using data from van Dongen *et al.* which reported an odds ratio of 2.71 (95% CI 1.44 to 5.10) for the risk of PTS in patients with symptomatic proximal DVT with good versus poor anticoagulation [defined as spending more than 50% of their time outside of the target international normalised ratio (INR) range].[111] The rate of PTS in asymptomatic distal DVT was not inflated because this would have increased the incidence to a level similar to that seen in symptomatic proximal DVT and the clinical experts believed that the rate in untreated distal DVT should be lower than for treated proximal DVT. The timing of PTS was based on information from van Dongen *et al.*, which reported the cumulative incidence over 4 years. This data was used to distribute the cumulative incidence reported by Hach-Wunderler *et al.* over 4 years. As van Dongen *et al.* reported no further incidence beyond 4 years we assumed no new incidence of PTS beyond 4 years in the model.

Mortality risks for adverse outcomes

Patients who survive the first 28 days after having an ICH have an increased risk of mortality in the long term. Folgelholm *et al.* report a standardised mortality ratio (SMR) of 4.5 in the first year and 2.2 in years two to six for patients who survived 28 days after ICH, compared to age- and sex-matched controls.[112] We have applied the latter in years 2–6 of the state-transition model to capture the increased risk of death in the long term for patients having non-fatal ICH. However, the SMR reported for the first year for patients having non-fatal ICH is lower than the SMR of 9.4 for medical inpatients and 4.9 for surgical inpatients.[83,85] Therefore, we have not applied any additional mortality risks for patients having non-fatal ICH in the first year as it did not seem logical that the mortality risks would be lower for those having ICH than for other medical or surgical inpatients not having ICH.

Two of the RCTs of LMWH versus placebo in medical inpatients reported the incidence of symptomatic PEs and the incidence of fatal PEs allowing the case-fatality rate to be calculated.[88,90] Overall, across both the LMWH and the placebo arms, 29% (5/17) of the PEs that occurred were fatal PEs. This is substantially higher than the case-fatality rate reported in registries of patients presenting with VTE, such as the RIETE registry where the case-fatality rate was 3.2% overall, with a rate of 4.1% in the inpatient population and 2.9% in the outpatient population.[113] However, given that the risk of death in the first 30 days reported by Moore *et al.* for all medical inpatients was 6.5%, it seems reasonable that the risk of death in those having PE would be higher than in all medical inpatients. It is also important to consider the fact that the RIETE registry only included patients diagnosed with PE and would miss cases where patients died suddenly and PE was only detected post-mortem. Studies that include PE

diagnosed post-mortem have found a high rate of mortality even when excluding cases where autopsy discovered PE is classified as non-causal for death. Heit *et al.* report a 7-day survival rate of only 71.1% when using this approach, but a survival rate of 93% when excluding immediately fatal PEs or PEs first diagnosed at autopsy.[114] This suggests that registries that recruit patients only after confirming PE using objective tests are likely to miss a substantial proportion of fatal PEs. Heit *et al.* also found that patients having a PE while in hospital had a higher risk of death than those having PE in a community setting, and those having surgery in the 90 days prior to their PE had a lower risk of death than those not having previous surgery. This suggests that we should expect higher case-fatality rates for inpatients compared to outpatients and higher case-fatality rates for medical inpatients compared to surgical inpatients. However, Heit *et al.* do not report an absolute case-fatality rate specifically for medical or surgical inpatients. An estimate of the case-fatality rate for PE for all surgical (6%) and medical patients (44.7%) is provided in CG92 (Table 4-3 of CG92) based on the average across all RCTs. These figures represent the ratio of fatal PE to symptomatic PE across multiple RCTs included in the systematic reviews that informed CG92. These figures were used in the model, in preference to rates from registry studies, to reflect the higher expected case-fatality rate for PEs in hospital inpatients, particularly in medical inpatients. However, the case-fatality rate for medical patients was re-estimated after excluding a single study which included sudden unexplained deaths in its calculation of fatal PEs, and which had a high rate of case-fatality (67%). Including this study was not considered appropriate in the calculation of the case-fatality rate as in the model the case-fatality rate is applied to confirmed PEs. After excluding this study, the average case-fatality rate across the remaining five RCTs was 26.8% and this was applied to medical inpatients in the base case.[88,90,115–117] However, as there is considerable uncertainty regarding the appropriate case-fatality rate we have explored the range of estimates observed in the RCTs (13% to 67%) for medical inpatients in sensitivity analyses.[88,118] We have also explored the impact of applying the higher average rate observed in medical inpatients (26.8%) to the surgical cohort.

Mortality risks in patients with CTEPH having either medical or surgical management were based on survival curves reported by Goodacre *et al.*, which were estimated from an international prospective registry of patients with CTEPH.[119] Deaths related to PE occurring within 6 months of PE are already accounted for in the model.[120] For this reason, the hazard of death for patients with CTEPH is only applied from 1 year onwards, with PE-specific mortality applied up to 6 months and all-cause mortality applied from 6 months to 1 year. To ensure that the risk of death in the CTEPH group was not artificially low compared with the risk of death in the general population, general population mortality risks were applied whenever these were higher than the risk in the CTEPH population, based on the survival curves.

Cost of prophylaxis

We have assumed that pharmacological prophylaxis is LMWH. Although NG89 recommends that LMWH is given for a minimum of 7 days, a survey of 25 exemplar centres suggests that the majority of hospitals give LMWH for the duration of admission, which is typically less than 7 days.[76] We have, therefore, assumed that LMWH is given only for the duration of admission.

The mean length of stay in admitted patients based on HES data is 5 days when excluding day cases (HES: Hospital Admitted Patient Care Activity 2018–19).[84] We were unable to obtain an estimate of the mean length of stay specifically for medical inpatients, as the breakdown is given by main speciality and some specialities include both medical and surgical patients. However, we note that the mean length of stay is similar for general medical patients and general surgical patients, and these are the two most common categories, suggesting that it is reasonable to apply the same estimate for both medical and surgical patients. We also identified a study by Fowler *et al.* which reported that the pooled mean duration of stay for surgical patients (excluding day cases) was 4.8 days in 2015, suggesting that this estimate of 5 days is reasonable at least for surgical inpatients.[81] We, therefore, assume that both medical and surgical patients receive 5 days of LMWH.

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It is assumed that the lowest cost preparation of LMWH is prescribed. Therefore, drug costs for LMWH were based on the cost of dalteparin (5000 units given every 24 hours by subcutaneous injection) as this had a cost of £14.12 over 5 days, which was lower than the cost for equivalent doses of enoxaparin (£15.14 for 40 mg every 24 hours) or tinzaparin (£17.82 for 4500 for units every 24 hours). In the base-case analysis, we assumed that LMWH is only continued until discharge and, therefore, the treatment can be administered by a hospital nurse. We have assumed that each administration requires 2.5 minutes of time for a band 6 hospital nurse, with a unit cost of £47 per working hour, giving an administration cost of £9.79 over 5 days.[78] Therefore, the total cost of prophylaxis is £23.91 for both medical and surgical inpatients.

We have also provided results for a scenario analysis in which LMWH is continued 2 days post-discharge to give a total of 7 days of LMWH, as this is recommended in NG89 as the minimum treatment duration. For this analysis, we have applied the costs for 2 days of outpatient administration of LMWH by adjusting the costs estimated by Menakaya *et al.* for outpatient LMWH.[121] The costs estimated by Menakaya *et al.* included clinical time for counselling and blood taking (including a 5-day platelet count), pharmacy dispensing and initial administration. These estimates include the costs of administration by a district nurse in 4% of patients to reflect the fact that not all patients will be able to self-administer. The costs were adjusted to reflect the shorter duration of outpatient administration in this case (2 days vs. 46 days). In this scenario analysis the costs of administration are increased to £81.26 and the drug costs are increased to £19.76, such that the total cost of prophylaxis is £101.03.

In the strategies examining the use of prophylaxis based on RAMs, we have assumed that the risk assessment will require 5 minutes of time spent by a hospital consultant, which is a cost of £9.08 when applying a unit cost per hour of £109.[78] This cost is applied to all strategies involving the use of a RAM, but not to the comparator strategies of prophylaxis for all and prophylaxis for none. A sensitivity analysis has also been conducted to explore whether the optimal strategy would be different if it could be assumed that the risk assessment would result in no additional cost, with the aim of exploring whether the cost of the risk assessment itself is a significant source of decision uncertainty.

Costs of treating VTE

The average time to VTE in medical inpatients reported by Barbar *et al.* was 42 days but this estimate is based on only 37 events.[15] The Million Women study reported by Sweetland *et al.* shows that postoperative VTE risk in women peaks at 3 weeks although it remains raised up to 12 weeks and the average time to VTE is not reported.[122] However, both these figures suggest that the majority of VTE occurs after discharge in both medical and surgical patients. Therefore, treatment costs for VTE are based on the same assumptions applied in a previous cost-effectiveness analysis of prophylaxis in patients having outpatient lower limb immobilisation. These include healthcare contacts for diagnosis, a short-stay inpatient admission where necessary, and 3 months of outpatient anticoagulant treatment. Resource use for diagnosis and admissions are summarised in *Appendix 2*, *Table 26*.

It is assumed that any VTE occurring prior to discharge, would extend hospital length of stay by up to 2 days and would, therefore, have a similar cost to that incurred by patients having VTE as an outpatient who require a short stay admission of up to 2 days. To determine whether the model is sensitive to uncertainties regarding the proportion of VTEs occurring pre-discharge and the likelihood that these will delay discharge, we have conducted a sensitivity analysis in which we assume that all VTEs occur pre-discharge and these VTEs result in no discharge delays.

Treatment for VTE is assumed to consist of 3 months of either a VKA (warfarin) or DOAC. Patients having treatment with a VKA are also assumed to have initial anticoagulation with LMWH until VKA treatment is established. It is assumed within the base-case model that 40% of patients will have a DOAC based on the usage of DOACs in the PREFER-VTE cohort from within those countries where DOACs had been launched.[105] An additional scenario analysis has been conducted to examine the potential impact of increased DOAC prescribing in the years since its launch. The costs for administering LMWH are

based on the costs reported by Menakaya, but these were adjusted to reflect the shorter duration of treatment (7 days compared with 42 days in Menakaya). Administration costs for oral anticoagulants include nine attendances at an anticoagulation service over 3 months for those receiving VKA, and a nurse-led telephone consultation at 10 days for DOACs. In addition, all patients are assumed to require an appointment with a consultant after 3 months to assess whether ongoing treatment is needed.

Costs of treating major bleeding

The cost over 90 days of fatal haemorrhagic stroke provided by Luengo-Fernandez *et al.* was uplifted to current prices and applied as the cost of fatal bleeds in the decision tree phase of the model.[123,124] This paper also provided costs over 90 days for non-fatal haemorrhagic stroke stratified by the level of disability. A weighted average cost was calculated across non-disabling, moderately disabling and totally disabling haemorrhagic strokes. This was then uplifted to current prices and applied as the cost of non-fatal ICH in the decision tree phase of the model. Luengo-Fernandez *et al.* also report the average costs per annum from 90 days to 5 years post-stroke, but these are not reported separately for haemorrhagic stroke. The costs of GP care and emergency care are reported to be statistically significantly higher post-stroke compared to the year before stroke. In addition, they report the cost of residential care in patients not living in residential care prior to their stroke. The total post-acute (beyond 90 days) costs for primary care, emergency care and residential care were calculated and uplifted to current prices and applied in the state-transition phase of the model to those having non-fatal ICH. A pro rata cost is also applied to those having stroke more than 90 days before the end of the decision tree phase of the model.

The cost of non-fatal non-ICH major bleeds was assumed to be similar to the cost of GI bleeds. This was estimated based on a weighted average cost for non-elective inpatient and non-elective short-stay management of GI bleeds using NHS reference costs for bleeds requiring single, multiple or no interventions (HRG codes FD03A to FD03H).[125] This was based on clinical expert advice that in surgical patients, the majority of major bleeds are distant from the site of surgery and, therefore, GI bleeding is a reasonable proxy for the cost of major bleeding even in surgical patients having non-GI surgery. In addition, the costs of GI bleeding are considered to be a reasonable proxy for the management of major bleeding in surgical patients, as the NHS reference cost data show that the majority of GI bleeds (87%) are managed without intervention, which is consistent with the data from XAMOS which shows that the majority of major bleeds in surgical patients are managed without a return to theatre.[103]

No costs are applied in the base-case analysis for CRNMB because it is assumed that these will be managed within the existing cost of inpatient care for those experiencing a CRNMB during inpatient prophylaxis. However, in the scenario analysis examining the use of LMWH for up to 7 days, a cost for ED attendance without admission is applied to a proportion of those having prophylaxis based on the ratio of CRNMBs to all major bleeds (2.05) reported in the PREFER-VTE registry.[105]

Costs of managing PTS and CTEPH

The management of PTS is assumed to involve one first and one follow-up vascular surgery outpatient appointment in the first year after diagnosis and two follow-up GP appointments every year thereafter. This is consistent with the assumption applied in a previous analysis.[74] An alternative cost based on the burden estimated in a US cohort is considered in a sensitivity analysis.[126]

Drug costs for medical management of CTEPH were based on the costs used in CG92, which were uplifted to give a cost of £18,507 per year. The costs for medically managed patients are applied each year to those surviving with CTEPH. The proportion of patients having surgical management for CTEPH (59%) is based on data from Delcroix *et al.*[120] The cost for surgical management of CTEPH is based on a weighted average of the reference costs for complex thoracic procedures (DZ02H/J/K) giving an average cost of £8175. A proportion of patients having surgical management (29%) are assumed to require medical treatment as a bridging therapy (average of 4.6 months). Including these costs brings the total cost in the first year to £10,237 for surgical management. No costs are applied beyond the first year for those managed surgically.

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Utility values

In our previous modelling of VTE prevention in lower limb injury, we identified a systematic review of utility values in VTE by Lubberts *et al.*[127] Forward citation searching was used to identify more recent systematic reviews on this topic and this identified a more recent review by Ghanima *et al.* but this yielded no more recent studies with relevant data.[128] Further forwards and backwards citation searching from the review by Ghanima identified one paper by Utne *et al.* which reported EQ-5D outcomes by trial arm in patients being treated with either rivaroxaban or warfarin for DVT.[129] Additional ad hoc searches using Google Scholar, which were limited to 2017 onwards, identified two more recent publications of health-related quality of life (HRQoL) data from the PREFER-VTE registry study, which had been previously used to obtain utility estimates in the model for lower limb injury.[113,130] The new data from this paper were extracted and used to calculate updated utility multipliers for DVT and PE giving utility multipliers of 0.962 and 0.960 for the first 6 months after DVT and PE, respectively. The utility multipliers in the second 6 months were 1.00 and 0.99, respectively. For PE these are higher than the multipliers applied in the previous model because the utility values reported in the recent paper were much higher than those reported previously from the same study. This is because the final publication reported results separately for patients with and without active cancer and we selected the data for those without cancer for use in the model. However, it should be noted that the difference in utility between those with and without active cancer is fairly constant across time for PE, suggesting that the utility decrement attributable to PE would be similar, but that there is an additional decrement due to active cancer. In the previous model, the average utility for PE over 6 months was compared to the utility achieved 6 months after DVT to determine the multiplier on the assumption that patients with DVT will have returned to full utility by 6 months. Whereas in the analysis of the new data, the utility multiplier was compared against the norm value index score for an age-/gender-matched general population (0.838 for PE and 0.852 for DVT) provided in the more recent papers. This method is preferable as it is not affected by differences in the characteristics of those experiencing PE and DVT.

Using forward citation searching from the review by Lubberts *et al.* we identified a systematic review of studies reporting HRQoL after adverse events associated with antithrombotic therapy for primary or secondary prevention of VTE. However, only four studies were identified in this review and they related to VTE prevention in populations with atrial fibrillation or following acute myocardial infarction. Two of these studies reported EQ-5D in patients with and without a bleeding adverse event,[131,132] but only one reported the EQ-5D for patients with major bleeding compared to no bleeding.[132] After adjusting for baseline differences in EQ-5D, Amin *et al.* (2016) report that the EQ-5D decrement for major bleeding (BRAC bleeding type 2–4) in the past 6 months compared to no bleeding in the past 6 months was (−0.0445, 95% CI 0.073 to 0.016, $p = 0.0022$). As the utility in those without bleeding was 0.86 at both baseline and 6 months, this decrement is equivalent to a 5% proportional decrement. In our previous analysis for lower limb immobilisations, we assumed that the utility in the month following a GI bleed would be equivalent to the utility in the month following PE. Using data from the more recent publication of the PREFER-VTE registry[130] would give a 16% decrement (0.718 compared to 0.838) when making this same assumption. The difficulty here is that the utility decrement associated with a major bleed is likely to reduce over time which is why we previously stated that any decrement would only persist for 1 month after a major bleed. Therefore, the study by Amin *et al.*, which is focused on bleeding at any time in the past 6 months, may miss the maximum period of utility decrement. For this reason, we have chosen to make the same assumption as before and to apply the utility decrement in the first month post-PE to the first month post-major bleeding using data from the more recent PREFER-VTE publication.[130]

Utility values following ICH were based on data from 5-year follow-up of the Oxford Vascular Study (OXVASC) study as these data were previously applied in our analysis of prophylaxis during lower limb injury.[123] A decrement of 0.22 was assumed in the decision tree part of the model where time since stroke was < 6 months and a decrement of 0.09 was assumed in the long-term part of the model. This study was chosen as the source of utility values previously as the duration of follow-up allowed time since stroke to be accounted for, and a comparison was made against general population norms.

In our previous analysis of prophylaxis during lower limb injury (Pandor *et al.* 2019[74]), we used utility data from the CaVenT study to estimate the utility decrement in patients with PTS.[133] An estimate of 10% was applied from diagnosis onwards, which was obtained from the CaVenT study by comparing the EQ-5D scores in those with and without PTS at 2 years. The CaVenT study did not stratify the utility estimates by severity of PTS, so this estimate was applied to all patients with PTS in the model regardless of severity. This may overestimate the utility decrement if the proportion of patients having severe PTS is lower in the modelled population than in the CaVenT study which recruited patients with acute iliofemoral DVT. A study by Lenert and Soetikno reported utility estimates for mild and severe PTS (0.98 and 0.93, respectively) obtained by using health state descriptions and a standard gamble valuation technique in a sample of volunteers.[134] These were not used in the base case as utility measured using the EQ-5D in patients with the condition is preferable to utility measured using standard gamble in volunteers based on descriptions of the condition. However, a scenario analysis was conducted in which the data from Lenert and Soetikno were combined with data on the proportion of PTS that is severe (6%) from Hach-Wunderle *et al.* to estimate a utility decrement of 2% across all patients with PTS. In the current analysis we have taken the same approach and have applied a 10% decrement in the base case and a 2% decrement in a scenario analysis.

The utility decrement in patients with CTEPH was estimated from a study by Meads *et al.* by comparing the utility in patients having CTEPH (0.56) and the utility in patients with disease categorised as New York Heart Association (NYHA) class 1 (0.89) in which the quality-of-life impact of symptoms would be expected to be minimal.[135] This gave a utility multiplier of 0.63 or a 37% decrement. This decrement is applied lifelong in the model to those having medical management of CTEPH, but only for 1 year in those having surgical management who have the utility multiplier for PE applied thereafter.

In our previous analysis of thromboprophylaxis during lower limb injury we identified several sources which estimated the utility decrement associated with VTE prophylaxis or VTE treatment.[74] The study selected for use in the previous model was a study by Marchetti *et al.* which reported that patients would be willing to trade 2.7 of 365 days to avoid treatment with LMWH and 4 of 365 days to avoid treatment with warfarin.[136] These data were previously used to estimate utility decrements of 0.007 for thromboprophylaxis and 0.011 for VTE treatment. These same decrements have been applied in this model.

Utility values for patients not experiencing any utility decrement due to prophylaxis, treatment, symptomatic VTE events, bleeding events (ICH or other major bleeds), long-term sequelae following VTE (PTS or CTEPH) or death are based on general population norms for a cohort of the same age and this is allowed to vary as the cohort ages during the model.[137]

Timing and duration of utility decrements applied in the decision tree

In order to calculate the QALYs gained by patients having different paths through the decision tree, it is necessary to make some assumptions regarding the timing of events as these are not explicitly modelled in a decision tree. We made the following assumptions when estimating QALYs in the decision tree:

- Baseline utilities using general population utility values for the starting age are applied to those not having treatment and not having any clinical events (e.g. VTE, bleeds).
- Bleeds during prophylaxis are assumed to occur halfway through the hospital admission (i.e. 2.5 days after starting prophylaxis).
- VTE is assumed to occur within 90 days of hospital admission and utility decrements for PE and DVT are applied from 42 days until the end of the decision tree period.
- Bleeds occurring during treatment for VTE are assumed to occur at 13, 32 and 12 days post diagnosis of VTE for fatal, ICH and other major bleeds, respectively (based on data from the RIETE registry reported by Nieto *et al.*).

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- Disutilities for ICH are applied lifelong but separate disutilities are applied in decision tree and state-transition phases of the model (i.e. during the first 6 months after admission and beyond 6 months after admission).
- Disutility of non-fatal non-ICH major bleeding is assumed to last a maximum of 28 days.
- Disutility of prophylaxis applies for the duration of prophylaxis (5 days) and is therefore less in those stopping early due to major bleeding.
- Disutility of treatment for VTE applies for the duration of treatment (3 months) and is therefore less in those stopping early due to major bleeding.

Although the utility decrements for VTE are assumed to apply from 42 days onwards based on the mean time to VTE reported by Barbar *et al.*,[15] there is likely to be considerable variability in the timing of VTE, which could occur before discharge or as late as 90 days after admission. Therefore, a sensitivity analysis was conducted in which the timing of VTE was varied from 3 to 90 days to determine if the model was sensitive to the assumption regarding the timing of VTE. We made the following assumptions when estimating QALYs in the state-transition model:

- Utility values for patents without any long-term sequelae (ICH, CTEPH, PTS) are taken from general population values and decrease as patients age in the model.
- All other utility values are applied as multipliers such that the absolute utility value decreases due to ageing in all patients.
- Utility decrements continue in the state-transition model for the remainder of the patient's lifetime for PE but not for DVT where patients are assumed to return to general population utility values at 6 months.
- Patients with CTEPH who are treated medically have a lifelong utility decrement, whereas those treated surgically return after 1 year to the same utility as those surviving PE without CTEPH.
- Patients with PTS have the same utility decrement from diagnosis to death.
- Patients with ICH have the same utility decrement from 6 months (i.e. the start of state-transition model) to death.

Sensitivity and specificity of RAMs

Sensitivity and specificity data have been extracted from the RAM studies listed in *Chapter 3*.[29,30,36,38,39,71] For many of the RAM studies we wished to examine in the model, the authors themselves have not reported sensitivity and specificity data. In this case, estimates of sensitivity and specificity have been extracted using reports of the incidence by risk score and graphical data, where possible. In some cases, estimates of sensitivity and specificity were extracted digitally from receiver operating characteristic (ROC) curves where these were reported.

Figure 7 shows the sensitivity and specificity data for RAMS in medical inpatients extracted from various studies. Overall, there is data reported for seven RAMs (Caprini, Kucher, Padua, IMPROVE, Intermountain, Geneva, Rothberg) and all except one (Rothberg) are reported in more than one cohort. It can be seen that there is not always consistency in the estimates of sensitivity and specificity for a particular RAM when reported across different cohorts. In particular, the estimates for IMPROVE and Intermountain obtained by Blondon *et al.* are more favourable than the estimates from Greene *et al.* However, several RAMs appear to have similar performance when estimates of sensitivity and specificity were taken from single cohort, as reported in papers by Greene *et al.* and Grant *et al.*

Figure 8 shows the sensitivity and specificity data for two RAMs in surgical inpatients. There were data on the Pannucci score reported by Pannucci *et al.* and data on the Caprini score reported by Bahl *et al.*

Figure 9 shows the sensitivity and specificity data available for mixed populations of both surgical and medical inpatients. Only one paper reported this information for a mixed population (Elias *et al.* 2017[36]). Elias *et al.* provide ROC curves for patients having prophylaxis and patients not having prophylaxis. They also provide a single estimate of sensitivity and specificity for the cohort as a whole.

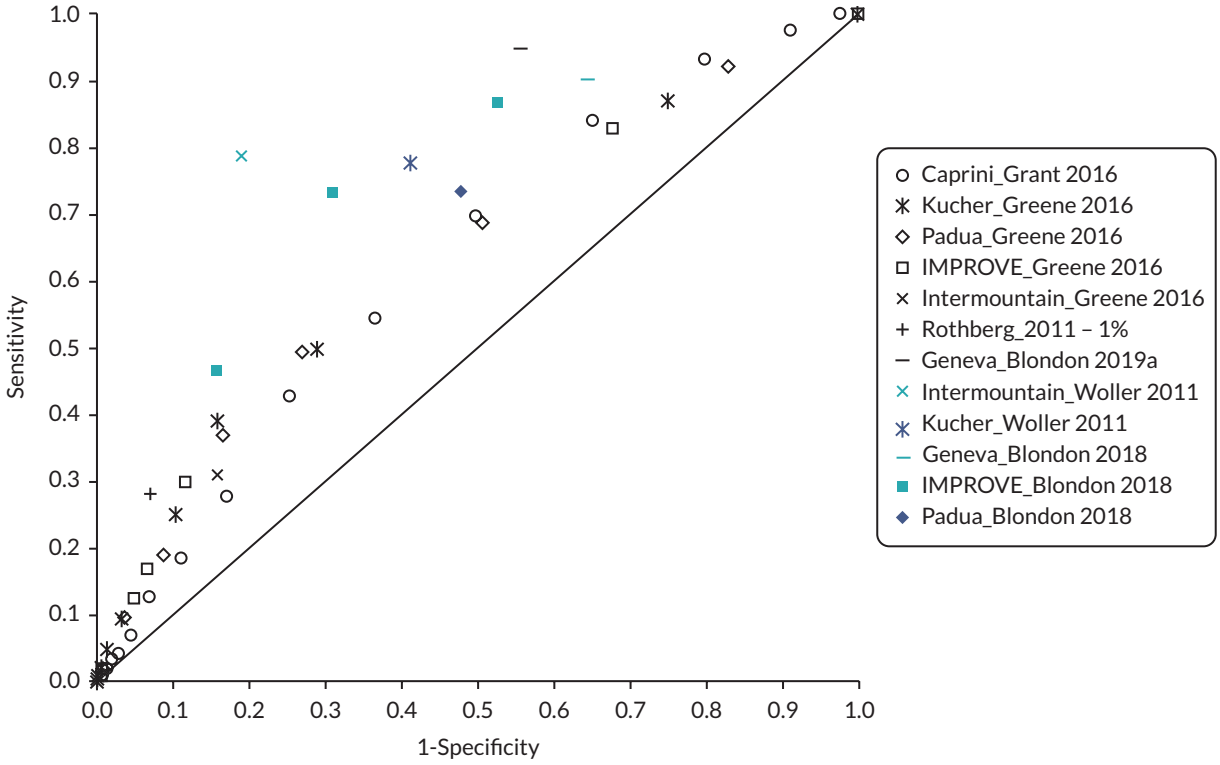

FIGURE 7 ROC curve for multiple risk assessment models evaluated in cohorts of medical inpatients.

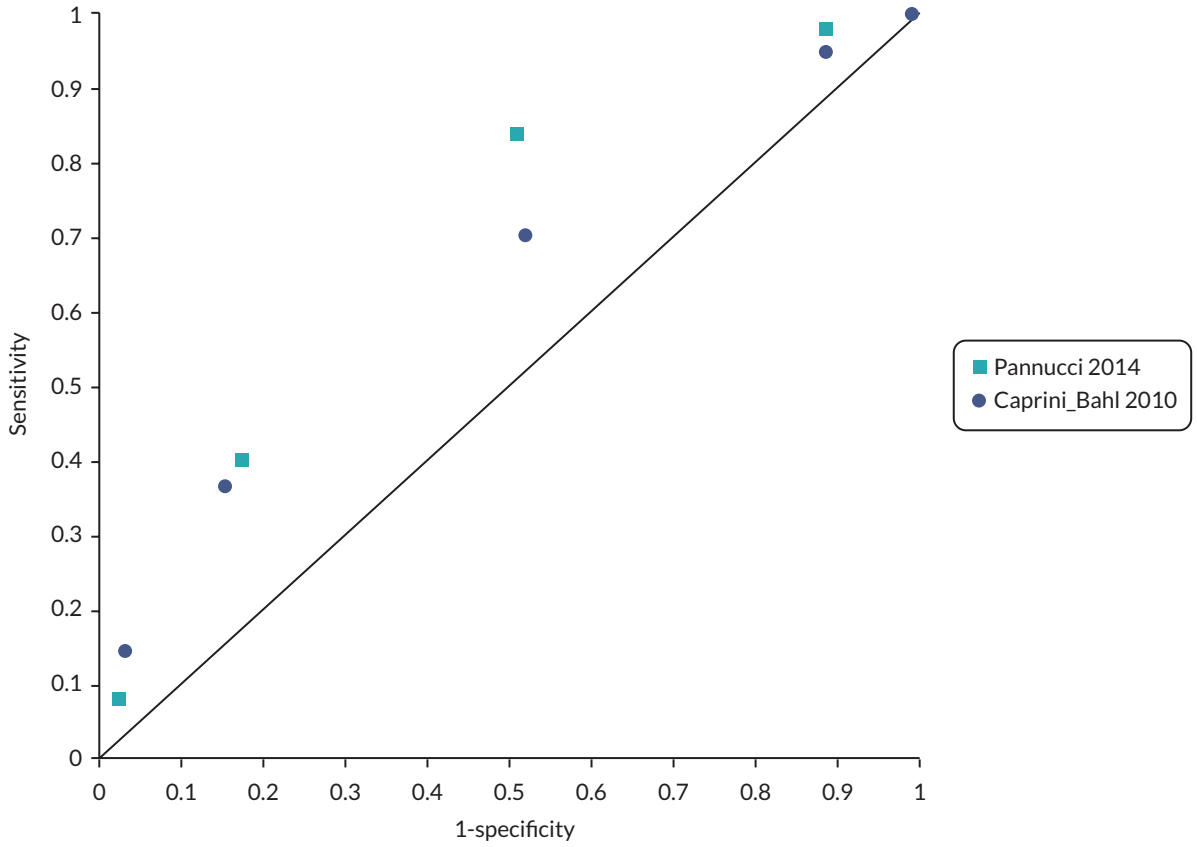

FIGURE 8 ROC curve for multiple risk assessment models evaluated in cohorts of surgical inpatients.

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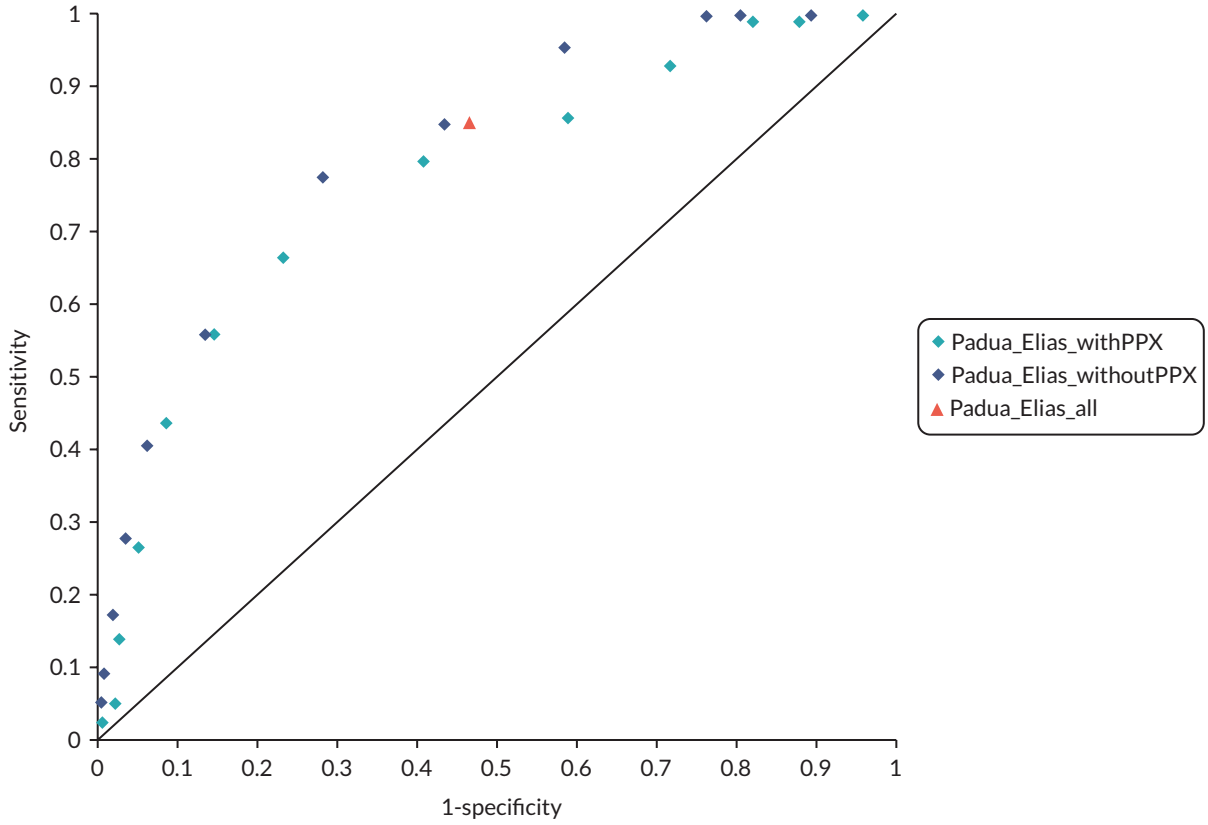

FIGURE 9 ROC curve for the Padua RAM in a mixed cohort of medical and surgical patients reported by Elias *et al.*[36] [with/without prophylaxis (PPX) and all].

The base-case deterministic analysis estimates the expected costs and QALYs for all available RAMs where performance data are available in that specific population (i.e. surgical or medical patients). In addition, because the usage of prophylaxis within the cohorts will tend to result in RAM performance being underestimated, we have also conducted a secondary analysis using the data from Elias *et al.* which was estimated in the subset of the cohort not receiving prophylaxis. This cohort included both surgical and medical inpatients and is therefore not used in the base-case scenario for either group.

Available data suggest that RAMs have generally weak predictive accuracy for VTE. There is insufficient evidence and too much heterogeneity to recommend one RAM over another. Hence, we have focused on using data from studies of RAMs to explore the trade-off between sensitivity and specificity, rather than try to identify the most cost-effective RAM. To do this we have used regression to estimate the trade-off between sensitivity and specificity for a typical RAM and have used this to explore how this trade-off affects the cost-effectiveness of using RAMs to select patients for prophylaxis.

Figure 10 shows the sensitivity and specificity data available across all populations with trend lines fitted firstly to all of the estimates across the multiple RAMS reported by Greene *et al.* and Grant *et al.* which were estimated in a single cohort, and secondly to the estimates from Elias *et al.*, which were estimated in the subset of the cohort not having pharmacological prophylaxis. The trend lines have been fitted by assuming that there is a linear relationship between logit (sensitivity) and logit (1-specificity). It should be noted that for the line fitting against the data from Greene *et al.* and Grant *et al.*, the fitted line assumes that each point is equally valid and does not take into account (1) the uncertainty around each pair of sensitivity and specificity estimates, (2) the relationship between multiple points that represent the ROC curve for a single RAM in a single study or (3) any relationship between estimates for different RAMs from the same study. The estimates from the Elias cohort were extracted for use in a sensitivity analysis exploring the potential for a more accurate RAM to be cost-effective. This was undertaken specifically

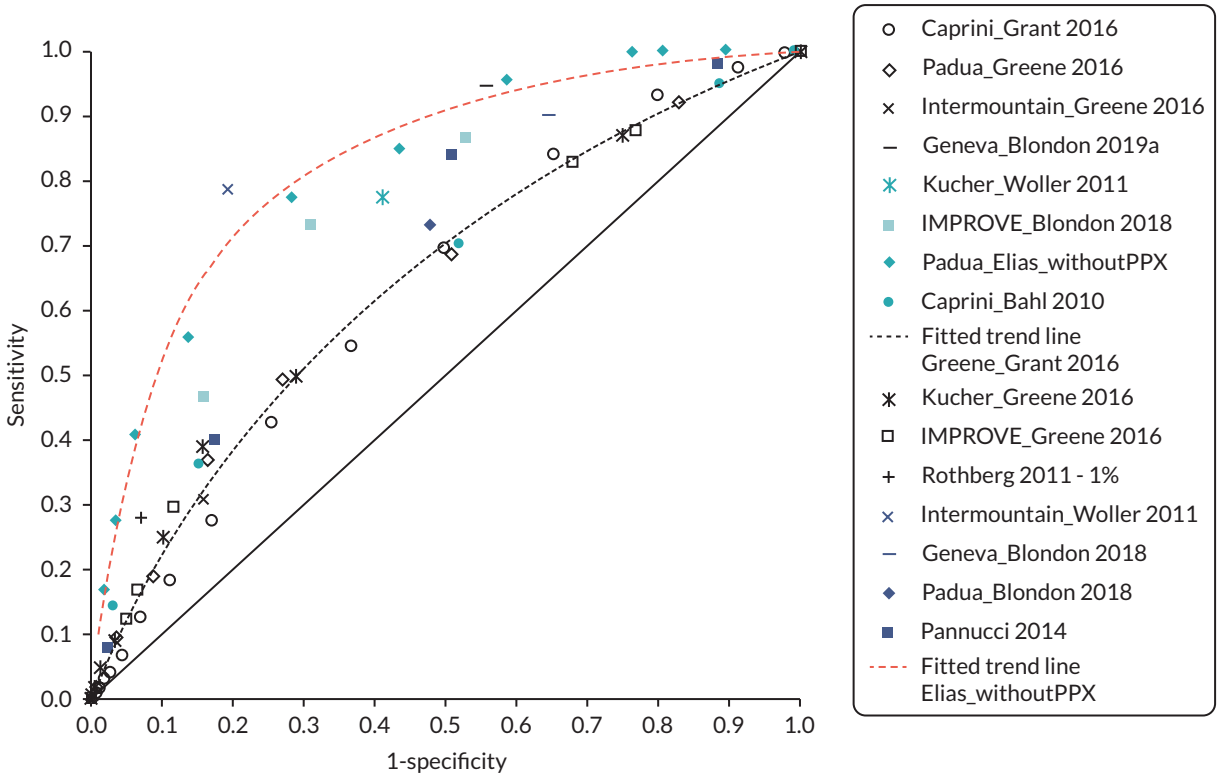

FIGURE 10 ROC curve for all studies (surgical, medical and mixed) with trend lines fitted.

to address the concern that use of VTE prophylaxis could lead to underestimation of the accuracy of the RAMs. It should be noted, however, that the Elias study reported higher accuracy for the Padua RAM than other studies in cohorts with and without prophylaxis. It is, therefore, unclear why accuracy was better in the Elias study, but it probably reflects features of the study design.

Model inputs for the elective hip replacement and elective knee replacement scenarios

In the main analysis for surgical inpatients, we excluded patients having elective hip and knee replacement surgery as the NICE guideline (NG89) recommends a more extended form of thromboprophylaxis in these groups. In knee replacement patients NG89 recommends LMWH for 14 days. In hip replacement patients NG89 recommends LMWH for 28 days. For comparison, in the majority of other categories of surgical patients, the duration of prophylaxis with LMWH recommended in NG89 is a minimum of 7 days.

If a single RAM is to be used across a broad range of surgical patients, encompassing populations that have a longer duration of prophylaxis, it is important to know whether the longer duration of prophylaxis in these groups would result in a different threshold for cost-effective use of prophylaxis. Therefore, we have conducted scenario analyses to determine what the risk threshold for thromboprophylaxis would be for elective hip and elective knee replacement patients and whether a prophylaxis for all strategies would be better in these specific populations.

In the scenario analyses for the two specific surgical populations of elective hip replacement patients and elective knee replacements, the overall modelling approach was the same as in the analysis for the general surgical cohort, but specific parameters were changed to make them more relevant to these groups. To identify relevant parameters, we used the cost-effectiveness models described for these populations in NG89. The key parameters for these populations are summarised in *Table 6*.

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TABLE 6 Summary of parameters for specific surgical populations requiring a longer duration of prophylaxis

Parameter	Elective hip replacement	Elective knee replacement
Average age at admission	68.7	69.2
% male	40%	44%
Duration of prophylaxis with LMWH	28 days	14 days
Absolute risk of PE without prophylaxis	1.42%	2.48%
Absolute risk of symptomatic DVT without prophylaxis	2.04%	1.35%
Absolute risk of asymptomatic DVT without prophylaxis	10.01%	28.62%
RR of VTE for prophylaxis (LMWH) vs. no prophylaxis	0.33	0.47
Absolute risk of PE with prophylaxis (LMWH)	1.08%	1.17%
Absolute of symptomatic DVT with prophylaxis (LMWH)	1.71%	0.63%
Absolute risk of symptomatic DVT with prophylaxis (LMWH)	3.30%	13.45%
Absolute risk of major bleeding without prophylaxis (including fatal, ICH and other)	1.26%	1.13%
Major bleed risk by type for patients without prophylaxis		
Fatal major bleeding	0.01%	0.01%
ICH	0.02%	0.02%
Other major bleeding	1.23% (including 0.16% surgical site bleeding requiring return to theatre)	1.10% (including 0.15% surgical site bleeding requiring return to theatre)
RR of bleeding for prophylaxis (LMWH) vs. no prophylaxis	2.55	1.09
Absolute risk of any major bleeding when receiving prophylaxis with LMWH (including fatal, ICH and other)	3.21%	1.23%
Major bleed risk by type for patients having prophylaxis		
Fatal major bleeding	0.03%	0.01%
ICH	0.06%	0.02%
Other major bleeding	3.12% (including 0.41% surgical site bleeding requiring return to theatre)	1.20% (including 0.16% surgical site bleeding requiring return to theatre)
Case-fatality rate for PE	17%	6%
SMR vs. general population in the year following admission	4.3	3.0

The absolute risks of VTE in elective hip and knee replacement patients were taken from the models in NG89. In NG89 these were estimated by combining information on the risk of symptomatic VTE in patients having prophylaxis taken from the National Joint Registry estimates of the ratio of asymptomatic to symptomatic DVTs provided by Quinlan *et al.* and information on the efficacy of prophylaxis taken from the NMAs conducted for NG89.[99,100,138]

The bleeding risk for elective hip and knee replacement patients has been taken from the model inputs for NG89. In the elective knee replacement population, the risk of major bleeding with LMWH was 1.23% (0.64% major bleeding at surgical site, 0.39% GI and ICH, 0.2% other major) in the NG89 model. For elective hip replacement patients, the baseline risk of major bleeding in those having standard

duration LMWH was 3.21% in the NG89 model (2.29% major surgical site bleeding, 0.72% ICH and GI, and 0.2% other major). This rate of major bleeding was applied to elective hip replacement patients having extended duration LMWH in the model, as although the NMA in NG89 predicted a lower risk of major bleeding for extended LMWH versus standard duration LMWH (0.78, 95% CI 0.11 to 3.85), the difference was not statistically significant and applying a lower risk of bleeding for a longer duration of prophylaxis was considered to lack clinical face validity.

The proportion of major bleeds that were fatal or non-fatal ICHs was taken from the same source as used in the main surgical cohort as this was a study of patients having major orthopaedic surgery.[103] Age at baseline and the proportion who are male were based on the estimates from the National Joint Registry used in NG89. The standardised mortality rates versus the general population were adjusted to give the same mortality rate at 12 months as applied in the NG89 model (1.49% for hip and 1.05% for knee), which again were based on data from the National Joint Registry. In hip replacement patients the case-fatality rate for PEs (17%) was taken from the model in NG89 and this was derived from the RCTs of elective hip replacement patients included in the reviews for NG89. However, in NG89 no equivalent data were available for knee replacement patients, so it was assumed that the case-fatality rate for knee replacement patients would be the same as for general surgical patients (6%).

The type of pharmacological prophylaxis used is assumed to be LMWH, but the duration of prophylaxis is assumed to be longer at 14 and 28 days, respectively, for knee and hip replacement patients compared with up to 7 days for the main surgical cohort. Also, because of the need for a longer duration of prophylaxis, it is assumed that prophylaxis will continue after discharge with outpatient prophylaxis used after discharge. For general surgical patients, in the scenario analysis in which we assumed that prophylaxis continues for 7 days, including 2 days of post-discharge prophylaxis, the total cost was £101.03. This total includes £67.55 for outpatient administration, which covers the cost of teaching patients to self-administer prophylaxis after discharge and the need for district nurse administration for a minority of patients (4%). In the elective knee replacement population, with a total of 14 days of LMWH, the total cost is increased to £141.71 due to the additional 7 days of LMWH. In the elective hip replacement population, with a total 28 days of LMWH, the total cost is £223.09.

NG89 also recommends prophylaxis with aspirin or DOACs as alternatives to LMWH in patients having elective hip or knee replacement. Therefore, we have conducted sensitivity analyses to see if adjusting the costs to reflect these alternative prophylaxis regimens, while assuming equivalent efficacy, results in different conclusions regarding the optimal use of RAMs in these cohorts. For the knee replacement population, the alternative regimens modelled consist or 14 days of rivaroxaban, at a cost of £25.20 or 14 days of aspirin, at a cost of £0.69. For the hip replacement population, the alternatives modelled consist of 35 days of rivaroxaban, at a cost of £63.00, or 10 days of LMWH followed by 28 days of aspirin, at a cost of £119.84.

Economic modelling results

Clinical outcomes predicted by the model with and without prophylaxis

Table 7 shows the clinical outcomes predicted by the model with and without prophylaxis in each of the modelled populations.

In medical inpatients, prophylaxis reduces serious adverse outcomes (fatal PEs, fatal bleeds and non-fatal ICHs) from 53 per 10,000 to 42 per 10,000. The reduction in symptomatic DVTs and non-fatal PEs is also higher than the increase in other bleed types. In the long-term outcomes (presented in *Table 7*) at 5 years, there is a large reduction in the number of patients experiencing PTS from prophylaxis from 787 per 10,000 to 385 per 10,000, but minimal difference in overall survival. Therefore, in medical inpatients, although prophylaxis increases the risk of major bleeding, this is more than outweighed by

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TABLE 7 Predicted clinical outcomes per 10,000 patients at 6 months and 5 years

	Outcomes at 6 months per 10,000 patients							Outcomes at 5 years per 10,000 patients				
	Fatal PE	Fatal bleed	Non-fatal ICH	Other major bleed[a]	Non-fatal PE	Symptomatic DVT	Asymptomatic DVT	PTS	PE survivor with CTEPH	PE survivor without CTEPH	ICH survivor	Dead (any cause)
Medical inpatients												
No prophylaxis	37	10	6	53	101	201	3041	787	2	83	5	1498
Prophylaxis	18	15	9	79	49	98	1489	385	1	41	7	1486
Surgical inpatients[b]												
No prophylaxis	4	1	2	122	58	78	1260	367	1	54	2	353
Prophylaxis	1	3	7	360	17	23	365	107	0	16	6	352
Elective hip replacement inpatients												
No prophylaxis	24	2	2	124	118	204	1000	294	3	100	2	1225
Prophylaxis	8	3	6	312	39	68	334	98	1	33	5	1212
Elective knee replacement inpatients												
No prophylaxis	16	2	2	112	247	134	2861	764	6	214	2	1079
Prophylaxis	7	2	2	121	116	63	1337	357	3	100	2	1070

a Patients having other major bleeds could also have a DVT or non-fatal PE.
b Surgical population includes patients having elective and emergency surgical procedures but excludes day cases and those having elective hip or knee replacement.

the number of VTE events avoided and there are additional benefits from preventing long-term VTE-related complications such as PTS.

In surgical inpatients, the risk of a serious adverse outcome (fatal PEs, fatal bleeds and ICH) is low at 7 per 10,000 but it is increased slightly by prophylaxis to 11 per 10,000 due to the additional risk of fatal bleeding or non-fatal ICH. Although the risk of any symptomatic VTE is reduced from 140 per 10,000 to 41 per 10,000, the risk of any major bleeding is increased from 125 per 10,000 to 370 per 10,000. Prophylaxis still reduces the risk of PTS in surgical inpatients, from 367 per 10,000 to 107 per 10,000, but PTS is less common in the surgical cohort than in the medical cohort due to the lower risk of DVT. Therefore, in the surgical population there is a more explicit trade-off between the short-term risk of major bleeding and the benefits of preventing VTEs and their long-term consequence.

In elective hip replacement patients, the risk of a serious adverse clinical outcome (fatal PEs, fatal bleeds and non-fatal ICH) is reduced by prophylaxis from 28 per 10,000 to 17 per 10,000. The risk of any symptomatic VTE is reduced from 346 per 10,000 to 116 per 10,000 and the risk of any major bleeding is increased from 128 per 10,000 to 321 per 10,000. The reduction in PTS is similar to that observed in the general surgical inpatient population (294 per 10,000 reduced to 98 per 10,000 by prophylaxis). Therefore, in the elective hip replacement population, the increase in rates of major bleeding is similar to the decrease in rates of symptomatic VTE, but overall there is a reduction in serious adverse clinical outcomes as only a very small minority of major bleeds are fatal or intracranial.

In elective knee replacement patients, the risk of a serious adverse clinical outcome (fatal PEs, fatal bleeds and non-fatal ICH) is reduced from 20 per 10,000 to 11 per 10,000 by prophylaxis. The risk of any symptomatic VTE is reduced from 397 per 10,000 to 186 per 10,000 but the increase in the risk of any major bleeding is smaller (116 per 10,000 to 125 per 10,000). The reduction in PTS is more similar to that observed in the medical inpatient population (764 per 10,000 reduced to 357 per 10,000), which is largely being driven by the high risk of asymptomatic DVT in the elective knee replacement population which is more similar to that observed in the medical inpatient population.

The 5-year survival is higher in surgical inpatients than in medical inpatients which is to be expected given the lower starting age of 54 years in surgical inpatients compared with 64 years in medical inpatients. In both the elective knee replacement population and the elective hip replacement population, all-cause mortality at 5 years is higher than in the general surgical population due to a higher starting age of 69 years in both groups. However, the impact of prophylaxis on all-cause mortality at 5 years is small regardless of the population selected.

Balance of benefits and harms of prophylaxis at different levels of risk

It can be seen from the clinical outcomes predicted by the model in *Table 7*, that there is always a trade-off between the benefits of using prophylaxis to reduce VTE risks and the potential harms that may occur due to the increased risk of bleeding. These differ between the medical and surgical populations largely because these groups have different average risks of VTE and major bleeding but also because some specific types of VTE outcomes and major bleeding events are more likely in some populations than others. It would, therefore, be useful to explore the overall impact of prophylaxis on health at differing levels of risk so that the balance of benefits and harms in individuals who have a higher or lower than average risk can be assessed. *Figures 11* and *12* present information on whether the overall impact of prophylaxis on QALYs over the patient's remaining lifetime is positive or negative for different levels of VTE risks and major bleeding risks. Where the overall impact of prophylaxis on lifetime QALYs is positive for a given level of VTE and major bleeding risk, the cell is coloured green and where it is negative the cell is coloured red. It should be noted that the steps in risks between rows and columns are not even across the table. In addition, although the risk levels presented for VTE without prophylaxis, and for major bleeding with prophylaxis are the same in *Figures 11* and *12*, the risk levels for VTE with prophylaxis and major bleeding without prophylaxis differ because the RRs for these outcomes

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Risk of major bleeding with prophylaxis	Risk of symptomatic VTE without prophylaxis																				Risk of major bleeding without prophylaxis
	0.20%	0.25%	0.30%	0.35%	0.40%	0.45%	0.50%	0.55%	0.60%	1.00%	1.40%	1.50%	2.00%	3.40%	4.00%	5.00%	6.00%	7.00%	8.00%	9.00%	
0.10%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.07%
0.20%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.13%
0.50%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.33%
1.02%	10	10	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.67%
2.00%	10	10	10	10	10	10	10	10	0	0	0	0	0	0	0	0	0	0	0	0	1.31%
3.00%	10	10	10	10	10	10	10	10	10	0	0	0	0	0	0	0	0	0	0	0	1.96%
3.70%	10	10	10	10	10	10	10	10	10	10	0	0	0	0	0	0	0	0	0	0	2.42%
5.00%	10	10	10	10	10	10	10	10	10	10	10	0	0	0	0	0	0	0	0	0	3.27%
6.00%	10	10	10	10	10	10	10	10	10	10	10	10	0	0	0	0	0	0	0	0	3.92%
7.00%	10	10	10	10	10	10	10	10	10	10	10	10	10	0	0	0	0	0	0	0	4.58%
8.00%	10	10	10	10	10	10	10	10	10	10	10	10	10	0	0	0	0	0	0	0	5.23%
9.00%	10	10	10	10	10	10	10	10	10	10	10	10	10	0	0	0	0	0	0	0	5.88%
10.0%	10	10	10	10	10	10	10	10	10	10	10	10	10	0	0	0	0	0	0	0	6.54%
11.0%	10	10	10	10	10	10	10	10	10	10	10	10	10	0	0	0	0	0	0	0	7.19%
12.0%	10	10	10	10	10	10	10	10	10	10	10	10	10	10	0	0	0	0	0	0	7.84%
13.0%	10	10	10	10	10	10	10	10	10	10	10	10	10	10	0	0	0	0	0	0	8.50%
14.0%	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	0	0	0	0	0	9.15%
15.0%	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	0	0	0	0	0	9.80%
16.0%	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	0	0	0	0	0	10.5%
18.0%	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	0	0	0	0	11.8%
	0.10%	0.12%	0.15%	0.17%	0.20%	0.22%	0.25%	0.27%	0.29%	0.49%	0.69%	0.74%	0.98%	1.66%	1.96%	2.45%	2.94%	3.43%	3.92%	4.41%	
	Risk of symptomatic VTE with prophylaxis																				

FIGURE 11 Balance of benefits and harms for medical inpatients with different levels of risk (blue and red indicate overall QALY gain and loss, respectively).

Risk of major bleeding with prophylaxis	Risk of symptomatic VTE without prophylaxis																				Risk of major bleeding without prophylaxis
	0.20%	0.25%	0.30%	0.35%	0.40%	0.45%	0.50%	0.55%	0.60%	1.00%	1.40%	1.50%	2.00%	3.40%	4.00%	5.00%	6.00%	7.00%	8.00%	9.00%	
0.10%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.03%
0.20%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.07%
0.50%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.17%
1.02%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.34%
2.00%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.67%
3.00%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.01%
3.70%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.24%
5.00%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.68%
6.00%	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2.01%
7.00%	10	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2.35%
8.00%	10	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2.68%
9.00%	10	10	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3.02%
10.00%	10	10	10	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3.36%
11.00%	10	10	10	10	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3.69%
12.00%	10	10	10	10	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4.03%
13.00%	10	10	10	10	10	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4.36%
14.00%	10	10	10	10	10	10	10	0	0	0	0	0	0	0	0	0	0	0	0	0	4.70%
15.00%	10	10	10	10	10	10	10	10	0	0	0	0	0	0	0	0	0	0	0	0	5.03%
16.00%	10	10	10	10	10	10	10	10	0	0	0	0	0	0	0	0	0	0	0	0	5.37%
18.00%	10	10	10	10	10	10	10	10	10	0	0	0	0	0	0	0	0	0	0	0	6.04%
	0.07%	0.09%	0.10%	0.12%	0.14%	0.15%	0.17%	0.19%	0.21%	0.34%	0.48%	0.51%	0.69%	1.16%	1.37%	1.71%	2.06%	2.40%	2.74%	3.08%	
	Risk of symptomatic VTE with prophylaxis																				

FIGURE 12 Balance of benefits and harms for surgical inpatients with different levels of risk (blue and red indicate overall QALY gain and loss, respectively).

are different in medical and surgical inpatients. The square outlined in bold is the average level of risk assumed for that population in the base-case analysis.

In *Figure 11*, it can be seen that prophylaxis for all results in QALY gains for medical inpatients with average levels of VTE and bleeding risks (3.4% and 1.02%, respectively). Prophylaxis for none would result in greater QALY gains if either the average VTE risk in the medical cohort was much lower (≤ 0.35%) or the average risk of bleeding in the medical cohort was much higher (≥ 11%). However, in a cohort of patients with both a higher risk of bleeding and a lower risk of VTE, for example, a 6% bleeding risk and a 1.5% VTE risk, prophylaxis would also do more harm than good.

In *Figure 12*, it can be seen that prophylaxis results in overall QALY gains over a much broader range of VTE and bleeding risks in surgical inpatients than in medical inpatients. In surgical inpatients a much lower proportion of major bleeding is fatal bleeding or a non-fatal ICH and, therefore, the overall impact of prophylaxis is positive over a broader range of bleeding risks. In addition, the average age assumed for patients in the surgical population is lower than the average age for patients assumed in the medical population. Therefore, any QALY losses due to long-term consequences of VTE, such as PTS, will be larger as they will have an impact over a longer time frame.

Figures 11 and *12* show exploratory analyses and should not be used to guide decision-making. The analysis assumes that the RR of bleeding with prophylaxis is constant and does not increase as the baseline bleeding risk increases, whereas it is conceivable that risk factors for bleeding also increase the RR of bleeding with prophylaxis. Furthermore, VTE and bleeding risk factors are often inter-related and there may be interactions between risk factors and between risks. These issues mean that the decision to prescribe prophylaxis for an individual patient with an increased bleeding risk is complex and unlikely to lend itself to determination by a simple trade-off.

Figures 11 and *12* show the balance of benefits and harms for prophylaxis in terms of the impact on overall lifetime QALYs, but they do not address the question of whether it is cost-effective to use prophylaxis at different levels of risk and whether it is cost-effective to use a RAM to select patients at higher risk for prophylaxis. These questions are addressed in *Deterministic base-case cost-effectiveness results for medical inpatients* to *Deterministic scenario analyses for elective hip and knee replacement populations* below.

Deterministic base-case cost-effectiveness results for medical inpatients

The deterministic base-case results obtained when applying the midpoint parameter estimates to the base-case scenario for medical inpatients using data for the five RAMS that were evaluated in a single cohort of patients (Green *et al.* 2016; Grant *et al.* 2016) are presented in *Figure 13*. For each RAM, several points are plotted which represent the costs and QALYs that can be achieved for different RAM cut-off points. It can be seen in *Figure 13* that the strategy of prophylaxis for all dominates all other options because it has a larger expected QALY gain and it also has a lower expected cost. *Figure 13* also shows the expected costs and QALYs for a RAM which has the average characteristics of all the RAMS evaluated in the cohort reported by Greene *et al.* and Grant *et al.* using the ROC curve regression described in *Sensitivity and specificity of RAMs*.

Figure 14 shows the secondary analysis introducing the data from RAMs evaluated in other cohorts. For some of these RAMs, only a single point is plotted as sensitive and specificity was only reported at

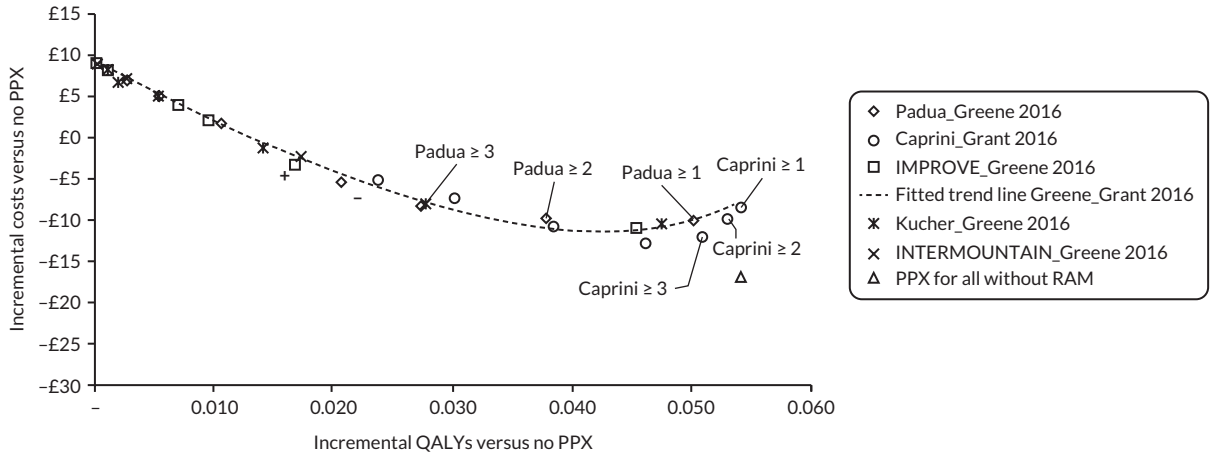

FIGURE 13 Deterministic base-case results for medical inpatients when using RAMs evaluated in a single cohort of patients (Greene *et al.*[39] and Grant *et al.*[38]).

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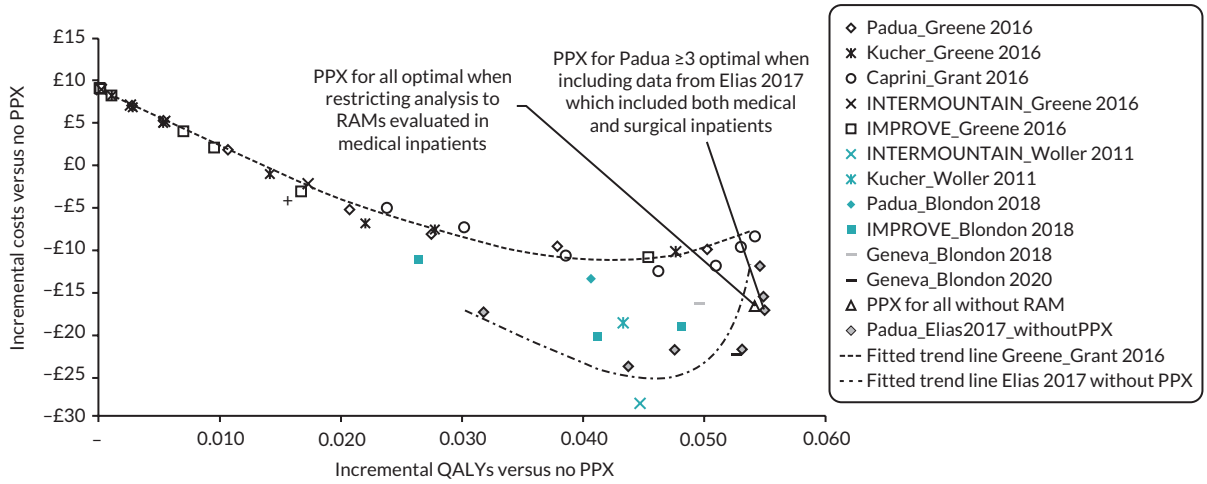

FIGURE 14 Deterministic base-case results for medical inpatients when using RAMs evaluated by Greene *et al.*[39] and Grant *et al.*[38] and RAMs evaluated in other cohorts (including the mixed cohort of surgical and medical patients reported by Elias *et al.*[36]).

a single threshold but for others multiple points are plotted showing different RAM thresholds. Several of these RAMs appear to perform better than the regression based on the average RAM evaluated in the cohort reported by Greene *et al.* and Grant *et al.* in that they provide a similar number of QALYs at a lower cost. The best-performing RAM reported in an alternative cohort, is the Geneva score with a cut-off of ≥ 3 (sensitivity of 94.6% and specificity of 44%) reported by Blondon *et al.*[29] However, prophylaxis for all would still be more cost-effective than using a Geneva score cut-off of ≥ 3, even when applying the performance data from Blondon *et al.*

Also shown in *Figure 14* is a sensitivity analysis using the Padua RAM performance data from Elias *et al.* which was obtained in the subgroup of the cohort not having prophylaxis.[36] When including this data, the optimal strategy would be a Padua score of ≥ 3 (sensitivity 99.9% and specificity of 23.7%), as this has slightly higher QALYs and slightly lower costs than prophylaxis for all. However, the caveat here is that Elias *et al.* recruited a mixed population of medical and surgical patients and, therefore, it is unclear if this RAM would perform equally well in an exclusively medical cohort. When the Padua score was evaluated by Greene *et al.* in an exclusively medical cohort, the performance was not as good, with a Padua score of ≥ 3 having a sensitivity and specificity of 49.3% and 73.0%, respectively. However, this sensitivity analysis suggests that if a RAM with sufficiently good performance could be developed and validated in an exclusively medical cohort, then prophylaxis for all would not be the optimal strategy in medical patients. Also shown are the expected costs and QALYs when using a regression fitted to the data points from Elias *et al.* It can be seen from this that the performance based on the regression is not as good as when using the observed sensitivity and specificity for the actual Padua RAM scores obtained by Elias *et al.* This is because the regression is not a good fit to the ROC curve for low RAM scores.

Probabilistic base-case results for medical inpatients

Based on these deterministic analyses, the probabilistic model was run for the strategies of no prophylaxis, prophylaxis for all and for the various cut-offs of the Padua score (assuming the RAM performance observed in Greene *et al.*). It should be noted that this probabilistic analysis does not explore the uncertainty regarding which RAM is optimal as this would require comparing all of the cut-offs from all of the various RAMs simultaneously. Instead, it uses the Padua RAM as an example RAM to answer the question of what the optimal strategy would be if the RAM chosen performed similarly to the Padua RAM.

The results based on the mean outcomes from 10,000 probabilistic model runs are summarised in *Table 8*. The broad conclusions are the same, in that prophylaxis for all is the optimal strategy when applying valuing a QALY at £20,000–30,000.

TABLE 8 Base-case results (mean from 10,000 PSA samples) in order of % receiving prophylaxis for medical inpatients

	% PPX	Sensitivity	Specificity	Absolute costs, £	Absolute QALYs	Cost vs. no PPX, £	QALYs vs. no PPX	ICER vs. PPX for none, £	INMB vs. PPX for none at £20K, £[a]	INMB vs. PPX for none at £30K, £[a]
PPX for none	0%	0	1	244.93	9.0033	-	NA	NA	NA	NA
PPX for Padua[b] ≥ 7	3%	5%	98%	251.40	9.0061	6.47	0.0028	2295.40	49.89	78.07
PPX for Padua[b] ≥ 6	6%	10%	96%	249.09	9.0087	4.16	0.0055	762.55	104.91	159.44
PPX for Padua[b] ≥ 5	12%	19%	91%	244.81	9.0141	−0.12	0.0108	Dominates	215.61	323.36
PPX for Padua[b] ≥ 4	23%	37%	84%	235.91	9.0243	−9.02	0.0210	Dominates	428.46	638.19
PPX for Padua[b] ≥ 3	35%	49%	73%	231.70	9.0311	−13.23	0.0279	Dominates	570.57	849.23
PPX for Padua[b] ≥ 2	57%	69%	49%	227.79	9.0417	−17.14	0.0384	Dominates	786.04	1170.49
PPX for Padua[b] ≥ 1	86%	92%	17%	224.43	9.0544	−20.50	0.0511	Dominates	1042.68	1553.77
PPX for all	100%	1	0	216.49	9.0585	−28.44	0.0552	Dominates	1132.39	1684.36

ICER, Incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; NA, not applicable; PPX, prophylaxis.

a INMB at £20K and INMB at £30K are the incremental net monetary benefits when valuing a QALY at £20,000 and £30,000 per QALY, respectively and the maximum value (shown in bold) shows you the optimal strategy.

b Assuming the Padua RAM performs according to the sensitivity and specificity data from Green *et al.* 2016.

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Figure 15 shows that while the average cost saving is £28.44 and the average QALY gain is 0.055 QALYs for prophylaxis for all versus prophylaxis for none, there are a broad range of estimates with 79% of samples resulting in a cost saving and the incremental cost having a CrI of £−113.66 to £46.28. The incremental QALY estimate has a CrI of 0.02 to 0.11, with 99.9% of samples resulting in a QALY gain compared to prophylaxis for none.

The cost-effectiveness acceptability curve (CEAC) is presented in *Figure 16* for medical inpatients. There is < 1% chance that prophylaxis for all is not the optimal strategy when valuing a QALY at £20,000. In addition, because prophylaxis for all is cost-saving compared to even the next most effective strategy, there is a 76% chance that it would be the optimal strategy when valuing a QALY at £0.

The overall expected value of perfect information (EVPI) associated with all parameters included in the probabilistic sensitivity analysis (PSA) when valuing a QALY at £20,000 was £0.06 per patient per year (£59.33 per 1000 patients per year) due to the high probability that prophylaxis for all is the optimal strategy. This suggests that there is minimal decision uncertainty regarding whether a RAM should be used in medical inpatients, when assuming the RAM will perform according to the performance of the Padua RAM in the Greene *et al.* cohort.

However, the results in *Figure 14* suggest that the optimal strategy may not be prophylaxis for all if a better-performing RAM could be developed in medical patients. Therefore, we decided to re-run the

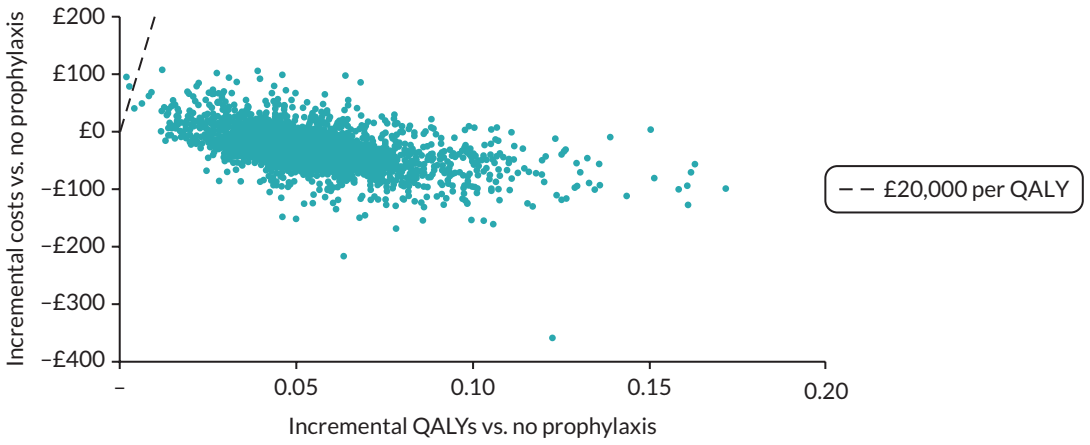

FIGURE 15 Cost-effectiveness plane for prophylaxis for all versus prophylaxis for none in medical inpatients.

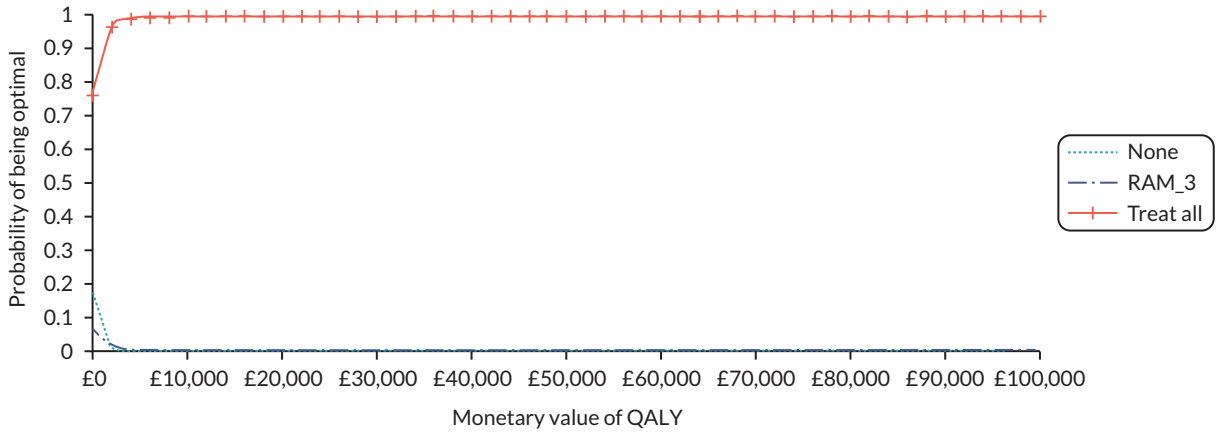

FIGURE 16 Cost-effectiveness acceptability curve (CEAC) for medical inpatients (applying performance of Padua RAM from Greene *et al.*[39]). Strategies with < 1% probability across all values of a QALY are not plotted.

EVPI analysis for the medical cohort when using the sensitivity and specificity data from the mixed cohort of medical and surgical patients reported by Elias *et al*. When using this sensitivity and specific data for medical inpatients, the EVPI is £2.42 per person per year (£2422.90 per 1000 patients per year). Offering prophylaxis at a RAM score of ≥ 3 has a 76.6% chance of being optimal and prophylaxis for all has a 17.6% chance of being optimal when valuing a QALY at £20,000. In addition, a large proportion of the global EVPI is attributable to the uncertainty around the RR of bleeding for prophylaxis versus no prophylaxis; expected value of partial perfect information (EVPPI) of £2.01 for this parameter with no other parameter having an EVPPI > £0.01. This sensitivity analysis suggests that if a better-performing RAM could be developed for medical inpatients, then the decision uncertainty would largely relate to the uncertainty around the increased risk of bleeding attributable to prophylaxis.

Deterministic scenario and sensitivity analyses for medical inpatients

Deterministic scenario and sensitivity analyses were conducted to explore which model assumptions and inputs were key drivers of decision uncertainty. To do this, deterministic results were generated using midpoint parameter inputs when varying individual model inputs or assumptions. These analyses assume that the RAM used is Padua and that it performs as observed in the cohort reported by Greene *et al*.

The results presented in *Table 9* show that the broad conclusion that prophylaxis for all is the optimal strategy (defined as most cost-effective when valuing a QALY at £20,000) does not vary under most of the scenarios and sensitivity analyses considered. The exceptions were scenarios that explored large changes to the risk of VTE and bleeding during PPX, with a sixfold decrease in VTE risk or a sixfold increase in risk of major bleeding needed to alter the optimal strategy.

On the basis of this, further analyses were conducted to explore how the optimal strategy varies when changing the average risks of VTE and major bleeding in the medical cohort. *Figure 17* shows that the optimum strategy is prophylaxis for all when the risk of VTE is high and the bleeding risk is low, but the optimum strategy is pharmacological prophylaxis for none when the risk of VTE is low and the bleeding risk is high. There is a band of combined VTE and bleeding risks where using a RAM to target prophylaxis at higher-risk patients would be optimal instead of a blanket strategy of either prophylaxis for all or prophylaxis for none. This suggests that it is important to gather good evidence on the average risks of VTE and major bleeding in the medical cohort as a whole in order to determine whether a RAM should be used to direct prophylaxis.

TABLE 9 Deterministic scenario and sensitivity analyses for medical inpatients when assuming the used RAM is Padua and performance is based on Greene *et al.*[39]

Scenario	Parameter varied	Parameter value in base-case scenario	Parameter value in current scenario	Optimal strategy in current scenario
Base case	N/A	N/A	N/A	PPX for all
Younger patients	Age	65.8	20	PPX for all
Older patients	Age	65.8	80	PPX for all
Double utility decrement for PPX	Utility decrement	0.007	0.015	PPX for all
Low discounting rate for costs and QALYs	Discount rate	3.5%	1.5%	PPX for all
High discounting rate for costs and QALYs	Discount rate	3.5%	6.0%	PPX for all

continued

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TABLE 9 Deterministic scenario and sensitivity analyses for medical inpatients when assuming the used RAM is Padua and performance is based on Greene *et al.* (*continued*)

Scenario	Parameter varied	Parameter value in base-case scenario	Parameter value in current scenario	Optimal strategy in current scenario
Utility decrement of PTS is halved	Utility decrement	10%	5%	PPX for all
Utility decrement of PTS from Lenert *et al.*	Utility decrement	10%	2%	PPX for all
Quadruple cost of administering RAM	Cost of RAM administration	£9.08	£36.33	PPX for all
No PTS risk in asymptomatic DVT (proximal or distal)	Risk of PTS in:			PPX for all
	Proximal	57.5%	0%	
	Distal	15.6%	0%	
Low risk of VTE (one-sixth of baseline risk)	VTE risk			Padua ≥ 2
	Symptomatic	3.4%	0.6%	
	Asymptomatic	30.5%	5.1%	
PTS cost from Caprini	Year 1 cost	£293	£1022	PPX for all
	Year 2 cost	£78	£423	
No asymptomatic DVTs	Asymptomatic DVT risk	30.5%	0%	PPX for all
7 days of LMWH (including 2 days post discharge)	Cost of PPX	£23.91	£101.03	PPX for all
Higher risk of death in year of admission	Risk of death in year 1	10%	22%	PPX for all
Bleed risk during VTE treatment reflects any HAS-BLED score	Risk of major bleeding during anticoagulation	0.9%	2.0%	PPX for all
Higher bleed risk during PPX (six times higher)	Risk of bleeding during PPX	1.02%	6.12%	Padua ≥ 1
No additional cost for administering RAM	Cost of RAM administration	£9.08	£0	PPX for all
Lower case-fatality rate of PE	Case-fatality rate of PE	26.8%	13%	PPX for all
Higher case-fatality rate of PE	Case-fatality rate of PE	26.8%	67%	PPX for all
No increase in inpatient care due to VTE	Distal DVT cost	£644.88	£386.10	PPX for all
	Proximal DVT cost	£765.05	£386.10	
	PE cost	£1850.68	£476.57	
VTE occurs 3 days after admission	Time of VTE	42	3	PPX for all
VTE occurs 90 days after admission	Time of VTE	42	90	PPX for all
Increased use of DOACs to treat VTE	% of VTE treatment that is DOACs	40%	100%	PPX for all

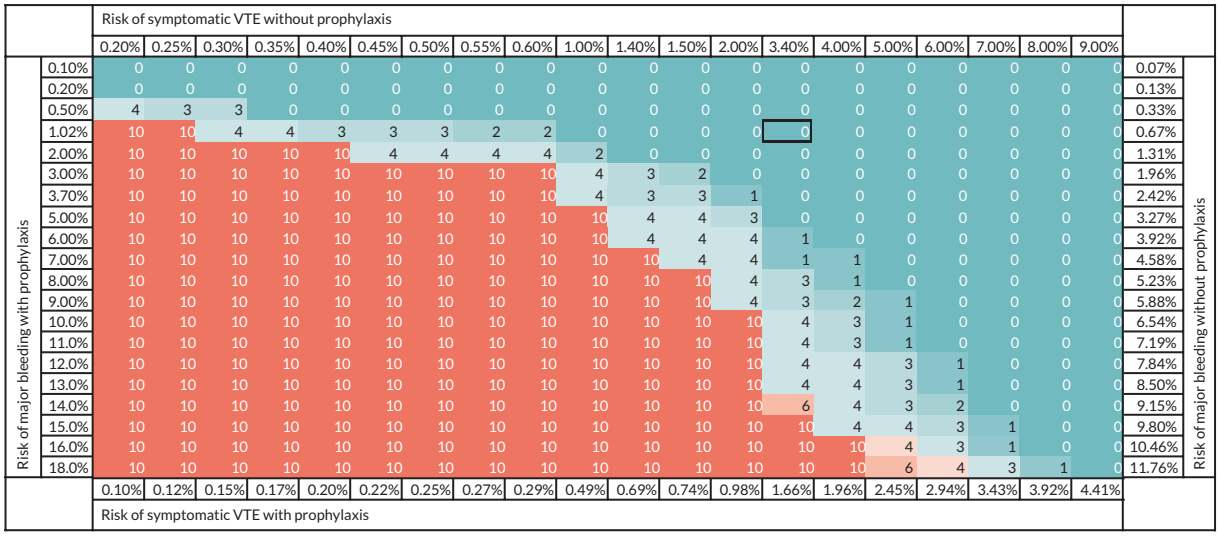

FIGURE 17 Optimal risk assessment strategy for cohorts of medical inpatients with varying levels of baseline risks (box indicates base-case scenario). It should be noted that the rows and columns do not represent equal steps in risk; red (10) indicates prophylaxis for none is optimal and blue (0) indicates prophylaxis for all is optimal; the numbers in cells of other colours represent the optimal Padua RAM score at which prophylaxis should be offered at that level of risk to maximise incremental net monetary benefit when valuing a QALY at £20,000.

The sensitivity and scenario analyses also suggest that various individual factors about which there was some uncertainty have no impact on the optimal strategy. These include the incidence of PTS after asymptomatic DVT, the costs and utility losses attributable to PTS, the case-fatality rate for PE and the exact timing of VTE within the 90-day post-admission period. In addition, it was found that the optimal strategy did not change when assuming no additional cost for administering the RAM or when assuming that patients continue LMWH for 7 days including 2 days of post-discharge administration.

Deterministic base-case results for surgical inpatients

The deterministic base-case results obtained when applying the midpoint parameter estimates to the base-case scenario for surgical inpatients using data for the two RAMS that were evaluated in either a surgical population (Caprini by Bahl *et al.*,[26] Pannucci by Pannucci *et al.*[54]) are presented in *Figure 18*. For each RAM, several points are plotted which represent the costs and QALYs that can be achieved for different RAM cut-off points. For the Pannucci RAM, the cut-offs shown are ≥ 6, ≥ 3 and ≥ 1. For the Caprini score the cut-offs shown are ≥ 7, ≥ 5, ≥ 3 and ≥ 2. From this it can be seen that the optimal strategy is pharmacological prophylaxis for all, if the analysis is restricted to RAMs evaluated exclusively in this cohort. *Figure 18* also includes results for the Padua RAM from the mixed cohort of both surgical and medical inpatients reported by Elias *et al*. When including the performance data from the Padua score evaluated by Elias *et al.*, the optimal strategy is a Padua score of ≥ 3 (sensitivity of 99.9% and specificity of 23.7%), which achieves more QALYs at a reduced cost compared to prophylaxis for all.

Figure 18 also shows the expected cost-effectiveness of a RAM whose performance is based on a regression fitted to the data from the ROC curve for Padua using the data observed in the cohort not having thromboprophylaxis reported Elias *et al*. The data for the lower Padua score cut-offs (≥ 1 to ≥ 3) were excluded from this regression as they did not fit the assumption that there is a linear relationship between logit (sensitivity) and logit (1-specificity). Therefore, the regression does not closely follow the performance of the Padua score for the cut-offs below 4 and the Padua score is predicted by the regression to perform less well than observed at cut-offs below 4. This results in thromboprophylaxis for all being the optimal strategy when assuming that the RAM would follow the ROC curve predicted by the regression. Based on this, we can say that a RAM would need to have a very high sensitivity, similar to that observed by Elias *et al.*, to make using a RAM more cost-effective than offering prophylaxis to all.

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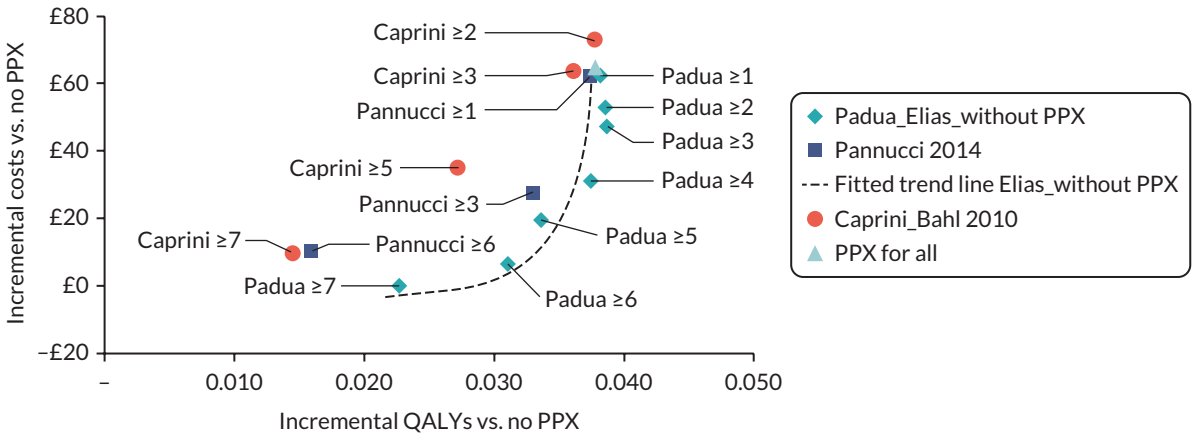

FIGURE 18 Deterministic base-case results for surgical inpatients when using RAMS evaluated in either surgical populations (Pannucci *et al.* 2014[54], Bahl *et al.* 2010[26]) or mixed populations of both surgical and medical inpatients [Elias without prophylaxis (PPX)].

Probabilistic base-case results for surgical inpatients

Based on these deterministic analyses, the probabilistic model was run for the strategies of no pharmacological thromboprophylaxis, prophylaxis for all and for the various cut-offs of the Pannucci score. It should be noted that this does not capture uncertainty related to which RAM is optimal as this would require a simultaneous comparison of all of the various cut-offs for all three RAMs.

The results based on the mean outcomes from 10,000 probabilistic model runs are summarised in *Table 10*. The broad conclusions are the same, in that offering prophylaxis to surgical patients with a Pannucci score ≥ 3 is the optimal strategy when applying valuing a QALY at £20,000 to £30,000.

Figure 19 shows the incremental costs and QALYs for pharmacological thromboprophylaxis for all versus prophylaxis for none in surgical inpatients. It can be seen that while the average cost saving is £47.88 and the average QALY gain is 0.035 QALYs, there are a broad range of estimates with 24% of PSA samples resulting in a cost saving and the incremental cost having a CrI of −£96 to £254. The incremental QALY estimate has a CrI of 0.002 to 0.080 with 98% of samples resulting in a QALY gain compared to prophylaxis for none.

The CEAC is presented in *Figure 20* for surgical inpatients. It can be seen from this that giving prophylaxis to all patients has the highest probability of being cost-effective at £20,000 per QALY, with a 70% likelihood of being optimal, but there is also a 17% likelihood that using a Pannucci score of ≥ 3 would be optimal and a 9% likelihood that using a Pannucci score of ≥ 1 would be optimal.

The overall EVPI associated with all parameters included in the PSA when valuing a QALY at £20,000 was £16.35 per person. This is calculated across all strategies including no prophylaxis, Pannucci scores of ≥ 6, ≥ 3 and ≥ 1 and thromboprophylaxis for all. It does not include the uncertainty of considering which RAM to use as the EVPPI has been run assuming that the Pannucci score is used. In addition, it should be noted that the EVPI analysis does not include any uncertainty not captured in the PSA such as uncertainty around the model assumptions or the choice of data sources, or uncertainty around the estimates of sensitivity and specificity.

In the analysis of parameter EVPI (EVPPI), only six individual parameters were found to have an EVPPI of more than £0.01 per person (see *Table 11* EVPI results for surgical in patients when using Pannucci RAM based on sensitivity and specificity from Pannucci *et al.*). The parameter with the largest EVPPI was the RR of VTE for patients having thromboprophylaxis compared to patients not having thromboprophylaxis. Other slightly less important parameters were the likelihood that major bleeding is intracranial (ICH) or fatal, the absolute and RRs of bleeding and the utility of patients experiencing PTS following DVT. These

TABLE 10 Base-case results (mean from 10,000 PSA samples) in order of per cent receiving thromboprophylaxis (PPX) for surgical inpatients

	% PPX	Sensitivity	Specificity	Absolute costs, £	Absolute QALYs	Cost vs. no PPX £	QALYs vs. no PPX	ICER vs. PPX for none, £	INMB vs. PPX for none at £20K, £[a]	INMB vs. PPX for none at £30K, £[a]
PPX for none	0%	0%	100%	159.13	13.9214	NA	NA	NA	NA	NA
PPX for Pannucci[b] ≥ 6	20%	40%	83%	165.89	13.9362	6.76	0.0148	457.59	288.62	436.31
PPX for Pannucci[b] ≥ 3	55%	84%	49%	176.99	13.9519	17.86	0.0306	584.51	593.17	898.68
PPX for Pannucci[b] ≥ 1	90%	98%	12%	206.09	13.9561	46.96	0.0347	1353.16	647.13	994.17
PPX for all	100%	100%	0%	207.01	13.9565	47.88	0.0351	1363.99	654.11	1005.11

ICER, Incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; NA, not applicable; PPX, prophylaxis

a INMB at £20K and INMB at £30K are the incremental net monetary benefits when valuing a QALY at £20,000 and £30,000 per QALY, respectively, and the maximum value shows you the optimal strategy.

b Assuming the Pannucci score performs as observed in Pannucci *et al.*

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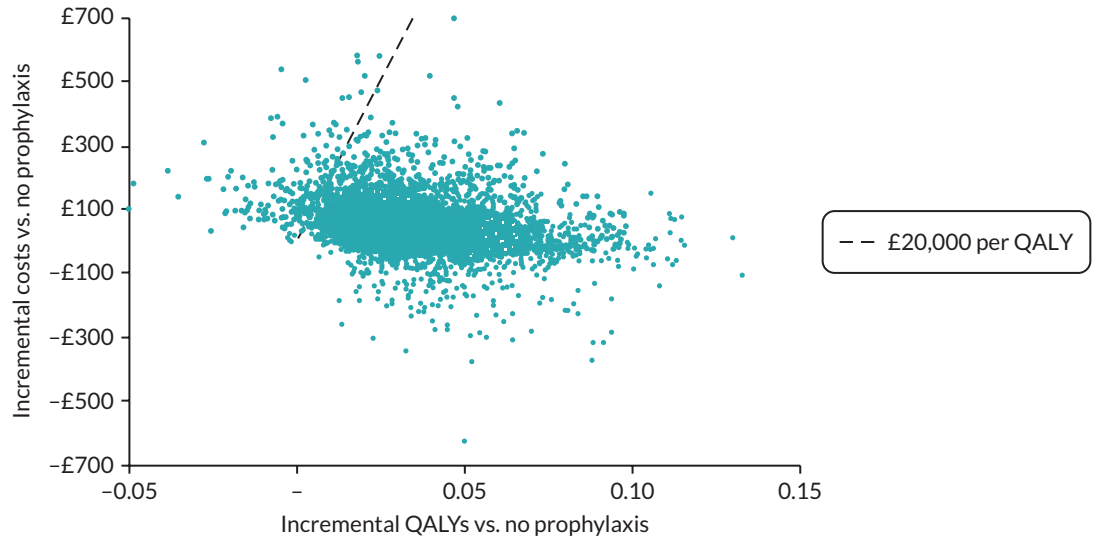

FIGURE 19 Cost-effectiveness plane for prophylaxis for all versus prophylaxis for none in surgical inpatients.

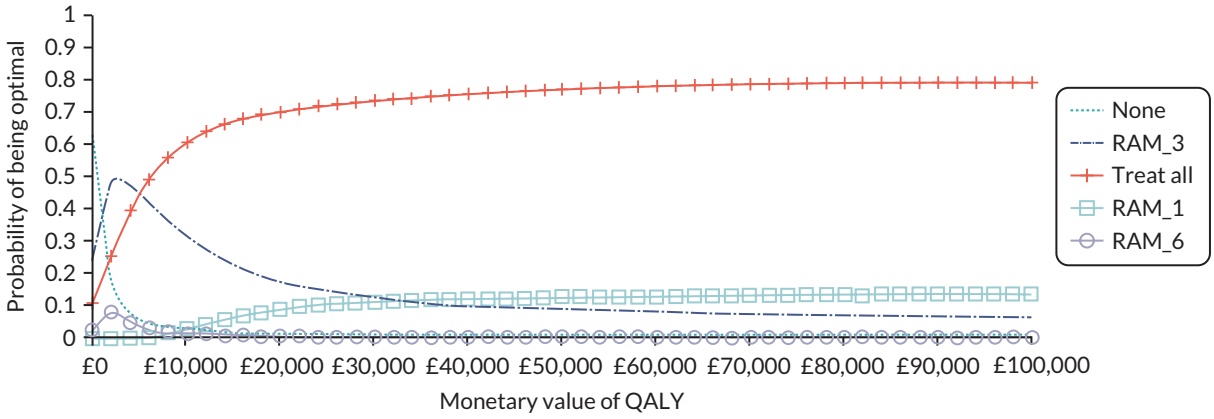

FIGURE 20 CEAC for surgical inpatients (assuming the RAM used is Pannucci).

TABLE 11 EVPI results for surgical in patients when using Pannucci RAM based on sensitivity and specificity from Pannucci *et al.*[54]

Parameter	Per person EVPPI (£)	Standard error	Indexed to overall EVPI = 1.00
RR of VTE for prophylaxis vs. no prophylaxis	5.95	0.99	0.36
% fatal if major bleed during prophylaxis	0.95	1.58	0.06
% of non-fatal major bleeds that are ICH during prophylaxis	0.59	1.32	0.04
RR of major bleed for prophylaxis vs. no prophylaxis	0.33	2.03	0.02
Absolute risk of major bleeding in patients having prophylaxis	0.13	1.49	0.01
Utility of PTS	0.01	1.05	< 0.01

findings reinforce the idea that it is the trade-off between the short-term risks of bleeding in patients receiving prophylaxis and the long-term risks of chronic complications that are most important to the decision regarding which surgical inpatients should be offered prophylaxis.

We also ran the PSA and EVPI analysis assuming that the Padua RAM is used and that it performs as seen in subset of the cohort reported by Elias *et al.* who did not receive prophylaxis. This was to explore whether further research would be more worthwhile if a RAM could be identified that performed better than the Pannucci RAM in surgical inpatients. The CEAC when assuming the RAM performance for Padua reported by Elias *et al.* is shown in *Figure 21*. When using the sensitivity and specificity data from Elias *et al.* the overall EVPI was £15.90 and the same set of parameters was identified as being the most important drivers of uncertainty.

Deterministic scenario and sensitivity analyses for surgical inpatients

Deterministic scenario and sensitivity analyses were conducted to determine whether the optimal strategy (when valuing a QALY at £20,000) varies under different assumptions or alternative sources of evidence. These analyses assume that the RAM used is Pannucci. The optimal strategy is defined as the most cost-effective strategy when valuing a QALY at £20,000.

These analyses (see *Table 12*) identified that prophylaxis for all is no longer the optimal strategy when the risk of VTE is halved, or when the risk of bleeding is doubled. It is also no longer optimal when the utility decrement of PTS is halved or estimated from alternative sources,[134] or when assuming there is no risk of PTS in asymptomatic DVTs. It is also no longer optimal when assuming that there are no asymptomatic DVTs. These analyses suggest that the cost-effectiveness of offering prophylaxis to surgical patients is being partly driven by the prevention of PTS in patients having asymptomatic DVT. The scenario exploring an increase in age to 80 changed the optimal strategy to a RAM score of ≥ 3, which suggests that the optimal strategy may differ for patients who have lower life expectancy and lower quality of life prior to admission as these patients have less potential to benefit from reducing the risk of long-term complications. An increase in the duration of prophylaxis to 7 days to cover 5 days of admission and 2 days of post-discharge prophylaxis also altered the optimal strategy to offering prophylaxis at a RAM score of ≥ 1. However, this was largely attributable to the additional 2 days of prophylaxis provided after discharge, as the duration of in-hospital prophylaxis had to be increased to 16 days before the optimal strategy changed. The use of extended prophylaxis for 28 days also resulted in an optimal strategy of offering prophylaxis for those with a RAM score ≥ 3.

The sensitivity and scenario analyses also suggest that various individual factors about which there was some uncertainty have no impact on the optimal strategy. These include the costs attributable to PTS, the case-fatality rate for PE and the exact timing of VTE within the 90-day post-admission period.

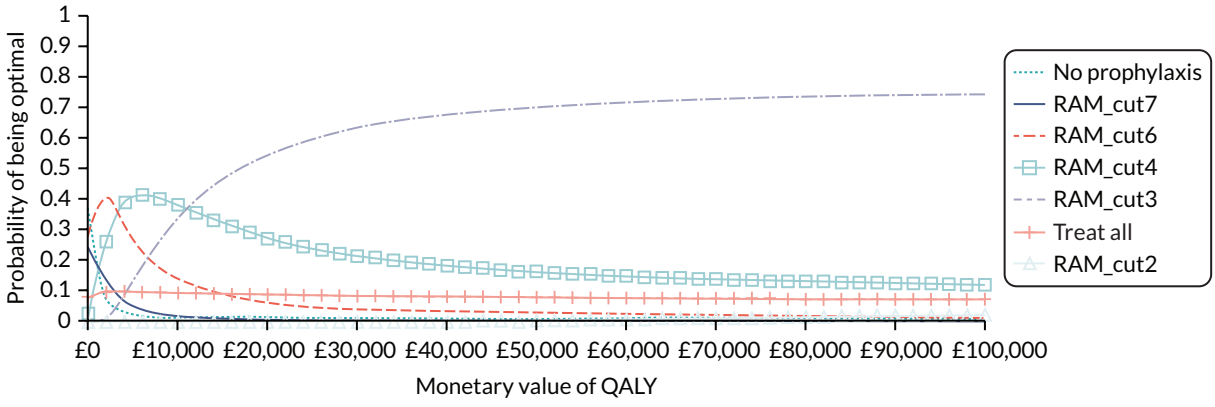

FIGURE 21 CEAC for surgical inpatients (assuming the RAM used is Padua from Ellias *et al.*[36]).

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TABLE 12 Deterministic scenario and sensitivity analyses for surgical inpatients when assuming RAM is Pannucci and performance is based on Pannucci *et al.*[54]

Scenario	Parameter varied	Parameter value in base-case scenario	Parameter value in current scenario	Optimal strategy in current scenario
Base case	N/A	N/A	N/A	PPX for all
Younger patients	Age	54.2	20	PPX for all
Older patients	Age	54.2	80	Pannucci ≥ 3
Double utility decrement for PPX	Utility decrement	0.007	0.015	PPX for all
Low discounting rate (same for costs and QALYs)	Discount rate	3.5%	1.5%	PPX for all
High discounting rate (same for costs and QALYs)	Discount rate	3.5%	6.0%	PPX for all
Utility decrement of PTS is halved	Utility decrement	10%	5%	Pannucci ≥ 1
Utility decrement of PTS from Lenert	Utility decrement	10%	2%	Pannucci ≥ 3
Quadruple time for administering RAM (5–20 minutes)	Cost of RAM administration	£9.08	£36.33	PPX for all
No PTS risk in asymptomatic DVT (proximal or distal)	Risk of PTS in:			Pannucci ≥ 6
	Proximal	57.5%	0%	
	Distal	15.6%	0%	
No PTS risk in asymptomatic distal DVT	Risk of PTS in:			Pannucci ≥ 1
	Proximal	57.5%	57.5%	
	Distal	15.6%	0%	
No PTS risk in asymptomatic proximal DVT	Risk of PTS in:			Pannucci ≥ 3
	Proximal	57.5%	0%	
	Distal	15.6%	15.6%	
Lower risk of VTE (halving rate vs. base case)	VTE risk			Pannucci ≥ 3
	Symptomatic	1.4%	0.7%	
	Asymptomatic	12.6%	6.3%	
PTS cost from Caprini	Year 1 cost	£293	£1022	PPX for all
	Year 2 cost	£78	£423	
No asymptomatic DVTs	Asymptomatic DVT risk	12.6%	0%	Pannucci ≥ 6
7 days of LMWH (including 2 days post discharge)	Cost of PPX	£23.91	£101.03	Pannucci ≥ 1
Longer duration of admission (16 days)	Cost of PPX	£23.91	£62.16	Pannucci ≥ 1
Higher risk of death in year of admission	Risk of death in year of admission	2%	12%	PPX for all
General population risk of mortality in year of admission	Risk of death in year of admission	2%	0.3%	PPX for all

TABLE 12 Deterministic scenario and sensitivity analyses for surgical inpatients when assuming RAM is Pannucci and performance is based on Pannucci *et al.* (*continued*)

Scenario	Parameter varied	Parameter value in base-case scenario	Parameter value in current scenario	Optimal strategy in current scenario
Bleed risk during VTE treatment reflects any HAS-BLED score	0.9%	2.0%	0.9%	PPX for all
Higher bleed risk during PPX	Risk of bleeding during PPX	3.7%	7.4%	Pannucci ≥ 3
No additional cost for administering RAM	Cost of RAM administration	£9.08	£0	Pannucci ≥ 1
Higher case-fatality rate for PE	Case-fatality rate	6%	26.8%	PPX for all
Use of extended prophylaxis	Duration of prophylaxis	5	28	Pannucci ≥ 3
No increase in inpatient care due to VTE	Distal DVT cost	£644.88	£386.10	PPX for all
	Proximal DVT cost	£765.05	£386.10	
	PE cost	£1850.68	£476.57	
VTE occurs 3 days after admission	Time of VTE	42	3	PPX for all
VTE occurs 90 days after admission	Time of VTE	42	90	PPX for all
Increased use of DOACs to treat VTE	% of VTE treatment that is DOACs	40%	100%	PPX for all

As these one-way scenario analyses identified that the conclusions were sensitive to the average risks of VTE and major bleeding in the cohort, we conducted a two-way scenario analysis to determine whether the optimal strategy would be different if the risk of VTE or the risk of major bleeding had been underestimated or overestimated in the base-case analysis. *Figure 22* shows, although prophylaxis for all is the optimal strategy at the exact level of VTE and bleed risk assumed in the base-case scenario, the use of a RAM would be optimal across a large range of VTE and bleeding risks if that RAM performed similarly to the Pannucci RAM. This suggests that obtaining good evidence on the average baseline risks of VTE and major bleeding in the surgical cohort being offered risk assessment is important for determining which patients should be offered thromboprophylaxis.

Deterministic scenario analyses for elective hip and knee replacement populations

Figure 23 shows the incremental costs and QALYs versus no prophylaxis for each RAM cut-off point. For each series of points, the point closest to the origin shows the costs and QALYs for a Pannucci ≥ 6, and then each successive point shows the next RAM cut-off (≥ 3, ≥ 1 etc.) until the last point shows prophylaxis for all. Separate lines show the results for the main surgical population and for the two specific populations of patients having either elective hip replacement or elective knee replacement. For the main surgical population, two alternative assumptions regarding whether thromboprophylaxis is stopped at discharge or continued post-discharge are shown for comparison.

The optimal strategy in the base case for the main surgical population, where LMWH is assumed to stop on discharge at 5 days, is prophylaxis for all. This is also the optimal strategy in the knee replacement population where LMWH is assumed to continue post discharge up to 14 days. For the main surgical population, when allowing patients to continue prophylaxis post discharge up to a maximum of 7 days, the optimal strategy (when valuing a QALY at £20,000) is offering prophylaxis using a RAM score cut-off of ≥ 1. The optimal strategy in the hip replacement population where LMWH is assumed to continue post discharge up to 28 days is offering prophylaxis using a RAM score cut-off of ≥ 3.

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Risk of major bleeding with prophylaxis	Risk of symptomatic VTE without prophylaxis																			Risk of major bleeding without prophylaxis
	0.20%	0.25%	0.30%	0.35%	0.40%	0.45%	0.50%	0.55%	0.60%	1.00%	1.40%	1.50%	2.00%	3.40%	4.00%	5.00%	6.00%	7.00%	8.00%	9.00%	
0.10%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.03%
0.20%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.07%
0.50%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.17%
1.02%	3	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.34%
2.00%	3	3	3	3	3	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.67%
3.00%	6	3	3	3	3	3	3	3	3	0	0	0	0	0	0	0	0	0	0	0	1.01%
3.70%	6	3	3	3	3	3	3	3	3	1	0	0	0	0	0	0	0	0	0	0	1.24%
5.00%	10	6	6	3	3	3	3	3	3	3	1	0	0	0	0	0	0	0	0	0	1.68%
6.00%	10	10	6	6	3	3	3	3	3	3	1	1	0	0	0	0	0	0	0	0	2.01%
7.00%	10	10	6	6	6	3	3	3	3	3	3	1	1	0	0	0	0	0	0	0	2.35%
8.00%	10	10	10	6	6	6	6	3	3	3	3	3	1	0	0	0	0	0	0	0	2.68%
9.00%	10	10	10	10	6	6	6	6	3	3	3	3	1	0	0	0	0	0	0	0	3.02%
10.0%	10	10	10	10	6	6	6	6	6	3	3	3	1	0	0	0	0	0	0	0	3.36%
11.0%	10	10	10	10	10	6	6	6	6	3	3	3	3	0	0	0	0	0	0	0	3.69%
12.0%	10	10	10	10	10	10	6	6	6	3	3	3	3	1	0	0	0	0	0	0	4.03%
13.0%	10	10	10	10	10	10	10	6	6	3	3	3	3	1	0	0	0	0	0	0	4.36%
14.0%	10	10	10	10	10	10	10	6	6	3	3	3	3	1	1	0	0	0	0	0	4.70%
15.0%	10	10	10	10	10	10	10	10	6	3	3	3	3	1	1	0	0	0	0	0	5.03%
16.0%	10	10	10	10	10	10	10	10	10	3	3	3	3	1	1	0	0	0	0	0	5.37%
18.0%	10	10	10	10	10	10	10	10	10	6	3	3	3	1	1	1	0	0	0	0	6.04%
	0.06%	0.07%	0.09%	0.10%	0.12%	0.13%	0.15%	0.16%	0.17%	0.29%	0.41%	0.44%	0.58%	0.99%	1.16%	1.45%	1.74%	2.03%	2.32%	2.61%	
	Risk of symptomatic VTE with prophylaxis																				

FIGURE 22 Optimal risk assessment strategy for cohorts of surgical inpatients with varying levels of baseline risks (box indicates base-case scenario). It should be noted that the rows and columns do not represent equal steps in risk; red (10) indicates prophylaxis for none is optimal and blue (0) indicates prophylaxis for all is optimal; the numbers in cells of other colours represent the optimal Pannucci RAM score at which prophylaxis should be offered at that level of risk to maximise incremental net monetary benefit when valuing a QALY at £20,000.

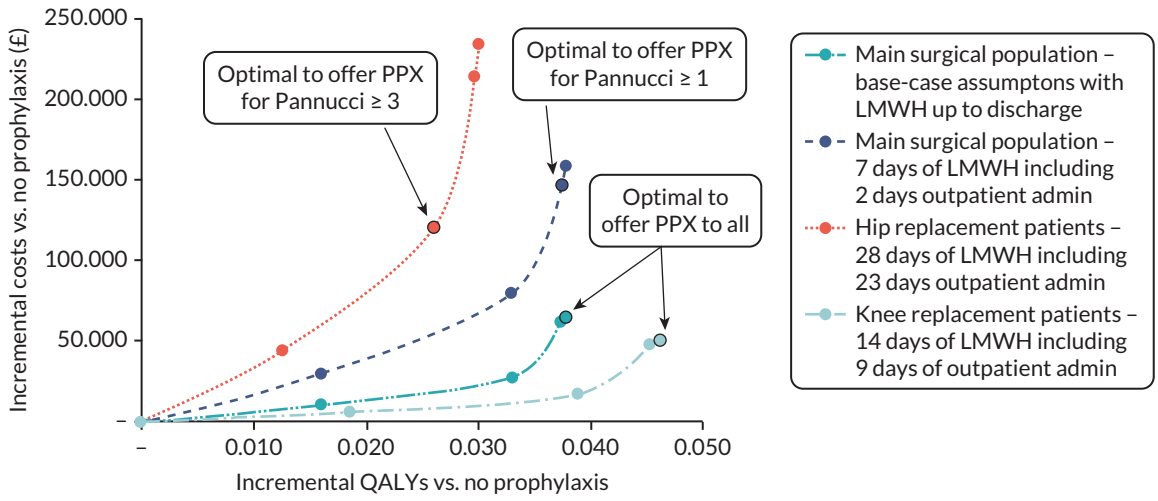

FIGURE 23 Incremental costs and QALYs versus no prophylaxis for various RAM cut-off points (Pannucci ≥ 6, Pannucci ≥ 3, Pannucci ≥ 1, PPX for all) for populations requiring PPX after discharge.

When applying the costs for the alternative pharmacological prophylaxis strategies using either aspirin or DOACs, but assuming equivalent efficacy to LMWH, the incremental costs were lower than the base-case scenario as these thromboprophylaxis strategies had lower costs. In the case of elective knee replacement patients, the optimal strategy was thromboprophylaxis for all when assuming either 14 days of aspirin or 14 days of a DOAC were offered. In hip replacement patients, thromboprophylaxis for all was optimal when assuming that DOACs were offered instead of LMWH and offering prophylaxis at a Pannucci score of ≥ 1 was optimal when assuming that prophylaxis consisted of 10 days of LMWH was followed by 28 days of aspirin.

The additional costs of offering extended duration prophylaxis, particularly with LMWH instead of DOACs or aspirin, mean that using a RAM to reduce the population being offered prophylaxis is optimal in patients having an elective hip replacement. However, in patients having elective knee replacement,

when the duration of prophylaxis is only 14 days, the optimal strategy is the same as in the main surgical cohort where prophylaxis is recommended up to 7 days.

Summary of key findings

- For medical inpatients, pharmacological prophylaxis for all patients without contraindications is likely to be the more cost-effective strategy, when valuing a QALY at £20,000. This assumes that any RAM applied in medical inpatients would perform in a similar manner to the average RAM performance estimated in a single cohort of medical inpatients.
- The optimal prophylaxis strategy was fairly robust under sensitivity analysis in the medical inpatient cohort. The key factors determining cost-effectiveness appear to be the baseline risks of VTE and major bleeding and the increased risk of major bleeding associated with prophylaxis.
- For surgical inpatients, pharmacological prophylaxis for all patients without contraindications is likely to be the more cost-effective strategy, when valuing a QALY at £20,000 and assuming that any RAM applied in a surgical population performs similarly to either the Pannucci or Caprini RAM.
- In the surgical inpatient cohort, the most cost-effective strategy was sensitive to many of the individual model inputs and assumptions tested, with the optimal strategy being a Pannucci score of ≥ 6 (sensitivity of 40% and specificity of 82%) when assuming no risk of PTS after asymptomatic proximal or distal DVT.
- In specific surgical populations who require longer durations of prophylaxis, it was found that pharmacological prophylaxis for all eligible patients is optimal in those having 14 days of LMWH following elective knee replacement whereas offering prophylaxis at a Pannucci score of ≥ 3 (sensitivity of 84% and specificity of 49%) was optimal when offering 28 days of LMWH to patients having elective hip replacement.
- Using a RAM to select patients for pharmacological prophylaxis in medical or surgical inpatients would only be optimal if that RAM had a high sensitivity, similar to that observed for the Padua RAM with a cut-off of ≥ 3 in a mixed cohort of medical and surgical patients (sensitivity 99.9%, specificity 23.7%).

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Chapter 8 Discussion

Statement of principal findings

Systematic review of RAMs

Sections of this chapter have been reproduced from Pandor *et al.* under licence CC BY 4.0.[17] In a systematic review of 51 observational studies evaluating RAMs for predicting the risk of developing VTE in hospital inpatients, we found that VTE RAMs have generally weak predictive accuracy. The studies validating these models are heterogeneous and most have a high risk of bias. Lack of methodological clarity was common, leading to difficulty in assessing the applicability of the individual study results. VTE prophylaxis was used in around half the study populations, with markedly varying frequency, and was not reported in most of the other studies. This is an important potential source of bias and heterogeneity between studies.

Our systematic review updated previous reviews to include more recent studies, but did not fundamentally alter the conclusions that the available evidence shows weak predictive accuracy and has significant methodological limitations.[8–10] VTE RAMs may be useful, despite the limited evidence and apparently weak accuracy, if they can identify patients with a higher risk of VTE who are more likely to benefit from prophylaxis. Decision-analytic modelling allowed us to explore whether VTE RAMs can provide more cost-effective use of VTE prophylaxis.

Economic evaluation

Using decision-analytic modelling to address the cost-effectiveness of VTE risk assessment, we made several key findings. For medical inpatients, the balance of VTE risk and risk of major bleeding, combined with the performance observed for RAMs in medical cohorts, means that prophylaxis for all is the optimal strategy within the model. The key factors determining cost-effectiveness in the medical cohort appear to be the baseline risks of VTE and major bleeding and the increased risk of major bleeding associated with prophylaxis. In the analysis for surgical inpatients, the optimal strategy within the model is to offer prophylaxis to all. However, the scenario analyses found that the optimal strategy was sensitive to many of the individual model inputs and assumptions tested, with the optimal strategy varying from a Pannucci score of ≥ 6 (sensitivity of 40% and specificity of 82%) to offering prophylaxis for all.

In the scenario analyses exploring specific surgical populations who require longer durations of prophylaxis, it was found that prophylaxis for all is optimal in patients having elective knee replacement whereas offering prophylaxis at a Pannucci score of ≥ 3 (sensitivity of 84% and specificity of 49%) was optimal when offering extended duration prophylaxis with LMWH to patients having elective hip replacement. The difference in optimal strategy between the elective hip replacement population and the main surgical cohort appear to be driven in part by the high cost of providing extended-duration prophylaxis, as the scenario analysis assuming 28 days of LMWH in the general surgical population also resulted in a Pannucci score of ≥ 3 being optimal. In the elective knee replacement population, the increased risk of bleeding associated with LMWH was lower meaning that there was less of a trade-off between a reduced VTE risk and an increased bleed risk in this group.

Our findings differ slightly from the previous cost-effectiveness analysis from a US health system perspective by Le *et al.*, which found that LMWH is cost-effective for medical inpatients when the risk of VTE is over 1%.[11] Le *et al.* discussed the use of RAMs to select patients with a risk of < 1% but did not explicitly model using a RAM to identify patients with a risk of < 1%. The difference is explained by the fact that Le *et al.* only included proximal symptomatic DVT and PE within their analysis and their average VTE risk in medical inpatients was assumed to be 1.4%. Under these conditions, the optimal strategy using our model would be a Padua score of ≥ 3 (when valuing a QALY at £20,000 or £30,000). Green

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et al. report a risk of < 1% in those with a Padua score < 3, suggesting the analyses are consistent when the VTE risk is defined in a similar manner.[39]

Assessing the feasibility of efficient data methods and estimating key parameters for future implementation research

The findings from our cohort study suggest that currently available, routine and efficient data methods which can potentially identify VTE or major bleeding events during hospital admission or within 90 days of discharge, are not sufficiently sensitive for use in a large data-enabled study. We failed to achieve feasibility for a number of predefined metrics and concluded that use of routine data to identify outcomes would be highly likely to miss important VTE and bleeding events, and may erroneously identify false-positive events. We also identify significant limitations in the ability of efficient methods to identify individual risk variables and facilitate RAM comparison at scale in any future work. The majority of our sites did not collect contemporaneous data on risk assessment in a digital, or easily accessible format.

In addition, we provide estimates of key parameters for any future implementation study, based on an observational cohort study of > 2000 patients across four NHS sites. We report a HAT event rate of 1.6% (95% CI 1.0% to 2.2%) and a major bleeding event rate of 2.5% (95% CI 1.8% to 3.2%) in the context of routine NHS care for hospital inpatients. We also identify high rates of pharmacological prophylaxis in the context of routine care and risk assessment using the Department of Health tool, noting prescribing rates of 86.2%, 80.4% and 93.7% for all, medical and surgical patients, respectively. When comparing RAMS with attempted validation, we demonstrate highly variable rates of potential pharmacological thromboprophylaxis within the same cohort of general medical and surgical patients, in a UK NHS setting. Prescribing recommendation rates at published thresholds varied from 13% to 91% between RAMs. These data provide key estimates of current and potential prescribing rates, and potential event rates for any future studies looking to compare VTE RAMs, or assess implementation of novel strategies.

Finally, recent survey work suggests that > 80% of UK NHS sites continue to use the Department of Health tool for VTE risk assessment and that a high proportion use weight-adjusted dosing of pharmacological thromboprophylaxis. Our survey data also found that many sites continue to conduct risk assessment via paper proforma only and that very few sites record the absence of risk characteristics. These findings suggest that further comparative research on individualised risk assessment reliant on routine data collection, is unlikely to be feasible or reliable. These are important points to consider in the design of any future study.

Strengths and limitations

Systematic review of RAMs

Our systematic review work has a number of strengths. The review was conducted with robust methodology in accordance with the PRISMA statement and the protocol was registered with the PROSPERO register. Clinical experts were involved throughout as checkers and to assess the validity and applicability of research during the review. We reported descriptive statistics to provide insight into the limited evidence base applicable to the subject matter, and the scientific concerns regarding validity of the data. However, there are a number of potential weaknesses. Decisions on study relevance, information gathering and validity were unblinded and could potentially have been influenced by pre-formed opinions. However, masking is resource intensive with uncertain benefits. The studies of risk prediction were a combination of prospective cohorts and retrospective health database registries. Both have significant limitations. Retrospective studies of health database registries may have large numbers but may be limited by poor data quality and failure to accurately ascertain outcomes. Prospective cohorts may have better quality data but with smaller numbers lack statistical power.

We were unable to undertake meta-analysis or statistical examination of the causes of the observed heterogeneity. Potential sources of heterogeneity include variation in study design, the study population, how RAMs are implemented, outcome definition and measurement and the use of thromboprophylaxis. The latter point is highlighted above as a key finding.

Economic evaluation

The main strength of the economic evaluation is that it is able to evaluate the trade-off between costs, benefits and harms in a systematic manner based on the existing evidence base. One of the key uncertainties in the modelling is the incidence of VTE in cohorts not having thromboprophylaxis and the incidence of major bleeds outside of clinical trials. To address this uncertainty, the two-way scenario analyses on VTE and bleeding risk provide information on how robust the conclusions would be if the average risk of bleeding and the average risk of VTE across the medical and surgical cohorts has been underestimated or overestimated. However, these analyses do not necessarily provide information on whether a different strategy would be optimal in a select cohort of patients known to have higher or lower risks of bleeding or VTE. This is because the performance of the RAMs has been measured in broad cohorts of patients and the RAMs may not perform as well in very select cohorts chosen to have a very high or very low risk of VTE or major bleeding.

The economic analysis assumed that the population did not have characteristics associated with an increased risk of bleeding, and therefore had a low risk of bleeding overall. The findings, and specifically the conclusion that prophylaxis for all is the optimal strategy, do not, therefore, apply to populations or individual patients with an increased bleeding risk. The analyses showing whether the overall health impact is positive or negative at varying levels of VTE and bleeding risk (see *Figures 11* and *12*) are intended to show how bleeding and VTE risks might interact but should not be used to guide individualised decisions for patients. Bleeding and VTE often share the same risk factors, and interactions may occur between risks and between risk factors. Furthermore, our analyses assume that the RR for bleeding associated with prophylaxis is constant and increases in proportion to baseline bleeding risk. It is conceivable, however, that the risk factors for bleeding could increase the RR associated with bleeding. Taken together, these issues mean that the decision to provide VTE prophylaxis in the presence of increased bleeding risk is extremely complex, and best undertaken on an individual patient basis by an experienced clinical decision-maker. In this scenario, there remains a potential option to use mechanical thromboprophylaxis through graduated compression stockings or intermittent pneumatic compression devices. However, the evidence to support use of either device in medically ill patients is limited. We opted not to evaluate alternative methods of mechanical prophylaxis for patients at high risk of bleeding within the model, for the reasons outlined in *Chapter 4*.

A key limitation of the economic analysis is the heterogeneity in the estimates of RAM performance across the various cohorts identified in the systematic review. The secondary analysis using performance data for the Padua RAM from the cohort reported by Elias *et al.* provides different conclusions about the optimal strategy than found in the base-case analysis, due to the better performance of the Padua RAM in this cohort compared to the performance of this and other RAMs in other cohorts. The Padua RAM did not perform consistently better than other RAMs in other studies, so the higher accuracy in the Elias study probably reflects study characteristics rather than superiority of the Padua RAM. Our use of these data was intended to explore the potential for an accurate RAM to be cost-effective, rather than draw conclusions regarding a specific RAM or population.

Estimating key parameters for future implementation research and assessing the feasibility of efficient data methods

We engaged a combination of digitally mature and paper-based NHS sites within our cohort study and supplemented the findings with survey work, to obtain an accurate picture of VTE risk assessment conduct in a contemporary UK setting. We based key parameter estimation on an updated systematic review (workstream 1) and strict consensus definitions for VTE and bleeding events. We used statistical support, topic experts and research staff to iteratively develop our data collection tool and designed

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a clear workflow diagram to ensure compliance with data collection methods and limit subjective interpretation of case note data.

However, there are a number of potential limitations with design which could impact on the outcomes from workstream 2. We recruited only teaching hospital sites with university affiliation, two of which were VTE exemplar centres and three of which were tertiary centres, which may limit the external validity of our key parameter estimates. Regarding the evaluation of risk variables and estimation of key parameters, we opted for a cohort design on the early assumption that VTE risk assessments would be completed prospectively and accurately at all sites, in line with NICE guidance and NHS contract standards,[86] and that these data would be retained within the healthcare record. Limitations in electronic data capture at several chosen sites led to this aspect of the project becoming single centre. As such, we were unable to undertake detailed work to determine whether other sites could implement efficient methods of recording risk assessment data, but the issues identified with limited IT and service pressures suggested that substantial work would have been required and success was unlikely.

In addition, the complexity of identified RAMs for comparison necessitated retrospective case note review to identify additional variables. This may have introduced bias in assessment and downgrading of other RAMs due to absence of inquiry and information in the case notes. Other limitations include a relatively small sample size and differential ascertainment for the Department of Health VTE risk tool (collected in real time by clinicians) compared to other RAMs (collected through case note review by research teams). In addition, we do not report estimation of bleeding risk within this work. Although this is a vital aspect of VTE risk assessment, the six RAMs presented for comparison do not integrate any form of bleeding assessment. It is therefore unclear how these RAMs would perform comparatively within a real-world population of medical and surgical inpatients. It is likely that the proportions of patients receiving prophylaxis in practice would be lower than those recommended once bleeding risk is taken into account. The exclusion criteria applied to this cohort limit the generalisability of our results.

Regarding the feasibility of efficient data methods, research assistants across sites varied in seniority and clinical experience. Although all sites had a principal investigator with clinical expertise available for queries and strict working definitions for outcome events, this may have introduced variation in reporting. Finally, we did not achieve our intended target of 3000 patients. Reasons for this are detailed in the above chapters. However, it is important to note that the overall results within our cohort of 2008 patients are well outside of feasibility targets and that sensitivity values using routine data sources to identify key outcomes are universally poor. We do not envisage that further cases would have significantly affected these values to the point of reaching feasibility, even with a high level of accuracy.

Research in context

Systematic review of RAMs

The present review is the largest and most comprehensive systematic review in this field to date. It includes 18 recent studies published since the completion of the previous systematic review. These studies are consistent with the previous literature in that they report modest performance of the assessed RAMs, with limitations in methodology and reporting preventing further analysis. The conclusion of this review therefore concurs with previous systematic reviews: there is insufficient evidence to recommend one RAM over another.

Economic evaluation

Although the optimal strategy of prophylaxis for all is the same in the medical and surgical cohorts, there is a more evident trade-off between the benefits of reduced VTE and the risks of increased bleeding for surgical patients as shown by the table of clinical outcomes in *Table 4*. This is why the optimal strategy is more sensitive to changes in the model inputs and assumptions in the surgical population. Parameters related to the long-term benefits of preventing VTE, such as the risk of PTS and the utility

decrement of PTS, were identified as being important in the EVPPI analysis and sensitivity analyses for the surgical cohort. Factors related to long-term risks of chronic complications such as PTS do not appear to be important in determining the optimal strategy in the medical cohort, which may be because the medical cohort is older and, therefore, has a shorter life expectancy over which to accrue benefits from avoiding long-term complications. It is also important to recognise that while the risk of any major bleeding is higher in the surgical population, the risk of fatal bleeding or a non-fatal ICH is higher in the medical population. Medical inpatients are also more likely to die following a PE, and more likely to die in the year following admission even without experiencing VTE or major bleeding. However, sensitivity analyses applying a lower case-fatality rate for PE in medical inpatients or a higher case-fatality rate for PE in surgical inpatients do not result in a change in the optimal strategy.

In the secondary analysis using RAM performance data from the study by Elias *et al.*, the optimal strategy was to use a RAM in both medical and surgical patients. This is because RAM performance from Elias *et al.* was better than assumed in the base case for either the medical or surgical patients. For example, Elias *et al.* reported a sensitivity of 99.9% and a specificity of 23.7% for a Padua score of ≥ 3, whereas the equivalent values reported by Greene *et al.* in an exclusively medical cohort, were 49.3% and 73.0%, respectively. Performance data for the Padua RAM were not evaluated in an exclusively surgical cohort so a direct comparison cannot be made. These results suggest that if a RAM were to be useful for determining which patients should receive prophylaxis, it would need to have very high sensitivity similar to that observed for the Padua RAM in the study by Elias *et al*. If a future RAM performed similar to the Padua score ≥ 3 and a cut-off of 3 was applied, the model predicts that we would expect 80% of surgical patients and 84% of medical patients to receive prophylaxis. NICE reported that according to national figures, over 70% of medical patients receive prophylaxis using the Department of Health Risk Assessment tool, with some trusts offering prophylaxis to over 90% of medical inpatients.[8]

Estimating key parameters for future implementation research and assessing the feasibility of efficient data methods

Our findings are in line with previous comparative research on VTE risk assessment. Systematic review data have reported prescribing recommendation rates ranging from 30% to 90% for medical patients with the application of different RAMs.[10,145,152,153] We have not identified previous work describing the comparative prescribing rates of different RAMS in a cohort of surgical patients and therefore provide new comparisons in this area. The baseline data on hospital length of stay, HAT event rates, major bleeding rates and prescribing rates are all in keeping with published evidence reviews, suggesting internal validity of our cohort.[8]

The findings in our study highlight the ongoing variation in clinical care, of both medical and surgical patients, when different RAMs are applied to similar populations. In addition, our findings support previous research regarding the risk thresholds employed using the Department of Health VTE risk tool; this RAM conferred the highest proportion of pharmacological prophylaxis to both medical and surgical patients than any of the other six RAMs, with a 36% increase in recommended prescribing for surgical patients, and a 21% increase in medical patients, compared to the next highest prescribing model. Such high prescribing recommendations invite two key questions. First, does this tool provide better clinical or cost-effectiveness compared to others? Second, if over 90% of patients are likely to receive pharmacological thromboprophylaxis following use of the RAM, is there any real value in asking clinical teams to perform subjective and complex risk assessment? Switching to an ‘opt-out’ approach based on contraindications and bleeding risk has the potential to confer advantage, through mitigation of time and opportunity costs while concurrently encouraging default and reliable prescribing options. Such changes could also mitigate the key recurring issues with preventable HAT, most commonly resulting from errors in assessment, linked prescribing or drug administration.[150]

Our findings of limited sensitivity using routine data methods within a UK setting are consistent with previous international work in this area. An early comparison of HES data to general practice records in

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England reported in 2012, initially concluded reliable identification of vascular disease using HES data (derived from ICD-10 coding data).[154] However, this analysis was restricted to PE from a VTE perspective and sought only to correlate disease states, rather than identify new case episodes. Several authors have also used primary care research data sets correlated to evidence of anticoagulation or other secondary care data to identify VTE events, with reported reliable capture. This work does not seek to discriminate between index presentation of VTE and HAT.[155,156] A systematic review, with searches run in July 2010, published in 2012, summarised findings on this topic from 19 studies. The positive predictive value (PPV) for PE ICD codes ranged from 24% to 92%, with higher values from certain combinations of codes. PPV values for DVT codes ranged from 31% to 97%. More recently, a cross-sectional North American study compared ICD-10 codes for VTE in hospitalised medical patients to a 'gold standard' manual review of clinical data in 4000 patients.[157] The authors report a sensitivity of 63%/PPV of 43% for any DVT and a sensitivity of 83%/PPV of 70% for PE, implying further discrepancy between types of VTE.

Several authors have also experimented with composite data sets and diagnostic/procedural/disease coding combinations. One study combined ICD codes for VTE with a common procedural terminology code for a VTE Diagnostic Study plus at least one of the following within 30 days of diagnosis: pharmacy script for anticoagulation, placement of an inferior vena cava filter, or death.[158] This algorithm still lacked sensitivity, reporting a value of 0.67 (0.60, 0.73), a specificity of 0.99 (0.98, 0.99), a PPV of 0.92 (0.87, 0.96) and a NPV of 0.94 (0.93, 0.95). Alotaibi *et al*. subsequently combined routinely collected ICD-10 coding data with imaging procedure codes to identify VTE events over a 10-year period compared to case note review and reported highly specific results but limited sensitivity, in line with our findings [74.83% (95% CI 67.01 to 81.62) and 75.24% (95% CI 65.86 to 83.14) for PE and DVT, respectively].[159] Verma *et al.* report findings using natural language processing (NLP) algorithms for digital interrogation of radiology reports in a large cohort of hospitalised medical patients.[157] The authors conclude a high level of accuracy for NLP algorithms, reporting sensitivities of 94%/91% and PPVs of 90%/89% for DVT and PE, respectively. Such algorithms would require external validation in a UK setting and would be unable to distinguish HAT from index presentation of VTE, in isolation. Reliance on such algorithms in the context of low event rates would also lead to potential bias from false-negative results.

In 2017, Baumgartner *et al.* highlighted further issues through interrogation of an administrative coding database, looking to determine the accuracy of ICD coding for new episodes of recurrent VTE in patients with a prior history.[160] Only 31.1% of coded encounters were verified by reviewers as true recurrent VTE. More recently, Pellathy *et al.* have conducted similar work to VTEAM within the USA, comparing accuracy of HAT diagnoses made through administrative coding to manual case note and radiology review.[161] The authors report only 40% of HAT cases identified through routine coding were confirmed by case note review and 45% of HAT confirmed through diagnostic test records lacked corresponding ICD codes. This body of evidence, now including our recent work, suggests caution with the use of routinely collected outcome data within any future study where HAT events are an outcome of significant importance.

There are multiple potential explanations for the limited performance of routine data to identify HAT. The condition is a temporal phenomenon and routine coding data can therefore mistake index presentation with VTE as HAT, or fail to code subsequent HAT following index admission with alternative pathology; there are clear international guidelines supporting outpatient diagnosis and management of VTE, so genuine cases of HAT may not necessarily require hospital admission or relevant administrative coding; and prior diagnosis of VTE can often be coded during repeat hospital attendance and mistaken as HAT. Many UK hospitals attempting root cause analysis of HAT cases in line with NHS contract standards have developed pathways to mitigate these issues and improve identification, through local reporting arrangements with radiology, ultrasound and pathology services. Such arrangements often work well transiently but are reliant on individuals and reporting systems subject to human error. These issues are reflected in our findings from workstream 2, which report a PPV of

100% for HAT RCA database findings, but limited sensitivity (implying missed cases still occur despite a systematic approach).

More generally, these findings raise questions about the current enthusiasm for data-enabled trials and epidemiological research using outcome measures reliant on routine data methods.[162] Such concepts are inherently attractive to researchers and patients, particularly in topic areas with low event rates. However, complex outcome measures which require temporal evaluation and qualification against prior disease states are unlikely to be reliably delivered through use of routinely collected data in isolation. Several explanations have been proposed for current demonstrations of inaccuracy. Relevant data may contain coding errors arising from ambiguous documentation by physicians and inconsistent handling of recurrent cases.[162,164] Recent case studies have reported significant amounts of missing data and poor interobserver agreement between routinely collected EHR data accessible through HES and case report form (CRF) evaluation.[165] Electronic records contain an abundance of free text, but often lack necessary intelligence to classify patient episodes appropriately, or allow processing and comparison of routinely collected data.[166] Recent evidence also suggests that more complex outcomes will be less easily identified through routine coding; a registry study of Medicare claims following mitral valve repair compared to formal adjudication, reported a PPV for mortality of 97%, heart failure requiring hospitalisation of 69%, bleeding of 40% and renal failure of 19%.[167] In addition, the time and effort needed to acquire necessary permissions for national routine coding data or to orchestrate data linkage can be substantial. A UK clinical trials unit recently reported a digital request to facilitate routine data comparison to CRFs in the context of a RCT, highlighting a negotiation process over consent that took several years and receipt of data 15 months following application.[168] Such time frames may only be realistic within the context of continually adaptive design trials and add further concern as to whether the juice is actually worth the squeeze.

In their call to action, Sydes *et al*. discuss supplementation of trial-specific follow-up as an option to realise the full potential of data-enabled research.[162] Such an approach has potential merit to attempt identification of potential HAT, given the high PPV and high specificity of routine data sources. These cases would require subsequent adjudication and this approach would still fail to address the low sensitivity reported using routine data methods. Our findings suggest the use of routine data sources in isolation would be insufficiently accurate to capture complex VTE and bleeding outcomes within the context of a pragmatic trial context, but supplementation may be a viable use of resources. In addition, routine data sources may have a role in other research contexts, such as identification of cases for qualitative work, case–control studies, targeted individual follow-up or downstream survey work.

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Chapter 9 Conclusions

Implications for patients, clinicians and policy-makers

The updated systematic review within workstream 1 highlights the lack of supporting evidence for RAMs in this area and clarifies the limitations of previous work. In particular, our systematic review provides contemporary evidence that no method of risk assessment has been extensively validated, or methodically studied by implementation research.[17] This work supports recommendations within recent current UK NICE guidance, which highlight the lack of evidence for an 'optimal RAM' and support use of any RAM published by a national UK body, professional network or peer reviewed-journal to aid risk assessment in medical and surgical inpatients.[8] However, our cohort study within workstream 2 draws attention to the potential impact on practice of such a broad recommendation. Applying the RAMs identified by systematic review to a cohort of medical and surgical NHS patients within a single centre resulted in overall recommendations for pharmacological prophylaxis ranging from 91% (95% CI 88.6% to 95.2%) to as low as 13% (95% CI 9.4% to 17.7%). Such potential variation has clinical, educational and medico-legal implications for clinicians and policy-makers. This variation would also clearly have a significant impact on patients. Multiple thrombosis societies and patient-facing organisations have worked hard to raise awareness on VTE risks over the last decade and empower patients to self-advocate for risk assessment and appropriately challenge medical decision-making.[169] If the strategy of risk assessment is variable and the supporting evidence limited, participation in shared decision-making may be difficult.

Furthermore, decision-analytic modelling suggests that routine VTE prophylaxis is likely to be more cost-effective for medical and surgical patients requiring hospital admission than a strategy based on any currently available RAM. When taken in context with the lack of supporting evidence for available RAMs and ongoing errors/omissions leading to preventable cases of hospital-acquired VTE,[150] these findings have significant implications for policy-makers. There is reasonable evidence for the clinical effectiveness of pharmacological prophylaxis (subject to contraindications) for prevention of VTE in all medical and surgical patients admitted to hospital.[4,13] If pharmacological prophylaxis for all is likely to also be the most cost-effective strategy, despite drug costs and potential harms, recommendation of unvalidated RAMs may be inappropriate. Based on our findings, it may be preferable for policy-makers to consider evaluating a new paradigm of 'opt-out' VTE prevention, in which all eligible patients are offered pharmacological prophylaxis on hospital admission without complex risk assessment. In this circumstance, patients who are ineligible for pharmacological prophylaxis due to contraindications, high bleeding risk or personal choice could still utilise mechanical thromboprophylaxis in accordance with current evidence.

In addition, during the course of this project we identified several pragmatic issues with RAM use and application which can lead to repeated system errors or disengagement. Several RAMs have subjective components with poor inter-rater reliability;[170,171] RAMs may not be completed accurately (or at all) by busy clinical teams if they are deemed unhelpful to the encounter; clinicians may complete RAMs in a biased fashion due to experience (or inexperience) based on seniority; RAM completion and identification of high VTE risk may not translate to reliable prescribing; multifactorial RAMs applied to every patient accrue a significant work burden; and some multifactorial and complex RAMs will actually accrue decision-making points from only a small number of key variables. Although these issues do not feature widely in the current literature due to lack of implementation research, several studies have highlighted the numerous pragmatic challenges of RAM use.[51,145,153] These cumulative issues also potentially support a paradigm shift towards an 'opt-out' strategy.

There are limitations in translating these research findings to practice. Our systematic review focused on RAMs which evaluate thrombosis risk (rather than bleeding risk). As such, our economic modelling

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work is also based on estimations in a population without an increased risk of bleeding. In addition, workstream 1 focused on population-level estimates. In reality, each individual patient encounter is likely to have a different risk profile regarding VTE and bleeding; practicalities of implementation may be different from the model and it may still be necessary to perform a degree of risk assessment, or to evaluate the contraindications for pharmacological prophylaxis in detail.

Finally, we highlight the limitations of using routine data methods in the context of future research. Such systems run the risk of identifying both false-negative and false-positive VTE cases, through failure to identify ambulatory (uncoded) cases and overdiagnosis of previous disease. Many of these issues reflect the changing approach to modern VTE management and would be challenging to mitigate within any future research studies. Our findings were similar with regard to bleeding events, showing poor sensitivity of ICD-10 coding data and multiple false-positive events identified across four NHS sites. These findings have implications for funders looking to support further work in this area and suggest large studies reliant on routine data collection methods for outcomes are likely to be inaccurate and therefore unfeasible.

Our PPI group highlighted at several points during the project that risk assessment in the UK setting still seems an uncertain process, with many clinicians underestimating the consequences of VTE and the importance of prophylaxis. In addition, several respondents in our survey of national leads (see *Chapter 7*) highlighted the 'tick box' nature of VTE risk assessment; many clinicians feel they have already made the decision to prescribe prophylaxis prior to any risk assessment, and therefore consider the assessment itself to be a futile exercise. These findings also potentially support a more implicit use of prophylaxis at the point of hospital admission, with a clinical focus on reliable and standardised implementation, summarised by the 'opt out' approach described above, in contrast to current practice (complex risk assessment followed by opting in). However, the PPI group was also clear that lack of information and discussion about VTE risk during hospital admission or in the periprocedural period, was an ongoing concern. It was further highlighted by the steering committee that risk assessment, for all its faults, offers a clear opportunity to educate junior clinicians and discuss the risk of VTE with patients and service users, raising awareness of the condition and improving dialogue on the topic. These softer benefits may be potentially lost through any process of routine and unqualified thromboprophylaxis prescribing.

Suggested research priorities

Similar to our previous work, we identified that the current evidence base for RAMs looking to select appropriate hospitalised patients for pharmacological thromboprophylaxis is very limited and estimates of prognostic accuracy are subject to substantial uncertainty.[74] However, any future research on RAMs would be subject to the same challenges faced by this project, of VTE risk assessment as a contract standard within NHS practice and subsequent high rates of prophylaxis, supported by clear NICE guidance.[8] It would therefore be unethical to expose patients to implementation research on RAMs incorporating any control arm without risk assessment, or thromboprophylaxis.

Alternatively, given our findings on cost-effectiveness it may be reasonable to consider implementation research focusing on assessment of a novel opt-out strategy, regarding pharmacological prophylaxis. Such work could be conducted in any NHS setting and allocate patients to an intervention arm (default prophylaxis subject to contraindications or high bleeding risk only) compared to standard care (formal risk assessment and tailored prophylaxis as per national guidance). Patients ineligible for pharmacological prophylaxis in either group could also be offered alternative mechanical prophylaxis using evidence-based strategies, to further evaluate impact. Our survey work would suggest such an approach to be of interest to the national VTE community, with more support for a cluster randomised design (rather than individual patient randomisation) at hospital level. Such work would need to consider the challenges of reliable follow-up and outcome ascertainment given our findings from workstream 2.

Proposals could include adjudicated co-primary outcome definitions for VTE and major bleeding, evaluated using a hybrid approach of digital patient follow-up, routine data sources and local VTE identification methods.

Within the context of such an implementation study (including high numbers of patients receiving pharmacological thromboprophylaxis), a large observational cohort could also be evaluated to determine which risk predictors are associated with potential thromboprophylaxis failure. Given the challenges identified by this project regarding the completion methods and accuracy of risk assessment, risk predictor variables would likely require reliable, real-time collection by research teams on admission, outside of clinical assessment. Serial evaluation over the first 48 hours would allow evaluation of temporal RAM trends and novel biomarkers (D-dimer, CRP) on risk profile, building on recent systematic review work.[172] Indeed, recently derived RAMs are heavily focused on objective biomarker variables at an early admission stage and echo concerns regarding inter-rater reliability with subjective RAM components.[173] Multivariate analysis could subsequently identify which of these features during the first 48 hours of admission best identify likely thromboprophylaxis failure, allowing further risk stratification during hospital admission. If validated, this approach could lead to future trials of enhanced thromboprophylaxis strategies for higher-risk populations, in keeping with the 'individualised approach' relevant to specific subgroups, already proposed by several topic experts.[174–176]

The same logic could be applied to patients at the lower end of the risk spectrum. Within the context of an implementation study, patients who do not receive pharmacological thromboprophylaxis during routine care could be followed in a similar fashion to evaluate risk characteristics, temporal trends and outcomes. These data could facilitate multivariate analysis and subsequent identification of patients at a particularly low risk of VTE, who could be considered for early cessation of prophylaxis.

Taken together, the above projects could evaluate a paradigm shift in clinical VTE risk management; evaluation of a novel opt-out approach on hospital admission with the majority of medical and surgical patients immediately commenced on a weight-adjusted standard dose of pharmacological thromboprophylaxis without detailed risk assessment; a further evaluation at 48 hours using enhanced risk prediction, temporal trends in clinical progress and biomarker data; and a subsequent 'rationalisation' of prophylaxis at this time point – to increase, to continue or to cease. Such an approach would obviate complex risk assessment at the front door, when information, time and accuracy of diagnosis are limited and the chances of error are high, and facilitate early reliable use of prophylaxis followed by considered transition.

We found limited evidence on the accuracy or validity of bleeding risk assessment tools for hospitalised medical and surgical patients. Given we found bleeding risk to be a key factor in determining cost-effectiveness, further studies of bleeding risk and outcomes in patients receiving pharmacological thromboprophylaxis are urgently required. The high number of patients receiving prophylaxis in routine care could facilitate the rapid development of large observational cohort studies in this area, designed to accurately capture risk variables at presentation and evaluate their association with standardised major and CRNMB risk during hospital admission. Our findings in workstream 2 suggest that such a study could not rely on routine data collection methods to determine outcomes of relevance and may require significant research support to ensure diligent and accurate follow-up.

Last, our work is restricted primarily to medical, surgical and orthopaedic patients. We did not evaluate bespoke RAMs in specific patient subgroups, such as cancer or neurosurgery. Further studies of prophylaxis in specific patient populations are warranted, in particular where risk profile may differ significantly due to higher risk of critical site bleeding. A recent commissioned call for research into prophylaxis for patients with traumatic brain injury exemplifies this point.[177] Future studies in bespoke populations are likely best delivered through RCTs, informed by our work on the accuracy of routine data regarding relevant outcomes in thrombosis research.

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Appendix 4 - Submitted work 3

Published source is acknowledged as:

Davis S, Pandor A, Sampson FC, Hamilton J, Nelson-Piercy C, Hunt BJ, *et al.* Thromboprophylaxis during pregnancy and the puerperium: a systematic review and economic evaluation to estimate the value of future research *Health Technol Assess*, 2024: **28**(9). https://doi.org/10.3310/DFWT3873

The submitted work is described in Chapters 4, 6,7 and 8 of the published source, and therefore only these Chapters are reproduced below. The full published source can be accessed here:

https://www.journalslibrary.nihr.ac.uk/hta/DFWT3873

The decision-analytic modelling described in submitted work 3 has also been published in a shorter-form peer-reviewed journal article. To avoid duplication, this article has not been included as a separate submitted work, and is not reproduced in this thesis. However, it is listed here as supportive evidence which demonstrates the candidate's ability to disseminate their research in journal article format.

Davis S, Pandor A, Sampson S, et al. Estimating the value of future research into thromboprophylaxis for women during pregnancy and after delivery: a value of information analysis. Journal Thromb Haemost. 2024 Apr;22(4):1105-1116.

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Chapter 4 Decision-analytic modelling

Decision problem

Aim

The cost-effectiveness analysis aims to estimate the expected costs, health benefits (QALYs) and INMB of providing thromboprophylaxis, to women who are pregnant or who are in the puerperium, using current and alternative risk stratification tools. The EVPI analysis aims to quantify the uncertainty around those estimates, given current evidence, and to determine which factors are the most important drivers of uncertainty when trying to determine the optimal risk-based thromboprophylaxis strategy in this population. The outcomes of the EVPI analysis are then used alongside the qualitative research (see *Chapter 5*) to identify potential future studies to gather additional evidence that would reduce the current decision uncertainty, while being feasible and acceptable to patients and clinicians. The EVSI aims to evaluate the value of the potential future research studies in terms of the net health benefits to patients and the cost of the research (see *Chapter 6*).

Population

The target population for the decision-analytic modelling is women who are pregnant or in the puerperium (within 6 weeks post delivery) receiving care in both hospital and primary care settings. The antenatal and postnatal populations are considered separately. In addition, the systematic review (see *Chapter 3*) identified RAMs that are specifically targeted at antenatal women at high risk of VTE due to either prior VTE and/or known thrombophilia, and RAMs that are specifically targeted at obese postpartum women and postpartum women following caesarean section. One RAM was identified for use in an unselected antepartum population, but the performance data for this RAM were poor. Therefore, the analysis in the unselected antepartum population was limited to exploratory analysis to determine the range of sensitivity and specificity values that would be required for a RAM in this population. As women who have a prior VTE or known thrombophilia are likely to have received antepartum risk assessment, the postpartum modelling excludes these groups. Therefore, the following subgroups are considered in the decision-analytic model:

- antepartum women identified as being at high risk (prior VTE or known thrombophilia)
- unselected postpartum women (excluding those with prior VTE or known thrombophilia)
- postpartum women identified due to specific risk factors (caesarean section, obesity)
- unselected antepartum women (exploratory analysis only).

Strategies for prophylaxis

Strategies for prophylaxis in women having antepartum risk assessment

The current NICE Guideline on the prevention of VTE in hospitalised women who are pregnant or who are in the puerperium recommends that clinicians use a tool published by a national UK body, professional network or peer-reviewed journal.[6] The NICE Guideline states that the most commonly used tool is the RCOG guideline;[6,7] this is considered to represent current practice in the decision analysis. No data were identified to assess the sensitivity and specificity of RCOG in predicting VTE in women having antepartum risk assessment. (The only study assessing the use of RCOG in antepartum women was not suitable for inclusion in the modelling because it was in a small cohort of hospitalised pregnant women with cancer and no sensitivity data were available.) However, two RAMs for antepartum VTE risk assessment [Lyon[32,33] and Efficacy of Thromboprophylaxis as an Intervention during Gravidity (EThIG)[27]] in women at high risk of VTE (prior VTE and/or thrombophilia) were identified in the systematic review (see *Chapter 3*). Therefore, in the high-risk antepartum population, the Lyon and EThIG RAMs are compared against each other and against strategies of prophylaxis for all and prophylaxis for none. *Table 5* summarises current RCOG guidance on antepartum thromboprophylaxis

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TABLE 5 Summary of antepartum prophylaxis recommendations for women at high risk of VTE (prior VTE/thrombophilia) according to RCOG and corresponding recommendations for two alternative RAMs[a]

Risk factors	RCOG[7]	Lyon[32]	EThIG[27]
Prior pregnancy-related VTE	LMWH from booking	LMWH from booking	LMWH from booking
Prior VTE which was unprovoked	LMWH from booking	LMWH from 28 weeks gestation	LMWH from booking
Prior VTE associated with major surgery	LMWH from 28 weeks gestation	Postnatal LMWH only	Postnatal LMWH only
Thrombophilia without prior VTE	Consider antenatal LMWH (depends on type of thrombophilia)	LMWH from 28 weeks gestation or postnatal only depending on type of thrombophilia	From booking or postnatal only depending on type of thrombophilia

a Guidance not replicated exactly, so please refer to the source guidance when making clinical decisions.

for high-risk women (prior VTE and/or thrombophilia),[7] and compares these with the two RAMs for high-risk patients.[27,32]

As the RAMs vary in their recommendations regarding the timing of prophylaxis for some groups, the base-case analysis assumes that risk assessment occurs at the time of the antenatal booking appointment and LMWH is offered from booking to women identified as being high risk using the RAM. Scenario analysis is then used to explore whether the conclusions are sensitive to prophylaxis being deferred to 28 weeks. In scenarios where antepartum prophylaxis is offered, it is assumed that prophylaxis is also continued for 6 weeks after delivery.

In the high-risk antepartum scenario, the model estimates outcomes for prophylaxis for the following strategies:

- antepartum prophylaxis followed by postpartum prophylaxis for all [prophylaxis (PPX) from booking]
- antepartum prophylaxis based on a RAM (Lyon/EThIG)[27,32] followed by postpartum prophylaxis for all
- postpartum prophylaxis for all but no antepartum prophylaxis [postpartum (PP) PPX only]
- no prophylaxis, either antepartum or postpartum (no PPX).

The exploratory analysis for unselected antepartum women makes similar assumptions regarding the timing of risk assessment (antenatal booking appointment) and the duration of prophylaxis offered to those identified as high risk (from booking until 6 weeks postpartum); however, the comparator strategy of postpartum prophylaxis for all (PP PPX only) is not included as unselected women not receiving antepartum prophylaxis are likely to receive a further risk assessment after delivery.

Strategies for prophylaxis in women having postpartum risk assessment

In the postpartum population model, the strategies compared are:

- postpartum prophylaxis for all (PP PPX for all)
- postpartum prophylaxis based on a RAM
- no postpartum prophylaxis (no PPX).

In each case, postpartum prophylaxis is assumed to be offered for 10 days. This is because for the majority of women receiving postpartum thromboprophylaxis, they would fit the criteria for short-term VTE prevention strategies based on their transient risk factors in line with the RCOG guidance. Extended postnatal prophylaxis lasting 6 weeks is mainly offered to those having antepartum

prophylaxis, who are excluded from this analysis, and some women with multiple or persistent risk factors. For the unselected postpartum population, the RAMs compared are RCOG,[11,39] SFOG,[11,36] Caprini[39] and the novel RAM reported by Sultan *et al*.[11] In the postpartum subgroups selected based on specific risk factors, the RAMs compared are RCOG and the novel RAM reported by Binstock *et al*.[28] in the post-caesarean section population and the novel RAM reported by Ellis-Kahana *et al*.[41] in the obese population.

Modelling methods

Context

The model estimates lifetime costs and QALYs for the different thromboprophylaxis strategies and the comparator of no thromboprophylaxis under an NHS and Personal Social Services (PSS) perspective. Future costs and benefits are both discounted to their net present value at a rate of 3.5% per annum in accordance with the 2013 NICE guide to the methods of technology appraisal.[44] Costs are reported in Great British pounds based on 2020 prices. To achieve this, historical prices used as model inputs were uplifted using the hospital and community health services pay and prices index up to 2016 and the NHS Cost Inflation Index thereafter.[45]

Conceptual model for antepartum women

The conceptual model has been developed in collaboration with the project management group (which included both clinical and patient experts). The group provided guidance on the selection of model outcomes based on clinical importance and assessed the appropriateness of data sources and model assumptions. An existing published model that has been used to evaluate RAM-based thromboprophylaxis strategies in other populations was used as a starting point for discussion.[46,47] Other models that were excluded from the systematic review of published economic evaluations, which addressed similar but not identical decision problems (see *Appendix 3*), were also used to inform discussions regarding relevant clinical outcomes for inclusion.

The model consists of a decision-tree phase, summarised in *Figure 3*, to capture short-term outcomes followed by a lifetime state-transition (Markov) model, summarised in *Figure 4*, to capture the impact of outcomes that result in death or ongoing morbidity. For women being assessed for antepartum prophylaxis, the decision-tree phase of the model is repeated to capture the antepartum and postpartum periods separately. Those patients who are well at the end of the antepartum decision tree remain at risk of postpartum VTE and enter into a postpartum decision tree with the same structure. Those patients who have experienced a symptomatic VTE or a non-fatal intracerebral haemorrhage (ICH) in the antepartum model are assumed to have ongoing costs and utility decrements [reductions in health-related quality of life (HRQoL)] driven mainly by these events, so they remain in the same health state in the postpartum phase.

The decision tree is used to estimate for each strategy: the number of patients receiving thromboprophylaxis; the impact of thromboprophylaxis on VTE outcomes (PEs and DVTs); and the incidence of major bleeds during either thromboprophylaxis or VTE treatment with anticoagulants. PEs were divided into fatal and non-fatal events. DVTs were divided first into symptomatic and asymptomatic DVTs and then into proximal and distal DVTs. Symptomatic DVTs and non-fatal PEs are assumed to result in 3 months of anticoagulant treatment, which should be continued until at least 6 weeks post delivery.

In our previous analysis of thromboprophylaxis strategies in patients having lower limb immobilisation following injury, we found that the prevention of post-thrombotic syndrome (PTS) following asymptomatic DVT was an important driver of both cost effectiveness and decision uncertainty due to asymptomatic DVTs being more common than symptomatic DVTs but their long-term consequences being more uncertain.[46] So while asymptomatic DVTs are assumed to remain undetected and untreated, it is important to capture these DVTs in the decision-tree phase of the model in order to capture any

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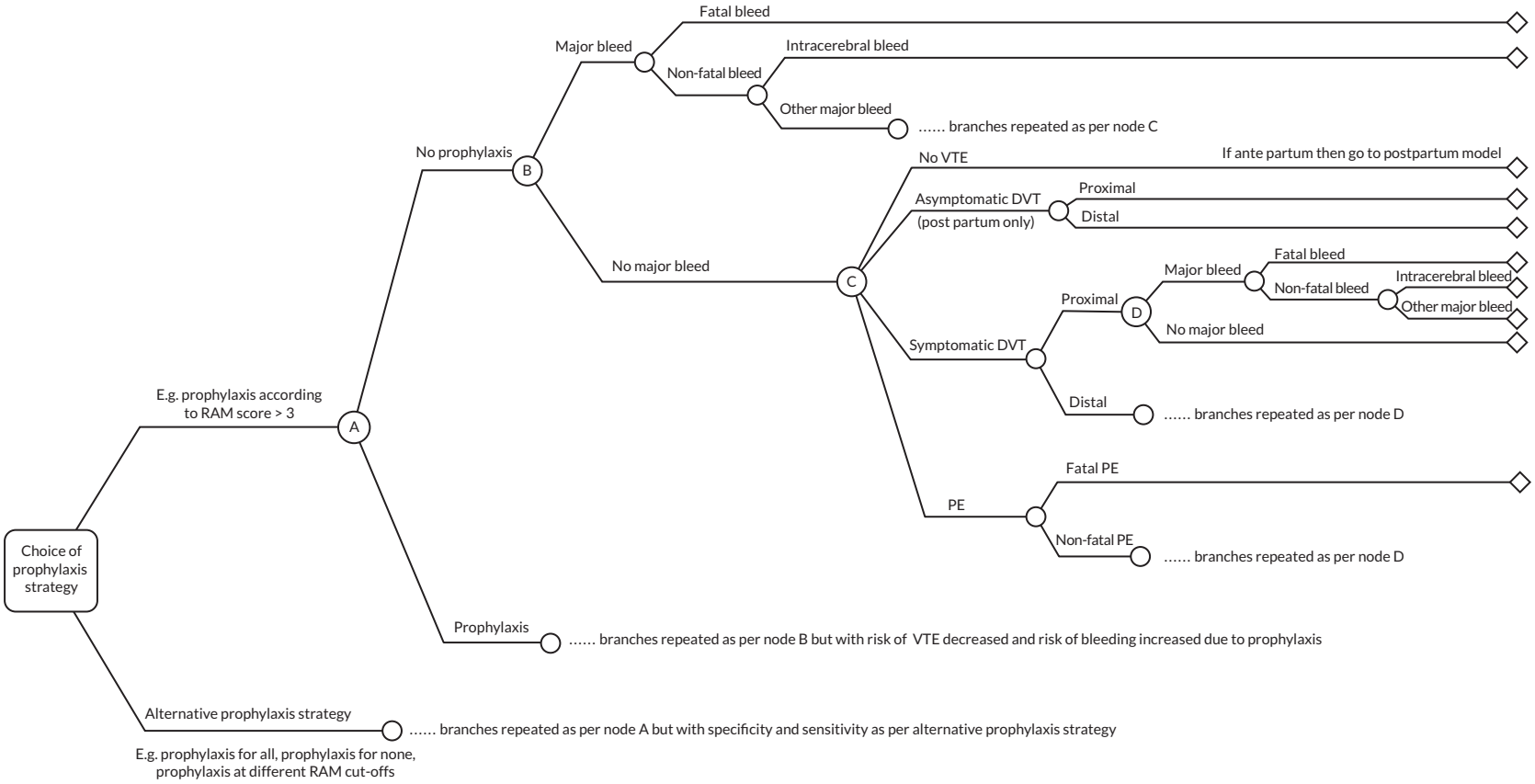

FIGURE 3 Short-term decision-tree model structure (repeated for antepartum and postpartum phases).

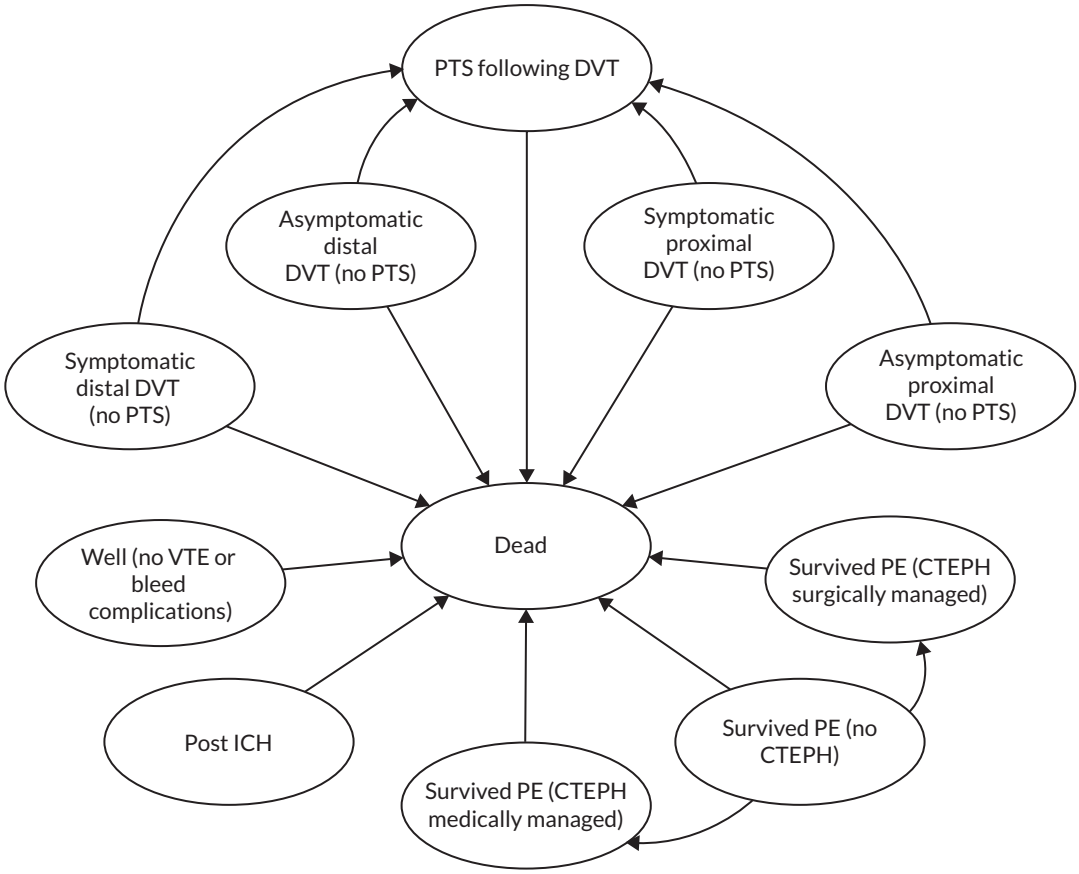

FIGURE 4 Long-term state-transition model. CTEPH, chronic thromboembolic pulmonary hypertension.

ongoing morbidity due to PTS in the long-term state-transition model. However, asymptomatic DVTs are only included in the postpartum model as this ensures that women without symptomatic VTE at delivery progress to the postpartum model where they remain at risk of symptomatic DVT. The risk of asymptomatic DVT is therefore only applied to those not experiencing symptomatic VTE in either the antepartum or postpartum periods. The total period covered by the decision-tree model is 1 year, with the first 30 weeks (from booking appointment at 10 weeks to delivery) covered by the antepartum model, and the remainder (155 days) covered by the postpartum model. This is considered sufficient to capture both the periods at risk of VTE (pregnancy and the 6 weeks after delivery) in addition to the period of VTE treatment if this occurs at the end of the period of risk. Diagnosis of PTS and chronic thromboembolic pulmonary hypertension (CTEPH) is assumed not to occur until the end of the decision-tree phase of the model, as it is difficult to distinguish these chronic complications from acute symptoms during the first 3 months after VTE. Major bleeding can occur both with and without prophylaxis. Major bleeds were considered to be those meeting the criteria proposed by the International Society on Thrombosis and Haemostasis (ISTH) subcommittee on the control of anticoagulation (Tardy *et al*. 2019).[48] Major bleeds were divided into fatal bleeds, non-fatal ICHs and other major bleeds (referred to as non-fatal non-ICH major bleeds). These other major bleeds were assumed to have no impact on costs or quality-of-life implications after 1 month, whereas ICHs are assumed to have long-term morbidity which is captured in the state-transition model. Wound haematomas can result in delayed discharge from hospital or women consulting at general practice (GP) surgeries or emergency departments (EDs) and they can also impact on HRQoL. These are included in the model as a form of clinically relevant non-major bleeding (CRNMB). Heparin-induced thrombocytopenia (HIT) was not included in the model because in a systematic review of 2777 pregnancies, there were no cases of HIT.[49] Heparin-related osteoporosis was not included as an adverse event in the model because use of LMWH in pregnancy has not been found to be associated with reduced bone mineral density.[50]

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The model estimates outcomes for a cohort of identical patients with average characteristics. In reality, the application of RAMs may lead to treated and untreated patients having different characteristics. This could lead to the cost effectiveness being over- or underestimated if the consequences of VTE are different for those selected for prophylaxis according to the RAMs. For example, if those being selected for prophylaxis by the RAMs are older, then any deaths prevented by prophylaxis will result in fewer life-years gained than for the model estimates based on women with an average age. Similarly, if the women offered prophylaxis have higher BMI than those not being offered prophylaxis, then the costs of prophylaxis will be higher than estimated based on average BMI. While the impact of these factors was expected to be small, this was checked by varying the starting age and BMI in scenario analysis to determine if the optimal prophylaxis strategy was sensitive to these characteristics. Age was found to have a bigger impact than BMI, but overall the cohort approach using average characteristics was considered a reasonable approximation for determining the optimal prophylaxis strategy.

The key model assumptions for the decision-tree phase are as follows:

- Patients who are well at the end of the antepartum decision-tree progress to the postpartum decision tree, while those experiencing an antepartum VTE event or ICH remain in their current state until entering the long-term state-transition model.
- No patient experiences an asymptomatic DVT in the antepartum decision tree as this ensures that they continue to be at risk of a symptomatic DVT in the postpartum model.
- Bleeding events are possible in both those having thromboprophylaxis and those having no thromboprophylaxis.
- VTE associated with pregnancy is assumed to occur within 6 weeks of delivery.
- Patients who stop or have a pause in prophylaxis due to major bleeding are assumed to have the same reduction in VTE risk as those who completed treatment.
- All patients with symptomatic DVT receive accurate diagnosis and initiate treatment with anticoagulants (LMWH until 6 weeks after delivery or a minimum or 3 months).
- Asymptomatic DVTs are not detected and are not treated.
- All PEs are symptomatic and lead to detection and treatment (LMWH until 6 weeks after delivery or a minimum or 3 months).
- Patients treated for symptomatic DVT and PE have a bleed risk associated with treatment, which is assumed to occur during the 3 months treatment period.
- Chronic complications of VTE (CTEPH following PE and PTS following DVT) are assumed to be diagnosed at least 3 months after VTE and therefore occur after any bleeds associated with VTE treatment.
- Patients having fatal PE are not at risk of other adverse outcomes prior to death (e.g. bleeding due to anticoagulant treatment).
- Risk of bleeding during treatment for VTE is independent of whether the patient bled during prophylaxis.
- Risk of VTE, risk of bleeding and risk of PTS/CTEPH are based on average patient characteristics (e.g. age and BMI) for the cohort being risk assessed.

A state-transition model (see *Figure 4*) was then used to extrapolate lifetime outcomes, including overall survival and ongoing morbidity related to either bleeds or VTE. The health states included within the state-transition model capture the risk of PTS following VTE and the risk of CTEPH following PE. The risk of PTS is modelled separately according to whether the DVT is asymptomatic or symptomatic and also whether the DVT is proximal or distal. All patients with PTS are combined in a single health state as costs, utilities (a measure of HRQoL on a scale of 0 to 1) and survival are not expected to be affected by whether PTS occurred following proximal or distal DVT. The PTS health state is not split into different severity levels as the utility estimates are based on the average utility across severity levels and the costs are not expected to differ by severity. The CTEPH health state is divided according to whether patients receive medical or surgical management to allow for differential costs and survival between these groups. There is also a post-ICH state to capture ongoing morbidity following ICHs.

Further adverse outcomes (PTS, CTEPH) are not modelled following ICH, as lifetime costs and QALYs are assumed to be predominantly determined by morbidity related to ICH. The state-transition model has annual cycles. All-cause mortality during the first year is applied before patients enter the state-transition model. Health state occupancy is half-cycle corrected such that all transitions between states, including mortality, is assumed to occur mid-cycle. The key model assumptions during the state-transition phase are as follows:

- All symptomatic DVTs are associated with a risk of PTS, but the rate is allowed to differ depending on whether the DVT is distal or proximal and whether it is symptomatic or asymptomatic.
- There is no risk of PTS following PE, and CTEPH is possible only after PE.
- Further outcomes (i.e. VTE, CTEPH and PTS) are not modelled for those who experience ICH as lifetime cost and QALYs will be determined predominantly by disability related to the ICH.
- All-cause mortality is applied to all transition states except CTEPH and post ICH which have state-specific mortality rates.
- Recurrent VTE (that is a second VTE occurring after the first VTE during the index pregnancy) is not modelled.

Conceptual model for postpartum women

The conceptual model for postpartum women is identical except that it starts at the point that women deliver and therefore no events occur during the antepartum phase of the model described above. Therefore, women spend 155 days in the postpartum model before progressing to the long-term state-transition model.

Data sources

The input parameters used in a previous analysis of thromboprophylaxis during hospitalisation were examined to identify any that were less relevant to women at risk of VTE during pregnancy and the puerperium.[47] The following data were updated to use data specific to our target population: data related to population characteristics (age, BMI and life expectancy); incidence of VTE; incidence of bleeding; incidence of PTS; costs of prophylaxis and cost of VTE treatment. Other data were generally based on the same sources used in the previous analysis with costs updated to reflect changes in prices. These included incidence of CTEPH following VTE; costs following PTS, CTEPH and ICH; the utility values for patients experiencing adverse outcomes and mortality risks following CTEPH and ICH.

A systematic review of published economic evaluations was conducted, which failed to identify any full economic evaluations that directly addressed the research question (see *Appendix 3*). However, several full-text articles that addressed similar research questions were examined to identify relevant data sources. These were supplemented with ad hoc searches for relevant literature, focusing where possible on systematic reviews.

When identifying data sources to populate the antepartum model for women at high risk of VTE, we focused on sources related to women with a prior VTE. Two-way scenario analysis was then used to explore whether the conclusions would differ if the target group had a higher or lower risk of VTE or major bleeding. When identifying data sources to populate the postpartum model, we focused first on sources related to women who have had a caesarean section as this is one of the most common risk factors that results in women requiring postpartum prophylaxis. O'Shaughnessy *et al*. estimated that the RCOG guideline would result in 85% of women having caesarean delivery receiving prophylaxis compared with only 15% of women having vaginal delivery.[15] Therefore, the consequences of postpartum prophylaxis are likely to be best represented by outcomes estimated in women having caesarean delivery even when modelling an unselected postpartum population. However, VTE risks have been estimated specifically for each of the postpartum populations and drug dosages, which are dependent on weight, have been adjusted for the obese postpartum population. In addition, two-way scenario analyses have been conducted to explore whether the

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conclusions would differ if the target group had a higher or lower risk of VTE or major bleeding than assumed in the base case.

Clinical input parameters are described below with a summary of the key parameters for each of the different populations provided in *Table 6* (for reference all parameters are provided in *Appendix 4*, *Tables 22–28*).

Population characteristics

The average age in the cohort (30 years) is based on the mean age reported by Sultan *et al*. (2016) from a large UK longitudinal primary care database (CPRD).[11] The cohort included 433,353 women, without a history of VTE, whose pregnancy ended in a live birth or still birth between 1997 and 2014 and who had at least 6 weeks of postpartum follow-up. The average weight, which is required for estimating LMWH dosing, is based on the average BMI of 27.4 kg/m^2 for 25- to 44-year-olds reported in the 2019 Health Survey for England.[51] For the obese subgroup, we have assumed a BMI of 35.8 kg/m^2, based on the average BMI in the RAM study in an obese cohort reported by Ellis-Kahana *et al*.[41]

Risk of venous thromboembolism in antepartum women with a prior venous thromboembolism

De Stefano *et al*. report 19 VTE events in 155 pregnancies where the women had a history of VTE prior to pregnancy but did not receive prophylaxis during pregnancy.[52] This gives an overall probability of 12.3% of having a VTE associated with the current pregnancy. The antepartum VTE risk was 5.8%, and the risk of postpartum VTE was of 6.9% (conditional on not having an antepartum VTE). Pabinger *et al*. reported similar VTE risks of 4% during pregnancy and 5% postpartum.[53] Brill-Edwards *et al*. reported a lower risk of VTE during pregnancy (2%), but their cohort excluded women with known thrombophilia and women could be recruited up to 20 weeks gestation, meaning that those having VTE early in pregnancy may have been excluded.[54] The risks from De Stefano *et al*. have been applied in the model. Higher and lower VTE risks have been explored in scenario analyses.

Risk of venous thromboembolism in unselected antepartum women

The risk of VTE in unselected antepartum women is based on the risk reported by Chauleur *et al*. in the cohort risk assessed using the STRATHEGE RAM.[31] There were nine VTE events in 2685 women (0.34%), of which four were antepartum and five were postpartum, giving absolute risks of 0.15% and 0.19% for antepartum and postpartum VTE, respectively. These data were only used in the exploratory analysis for unselected antepartum women.

Risk of venous thromboembolism in postpartum women

The risk of VTE in women following caesarean section has been estimated from an earlier analysis of the CPRD database (data from 1997 to 2010) reported by Sultan *et al*. (2014) in which women with prior VTE were excluded from the analysis.[55] For comparison, the risk of VTE within 6 weeks was 0.071% in this earlier cohort (158 in 222,334 deliveries) compared with 0.072% in the later cohort used to derive the Sultan RAM.[11,55] In this earlier study, the incidence of VTE within 6 weeks of any caesarean delivery was estimated to be 0.137% (74 VTEs occurring within 6 weeks across 31,843 emergency and 22,341 elective caesarean sections).[55] The risk of postpartum VTE within 6 weeks of delivery in women with obesity (BMI ≥ 30 kg/m^2) was 0.153% (37 VTEs in 24,141 women). The risk of VTE over 6 weeks in unselected postpartum women was taken to be 0.072% based on the later study by Sultan *et al*.[11]

Ratio of asymptomatic deep-vein thrombosis to symptomatic deep-vein thrombosis in postpartum women

A review by Blondon *et al*.[56] examining the incidence of VTE following caesarean section or vaginal delivery identified six studies which screened women postnatally to identify asymptomatic DVT. Over the 6 studies, we identified 1 symptomatic and 4 asymptomatic cases in a combined cohort of 717

TABLE 6 Summary of key parameters in each population

Parameter	High-risk antepartum women (e.g. prior VTE)	Postpartum women (unselected, C-section or obese)	Report section
Age (years)	30	30	*Population characteristics*
BMI (kg/m^2)	27	27 36 (obese subgroup)	*Population characteristics*
Duration of prophylaxis	From booking until 6 weeks PP	10 days	*Strategies for prophylaxis in women having antepartum risk assessment* and *Strategies for prophylaxis in women having postpartum risk assessment*
Absolute risk of PE without prophylaxis	1.40% AP and 1.65% PP	0.017% (unselected) 0.029% (C-section) 0.037% (obese)	*Risk of venous thromboembolism in antepartum women with a prior venous thromboembolism*, *Risk of venous thromboembolism in postpartum women* and *Proportion of venous thromboembolism that is deep-vein thrombosis without pulmonary embolism*
Absolute risk of symptomatic DVT without prophylaxis	4.41% AP and 5.20% PP	0.055% (unselected) 0.092% (C-section) 0.116% (obese)	*Risk of venous thromboembolism in antepartum women with a prior venous thromboembolism*, *Risk of venous thromboembolism in postpartum women* and *Proportion of venous thromboembolism that is deep-vein thrombosis without pulmonary embolism*
Absolute risk of asymptomatic DVT without prophylaxis	0% AP[a] 20.80% PP	0.229% (unselected) 0.370% (C-section) 0.460% (obese)	*Ratio of asymptomatic deep-vein thrombosis to symptomatic deep-vein thrombosis in postpartum women*
RR of VTE for prophylaxis (LMWH) vs. no prophylaxis	0.33	0.53[b]	*Relative risk of venous thromboembolism in women having antepartum prophylaxis* and *Relative risk of venous thromboembolism in women having postpartum prophylaxis*
Absolute risk of major bleeding with prophylaxis (LMWH)	0.24% AP and 5.49% PP	4.58%	*Risk of major bleeding in women having antepartum and postpartum prophylaxis* and *Risk of major bleeding in women having postpartum prophylaxis*
RR of bleeding for prophylaxis (LMWH) vs. no prophylaxis	1.53	1.53	*Relative risk of major bleeding in women having antepartum prophylaxis compared to no antepartum prophylaxis* and *Relative risk of major bleeding for postpartum prophylaxis compared to no postpartum prophylaxis*
Absolute risk of fatal major bleeding (without LMWH)	0.5 in 100,000 AP 0.6 in 100,000 PP	0.6 in 100,000	*Risk of fatal bleeding and non-fatal intracerebral haemorrhage*
Absolute risk of non-fatal ICH (without LMWH)	0.9 in 100,000 AP 1.1 in 100,000 PP	1.1 in 100,000	*Risk of fatal bleeding and non-fatal intracerebral haemorrhage*
Increased risk of wound haematoma for LMWH	2.1%	0.6%	*Risk of wound haematoma in women having antepartum and postpartum prophylaxis* and *Risk of wound haematoma in women having postpartum prophylaxis*

a Risk of asymptomatic VTE is assumed to be zero in the AP model to ensure women remain at risk of symptomatic VTE in the PP model.
b Average over 6 weeks based on RR of 0.33 applied for 3 weeks and no efficacy thereafter.

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patients.[57–62] Therefore, a ratio of 4:1 is applied in the base case. All of the asymptomatic cases of DVT identified were distal calf DVTs. A zero rate of asymptomatic DVT is explored in scenario analyses as the clinical significance of asymptomatic distal calf DVTs is unclear.

Proportion of venous thromboembolism that is deep-vein thrombosis without pulmonary embolism

The proportion of symptomatic VTE that is PE compared with DVT without PE has been estimated from studies included in the systematic review by Meng *et al*., which reported the incidence of PE and DVT without PE (24% of VTE is PE based on ratio of 17,035 DVT without PE to 5401 PE).[5] The review included both antepartum and postpartum VTE and the same ratio is applied to both the antepartum and postpartum incidences of VTE.

Proportion of deep-vein thrombosis that is distal

Data from the Computerized Registry of Patients with VTE (RIETE) were used to determine the proportion of symptomatic DVTs that are distal versus proximal. RIETE is an ongoing prospective registry of patients with objectively confirmed VTE and Elgendy *et al*. describe clinical characteristics for the subset of women who were pregnant or postpartum (within 2 months of delivery) at the time of VTE presentation.[63] Elgendy *et al*. report that 71% of postpartum DVTs (215 of 301) were proximal, whereas 78% of antepartum DVTs (342 of 438) were proximal.[63]

We assumed that all asymptomatic DVTs are distal as none of the asymptomatic DVTs identified through systematic screening of postnatal women in the six studies described in section *Ratio of asymptomatic deep-vein thrombosis to symptomatic deep-vein thrombosis in postpartum women* were proximal.

Relative risk of venous thromboembolism in women having antepartum prophylaxis

The relative risk (RR) of symptomatic VTE for antenatal LMWH (with or without postnatal prophylaxis) compared with no prophylaxis is reported as being 0.39 (95% CI 0.08 to 1.98) based on four randomised controlled trials (RCTs) included in the updated Cochrane review by Middleton *et al*.[8] However, three of the RCTs included in this meta-analysis were considered by our clinical experts to be less applicable to the modelled population of high-risk women with a prior VTE. Two of the papers related to the LMWH (FRagmin®) in pregnant women with a history of Uteroplacental Insufficiency and Thrombophilia (FRUIT) trial, which aimed to investigate LMWH combined with aspirin to prevent recurrent early-onset pre-eclampsia. This trial specifically excluded women at high risk of VTE due to prior history of VTE.[64,65] The third study was the Thrombophilia in Pregnancy Prophylaxis Study (TIPPS), in which LMWH was not given specifically for the indication of reducing VTE risk and less than half of the cohort had risk factors for VTE.[66] The dose of LMWH used in the TIPPS study was also higher than recommended for prophylaxis by RCOG.[7,66] The remaining RCT by Gates *et al*. was the only study included in the previous Cochrane review, and this had a RR of 0.33 (95% CI 0.02 to 7.14).[67] It should be noted that this was in fact a pilot study and the numbers recruited were small (n = 8 in each arm), and only one VTE event was observed, hence the wide CIs. The RR from this single pilot RCT was used in the base-case analysis due to the indirectness of the populations recruited in the FRUIT and TIPPS RCTs and also because of concerns regarding the dose used in the TIPPS study and the use of aspirin in the FRUIT study. However, scenario analysis was conducted using the meta-analysed estimate from all four papers reported by Middleton *et al*.[8]

Relative risk of venous thromboembolism in women having postpartum prophylaxis

The updated Cochrane review reports a RR for VTE of 2.97 (95% CI 0.31 to 28.03) for LMWH versus no prophylaxis following caesarean section based on two studies.[67,68] Both of these were pilot studies. The dose used in one was lower than recommended in the RCOG guideline [2500 IU of dalteparin (Fragmin, Roche) daily for 4–5 days].[68] For symptomatic DVT, an estimate of 1.40 (95% CI 0.17 to 11.55) is reported by Middleton *et al*.[8] based on two RCTs.[68,69] Two feasibility studies on postnatal prophylaxis

in higher-risk postpartum women (low-risk thrombophilia, immobilisation or two or more risk factors) were also included in the updated Cochrane review (Rodger *et al.* 2015, 2016),[18,19] but neither of these reported any VTE outcomes and both struggled to recruit. There is therefore a paucity of data on the efficacy of LMWH when used as postpartum prophylaxis and those studies that do exist estimate a higher risk of VTE compared with no LMWH, which is the opposite of what is expected based on studies in medical (RR = 0.49, 95% CI 0.37 to 0.67) and surgical cohorts [odds ratio (OR) = 0.26, 95% CI 0.09 to 0.87].[47] To conduct EVPI analysis to estimate the value of future research, it is necessary to have some prior estimate of treatment efficacy even if that is based on indirect sources or expert consensus. In order to capture both our experience from other populations that LMWH is expected to reduce VTE, and the high degree of uncertainty in the efficacy of LMWH when used as postpartum prophylaxis, we decided to use the RR applied for antepartum prophylaxis (0.33, 95% CI 0.02 to 7.14).

It is unclear whether giving 10 days of LMWH provides protection from VTE for 10 days or for a longer period. Studies in general medical and surgical patients usually involve patients being offered LMWH during admission, or for a defined period such as 7 or 10 days and then they report the RR for VTE over a longer period such as 90 days post admission. Therefore, in these studies, the RR attributed to a short period of LMWH has been estimated over a longer time. Therefore, in previous models of thromboprophylaxis in medical and surgical in patients, the RR estimated from the meta-analyses of RCTs has been applied to the whole period at risk.[47] However, in this case, the RR has been taken from a study of antenatal prophylaxis in which LMWH was continued over the whole period at risk. It is therefore unclear whether the RR estimated in this setting should be applied to the whole 6 weeks over which patients are at risk of VTE, or just to the 10 days during which they received treatment. It was considered that giving 10 days of postpartum thromboprophylaxis would provide a risk reduction of VTE for longer than 10 days. This is because the development of clots occurs in the early postpartum period but may present symptomatically after 10 days, but not beyond 6 weeks postpartum. Given this uncertainty, we have assumed in the base-case scenario that risk falling in the first 3 weeks has the full treatment effect and risk falling beyond this has no treatment effect. This gives an average RR of 0.53 across the 6 weeks when applying a RR of 0.33 to risk falling in the first 3 weeks and a RR of 1 to risk falling from then up to 6 weeks. We have also conducted scenarios exploring the two extreme scenarios of having the RR apply to all 6 weeks and only the first 10 days. The proportion of the 6-week VTE risk falling within each time frame was estimated from the data provided by Sultan *et al.*[55] The RRs applied when assuming that the efficacy applies for 3 weeks (base case), 10 days (pessimistic scenario) and 6 weeks (optimistic scenario) are 0.53, 0.69 and 0.33, respectively.

Risk of major bleeding in women having antepartum and postpartum prophylaxis

A paper by Nelson-Piercy *et al*. reports the incidence of serious antepartum bleeds within their reporting of adverse events in a cohort of women having antenatal tinzaparin (Innohep®, LEO Pharma).[70] Serious was defined as '*clinical events that: resulted in death; were life-threatening; required inpatient hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability/incapacity; were congenital anomalies/birth defects; were other medically important conditions*'. The incidence was 3 in 1267 (0.24%), but this included 1013 women having LMWH as prophylaxis and 254 having LMWH as treatment for VTE.[70] Therefore, this may overestimate the risk of major antepartum bleeding for prophylaxis doses of LMWH as some women were having higher doses of LMWH for VTE treatment. All three of the serious bleeds were recorded as possibly, but not probably, related to LMWH. In a UK cohort, reported by Schoenbeck *et al*., one of the 91 women who received both antepartum and postpartum prophylaxis experienced major obstetric haemorrhage (placental abruption requiring caesarean section at full term) giving a major antepartum bleeding risk of 1%.[71] In contrast, Cox *et al*. reported four severe antepartum bleeds requiring urgent delivery in 98 pregnancies (4.08%) exposed to LMWH in a New Zealand cohort.[72] Therefore, the risks of antepartum major bleeding appear to vary greatly (0.24–4.08%). Some of this variation is likely to be due to inconsistent definitions of what constitutes major bleeding and some due to differences in the cohorts of women described.

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Tardy *et al*. conducted a review of RCTs of pregnant women having heparin to identify how RCTs have reported bleeding complications from heparin in the past.[48] Tardy *et al.* conclude, '*at present it is impossible to estimate the rates and severities of either antepartum bleeding or primary PPH occurring during prophylactic treatment with heparin*'.[48] They propose a definition for major bleeding in antepartum women that includes both the standard definition for major bleeding applied in medical inpatients and risks specific to pregnancy.[48,73] Although the definition proposed by the ISTH includes outcomes such as placenta previa requiring delivery and placenta abruption, it is unclear if these are likely to be causally related to the use of LMWH. Tardy *et al*. also state that antepartum bleeding due to placenta previa and placenta abruption is observed in 2–5% of all pregnancies in the absence of thromboprophylaxis.[48] We have applied the risk of serious antepartum bleeding from Nelson-Piercy *et al*. in the base case (0.24%), because it has been estimated in a large cohort of women receiving antenatal LMWH (*N* = 1267) and the definition of serious antepartum bleeding is specified.[70] However, given the uncertainty associated with this parameter, a range of major antepartum bleeding risk up to 4.08% is explored in sensitivity analysis to determine the significance of this parameter for decision-making.

The rate of postpartum major bleeding in women having both antepartum and postpartum prophylaxis has been estimated from a cohort reported by Schoenbeck *et al*.[71] In this cohort, that 5 of 91 women (5.5%) having antepartum prophylaxis followed by postpartum prophylaxis required a postpartum transfusion due to bleeding. This is higher than the risk of serious postpartum haemorrhage (PPH) (3.2%) reported by Nelson-Piercy *et al*., which was estimated across both treatment and prophylaxis doses of LMWH.[70] Nelson-Piercy *et al*. also report that 2.9% of women having prophylaxis doses of LMWH had bleeding requiring intervention, although this is not divided into antepartum and postpartum bleeding.[70] Given that postpartum bleeding requiring transfusion clearly meets the ISTH criteria for major PPH, we have applied the risk of 5.5% from Schoenbeck *et al*. in the base case, but higher and lower bleeding risks have been explored in sensitivity analysis.

Relative risk of major bleeding in women having antepartum prophylaxis compared to no antepartum prophylaxis

The only RCT reporting the RR of major bleeding in women having antepartum prophylaxis was the TIPPS study (RR = 1.48, 95% CI 0.25 to 8.72).[66] However, this population was considered somewhat indirect because not all women were included due to their VTE risk, and the dose used in this study was higher than the dose usually given to prevent VTE (women had the RCOG recommended dose of 5000 IU of dalteparin daily from randomisation until 20 weeks gestation but the dose was then doubled to 5000 IU twice daily until at least 37 weeks).[66] Furthermore, the timing of the major bleeding was not reported in the TIPPS study, so it is unclear if the bleeding occurred during the antepartum prophylaxis or during the postpartum period when both study arms received LMWH for 6 weeks. The RR of major bleeding in medical patients has been previously reported as 1.53 (95% CI 0.80 to 2.92), based on a meta-analysis of three RCTs.[6] Although it is expected that the absolute risk of bleeding is likely to differ between pregnant women and general medical inpatients, it was decided that the RR of bleeding from the medical cohort could be applied to women having antepartum prophylaxis, as the dose of LMWH used in medical in patients is consistent with that recommended by RCOG. Use of the alternative estimate provided by the TIPPS study is explored in scenario analysis.

Risk of wound haematoma in women having antepartum and postpartum prophylaxis

Lindqvist *et al*. recorded a risk of 2.5% for haematoma in women who had a prior VTE who were having LMWH during and after pregnancy and a risk of 0.4% in controls not having LMWH ($p < 0.001$).[74] We have therefore assumed an increased risk of wound haematoma attributable to LMWH of 2.1% in women having antepartum and postpartum prophylaxis.

Risk of major bleeding in women having postpartum prophylaxis

Although the severity of PPH is often defined according to volume of blood loss, with major PPH usually defined as blood loss > 1000 ml,[75] the definition of major bleeding for postpartum women proposed by

Tardy *et al*. includes blood loss < 1000 ml leading to transfusion.[48] In addition, blood loss of > 1000 ml is not defined as major bleeding by Tardy *et al*. unless it is combined with the need for transfusion or other intervention (e.g. second-line uterotonics or surgical intervention). Therefore, we tried to identify a study which reported the incidence of major postpartum bleeding that is consistent with the definition proposed by Tardy *et al*. rather than one based purely on volume of blood loss.

The risk of major bleeding in women having postpartum prophylaxis following a caesarean section is taken from a study by Gizzo *et al*.[76] In this study, the incidence of bleeding requiring transfusion after starting prophylaxis (12 hours after caesarean section) was reported as 4.6% (16/349). In this study, haemoglobin levels both post caesarean section and pre transfusion are reported, along with units of blood transfused, and transfusion was considered necessary if the haemoglobin fell below 8 g/dl. Based on these data, it was considered that the outcome of requiring transfusion in this study was reasonably consistent with one of the definitions of major bleeding proposed by ISTH, which is transfusion of two or more units of whole blood or red cells to maintain a haemoglobin level > 7–9 g/dl.[48,76] However, it is acknowledged that there is significant uncertainty regarding the incidence of PPH meeting the ISTH proposed definition and therefore both higher and lower incidence of major bleeding are explored in sensitivity analysis.

Relative risk of major bleeding for postpartum prophylaxis compared to no postpartum prophylaxis

There were no useful data on major bleeding in women having postpartum prophylaxis following a caesarean section from studies included in the Cochrane review.[8] Although some data were reported for bleeding-related adverse events, none of the studies reported any cases of major bleeding using a definition consistent with that proposed by the ISTH. The open-label pilot study by Rodger *et al*. (2016) reported one major bleeding episode in the LMWH arm and none in the prophylaxis arm giving a RR for major bleeding of 3.53 (95% CI 0.15 to 81.11).[19] However, the wide CIs produced by this single-pilot RCT were considered to be unrepresentative of the broader evidence on the safety of LMWH in indirect populations (i.e. medical and surgical patients who are not pregnant or in the puerperium). Therefore, the RR of major bleeding for medical inpatients receiving LMWH for VTE prophylaxis was used in the base-case analysis and the data from Rodger *et al*. were applied in a sensitivity analysis.

Risk of wound haematoma in women having postpartum prophylaxis

Ferres *et al*. reported an incidence of wound haematoma of 1.7% (11/653) in women at high risk of VTE after caesarean section who had received enoxaparin (Clexane®, Sanofi) and an incidence of 1.1% in those who were eligible but who were not offered enoxaparin (11/1042).[77] Although this difference was not statistically significant, we were keen to capture the potential for increased wound haematoma as this was considered an important side effect of LMWH for women. We therefore assumed in the base case that postpartum prophylaxis increases the risk of wound haematoma by 0.6%.

Risk of fatal bleeding and non-fatal intracerebral haemorrhage

From the report published by MBRRACE-UK, we estimated that the rate of fatal bleeds, including either obstetric haemorrhages or ICH, was 0.53 per 100,000 maternities in the antepartum period and 0.57 per 100,000 maternities in the postpartum period.[78]

The incidence of ICH has been estimated from a study by Ban *et al*. which used routine hospital (HES) and GP records (CPRD) to estimate the incidence of strokes in the antepartum, peripartum (1 day prior to 1 day after delivery) and early postpartum (within 6 weeks of delivery) periods.[79] This study reported the incidences separately for ischaemic stroke, ICH, subarachnoid haemorrhage and unspecified strokes. We used the data reported to estimate an incidence of 0.9 per 100,000 pregnancies and 1.1 per 100,000 pregnancies for non-fatal ICH in the antepartum and postpartum groups, respectively. As it is unclear whether the risk of fatal bleeding and non-fatal ICH is causally linked to women receiving LMWH as prophylaxis for VTE, we have also conducted a scenario analysis in which these outcomes are excluded from the model.

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Risk of major bleeding during treatment for venous thromboembolism

The Global Anticoagulant Registry in the FIELD (GARFIELD) and RIETE registries report subgroup analyses for women who are pregnant or postpartum at the time of their acute VTE diagnosis.[63,80] They report the incidence of major bleeding during treatment for pregnancy-associated VTE. The RIETE registry provides a larger sample than the GARFIELD registry. The incidence of major bleeding reported in the RIETE registry is 0.8% for women having pregnancy-related VTE and this has been applied in the model.[63]

No fatal bleeds on VTE treatment doses are reported for the postpartum VTE subgroup in the RIETE cohort and only one was reported in the pregnancy-associated VTE subgroup of the RIETE cohort.[63] However, data are also presented for a subgroup of younger women (aged under 50) with non-pregnancy-associated VTE who were used as a comparative cohort for the pregnant/postpartum subgroups. As this provided a larger sample size (*N* = 8084), the data from the non-pregnant cohort were used to estimate the proportion of major bleeds that are fatal (6.3% = 4/63).[63] When combined with the 1.1% absolute risk of major bleeding, this gives an absolute risk of fatal bleeds during VTE treatment of 0.07% (7 in 10,000), which is similar to the lowest risk category for fatal bleeding identified from a separate analysis of the whole RIETE cohort.[81] There are two limitations with this: the non-pregnant cohort diagnosed with VTE may have other risk factors for VTE that place them at increased risk of death such as cancer; and there is a higher rate of direct oral anticoagulant (DOAC) use for long-term anticoagulation in the non-pregnant cohort (9.4% for non-pregnancy-related VTE vs. 4.7% for postpartum VTE).[63] Given the uncertainty regarding the risk of fatal bleeding during treatment of pregnancy-related VTE, we have conducted a scenario analysis exploring a zero rate of fatal bleeding to see how important this parameter is to the decision analysis.

Data on the incidence of non-fatal ICH for VTE treatment doses of LMWH for women having pregnancy-associated VTE are sparse. The RIETE registry does not report the site of major bleeding.[63] The GARFIELD registry does report the site of any major or minor bleed and none of these are reported to be intracranial, although 11 bleeds in the non-pregnancy-associated VTE group and 1 in the pregnancy-associated VTE group are reported to as being 'other'.[80] The GARFIELD registry does report 2 events as stroke/transient ischaemic attack in 29 women having major bleeding during treatment of non-pregnancy-related VTE, but these could be ischaemic events.[80] If we assume that half of these strokes were haemorrhagic events,[79] then the proportion of major bleeding events in GARFIELD which were ICH would be 3.4% (= 1/29) in the non-pregnancy-associated VTE subgroup.[80] This is slightly lower than the proportion of non-fatal major bleeding events which are ICH in the RIETE registry as a whole (9%).[81] This gives an absolute risk of non-fatal ICH on treatment doses of LMWH of 0.04% (4 in 10,000), which is applied in the base-case analysis. A scenario analysis exploring a zero rate of non-fatal ICH is also explored to determine how important this parameter is to the decision analysis.

Risk of chronic complications

The risk of CTEPH in patients having PE was taken from a systematic review by Ende-Verhaar *et al*.[82] A cumulative incidence of 3.2% (95% CI 2.0 to 4.4) over 2 years was reported in those who survived the initial 3-month period after PE and this was applied to the model giving a risk of 1.6% per annum. We assumed no risk of new CTEPH beyond 2 years based on a study with a median follow-up of 94 months, which reported no new cases of CTEPH after 2 years.[83]

A study describing the risk of PTS following VTE related to pregnancy was identified from a review by Kourlaba *et al*.[84] This paper by Wik *et al*. reported that the risk of PTS, defined as a Villalta score ≥ 5 was 42% following DVT.[85] Wik *et al*. also report that age, smoking, timing of VTE (postnatal rather than antenatal) and location (proximal rather than distal) were significant predictors of the risk of PTS in pregnancy-related VTE. Wik *et al*. also found a significant interaction between timing and location of DVT such that proximal DVT occurring postpartum gave the highest risk of PTS. However, this association between timing and location did not occur in women having antenatal DVT. We, therefore,

used the data from Wik *et al*. to estimate separate risks of PTS for antenatal DVT (34%), distal postpartum DVT (31%) and proximal postpartum DVT (66%). In the base-case scenario, asymptomatic DVTs are assumed to carry the same risk of PTS as symptomatic DVTs, but in a scenario analysis we have assumed no risk of PTS from asymptomatic DVTs. The proportion of cumulative PTS risk falling in years 1–5 after DVT was based on a study by van Dongen *et al*. which followed up patients with a DVT (not specifically pregnancy-related DVT) every 6 months for a maximum of 5 years (median follow-up 4.9 years) to assess them for signs and symptoms of PTS.[86]

To explore how sensitive the model is to the risk of PTS, we have also conducted a scenario analysis in which the risk of PTS (15.6% and 32.4% in distal and proximal DVT, respectively) were estimated from a non-pregnant population.[46]

Mortality risks

Patients who survive the first 28 days after having an ICH have an increased risk of mortality in the long term. Fogelholm *et al*. report a standardised mortality ratio (SMR) of 4.5 in the first year and 2.2 in years two to six for patients who survived 28 days after ICH, compared to age- and sex-matched controls.[87] These SMRs have been applied as multipliers to the risks of all-cause mortality in women having non-fatal ICH. This means that women having ICH have an increased risk of death in the long term compared to women not having an ICH, but the absolute risk of death in women having ICH is much lower than in the study reported by Fogelholm, where the average age was > 65 years in both men and women recruited to the study. Given that the SMRs have been calculated in a predominantly older cohort, and the relationship between ICH and increased mortality may not translate to younger patients, we have conducted a scenario analysis in which women who have a non-fatal ICH (i.e. survive 28 days after an ICH) do not have any increased mortality in the long term.

A review by Kourlaba *et al*. reports a case fatality rate for PE of 2% (95% CI 1.44 to 2.56), which was based on a meta-analysis of four studies.[84] This estimate was largely dependent on the rates from two large studies based on discharge records which reported case-fatality rates of 1.73% (Liu *et al*.) and 2.43% (James *et al*.), respectively.[3,88] Case-fatality rates from registry studies such as RIETE were lower (< 1%),[63] but these may be biased because women who die shortly after PE would not necessarily be recruited into registry studies of anticoagulant treatment. A case-fatality rate of 2% has therefore been applied in the model.

Mortality risks in patients with CTEPH having either medical or surgical management were based on survival curves reported by Goodacre *et al*., which were estimated from an international prospective registry of patients with CTEPH.[89] Deaths related to PE occurring within 1 year of PE are already accounted for in the model.[90] For this reason, the hazard of death for patients with CTEPH are only applied from 1 year onwards. To ensure that the risk of death in the CTEPH group was not artificially low compared with the risk of death in the general population, general population mortality risks were applied whenever these were higher than the risk in the CTEPH population, based on the survival curves.

All-cause mortality is estimated from age- and sex-specific general population mortality estimates and is applied to all women not experiencing CTEPH, ICH, fatal bleeds or fatal PE.[91] These have not been adjusted to account for any increased risk of mortality associated with pregnancy.

Cost of prophylaxis

We have assumed that the pharmacological prophylaxis used is LMWH as the use of oral anticoagulants including vitamin K antagonists, such as warfarin, and DOACs should be avoided in women who are pregnant.[7] Although warfarin can be used postpartum in women who are breastfeeding, clinical expert advice was that most women preferred to use LMWH postnatally due to the monitoring requirements associated with warfarin.

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Women having antepartum prophylaxis are assumed to receive prophylaxis from 10 weeks as this is the typical time of the antenatal booking appointment. It is acknowledged that some women with a prior VTE may be on anticoagulant treatment prior to pregnancy and may immediately switch to LMWH as soon as pregnancy is confirmed, and some women may take longer than 10 weeks to have their risk assessed and start prophylaxis, but 10 weeks was considered a reasonable average starting time. Prophylaxis started antenatally is assumed to continue until 6 weeks after delivery.

As some women are recommended to have antepartum prophylaxis only from 28 weeks under the RCOG guidance, a scenario analysis exploring the impact of delaying antepartum prophylaxis until 28 weeks in this population is described in the section *Exploratory deterministic analysis for antepartum women with three risk factors.* In addition, the Lyon score recommends that some women having antepartum prophylaxis from booking and some from 28 weeks. Therefore, a scenario analysis exploring the impact of delaying prophylaxis to 28 weeks is described in the section *Deterministic scenario analyses for antepartum women with a prior venous thromboembolism*.

Women starting prophylaxis postnatally are assumed to be offered 10 days of postpartum prophylaxis in line with current RCOG guidance for those at intermediate risk. Six weeks of postpartum prophylaxis is only offered to those at high risk of VTE, many of whom will already be identified as requiring antepartum prophylaxis.

Patients having a major bleed while taking antenatal prophylaxis would be likely to stop antepartum prophylaxis and restart postnatally. We assumed a 66% reduction in their antepartum prophylaxis cost in such cases. The cost of postpartum prophylaxis is not assumed to reduce if a major bleed occurs postnatally, because even if treatment is discontinued, it is likely that the rest of the 10 days or 6 weeks course would be wasted.

It is assumed that the lowest cost preparation of LMWH is prescribed. Therefore, drug costs for LMWH were based on the cost of dalteparin (5000 units given every 24 hours by subcutaneous injection, based on a weight of 73 kg) as this had a lower cost per day (£2.82) than either enoxaparin or tinzaparin (based on NHS drug tariff prices for lowest cost preparation).[92] The cost was increased to £4.23 per day in the obese cohort (7500 units per day for a 95 kg woman).[92] The cost for administration of LMWH has been estimated by adjusting the costs estimated by Menakaya *et al*. for outpatient LMWH.[93] This includes the cost of counselling women to self-inject when they first start prophylaxis with LMWH and the cost of administration by a district nurse in the small minority of women (4%) who are unable to self-inject. The cost of administration is £74.94 for 10 days of postnatal LMWH and £321.64 for those starting LMWH antenatally and continuing until 6 weeks after delivery (see *Appendix 4*, *Table 23*). In addition, for women having antepartum prophylaxis, it is assumed that they will receive one additional outpatient appointment (£205 for a multiprofessional face-to-face follow-up appointment)[94] in late pregnancy to discuss the need to discontinue LMWH at the onset of labour or prior to any planned delivery.

In the strategies examining the use of prophylaxis based on RAMs, we have assumed that the risk assessment will require 5 minutes of time spent by a hospital consultant, which is a cost of £9.92 when applying a unit cost per hour of £119.[45] This cost is applied to all strategies involving the use of a RAM, but not to the comparator strategies of prophylaxis for all and prophylaxis for none. A sensitivity analysis has also been conducted to explore whether the optimal strategy would be different if it could be assumed that the risk assessment would result in no additional cost, with the aim of exploring whether the cost of the risk assessment itself is a significant source of decision uncertainty.

Costs of treating venous thromboembolism

Treatment for VTE (PE or DVT) in the model is assumed to consist of 3 months of LMWH, because warfarin and DOACs are not safe during pregnancy. Although warfarin is a possible alternative treatment for postnatal women, it is less commonly used because of the need for regular blood tests and many mothers would prefer subcutaneous injections without monitoring. Equally, although DOACs

can be offered postnatally, these are limited to women who are not breastfeeding. The recommended doses for each of the three available LMWHs (enoxaparin, dalteparin and tinzaparin) have been based on Table 1a–c of the RCOG guideline on the acute management of thromboembolic disease (Green-top guideline no. 37b).[75] A weight of 73 kg has been assumed based on the average weight of women aged 25–44 years in the 2019 Health Survey for England.[51] Where the dose required does not match exactly one of syringe sizes provided by manufacturers, it is assumed that the next size up is used and any excess is discarded so that a new syringe is used each time. The proportion of patients receiving each of the three LMWH preparations (enoxaparin 65.2%, dalteparin 21.6%, tinzaparin 13.2%) was based on data from a recent survey of clinicians by McFarlane *et al.*,[95] which also reported that 56.5% used once daily rather than twice daily dosing. This was used to estimate the proportion using once daily dosing (51%) for dalteparin and enoxaparin after accounting for the fact that tinzaparin is only recommended for once daily dosing. The total cost for drug acquisition for 91 days of treatment is £887.21. This was increased to £1155.32 when using the higher weight of 95 kg for the obese postpartum population.

Women having VTE treatment with LMWH who experience major bleeding are assumed to stop LMWH while actively bleeding, but it is assumed that treatment dose LMWH will be started as soon as it is safe to do so. Therefore, no reduction in VTE drug treatment cost is assumed in the base-case analysis. However, a scenario analysis is conducted assuming that LMWH is stopped for 4 weeks to see whether this factor is an important driver of cost-effectiveness. This reduces the costs of VTE treatment by 11% for those having antepartum VTE and by 18% for those having postpartum VTE.

The costs for administering LMWH, including the cost of training patients to self-administer and the cost of administration by a district nurse for a small minority of patients (4%), are based on the costs reported by Menakaya *et al.*,[93] but these were adjusted to reflect the longer duration of treatment (91 days compared with 42 days in Menakaya), giving a cost of £157.51 for administration. In the base-case analysis, it is assumed that women having treatment dose LMWH for either antepartum or postpartum VTE will have monthly joint outpatient clinic appointments with a haematologist and obstetrician while receiving treatment dose LMWH [£205; Healthcare resource group (HRG) WF02A Service code 303].[94] However, it was noted that many women experiencing antepartum VTE will already be having regular clinical appointments to manage the comorbidities that put them at increased risk of VTE and not all of the monthly appointments will be required solely due to the LMWH treatment. To explore this, a scenario analysis was conducted where it was assumed that women having antepartum LMWH have three additional clinic appointments and those having postpartum LMWH have one additional clinic appointment. The total cost of drug treatment for VTE is £1659.79 for those having postpartum VTE and £2748.29 for those having antepartum VTE (see *Appendix 4*, *Table 24*). This is because women having antepartum VTE are assumed to experience VTE on average at 24 weeks gestation (see section *Timing and duration of utility decrements applied in the decision tree*), resulting in 154 days of VTE treatment.

Resource use for management of acute VTE is provided in a summary table (see *Appendix 4*, *Table 25*). The costs of diagnosing DVT and PE in patients having these outcomes postnatally have been based on the costs used previously in non-pregnant populations having DVT or PE in an outpatient setting.[46] These previous analyses assumed that 10% of patients having proximal DVTs and 60% of patients having PEs would be admitted but none having distal DVTs would be admitted. In addition, it was assumed that 10% of those having PE would be admitted to critical care. For women having an antenatal DVT or PE, we would expect a greater likelihood of admission compared to a non-pregnant population. We have assumed that the likelihood of admission for proximal DVT is double that assumed in the non-pregnant population (20% vs. 10%) but remains zero for distal DVT. We have assumed that the likelihood of admission increases from 60% to 90% in women having antenatal PE. We have also assumed that the risk of admission to critical care is double for pregnant women having a PE compared to non-pregnant people having a PE (20% vs. 10%). We assumed maximum resource use for people having fatal PE (i.e. ambulance transfer to the ED leading to a short-stay admission including a critical care unit stay) but have excluded the long-term cost of VTE drug treatment.

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For patients having antenatal PE, we have taken the diagnostic tests used from the Diagnosis of Pulmonary Embolism in Pregnancy (DiPEP) study.[96] We have assumed a 50 : 50 split between ventilation/perfusion (V/Q) single photon emission computed tomography (SPECT) and V/Q planar as Goodacre *et al*. only report the frequency of ventilation-perfusion scanning and not the specific type. As the DiPEP study did not report on the use of echocardiogram, we have taken the proportion from a previous UK Obstetric Surveillance System (UKOSS) data set reported by Knight *et al*.[97] (*Appendix 4*, *Table 25*). The total cost for acute management of VTE (i.e. excluding long-term drug treatment) ranged from £311.32 for symptomatic distal DVT to £3261.24 for fatal PE (details provided in *Appendix 4*, *Table 25*). Given that many assumptions have been employed to estimate resource use associated with diagnosis and management of VTE, the importance of these costs is explored in a scenario analysis. In this scenario, we assume that all antenatal VTE results in admission and 50% of antenatal PE also results in a critical care stay.

Costs of treating major bleeding

The cost over 90 days of fatal haemorrhagic stroke provided by Luengo-Fernandez *et al*. was uplifted to current prices and applied as the cost of fatal bleeds in the decision-tree phase of the model.[98] This paper also provided costs over 90 days for non-fatal haemorrhagic stroke stratified by the level of disability. A weighed average cost was calculated across non-disabling, moderately disabling and totally disabling haemorrhagic strokes.[98] This was then uplifted to current prices and applied as the cost of non-fatal ICH in the decision-tree phase of the model. Luengo-Fernandez *et al*. also report the average costs per annum from 90 days to 5 years post stroke, but these are not reported separately for haemorrhagic stroke. The costs of GP care and emergency care are reported to be statistically significantly higher post stroke compared to the year before stroke. In addition, they report the cost of residential care in patients not living in residential care prior to their stroke. The total post-acute (beyond 90 days) costs for primary care, emergency care and residential care were calculated and uplifted to current prices and applied in the state-transition phase of the model to those having non-fatal ICH. A pro rata cost is also applied to those having stroke more than 90 days before the end of the decision-tree phase of the model.

There are limited data available to determine the cost of managing non-fatal, non-ICH bleeds in pregnant women. The cost of managing non-fatal non-ICH major bleeds was assumed to be similar to the cost of managing a gastrointestinal (GI) bleed, despite these being different pathologies. This is consistent with the approach that has been taken in previous published models of VTE prevention covering both patients having outpatient lower limb immobilisation and patients at risk of hospital acquired VTE.[46,47] It was also the approach taken in a US economic evaluation of heparin use in pregnant women reported by Johnston *et al*. (2005).[99] The cost of GI bleeding was estimated based on a weighted average cost for non-elective inpatient and non-elective short-stay management of GI bleeds using NHS reference costs for bleeds requiring single, multiple or no interventions (HRG codes FD03A to FD03H).[94] The average length of stay was 3 days for the most common HRG code for GI bleeding which comprised 46% of the spells for GI bleeding, suggesting that the median length of stay is around 3 days. Costs estimated using GI bleeding as a proxy are probably more applicable to women having a major non-obstetric bleed, where the bleed itself would be the reason for admission. This is because it is assumed that many women having major bleeding at the time of delivery (i.e. a PPH) are likely to already be receiving inpatient care. A cost-effectiveness model examining the use of uterotonics to prevent PPH estimated that the average length of stay would be 1.5 days in women without PPH (< 500 ml blood loss), increasing to 3 days in women who have > 1500 ml of blood loss, who are also assumed to require transfusion of two units of blood,[100] in which case the additional length of stay attributable to major PPH would be closer to 1.5 days. An international survey of midwives (N = 100) estimated that women having a major PPH would have an increased length of stay of 1 day compared to women not having a PPH. However, when UK-specific midwives were questioned (N = 25), it was suggested the estimated additional length of stay attributable to a major PPH would be longer at 2.3 days.[101] Based on these data, it is possible that the cost of an admission for GI bleeding is higher than the additional cost of managing a major PPH in a woman already admitted for delivery. Given the likely heterogeneity associated with

the costs of major bleeding in this population, we have conducted a scenario analysis in which we assume no additional cost, and a scenario analysis in which we assume the cost is twice that expected for GI bleeding, to determine how sensitive the results are to this parameter.

Costs of wound haematoma

Wound haematomas can lead to a delay in discharge for women after delivery. Therefore, we assumed that a wound haematoma would result in a long-stay admission instead of a short-stay admission using the reference costs for normal delivery (cost difference of £1372 between non-elective and short-stay admission NZ30C).[94] We explored a more conservative scenario in which a wound haematoma only leads to one ED attendance in a scenario analysis.

Costs of managing post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension

The management of PTS is assumed to involve one first and one follow-up vascular surgery outpatient appointment in the first year after diagnosis and two follow-up GP appointments every year thereafter. This is consistent with the assumption applied in a previous analysis.[46] An alternative cost based on the burden estimated in a US cohort is considered in a sensitivity analysis.[102]

Drug costs for medical management of CTEPH were based on the costs used in CG92, which were uplifted to give a cost of £18,980 per year. The costs for medically managed patients are applied each year to those surviving with CTEPH. The proportion of patients having surgical management for CTEPH (59%) is based on data from Delcroix *et al*.[90] The cost for surgical management of CTEPH is based on a weighted average of the reference costs for complex thoracic procedures (DZ02H/J/K) giving an average cost of £8175.[94] A proportion of patients having surgical management (29%) are assumed to require medical treatment as a bridging therapy (average of 4.6 months). Including these costs brings the total cost in the first year to £10,282 for surgical management. No costs are applied beyond the first year for those managed surgically.

Utility values

A recent systematic review of utility values by Etxeandia-Ikobaltzeta *et al*. was identified which included utilities values in studies published up to April 2018.[103] This review identified only one study of relevance to pregnant/postpartum women, but this study used the EuroQol-5 Dimensions (EQ-5D) visual analogue scale (VAS) which is not a preference-based measure of utility. Estimates of utility following DVT and PE in the general population from the Prevention of Thromboembolic Events – European Registry in VTE (PREFER-VTE) study (not specific to pregnancy or puerperium)[104,105] have been used in a previous model of thromboprophylaxis in hospitalised patients.[46,47] As no additional utility values were identified from the review by Etxeandia-Ikobaltzeta *et al*., the utility values from the PREFER-VTE study applied in previous VTE prevention models were maintained in this model. These gave utility multipliers of 0.962 and 0.960 when averaging the reported utility values over the first 6 months after DVT and PE, respectively (see *Appendix 4*, *Table 26*), and long-term utility multipliers of 1.00 and 0.99, respectively (see *Appendix 4*, *Table 27*).

One of the key assumptions in previous models was that the utility decrement of PE and non-ICH major bleeding is similar in the month following these events.[46,47] This assumption is somewhat supported by Etxeandia-Ikobaltzeta *et al*., who found that the EQ-5D VAS score was 30 for both PE and major obstetric bleeding.[103] Therefore, it seemed reasonable to maintain this assumption in the model for pregnant women. However, it should be noted that the utility decrement for major non-ICH bleeding is applied for only 1 month, whereas an ongoing utility decrement is applied for PE, so PE has a larger impact on QALYs than major bleeding. Given the lack of utility values measured directly in women following major bleeding, a scenario analysis in which no utility decrement is applied for those having major non-ICH bleeding has been conducted to explore the importance of this parameter. For wound haematoma, we have assumed a utility decrement equivalent to major non-ICH bleeding for 1 week to

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capture any adverse impact on HRQoL. A scenario analysis removing this utility decrement for wound haematoma was also explored.

No pregnancy-specific estimates of utility following PTS or CTEPH were identified in the review by Etxeandia-Ikobaltzeta *et al*.,[103] so the sources applied in previous models were maintained.[46,47] In our previous analysis of prophylaxis during lower limb injury, we used utility data from the Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis (CaVenT) study to estimate the utility decrement in patients with PTS.[106] An estimate of 10% was applied from diagnosis onwards which was obtained from the CaVenT study by comparing the EQ-5D scores in those with and without PTS at 2 years. The CaVenT study did not stratify the utility estimates by severity of PTS, so this estimate was applied to all patients with PTS in the model regardless of severity. This may overestimate the utility decrement if the proportion of patients having severe PTS is lower in the modelled population than in the CaVenT study which recruited patients with acute iliofemoral DVT. A study by Lenert and Soetikno reported utility estimates for mild and severe PTS (0.98 and 0.93, respectively) obtained by using health state descriptions and a standard gamble valuation technique in a sample of volunteers.[107] These were not used in the base case as utility measured using the EQ-5D in patients with the condition is preferable to utility measured using standard gamble in volunteers based on descriptions of the condition. However, a scenario analysis was conducted in which the data from Lenert and Soetikno[107] were combined with data on the proportion of PTS that is severe (6%) from a registry study in outpatients having VTE,[108] to estimate a utility decrement of 2% across all patients with PTS. In the current analysis, we have taken the same approach and have applied a 10% decrement in the base case and a 2% decrement in a scenario analysis.

The utility decrement in patients with CTEPH was estimated from a study by Meads *et al*. by comparing the utility in patients having CTEPH (0.56) and the utility in patients with disease categorised as New York Heart Association (NYHA) class 1 (0.89) in which the HRQoL impact of symptoms would be expected to be minimal.[109] This gave a utility multiplier of 0.63 or a 37% decrement. This decrement is applied lifelong in the model to those having medical management of CTEPH, but only for 1 year in those having surgical management who have the utility multiplier for PE applied thereafter.

The values applied following non-fatal ICH were also taken from those used in previous VTE prevention models. Utility values following ICH were based on data from 5-year follow-up of the Oxford Vascular Study (OXVASC) study as these data were applied in a previous analysis of thromboprophylaxis after lower limb injury.[110] An absolute decrement of 0.22 was assumed in the decision-tree part of the model where time since stroke was < 1 year and a decrement of 0.09 was assumed in the long-term part of the model. This study was chosen as the source of utility values previously as the duration of follow-up allowed time since stroke to be accounted for, and a comparison was made against general population norms.

In the previous analysis of thromboprophylaxis after lower limb injury, we identified several sources which estimated the utility decrement associated with VTE prophylaxis or VTE treatment.[46] The study selected for use in the previous model was a study by Marchetti *et al*. which reported that patients would be willing to trade 2.7 of 365 days to avoid treatment with LMWH.[111] These data were previously used to estimate a utility decrement of 0.007 for LMWH. These same decrements have been applied in this model. However, it is noted that the utility decrement may differ for women during pregnancy or the puerperium. Therefore, to determine how sensitive the model results are to this parameter, we conducted scenario analyses in which we assumed that the utility decrement is either double the value assumed in the base case or zero.

Utility values for patients not experiencing any utility decrement due to prophylaxis, treatment, symptomatic VTE events, bleeding events (ICH or other major bleeds), long-term sequelae following VTE (PTS or CTEPH) or death are based on general population norms for a cohort of the same age and this is allowed to vary as the cohort ages during the model.[112]

Timing and duration of utility decrements applied in the decision tree

To calculate the QALYs gained by patients having different paths through the decision tree, it is necessary to make some assumptions regarding the timing of events as these are not explicitly modelled in a decision tree. The average timing of postpartum VTE is 21 days based on the timings reported by Sultan *et al.*[55] However, we are interested in the timing of the VTE that is prevented by prophylaxis. If you assume that the VTE events prevented by prophylaxis occur on average halfway through the prophylaxis, then that would mean assuming they occur at 5 days. However, it is also possible that early prophylaxis for 10 days prevents VTEs that would have been diagnosed later in the puerperium after prophylaxis has ended. Therefore, in our base-case analysis, we have assumed that the VTEs being prevented occur on average at 21 days, and we explore the impact of varying this from 5 to 42 days in scenario analysis.

The average timing of VTE occurring during pregnancy was estimated using data from Voke *et al*. which provides a scatter plot of timing of VTE events.[113] From this it was estimated that the average timing of VTE was 24 weeks.

Timing of postpartum bleeds during prophylaxis (3 days) was based on the average timing reported by Gizzo *et al.*[76] Bleeds occurring during antepartum prophylaxis are assumed to occur 28 days before the timing of VTE. Bleeds occurring during treatment for VTE are assumed to occur at 13, 32 and 12 days post diagnosis of VTE for fatal, ICH and other major bleeds, respectively (based on data from the RIETE registry reported by Nieto *et al.*).[81]

We made the following assumptions when estimating QALYs in the decision tree:

- Baseline utilities using general population utility values for the starting age are applied to those not having treatment and not having any clinical events (e.g. VTE, bleeds).
- A disutility for ICH is applied lifelong, but separate values are applied in decision-tree and state-transition phases of the model.
- Disutility of non-fatal non-ICH major bleeding is assumed to last a maximum of 28 days.
- Disutility of prophylaxis applies for the duration of prophylaxis.
- Disutility of treatment for VTE applies for the duration of treatment.

We made the following assumptions when estimating QALYs in the state-transition model:

- Utility values for patents without any long-term sequelae (ICH, CTEPH, PTS) are taken from general population values and decrease as patients age in the model.
- All other utility values are applied as multipliers such that the absolute utility value decreases due to ageing in all patients.
- Utility decrements continue in the state-transition model for the remainder of the patients' lifetime for PE but not for DVT where patients are assumed to return to general population utility values at 1 year.
- Patients with CTEPH who are treated medically have a lifelong utility decrement, whereas those treated surgically return after 1 year to the same utility as those surviving PE without CTEPH.
- Patients with PTS have the same utility decrement from diagnosis to death.
- Patients with ICH have the same utility decrement from the start of state-transition model to death.

Sensitivity and specificity of risk assessment models

Estimates of sensitivity and specificity are based on the data presented in the systematic review (see *Chapter 3*). Only those studies that reported both sensitivity and specificity could be included in the modelling and any study reporting a sensitivity of 0% was excluded from the modelling. In the antepartum model for high-risk women, only the EThIG and Lyon RAMs had data suitable for inclusion. The modelling for high-risk women assumes that patients classified as low risk by the EThIG and Lyon

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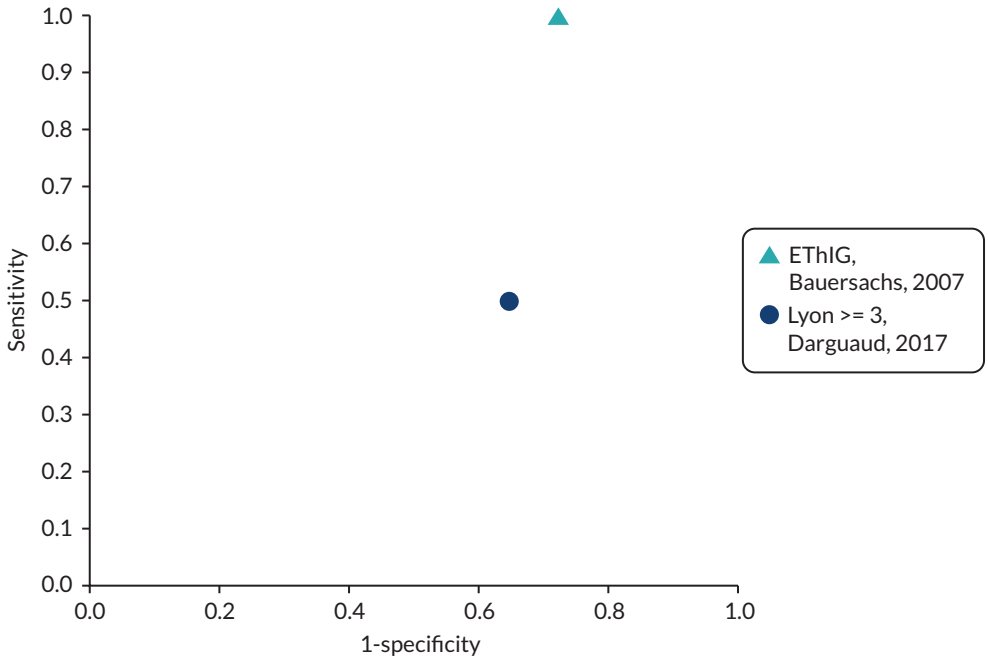

FIGURE 5 Receiver operating characteristics curve for RAMs to predict antepartum VTE in high-risk women. (References for figure: Bauersachs 2007,[27] Dargaud 2017.[32])

RAMs will receive postpartum prophylaxis and those categorised as high risk based on the RAMs will receive antepartum prophylaxis in addition to postpartum prophylaxis. Therefore, it is the sensitivity and specificity of the RAMs in predicting antepartum VTE that are relevant to the economic analysis. The data available for the high-risk antepartum women for the EThIG and Lyon RAMs are summarised in *Figure 5* as a receiver operating characteristics (ROC) curve.

In the unselected postpartum population, data were available for the RCOG,[11,39] SFOG[11,36] and Caprini[39] RAMs and the novel RAM reported by Sultan *et al.*,[11] for which performance data were reported for multiple cut-offs (defined according to those falling in the top 1%, 5%, 10%, 20% and 25% of absolute risk). In the postpartum population with obesity, only the novel RAM reported by Ellis-Kahana *et al.*,[41] is available, but performance data are provided for two versions of this RAM, in which thrombophilia was either included or excluded from the risk algorithm. In the post-caesarean section population, a novel RAM is reported by Binstock *et al.* along with data for the RCOG RAM.[28] The data for postpartum RAMs across the three populations are summarised in *Figure 6*.

In the unselected antepartum population, the only RAM identified with available performance data was the STRATHEGE RAM,[31] but the data suggested that it had poor performance (sensitivity of 0% and specificity of 98%). Therefore, the analysis in the unselected antepartum population was limited to exploratory analysis. In this analysis, various theoretical combinations of sensitivity and specificity values were tested to determine the range of sensitivity and specificity values that would be required for a RAM to be cost-effective in this population.

Model inputs for secondary scenarios where antepartum prophylaxis is offered at 28 weeks

In the main analysis for antepartum prophylaxis in women at high risk of VTE, we have assumed that women are offered prophylaxis from booking if they are identified as being at high risk by either the EThIG or Lyon RAMs. However, for the Lyon RAM, some women are offered antepartum prophylaxis from 28 weeks only.[32,33] Therefore, we have conducted a scenario analysis where prophylaxis is only offered from 28 weeks in the high-risk subgroup to explore whether this results in a different strategy being most cost-effective. For this analysis, the efficacy of prophylaxis

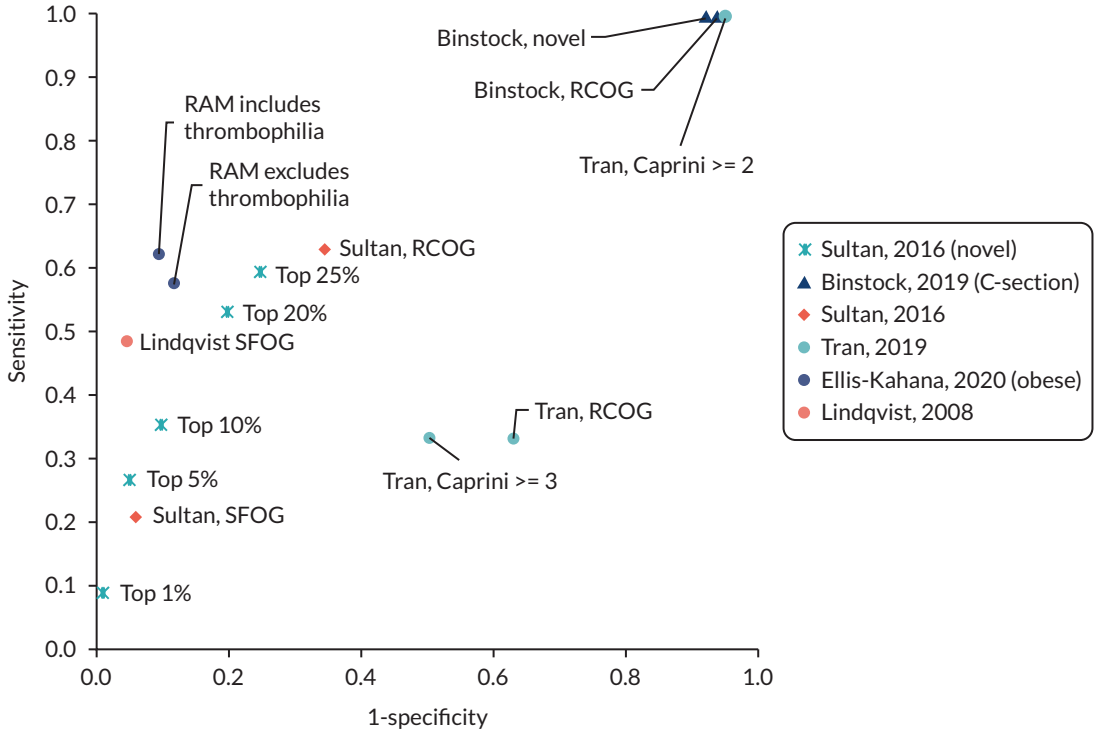

FIGURE 6 Receiver operating characteristics curve for postpartum VTE in unselected postpartum women and women with specific risk factors (obesity, caesarean section). (References for figure: Binstock 2019,[28] Ellis-Kahan 2020,[41] Lindqvist 2008,[36] Tran 2019,[39] Sultan 2016.[11])

is adjusted so that it only applies to the 40% of antepartum VTE risk occurring after 28 weeks gestation and the average timing of VTE is moved from 24 to 34 weeks, with consequent impacts on the cost of VTE treatment. The average timing of VTE occurring after 28 weeks was based on the scatterplot provided by Voke *et al.*[113] Other risks, such as the risks of major antepartum bleeding, are not adjusted.

In the main analysis for women being offered antepartum prophylaxis, we have focused on women at high risk being offered prophylaxis from booking. However, within the RCOG guidance, antepartum prophylaxis is also recommended from 28 weeks in women having three risk factors.[7] A secondary scenario has been conducted to explore whether this is cost-effective. Some data on the risk of antepartum VTE for specific risk factors and for some combinations of risk factors were available from an analysis of a GP database by Sultan *et al.* (2013).[114] This used a different GP database (The Health Improvement Network) from that used to generate the postpartum RAM (CPRD),[11] but again it excluded women with a prior history of VTE. This provided the risk of VTE for women with any 2 or more risk factors as being 95 antepartum events per 100,000 pregnancies and 111 postpartum events per 100,000 risk factors (0.20% VTE risk overall).[114] The risk for women with three or more risk factors is not provided; however, if we applied the RR for the strongest individual risk factor, which was varicose veins (RR of 2.21 for antepartum VTE and 3.90 for postpartum VTE), to the absolute risks for two or more risk factors, then this would suggest an upper limit for the absolute risk of 217 antepartum VTEs per 100,000 pregnancies and 433 postpartum VTEs per 100,000 pregnancies. This suggests an upper limit for women with three risk factors of around 0.6%. As an exact risk cannot be identified for women with three or more risk factors, we have used the model to identify the level of risk that would be required in this group for prophylaxis at 28 weeks to be cost-effective.

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Approach to quantifying decision uncertainty

A probabilistic sensitivity analysis (PSA) has been conducted to incorporate uncertainty regarding the model inputs and determine how this uncertainty propagates through the model to translate into uncertainty in the incremental costs and QALYs and therefore decision uncertainty regarding the optimal prophylaxis strategy. The PSA is based on 10,000 parameter samples (probability distributions are provided, see *Appendix 4*, *Tables 22* and *28*). In the PSA, the OR for VTE was sampled using the event rates from the study by Gates *et al.*[67] (OR 0.29, 95% CI 0.01 to 8.37), and this was used to calculate the expected RR given the sampled absolute risk of VTE in the model for people not receiving prophylaxis.

In addition, the decision uncertainty associated with not having perfect information on all model parameters is estimated by the EVPI analysis. The overall EVPI provides an estimate of the increase in net monetary benefit that could be achieved by having perfect information on all model parameters simultaneously. The increase in net monetary benefit that can be achieved by obtaining perfect information on individual parameters or groups of parameters is known as the expected value of perfect parameter information (EVPPI). We have estimated EVPPI using the online Sheffield Accelerated Value of Information (SAVI) tool which uses a regression-based approach to obtain estimates of EVPPI directly from the outcomes of the PSA and the set of parameter inputs that generated those PSA outputs.[115,116] We provide EVPI and EVPPI estimates per patient and we also estimate the EVPI and EVPPI over 5 years of births, assuming 640,370 live births per annum in England and Wales,[117] and discounting of future costs and benefits at 3.5%.

Aspects of structural uncertainty such as the choice of one data source over another to inform the parameter distribution, or the impact of various model assumptions, are explored within scenario analyses using the mean estimates for the parameter inputs (referred to as the deterministic model).

Results – cost-effectiveness and value of perfect information

Clinical outcomes predicted by the model with and without prophylaxis

Table 7 shows the clinical outcomes predicted by the model with and without prophylaxis in each of the modelled populations when using the deterministic model (i.e. mean parameter inputs).

In the population of high-risk antepartum women, prophylaxis reduces serious adverse outcomes (fatal PEs, fatal bleeds and non-fatal ICHs) from 71 per 100,000 to 28 per 100,000. Prophylaxis reduces the risk of fatal bleeding and non-fatal ICH because it reduces the risk of VTE and therefore the risk of requiring anticoagulant treatment, which itself has a risk of fatal bleeding and non-fatal ICH. The reduction in symptomatic DVTs is higher than the increase in other major bleeds. In the long-term outcomes, presented in *Table 7* at 5 years, there are also reductions in both PTS (7127 per 100,000) and CTEPH (49 per 100,000).

The absolute risks of VTE are much lower in the unselected postpartum population, but the bleeding risks are of the same order of magnitude. Prophylaxis for all would result in one additional serious adverse outcome (1 additional ICH per 100,000) but would reduce symptomatic VTE by 34 per 100,000. However, the risk of other major bleeding is significant at 1586 per 100,000. In the postpartum subgroups selected for specific risk factors (obesity, post caesarean section), the benefits of prophylaxis are slightly higher, because the risks of VTE are slightly higher, but these are still outweighed by the increased risks of major bleeding.

TABLE 7 Predicted clinical outcomes per 100,000 patients at 6 months and 5 years

	Outcomes at 6 months per 100,000 patients							Outcomes at 5 years per 100,000 patients				
	Fatal PE	Fatal bleed	Non-fatal ICH	Other major bleed[a]	Non-fatal PE	Symptomatic DVT	Asymptomatic DVT	PTS	PE survivor with CTEPH	PE survivor without CTEPH	ICH survivor	Dead (any cause)
High-risk antepartum women (e.g. prior VTE)												
No prophylaxis	59	7	5	3423	2890	9300	19,593	10,824	74	2790	5	321
Prophylaxis[b]	20	4	4	5400	974	3136	6733	3696	25	941	4	266
Unselected postpartum women												
No prophylaxis	0	1	1	2996	17	55	219	101	0	16	1	238
Prophylaxis[c]	0	1	2	4582	9	29	116	53	0	9	2	238
Obese postpartum women												
No prophylaxis	1	1	1	2996	36	116	465	215	1	35	1	238
Prophylaxis[c]	0	1	2	4582	19	62	246	114	0	18	2	238
Postpartum women following caesarean section												
No prophylaxis	1	1	1	2996	32	104	415	192	1	31	1	238
Prophylaxis[c]	0	1	2	4582	17	55	219	101	0	16	2	238

a Patients having other major bleeds could also have a DVT or non-fatal PE.
b Prophylaxis for all from booking until 6 weeks postpartum.
c Ten days of postpartum prophylaxis for all.

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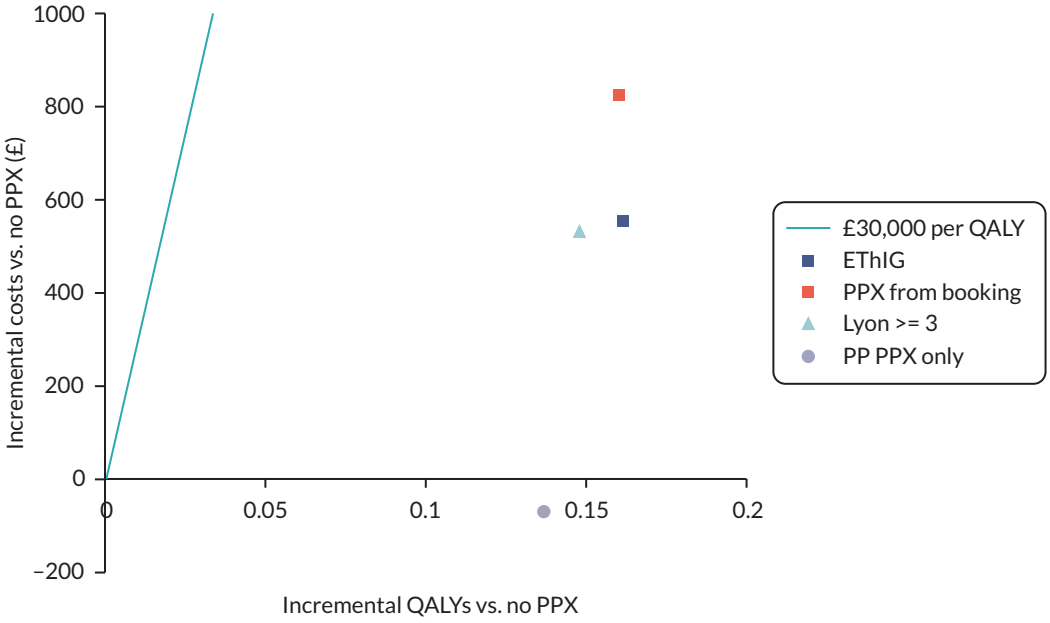

FIGURE 7 Deterministic base-case results for RAMs validated in antepartum women at high risk of VTE. (References for figure: EThiG,[27] Lyon.[32])

Antepartum women with a prior venous thromboembolism

Deterministic base-case results for antepartum women with a prior venous thromboembolism

The deterministic base-case results obtained when applying the midpoint parameters estimates to the base-case scenario for antepartum women with a prior VTE are shown in *Figure 7*. It can be seen that all of the strategies have an incremental cost-effectiveness ratio (ICER) under £30,000 per QALY when compared to a strategy of offering no antepartum or postpartum prophylaxis (no PPX). The strategy of offering only postpartum prophylaxis (PP PPX only) is cost saving compared to no PPX and generates additional QALYs and therefore dominates no PPX. The EThIG RAM has the highest QALY gains and it has lower costs that offer prophylaxis to all from booking (PPX from booking). Therefore, PPX from booking is said to be dominated by the EThIG RAM. The ICER for the Lyon RAM compared to PP PPX only is £53,757 per QALY, whereas the ICER for the EThIG RAM compared to the Lyon RAM is less at £1468 per QALY. Therefore, the Lyon RAM is extendedly dominated because it would never be preferable when the EThIG RAM and PP PPX only strategies are available. The ICER for the EThIG RAM compared to PP PPX for all is £24,982. Therefore, based on the deterministic analysis, PP PPX only would be most cost-effective when applying a cost per QALY threshold of £20,000 and the EThIG RAM would be most cost-effective when applying a cost per QALY threshold or £30,000.

Probabilistic base-case results for antepartum women with a prior venous thromboembolism

The results based on the mean outcomes from 10,000 probabilistic model runs are summarised in *Table 8*. The broad conclusions are the same, in that all of the strategies are cost-effective compared to no prophylaxis, and the optimal strategy when valuing a QALY at £20,000 is PP PPX only. However, the ICER for the EThIG RAM compared to PP PPX only is £56,761 per QALY in the probabilistic analysis, whereas the ICER for this comparison was under £30,000 in the deterministic analysis. This means that the optimal strategy when valuing a QALY at £30,000 is the PP PPX only strategy based on the probabilistic analysis.

TABLE 8 Base-case results (mean from 10,000 PSA samples) in order of % receiving antepartum prophylaxis for high-risk antepartum women

	% AP PPX (%)	Sensitivity for predicting AP VTE (%)	Specificity for predicting AP VTE (%)	Absolute costs, (£)	Absolute QALYs	Cost vs. no PPX, (£)	QALYs vs. no PPX	ICER vs. no PPX, (£)	ICER vs. next least effective strategy, (£)	INMB vs. no PPX at £20K, (£)[a]	INMB vs. no PPX at £30K, (£)[a]
No PPX	0	0	100	729.26	20.802	NA	NA	NA	NA	NA	NA
PP PPX only	0[b]	0[c]	100[d]	757.52	20.877	28.26	0.075	375	375	**1477.17**	**2229.88**
Lyon ≥ 3	64	50	35	1388.52	20.884	659.27	0.082	7994	Extendedly dominated	990.22	1814.96
EThIG	74	100	28	1449.76	20.889	720.51	0.087	8237	56,761	1028.84	1903.52
PPX from booking	100	100	0	1709.13	20.893	979.88	0.091	10,796	78,722	835.37	1742.99

NA, not applicable.
a INMB at £20K and INMB at £30K are the INMBs when valuing a QALY at £20,000 and £30,000 per QALY, respectively, and the maximum value (shown in bold) shows you the optimal strategy.
b The PP PPX only strategy has 0% antepartum prophylaxis, but 100% postpartum prophylaxis.
c Zero per cent sensitivity for antepartum VTE, but 100% for postpartum VTE.
d 100% specificity for antepartum prophylaxis, but 0% for postpartum prophylaxis.

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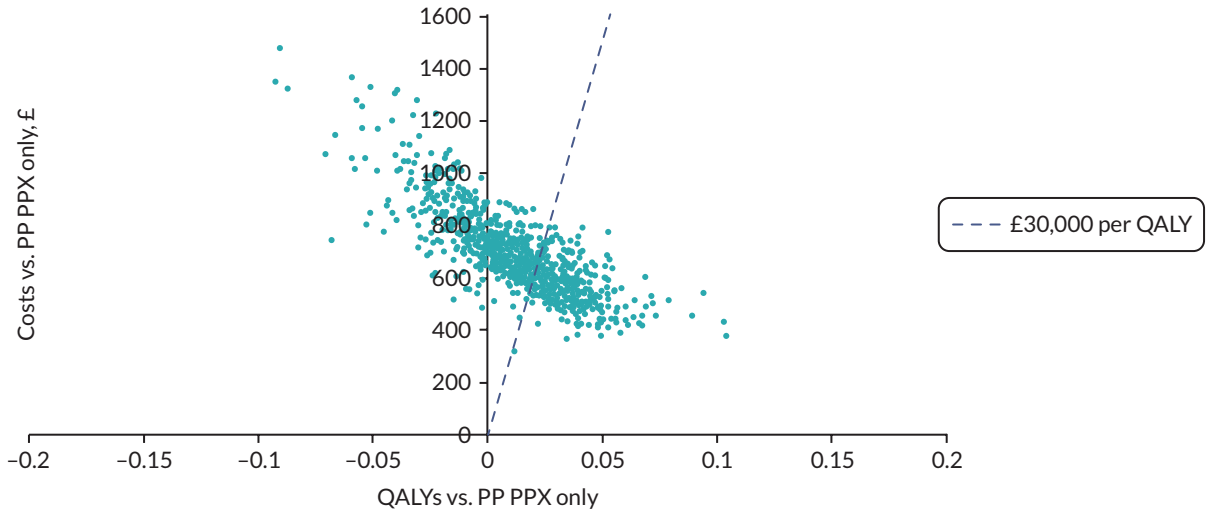

FIGURE 8 Probabilistic base-case results for antepartum prophylaxis according to the EThIG RAM vs. postpartum prophylaxis only (PP PPX only).

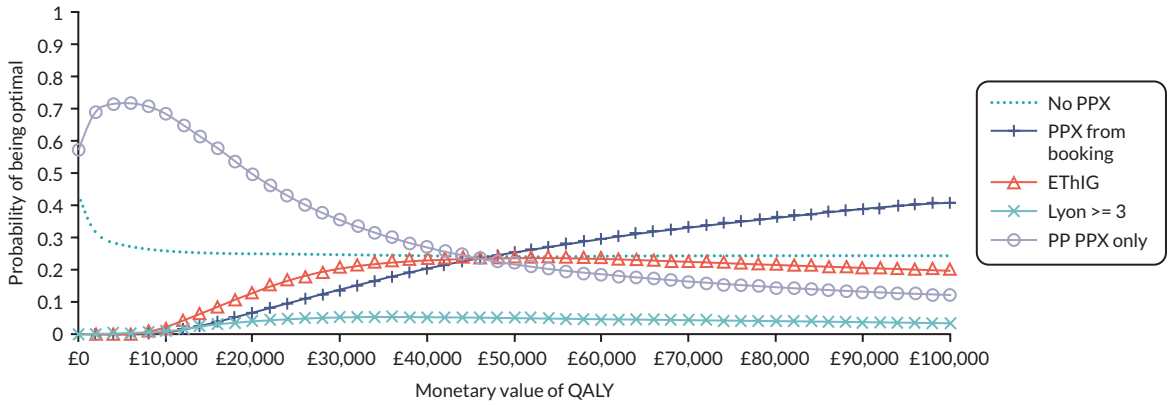

FIGURE 9 Cost-effectiveness acceptability curve for high-risk antepartum women. (References for figure: EThiG,[27] Lyon.[32])

However, there is significant uncertainty in the incremental costs and QALYs as demonstrated by *Figure 8*, which shows the spread of incremental costs and QALYs for antepartum prophylaxis based on the EThIG RAM compared to a strategy of PP PPX only, with 42% of the PSA samples providing an ICER of under £30,000 per QALY for the EThIG RAM compared to PP PPX only. The cost-effectiveness acceptability curve (CEAC) is presented in *Figure 9*. This shows that the PP PPX only strategy has the highest probability of being most cost-effective (36%), when valuing a QALY at £30,000. However, no PPX, and PPX according to the EThIG RAM both have a > 20% probability of being optimal.

Due to this high degree of uncertainty regarding the optimal strategy, the overall EVPI associated with all parameters included in the PSA, when valuing a QALY at £30,000, was £1454 per patient. Therefore, the population EVPI over 5 years of births would be £21.8 million when taking into account that there are 640,000 births per year, and 0.5% of these are in women with a prior history of VTE.[15,117]

Expected value of perfect parameter information was used to determine which individual parameters and groups of parameters were the greatest drivers of uncertainty regarding the optimal strategy. Full results for individual parameters are provided (see *Appendix 5*, *Table 29*), but the single most important parameter was the RR of VTE which accounted for 94% of the overall EVPI. Given that any study which

provides additional evidence on the RR of VTE could also be used to capture additional information on the RR of bleeding, we estimated the EVPI for these two parameters, which was £1363 per patient, or £20.4 million over 5 years of births (see *Appendix 5*, *Table 30*). The remaining groups of parameters examined all had an EVPPI that was less than 1% of the total EVPI.

Deterministic scenario analyses for antepartum women with a prior venous thromboembolism

The deterministic scenario analyses were conducted to explore which model assumptions and inputs were key drivers of decision uncertainty. To do this, deterministic results were generated using midpoint parameter inputs when varying individual model inputs or assumptions. In the base-case deterministic analysis, the optimal strategy, when valuing a QALY at £30,000, was using the EThIG RAM to determine antepartum prophylaxis. The sensitivity of the model results to the various alternative assumptions and data inputs are expressed using INMB benefit for EThIG RAM compared to no prophylaxis. A negative INMB would mean that antepartum prophylaxis using the EThIG RAM has an ICER over £30,000 per QALY compared to a strategy of no prophylaxis.

Figure 10 shows the results for the scenario analyses that had the greatest impact on the INMB when comparing antepartum prophylaxis according to the EThIG RAM against a strategy of no PPX. (Full

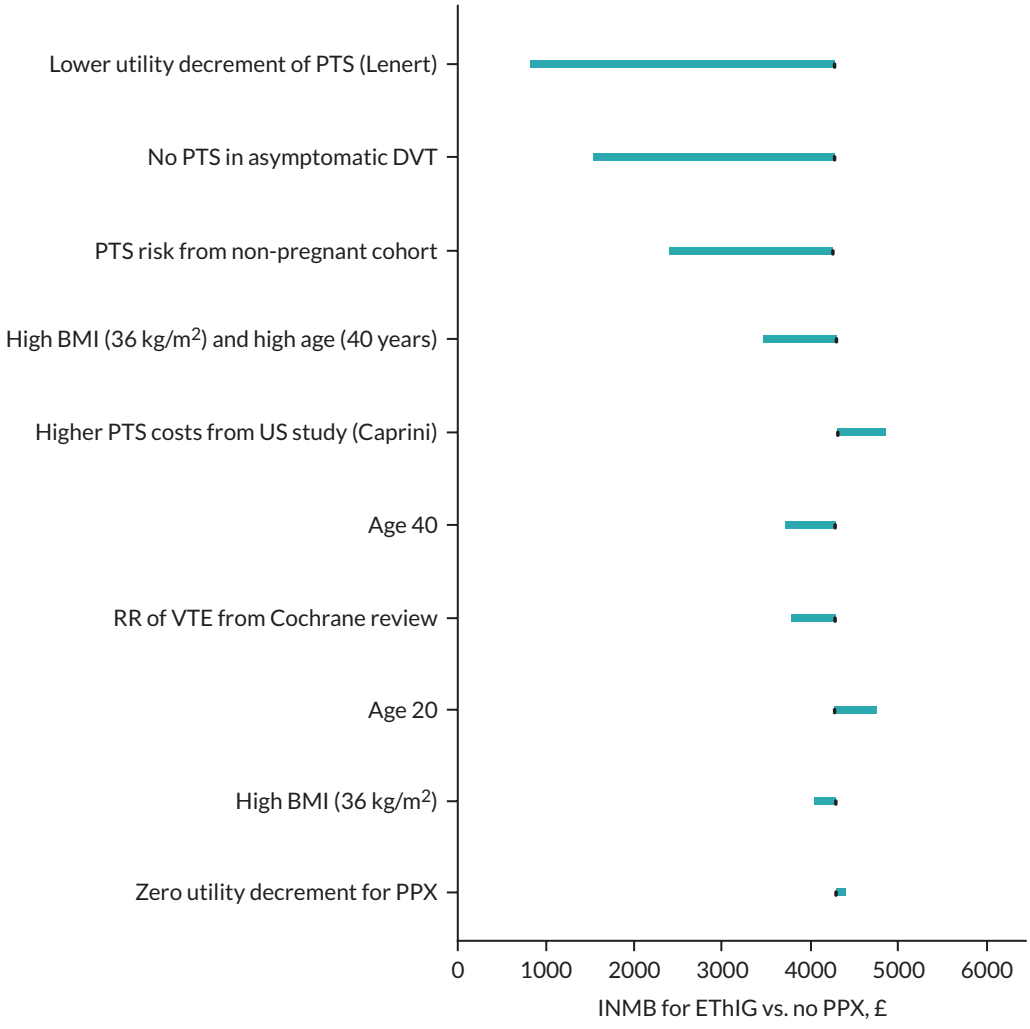

FIGURE 10 Deterministic scenario analyses for antepartum prophylaxis in high-risk women using EThIG RAM[27] compared to offering no prophylaxis (no PPX). (References for figure: Cochrane review,[8] Caprini,[102] Lenert.[107])

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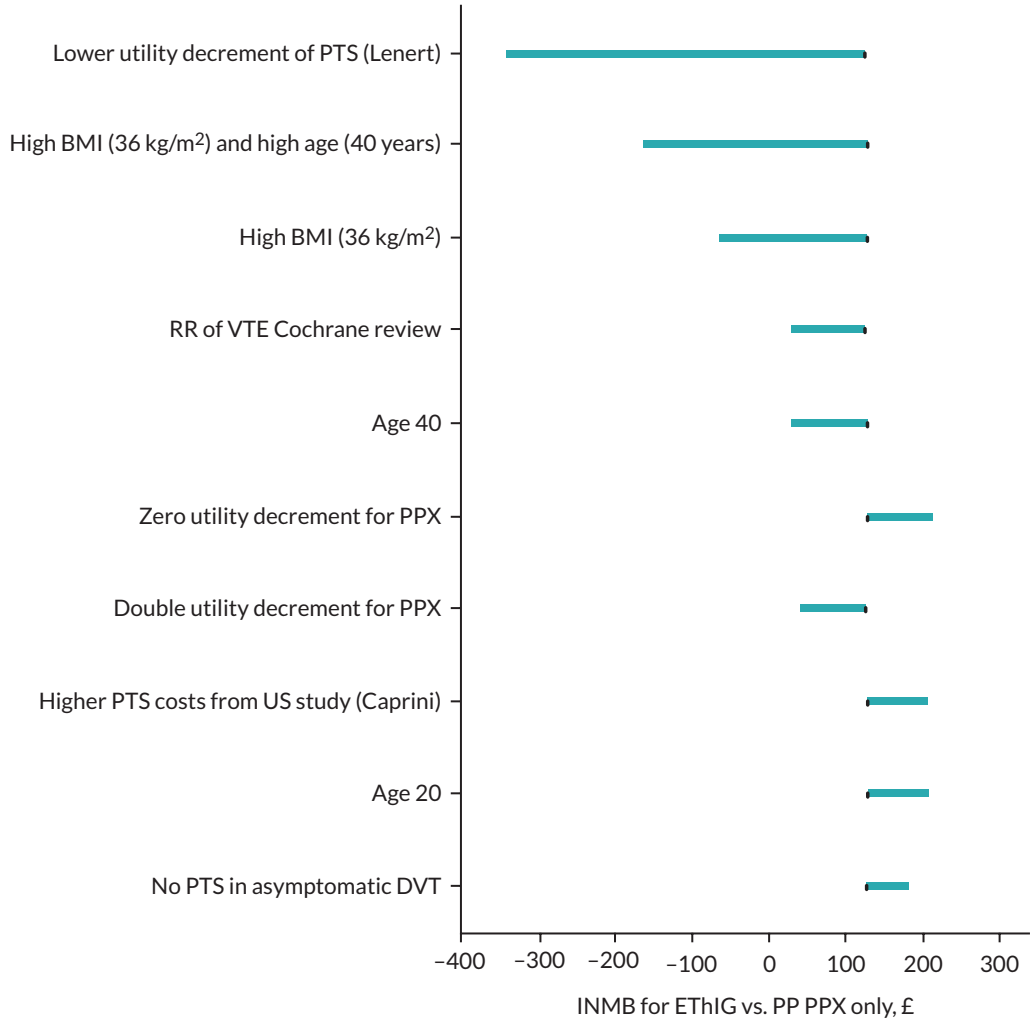

FIGURE 11 Deterministic scenario analyses for antepartum prophylaxis in high-risk women using EThIG RAM[27] compared to offering postpartum prophylaxis only (PP PPX only). (References for figure: Cochrane review,[8] Caprini,[102] Lenert.[107])

results for the deterministic scenario analyses are provided, see *Appendix 6*, *Table 40*.) It can be seen that none of the scenario analyses result in a negative INMB. Also, it can be seen that the factors that had the greatest impact were those related to PTS, patient characteristics, efficacy and safety of LMWH and the utility decrement associated with daily LMWH injections.

Figure 11 shows the deterministic scenario analyses when comparing antepartum prophylaxis according to the EThIG RAM against a strategy of postpartum prophylaxis only (PP PPX only). In this comparison, many of the same factors are important, but for three scenario analyses, the INMB was negative meaning the optimal strategy switched from antepartum prophylaxis according to the EThIG RAM to PP PPX only. This was true when assuming a lower utility decrement for PTS and in the two scenarios which assumed higher BMI (36 kg/m^2), which affects the dosage and therefore the costs of prophylaxis.

In the base-case analysis for high-risk antepartum women, we have assumed that those identified as high risk according to the RAM receive antepartum prophylaxis from their booking appointment. However, the Lyon RAM actually recommends antepartum prophylaxis from 28 weeks for those with a score 3–6 and only recommends prophylaxis from booking in those with a score of 6 or more. As this will affect both the costs and efficacy of offering antepartum prophylaxis using the Lyon RAM, we have therefore conducted a scenario analysis to determine the impact of assuming that antepartum prophylaxis is deferred until 28 weeks. The results for this scenario analysis are provided in *Figure 12*.

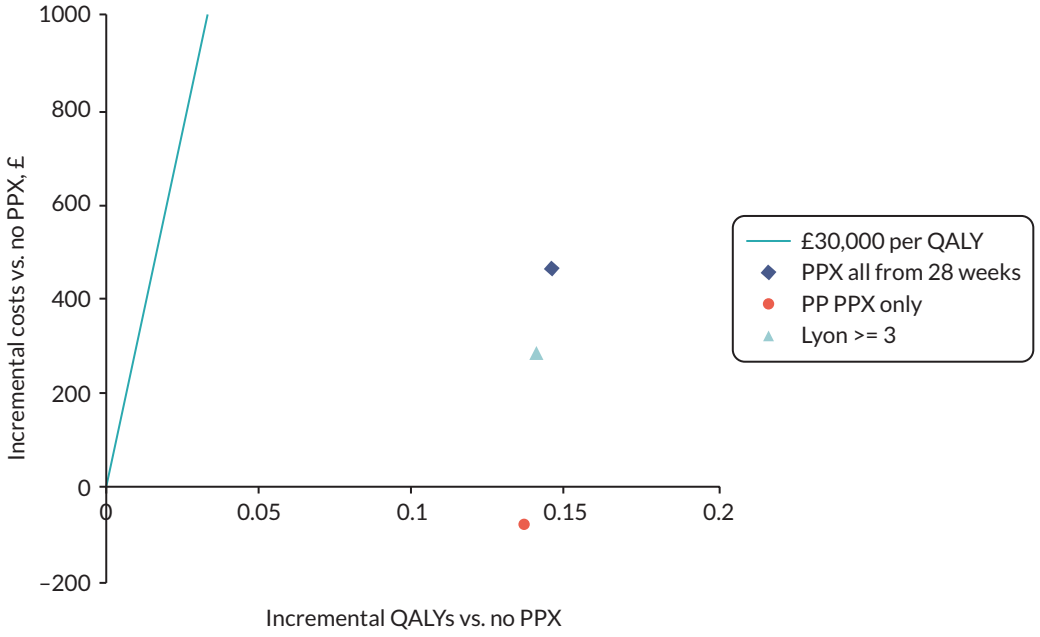

FIGURE 12 Deterministic scenario analysis for the Lyon RAM in women at high risk of VTE when assuming that antepartum prophylaxis is delayed until 28 weeks. (Reference for figure: Lyon.[32])

In this scenario, the Lyon RAM has an ICER of £83,144 per QALY compared to PP PPX only, which is less favourable than the deterministic ICER in the base case (£53,757 per QALY). This is because, although delaying prophylaxis to 28 weeks reduces the costs of prophylaxis, it also reduces the period of effective prophylaxis and therefore lowers the QALY gains and the cost savings. This scenario analysis suggests that the benefits of the Lyon RAM may be overestimated in the base-case scenario because it recommends a mixture of prophylaxis from booking and prophylaxis from 28 weeks gestation, but the base-case analysis assumes prophylaxis is given from booking in any patient with a Lyon score ≥ 3 as this is the cut-off for offering any antepartum prophylaxis.

Given that there were uncertainties in the evidence used to determine the risk of VTE and major bleeding in the cohort of high-risk antepartum patients, a two-way scenario analysis was conducted to explore whether the optimal prophylaxis strategy would vary if the average risks of VTE and major bleeding were higher or lower. The results (see *Appendix 6*, *Table 35*) show that the optimal strategy would be to offer only postpartum prophylaxis if the VTE risk was under 10%. The results are not

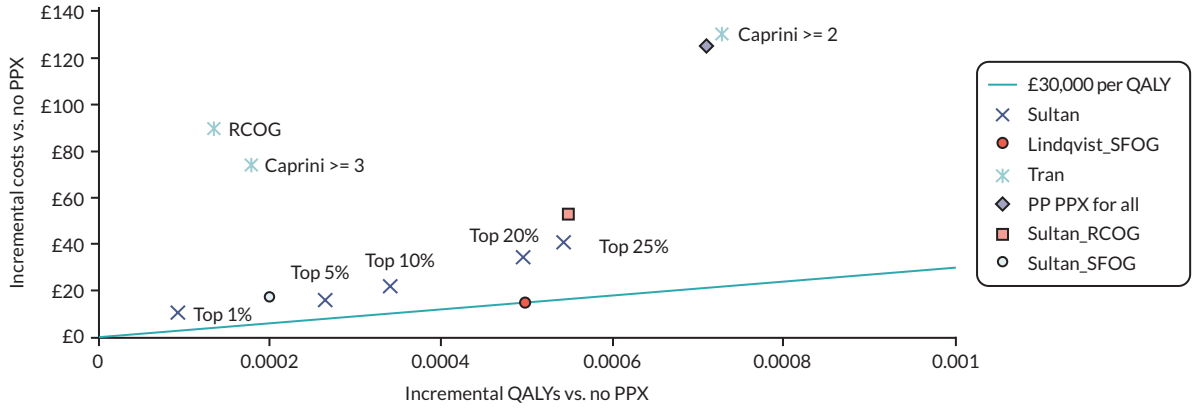

FIGURE 13 Deterministic base-case results for unselected postpartum women being offered prophylaxis according to various RAMs (RCOG, SFOG, Caprini, Sultan) compared to no prophylaxis (no PPX). (References for figure: Lindqvist 2008,[36] Tran 2019,[39] Sultan 2016.[11])

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particularly sensitive to the risks of major bleeding, although the optimal strategy does change for higher bleeding risks (> 7%) when the VTE risk is in the range of 11–12%.

Unselected postpartum women

Deterministic base-case results for unselected postpartum women

The deterministic base-case results obtained when applying the midpoint parameter estimates to the base-case scenario for unselected postpartum women are presented in *Figure 13*. For the Sultan RAM, results are presented for various cut-offs defined according to the proportion of women defined as being high risk (e.g. top 1%) when using the Sultan calculator to determine absolute risk. The ICER for the SFOG RAM when using the sensitivity and specificity data reported by Lindqvist *et al.*[36] is £29,777 compared to no prophylaxis. However, this was a low-quality study, and this RAM did not perform as well in the higher-quality study conducted by Sultan *et al*. and using this performance data resulted in a deterministic ICER of £86,142 compared to no prophylaxis.

Probabilistic base-case results for unselected postpartum women

The PSA was run to compare the RCOG, SFOG and Sultan RAMs using performance data from the Sultan paper. This was chosen as it was the highest-quality study and was considered to provide the most robust estimates of performance for these three RAMs. Also, it had the benefit of estimating the performance of all three RAMs in the same cohort which minimises the risk of bias due to difference in the cohort characteristics or differences in the methods employed.

The results based on the mean outcomes from 10,000 probabilistic model runs are summarised in *Table 9*. It can be seen that the average QALY gains for all RAM-based strategies are now negative. This means that no PPX is the dominant strategy when incorporating uncertainty regarding the parameter inputs. *Figure 14* shows the incremental costs and QALYs for using the Sultan RAM to offer prophylaxis to the top 1% of VTE risk versus no PPX. It can be seen that there is significant uncertainty regarding the incremental QALYs, with a 95% CI of −0.0011 to 0.0003 and 24% of PSA samples resulting in a negative incremental QALY gain.

The CEAC for postpartum prophylaxis in unselected women is presented in *Figure 15*. When valuing a QALY at £30,000, a strategy of offering no prophylaxis has an 89% probability of being optimal, whereas all of the remaining strategies have less than a 10% chance of being optimal.

The overall EVPI associated with all parameters included in the PSA when valuing a QALY at £30,000 was £0.68 per person. Although this is a small amount of EVPI per person, the amount across 5 years of births, assuming 640,000 births per annum,[117] would be £2.0 million. No individual parameter had an EVPPI of more than £0.01 per person.

The broad spread of incremental QALY estimates appears to be driven by the uncertainty in the RR of VTE. However, in this case, there is not a large EVPI associated with this parameter as only 11% of the PSA samples resulted in a strategy other than no PPX being optimal (defined as having the maximum INMB when valuing a QALY at £30,000).

Deterministic scenario analyses for unselected postpartum women

Deterministic scenario analyses were conducted to explore which model assumptions and inputs were key drivers of decision uncertainty. To do this, deterministic results were generated using midpoint parameter inputs when varying individual model inputs or assumptions. In the base-case deterministic analysis, the optimal strategy, when valuing a QALY at £30,000, was no prophylaxis, but the strategy with the second highest INMB was offering prophylaxis to patients in the top 5% of VTE risk using the Sultan RAM. Therefore, the sensitivity of the model results to the various alternative assumptions and data inputs are expressed using INMB benefit for Sultan (top 5%) compared to no prophylaxis. A positive INMB would mean Sultan (top 5%) has an ICER of under £30,000 per QALY compared to a strategy of

TABLE 9 Base-case results (mean from 10,000 PSA samples) in order of % receiving prophylaxis for unselected postpartum women

	% PPX	Sensitivity (%)	Specificity (%)	Absolute costs, (£)	Absolute QALYs	Cost vs. no PPX, (£)	QALYs vs. no PPX	ICER vs. no PPX, (£)	ICER vs. next least effective strategy, (£)	INMB vs. no PPX at £20K, (£)[a]	INMB vs. no PPX at £30K, (£)[a]
No PPX	0	0	100	43.66	20.5549	NA	NA	NA	NA	NA	NA
Sultan top 1%	1	9	99	54.60	20.5549	10.94	−0.0000	Dominated	Dominated	−11.71	−12.09
Sultan top 5%	5	27	95	59.84	20.5548	16.17	−0.0001	Dominated	Dominated	−18.59	−19.79
SFOG	6	21	94	61.29	20.5548	17.63	−0.0001	Dominated	Dominated	−19.71	−20.75
Sultan top 10%	10	36	90	66.24	20.5547	22.57	−0.0002	Dominated	Dominated	−26.01	−27.73
Sultan top 20%	20	53	80	79.04	20.5546	35.38	−0.0003	Dominated	Dominated	−40.89	−43.65
Sultan top 25%	25	60	75	85.41	20.5546	41.75	−0.0003	Dominated	Dominated	−48.08	−51.24
RCOG	35	63	66	97.32	20.5545	53.65	−0.0004	Dominated	Dominated	−61.02	−64.71
PPX for all	100	100	0	170.86	20.5542	127.20	−0.0007	Dominated	Dominated	−141.75	−149.02

NA, not applicable.
a INMB at £20K and INMB at £30K are the INMBs when valuing a QALY at £20,000 and £30,000 per QALY, respectively, and the maximum value shows you the optimal strategy.

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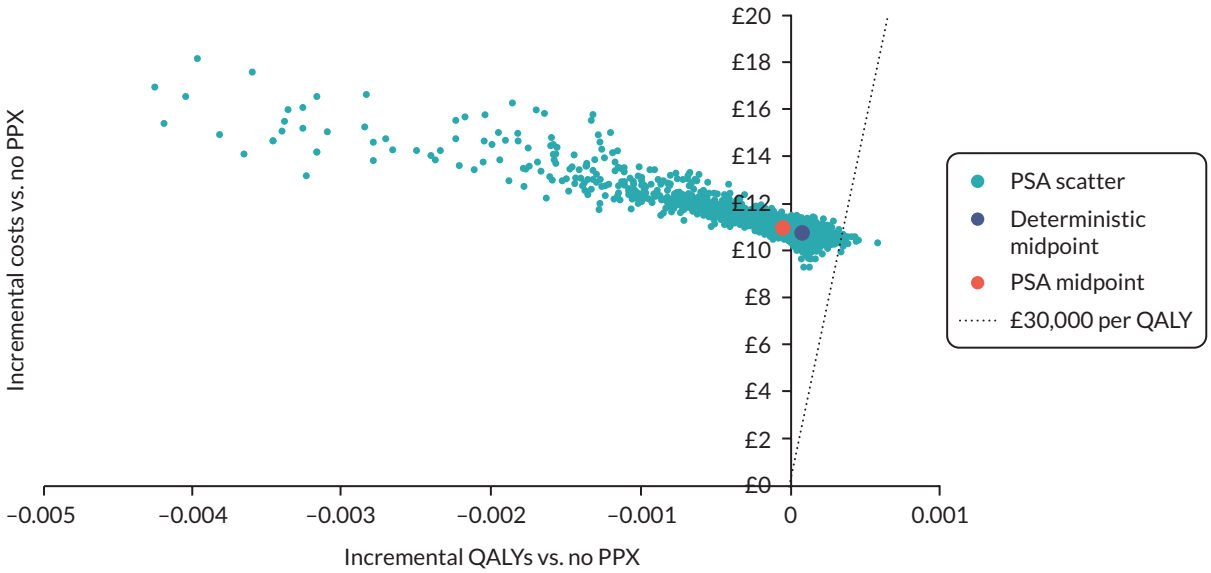

FIGURE 14 Probabilistic base-case results for using the Sultan RAM (top 1%) vs. no prophylaxis (no PPX) in unselected postpartum women.

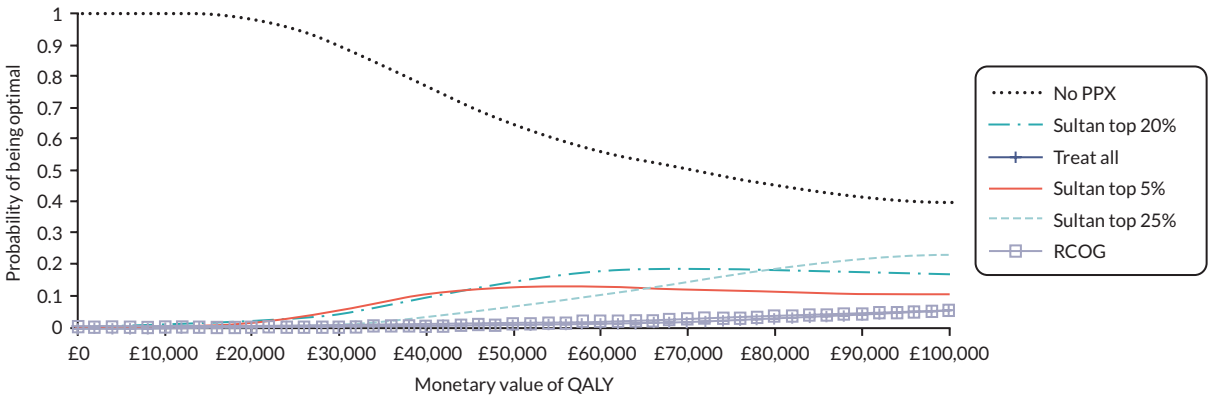

FIGURE 15 Cost-effectiveness acceptability curve for prophylaxis strategies in unselected postpartum women.

no prophylaxis, whereas a negative INMB would mean that no prophylaxis remains the optimal strategy as in the base case.

The 10 scenario analyses that had the greatest impact on the INMB are presented in *Figure 16*. (Full results for the deterministic scenario analyses are provided, see *Appendix 6*, *Table 41*.) It can be seen that the only one that resulted in Sultan (top 5%) having a positive INMB, and therefore an ICER under £30,000 per QALY, was when we assumed no cost for conducting the risk assessment. It should be noted that this also resulted in a positive INMB for Sultan (top 1%) but the INMB for Sultan (top 5%) was higher meaning that the latter would be the optimal strategy in this scenario. Other factors that appear to be important based on the deterministic scenario analyses were those related to PTS, patient characteristics, safety and efficacy of LMWH and finally the cost and utility impact of non-fatal non-ICH bleeding. The assumption regarding the duration of efficacy applied for 10 days of LMWH was fairly influential, but even assuming a full 6 weeks of efficacy, instead of the 3 weeks assumed in the base case, did not result in a positive INMB for Sultan (top 5%) compared to no prophylaxis.

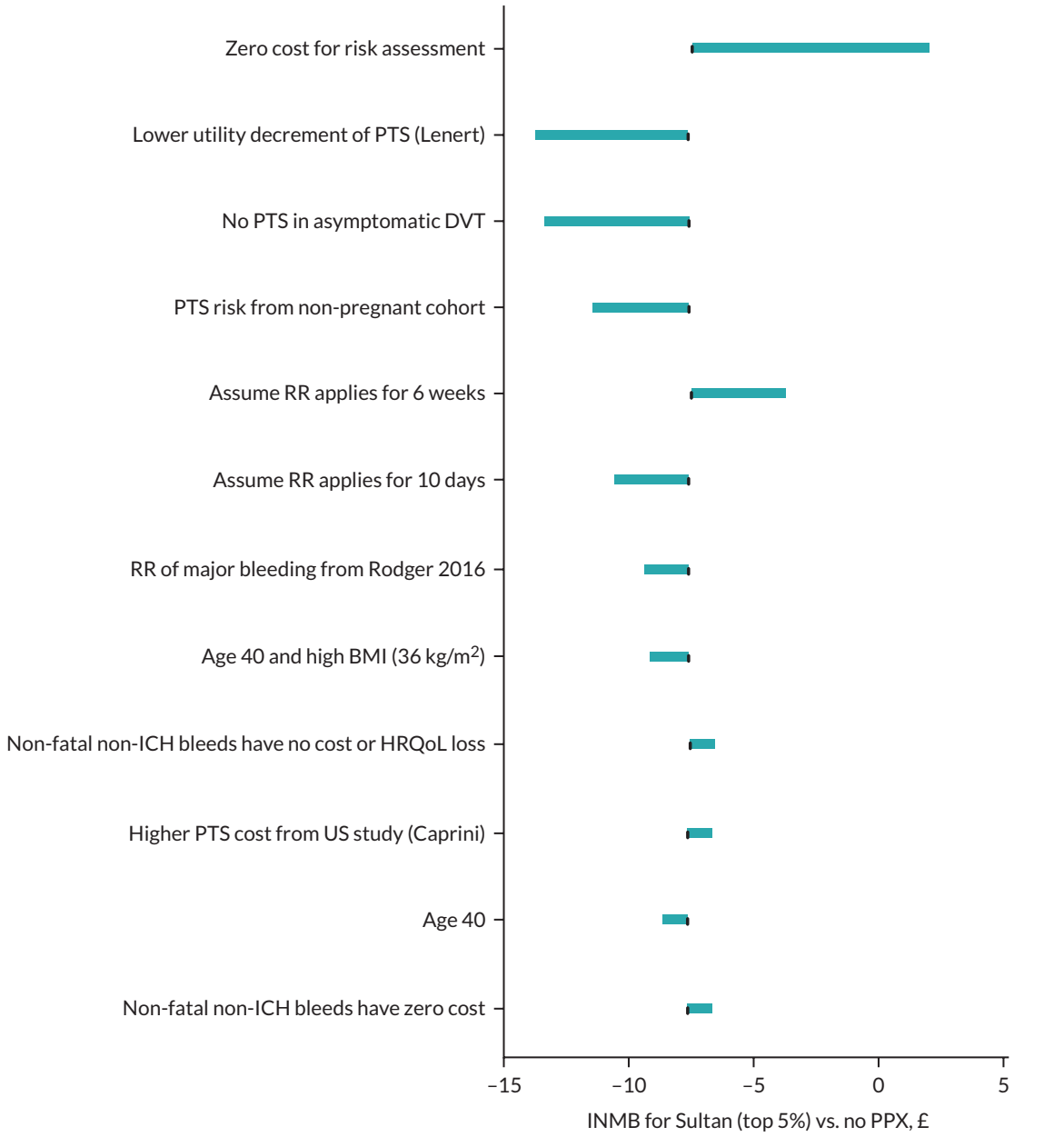

FIGURE 16 Deterministic scenario analysis for Sultan (top 5%) vs. no prophylaxis (no PPX) in unselected postpartum women. [References for figure: Sultan (top 5%),[11] Caprini,[102] Lenert,[107] Rodger.[19]]

A two-way scenario analysis was also conducted to determine how sensitive the conclusions are to the absolute risks of VTE and major bleeding. The results (see *Appendix 6*, *Table 36*) show that using a RAM to select patient for postpartum prophylaxis would be cost-effective (when valuing a QALY at £30,000) if the risks of VTE were higher than assumed in the base-case analysis. For example, an increase in VTE risk from 0.07% to 0.14% would mean that offering prophylaxis using the Sultan (top 5%) would be most cost-effective, but only if the risks of bleeding were 2–7%. Offering prophylaxis to a broader group, using Sultan (top 20%), would be optimal if the risks of VTE were 0.14% and the bleeding risks were under 2%. However, at the level of VTE risk assumed in the base-case scenario, the optimal strategy is not sensitive to the risks of major bleeding.

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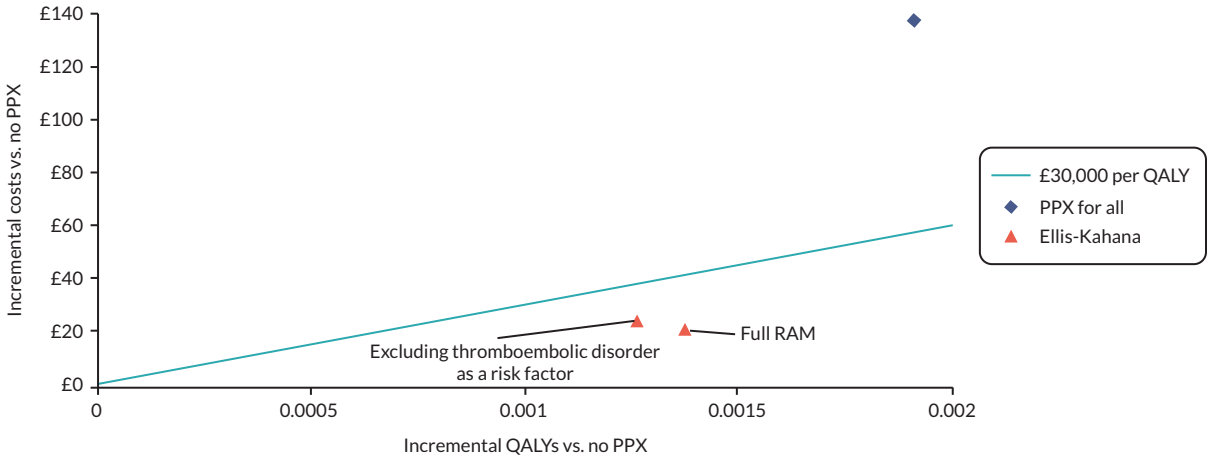

FIGURE 17 Deterministic base-case results for Ellis-Kahana RAM vs. no prophylaxis (no PPX) in obese postpartum women. (References for figure: Ellis-Kahan 2020.[41])

Obese postpartum women

Deterministic base-case analysis for obese postpartum women

Figure 17 shows the incremental costs and QALYs versus no prophylaxis (no PPX) for the subgroup of postpartum women with obesity as a specific risk factor. It can be seen that prophylaxis for all (PPX for all) would not be the optimal strategy in this population as the ICER is above £30,000 per QALY. In comparison, both versions of the RAM developed by Ellis-Kahana *et al*. have ICERs under £30,000 per QALY. The two RAMs presented by Ellis-Kahana differ in that one included thromboembolic disorder within the risk score (referred to as the full RAM) and the other excluded this specific risk factor.

Probabilistic base-case analysis for obese postpartum women

In the PSA, we have compared the Ellis-Kahana RAM (full RAM) with a strategy of no prophylaxis. Results based on mean costs and QALYs are summarised in *Table 10*. *Figure 18* shows the spread of incremental costs and QALYs on the cost-effectiveness plane for the Ellis-Kahana RAM (full RAM) compared to no prophylaxis. The mean QALY gain is negative (−0.0001), but there is a wide spread of incremental QALY estimates, with a 95% CI of −0.013 to 0.004. Therefore, although using the Ellis-Kahana RAM (full RAM) has an ICER under £30,000 versus no prophylaxis in the deterministic analysis, this strategy is dominated by no prophylaxis when using the mean outputs of the PSA as on average it has lower QALYs and higher costs (see *Table 10*). This is despite the fact that the ICER falls under £30,000 for 64% of the PSA samples. The CEAC for the alternative prophylaxis strategies in obese postpartum women is shown in *Figure 19*. This shows that the strategy of using the Ellis-Kahana RAM (full RAM) to determine postpartum prophylaxis in obese women has the highest probability (64%) of being the optimal strategy, when valuing a QALY at £30,000.

The overall EVPI for this population when comparing these three prophylaxis strategies is £22.35 per patient. This would mean an overall EVPI of £13.4 million over 5 years of births[117] when assuming that around 20% of pregnant women are obese.[118] The single most important individual parameter in the EVPPI analysis was the RR of VTE which had an EVPPI that was 99% of the overall EVPI, meaning that obtaining perfect information on this individual parameter would lead to an expected gain of £13.4 million over 5 years of births (see *Appendix 5*, *Table 31*). The EVPPI for both the RR of VTE and the RR of bleeding combined was similar (see *Appendix 5*, *Table 32*).

The broad spread of incremental QALY estimates appears to be driven by the uncertainty in the RR of VTE. In the population of obese postpartum women, there is a large EVPI associated with this parameter as the wide spread of incremental QALY gains, which is driven by uncertainty in the efficacy of LMWH

TABLE 10 Base-case results (mean from 10,000 PSA samples) in order of % receiving prophylaxis for obese postpartum women

	% PPX	Sensitivity (%)	Specificity (%)	Absolute costs, (£)	Absolute QALYs	Cost vs. no PPX, (£)	QALYs vs. no PPX	ICER vs. no PPX, (£)	ICER vs. next least effective strategy, (£)	INMB vs. no PPX at £20K, (£)[a]	INMB vs. no PPX at £30K, (£)[a]
No PPX	0	0	100	49.01	20.552	NA	NA	NA	NA	NA	NA
Ellis-Kahana (full RAM)	10	62	90	73.20	20.552	24.20	−0.0004	Dominated	Dominated	−33.17	−37.65
Ellis-Kahana (excluding thrombophilia)	12	58	88	76.44	20.552	27.43	−0.0004	Dominated	Dominated	−36.13	−40.48
PPX for all	100	100	0	190.62	20.551	141.61	−0.0010	Dominated	Dominated	−162.27	−172.59

NA, not applicable.
a INMB at £20K and INMB at £30K are the INMBs when valuing a QALY at £20,000 and £30,000 per QALY, respectively, and the maximum value shows you the optimal strategy.

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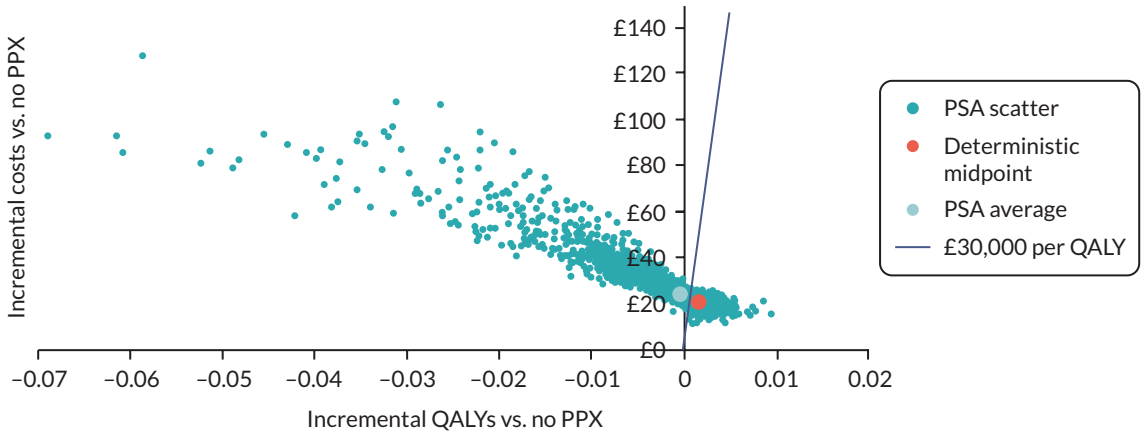

FIGURE 18 Probabilistic results for Ellis-Kahana RAM (full RAM including thromboembolic disorder) vs. no prophylaxis (no PPX) in obese postpartum women.

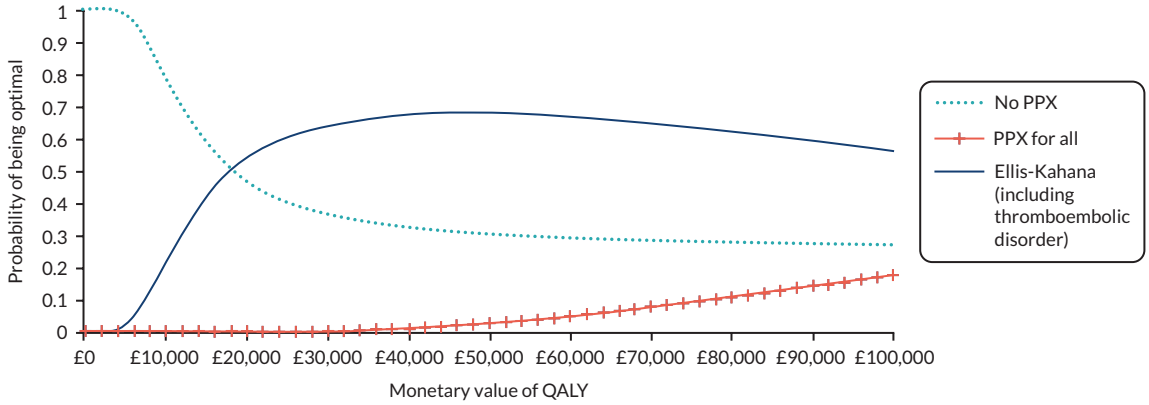

FIGURE 19 Cost-effectiveness acceptability curve for prophylaxis strategies in obese postpartum women. (References for figure: Ellis-Kahana.[41])

to prevent VTE, results in the optimal prophylaxis strategy (defined as having the maximum INMB when valuing a QALY at £30,000) being uncertain.

Deterministic scenario analysis for obese postpartum women

The deterministic scenario analyses were conducted to explore which model assumptions and inputs were key drivers of decision uncertainty. To do this, deterministic results were generated using midpoint parameter inputs when varying individual model inputs or assumptions. In the base-case deterministic analysis, the optimal strategy when valuing a QALY at £30,000, was using the Ellis-Kahana RAM (full RAM). Therefore, the sensitivity of the model results to the various alternative assumptions and data inputs are expressed using INMB for Ellis-Kahana RAM (full RAM) compared to no prophylaxis. A negative INMB would mean that the Ellis-Kahana RAM has an ICER of over £30,000 per QALY compared to a strategy of no prophylaxis in that scenario, whereas a positive INMB would mean that using the RAM remains optimal as in the base case.

It can be seen from *Figure 20* that the factors that have the largest impact on the INMB were related to PTS and the efficacy of 10 days of LMWH to prevent VTE over 6 weeks. However, only two of these scenarios result in a negative INMB and these were assuming a lower utility decrement for PTS and assuming no risk of PTS in asymptomatic DVT. Other factors that are moderately important are patient characteristics, the RR of major bleeding and cost and QALY implications of non-fatal, non-ICH bleeds,

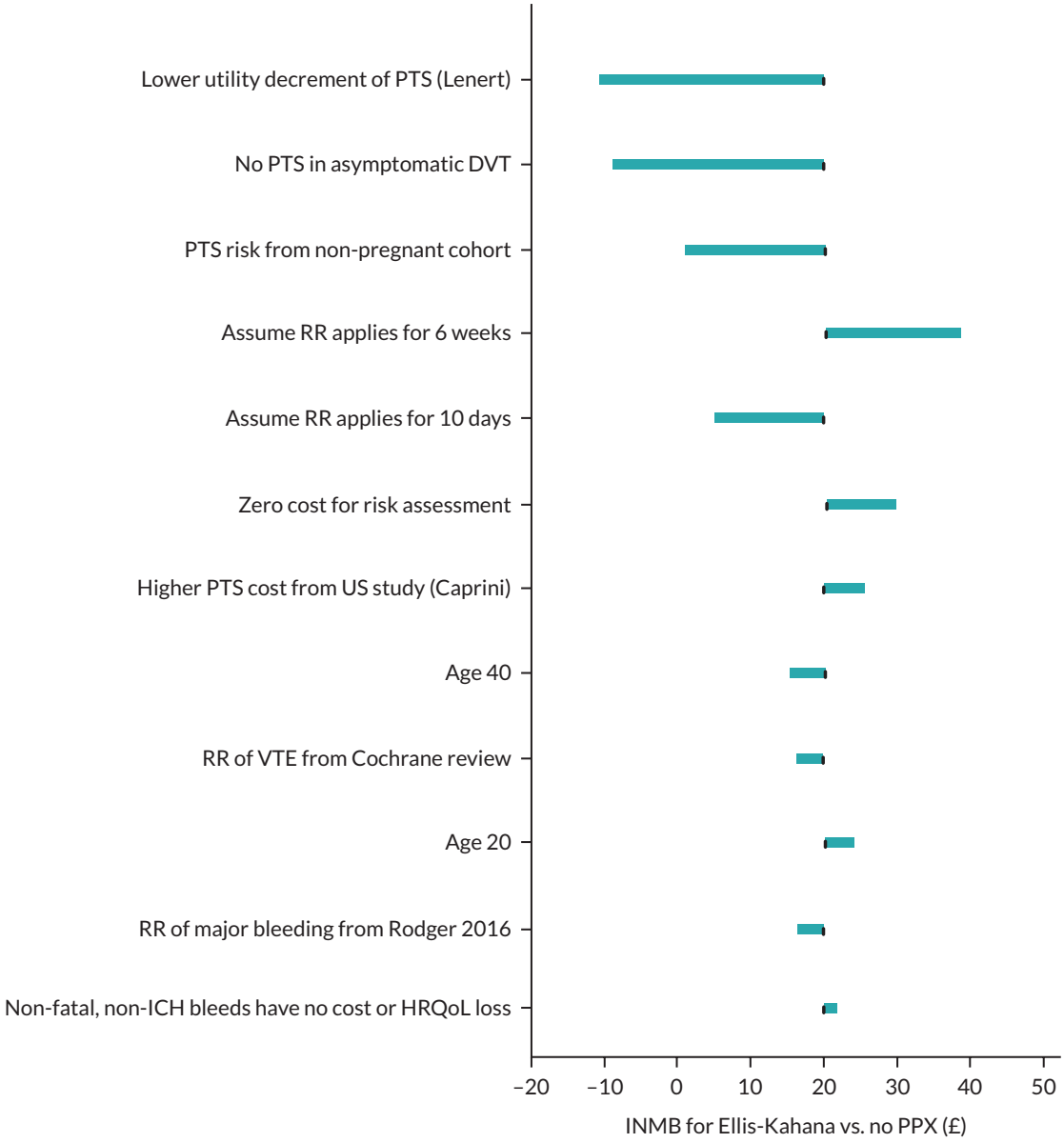

FIGURE 20 Deterministic scenario analyses for Ellis-Kahana (full RAM) vs. no prophylaxis (no PPX) in obese postpartum women. (References for figure: Cochrane review,[8] Caprini,[102] Ellis-Kahana,[41] Lenert,[107] Rodger.[19])

although the impact of these is smaller. Results for the deterministic scenario analyses are provided in full (see *Appendix 6*, *Table 42*).

The two-way scenario analysis (see *Appendix 6*, *Table 37*) demonstrates that the choice of optimal strategy is not particularly sensitive to the risk of major bleeding when the VTE risk is below 0.6%. However, a strategy of no PPX would be optimal if the VTE risk was 0.07%, similar to that in unselected postpartum women. This suggests that the difference in optimal strategy between this specific at-risk subgroup and the general postpartum population is the level of VTE risk.

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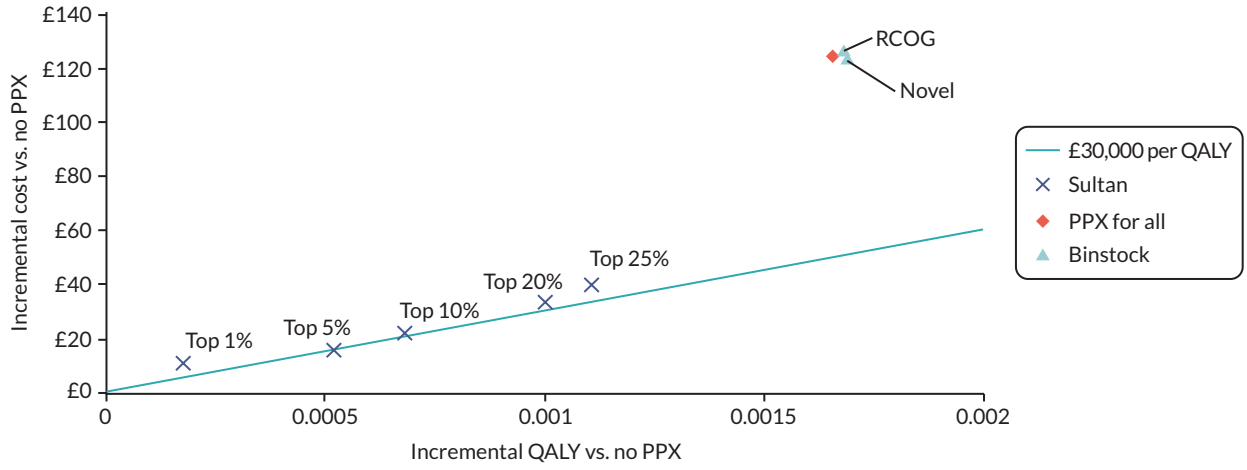

FIGURE 21 Deterministic base-case results for RCOG, novel RAM (Binstock *et al.*) and Sultan RAM compared to no prophylaxis (no PPX) in women following caesarean section (NB: Sultan RAM not validated in this specific group). (References for figure: Binstock,[28] Sultan.[11])

Postpartum women after caesarean section

Deterministic base-case results for postpartum women after caesarean section

It can be seen from *Figure 21* that neither the RCOG RAM nor the novel RAM reported by Binstock *et al.*[28] is cost-effective when used in postpartum women after caesarean section. This is because both these RAMs had poor specificity in the cohort reported by Binstock *et al.* and therefore result in over 90% of women being offered prophylaxis after caesarean section in the model. However, given that the risks of VTE are similar in the post-caesarean section group and the obese postpartum group, we considered it likely that a RAM with a better performance would be cost-effective in this subgroup. Therefore, we decided to include the Sultan RAM in the analysis for post-caesarean section women to explore whether a RAM with similar performance to the Sultan RAM would be cost-effective. The results should be interpreted with caution as the novel RAM reported by Sultan *et al.*[11] has been validated in a broad population of postpartum women and the sensitivity and specificity may be different in the specific subgroup of postpartum women with obesity. However, it can be seen that a RAM with performance similar to the Sultan RAM would need to select the 5% of patients with the highest risk of VTE for prophylaxis to have an ICER under £30,000.

Probabilistic base-case results for postpartum women after caesarean section

Based on the results of the deterministic analysis, we decided to include the Sultan RAM in the probabilistic analysis along with the RCOG and novel RAMs reported by Binstock *et al.*[28] This was to explore whether a RAM with performance similar to the Sultan RAM would be cost-effective in the post-caesarean section population. The mean outputs of the PSA are shown in *Table 11*, where it can be seen that no PPX dominates (i.e., has lower costs and higher QALYs than) all alternative strategies. This is due to the wide spread of incremental QALYs on the cost-effectiveness plane, which is shown in *Figure 22* for the Binstock novel RAM and for the Sultan RAM (top 5%). For the Binstock RAM, 41% of PSA samples resulted in a negative incremental QALY gain compared to no prophylaxis, whereas for the Sultan RAM (top 5%) this occurred in only 24% of PSA samples. The CEAC in *Figure 23* shows that no PPX had the highest probability of being optimal (57%) in the post-caesarean section population when valuing a QALY at £30,000.

The overall EVPI was £7.74 per patient, which is equivalent to £5.6 million over 5 years of births[117] taking into account that 24% of births are by elective or emergency caesarean section.[55] The parameter with the highest EVPPI was the RR of VTE, which has an EVPPI equivalent to 68% of the overall EVPPI (see *Appendix 5*, *Table 33*). This is equivalent to £3.8 million over 5 years of births. No other individual

TABLE 11 Base-case results (mean from 10,000 PSA samples) in order of % receiving prophylaxis for women following caesarean section

	% PPX	Sensitivity (%)	Specificity (%)	Absolute costs, (£)	Absolute QALYs	Cost vs. no PPX, (£)	QALYs vs. no PPX	ICER vs. no PPX, (£)	ICER vs. next least effective strategy, (£)	INMB vs. no PPX at £20K, (£)[a]	INMB vs. no PPX at £30K, (£)[a]
No PPX	0	0	100	47.29	20.5527	NA	NA	NA	NA	NA	NA
Sultan top 1%[b]	1	9	99	58.28	20.5527	10.99	−0.0000	Dominated	Dominated	−11.93	−12.40
Sultan top 5%[b]	5	27	95	63.59	20.5526	16.30	−0.0001	Dominated	Dominated	−19.06	−20.44
Sultan top 10%[b]	10	36	90	70.05	20.5525	22.75	−0.0002	Dominated	Dominated	−26.62	−28.55
Sultan top 20%[b]	20	53	80	82.95	20.5524	35.66	−0.0003	Dominated	Dominated	−41.72	−44.75
Sultan top 25%[b]	25	60	75	89.36	20.5524	42.07	−0.0003	Dominated	Dominated	−49.01	−52.48
Binstock novel	92	100	8	173.89	20.5522	126.60	−0.0005	Dominated	Dominated	−136.51	−141.46
RCOG	94	100	6	176.40	20.5522	129.11	−0.0005	Dominated	Dominated	−139.66	−144.94
PPX for all	100	100	0	175.21	20.5519	127.92	−0.0008	Dominated	Dominated	−143.40	−151.14

NA, not applicable.
a INMB at £20K and INMB at £30K are the INMBs when valuing a QALY at £20,000 and £30,000 per QALY, respectively, and the maximum value shows you the optimal strategy.
b Assuming the Sultan RAM performs similarly in the post-caesarean section population to how it did in the general postpartum population.[11]

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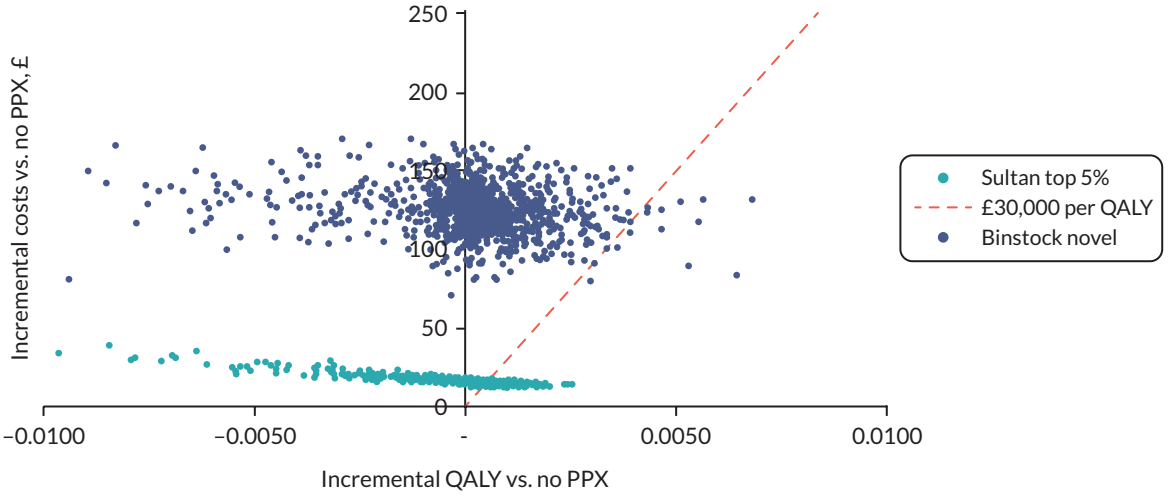

FIGURE 22 Probabilistic results for the Binstock novel RAM and the Sultan RAM (top 5%) compared to no prophylaxis (no PPX) in women following caesarean section. (References for figure: Binstock,[28] Sultan 2016.[11])

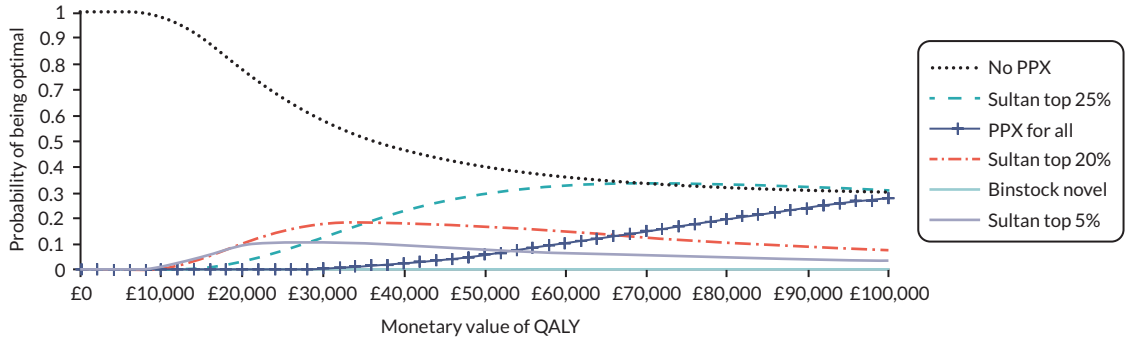

FIGURE 23 Cost-effectiveness acceptability curve for prophylaxis strategies in women following caesarean section. (References for figure: Binstock,[28] Sultan 2016.[11])

parameter had significant EVPPI (i.e. none >£1 per person). An analysis exploring the EVPPI for various groups of parameters is reported in full (see *Appendix 5*, *Table 34*). The EVPPI for both the RR of VTE and the RR of bleeding is estimated to be £5.47 per person or £4.0 million over 5 years of births. All other groups of parameters had an EVPPI that was much lower (≤£1 per person).

If the Sultan RAM is excluded from the analysis, the overall EVPI is lower at £2.06 per person, but none of the individual parameters have significant EVPPI (i.e. none >£1 per person). This is because the optimal strategy is less uncertain with no PPX having a 93% probability of being optimal (i.e. maximising INMB when valuing a QALY at £30,000) when compared to PPX for all and prophylaxis using either the novel Binstock RAM or the RCOG RAM.

In the population of postpartum women who have had a caesarean section, there is significant EVPPI associated with the RR of VTE but only when assuming that a RAM that performs similarly to the Sultan RAM is available. When assuming that only the RCOG or Binstock novel RAMs are available in the post-caesarean section population, the uncertainty regarding the optimal strategy (defined as having the maximum INMB when valuing a QALY at £30,000) is much lower and choice of optimal strategy is less sensitive to the uncertainty regarding the efficacy of LMWH in preventing VTE.

Deterministic scenario analyses for postpartum women after caesarean section

We decided to use the Sultan RAM (top 5%) to explore the sensitivity of the model to the various assumptions and data sources as this strategy was the only strategy with an ICER under £30,000 per QALY in the deterministic analysis. Therefore, in the scenario analyses, if the INMB becomes

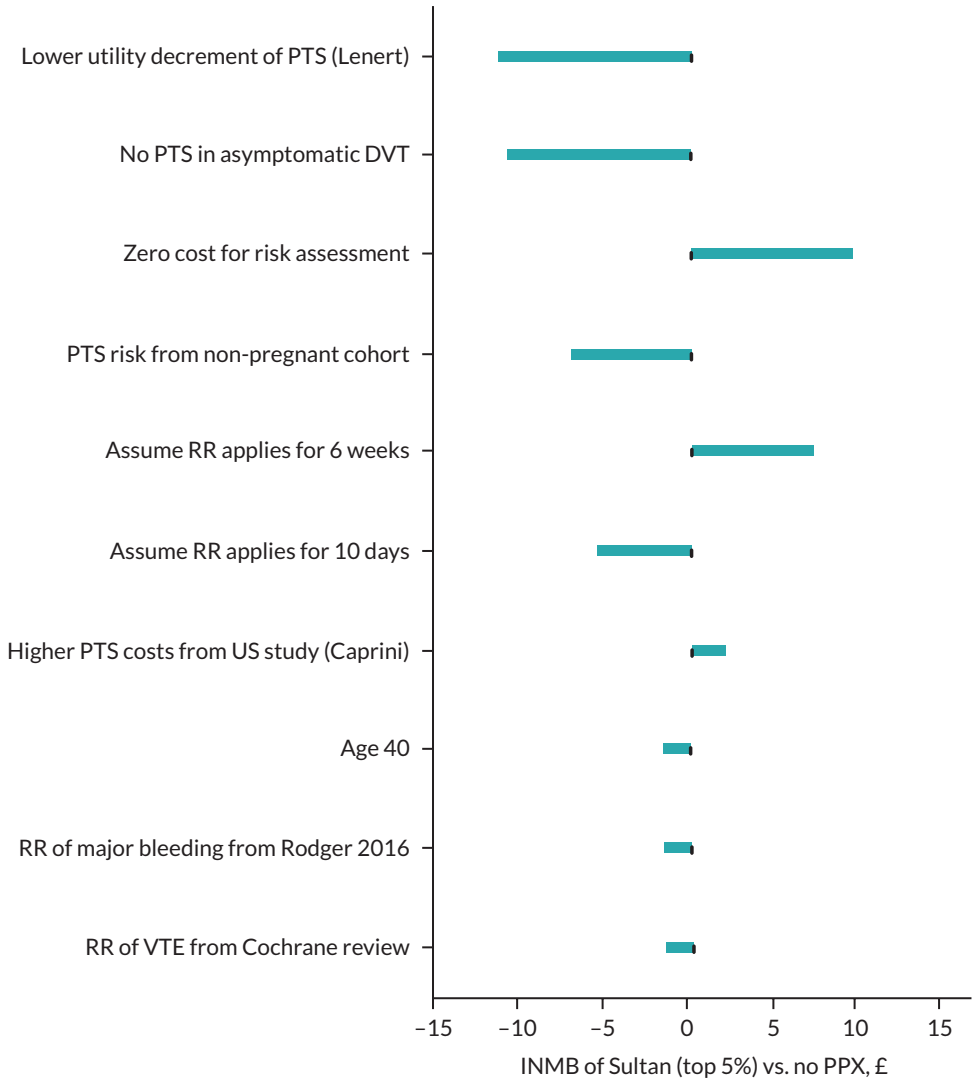

FIGURE 24 Deterministic scenario analyses for Sultan RAM (top 5%) vs. no prophylaxis (no PPX) in the post-caesarean section population (NB: Sultan RAM not validated in this specific subgroup). (References for figure: Cochrane review,[8] Caprini,[102] Lenert,[107] Rodger.[19])

negative, this means that the Sultan RAM (top 5%) has an ICER over £30,000 per QALY compared to no prophylaxis and the optimal strategy has changed to become no prophylaxis.

The optimal strategy is sensitive to many assumptions because the ICER for using the Sultan RAM (top 5%) compared to no prophylaxis is £29,281 per QALY meaning that factors that have a small impact on the costs and benefits have the potential to change the optimal strategy (see *Appendix 6*, *Table 43* for full deterministic scenario analysis results). However, it can be seen in *Figure 24* that factors related to PTS are again important drivers of the INMB with a lower utility decrement for PTS and a lower incidence of PTS resulting in no prophylaxis becoming the optimal strategy. The results are also particularly sensitive to the assumptions regarding whether the efficacy of LMWH is applied for 10 days or 6 weeks rather than the 3 weeks assumed in the base case.

We also conducted the deterministic scenario analyses for the Binstock Novel RAM compared to no prophylaxis, but none of the scenarios explored resulted in the Binstock novel RAM having an ICER under £30,000 per QALY. The same was true when we used the data from Binstock for the RCOG RAM in the post-caesarean section population.

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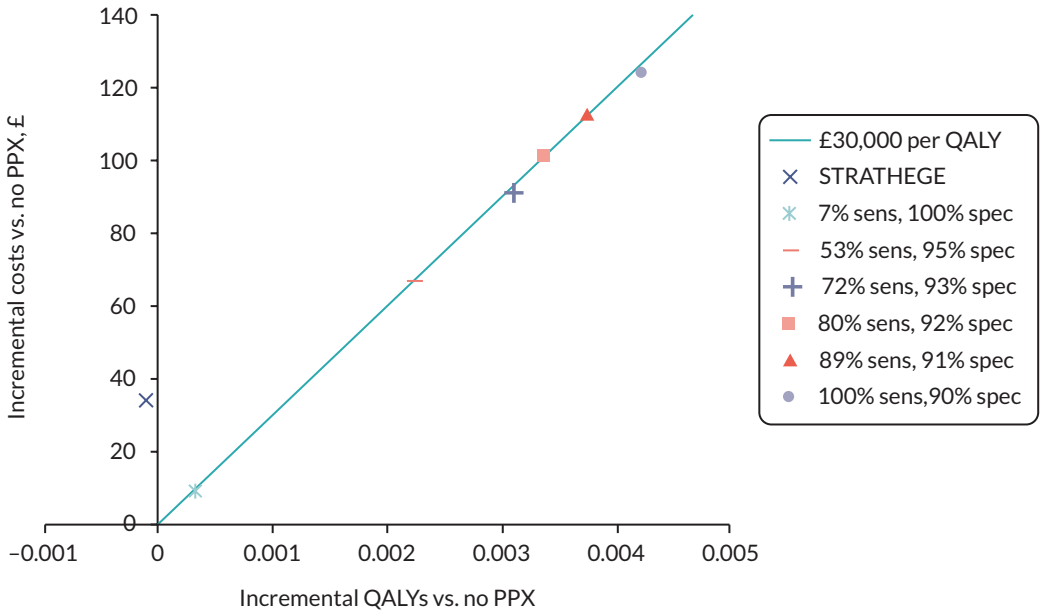

FIGURE 25 Deterministic results for using the STRATHEGE RAM or a theoretical RAM (shown for various combinations of sensitivity and specificity) compared to no prophylaxis (no PPX) in an unselected antepartum cohort. (References for figure: STATHEGE.[31])

The two-way scenario analysis (see *Appendix 6*, *Table 38*) demonstrates that the VTE risk would need to be much higher for the Binstock novel RAM to be more cost-effective (when valuing a QALY at £30,000), than using a RAM with performance similar to the Sultan RAM. In addition, the risk of VTE would need to be similar to that observed in the unselected postpartum population (0.07%) before no prophylaxis became the optimal strategy. Also, if the risk of VTE was above 0.5%, then the optimal strategy would depend on the risk of major bleeding. For example, prophylaxis for all would be optimal if the risk of bleeding was lower than assumed in the base case and prophylaxis using the Binstock RAM would be optimal if the bleeding risk was similar to that assumed in the base case.

Exploratory analyses for antepartum women

Exploratory deterministic analysis for unselected antepartum women

The deterministic results for the STRATHEGE RAM[31] are shown in *Figure 25* alongside various theoretical combinations of sensitivity and specificity. These theoretical combinations are provided to explore the trade-off between sensitivity and specificity that would be required for a RAM to achieve a cost per QALY under £30,000, when being used to determine antepartum prophylaxis in an unselected cohort. It can be seen from *Figure 25* that the poor sensitivity (0%) of the STRATHEGE RAM,[31] which results in 2% of women having antepartum prophylaxis, results in negative QALYs compared with no prophylaxis but at additional cost and it is therefore dominated by a strategy of offering no prophylaxis. From the theoretical combinations of sensitivity and specificity explored, it can be seen that a high degree of specificity would be required for a RAM used in this population, with a specificity of 90–95% being required for a RAM whose sensitivity is between 100% and 53%, respectively.

Exploratory deterministic analysis for antepartum women with three risk factors

Antepartum women with three risk factors are currently offered antepartum prophylaxis from 28 weeks gestation according to the RCOG guidance (provided none of the risk factors is prior VTE or another risk factor that warrants earlier prophylaxis).[7] Any woman offered antepartum prophylaxis within RCOG is then eligible for 6 weeks of postpartum prophylaxis. As we were unable to obtain an exact estimate for absolute VTE risk in the group with three antepartum risk factors (see *Model inputs for secondary scenarios where antepartum prophylaxis is offered at 28 weeks*), we have conducted an exploratory analysis to determine the optimal strategy in this group across differing levels of VTE and bleeding risk. The strategy

of prophylaxis from 28 weeks gestation (followed by postpartum prophylaxis for 6 weeks) is compared against a strategy of offering no prophylaxis at all and a strategy of offering no antepartum prophylaxis but assuming that all women will receive 6 weeks of postpartum prophylaxis. The results (see *Appendix 6*, *Table 39*) show that for the level of bleeding risk assumed in the base case (4.58%), an absolute risk of VTE of >0.5% would be required for 6 weeks of postpartum prophylaxis for all to be optimal. A more precise threshold analysis identified that 6 weeks of postpartum prophylaxis had an ICER under £30,000 compared to thromboprophylaxis for none only when the risk of VTE was >0.57%. We estimated in section *Model inputs for secondary scenarios where antepartum prophylaxis is offered at 28 weeks* that the upper limit of VTE risk in antepartum women with three risk factors (excluding a prior VTE) was likely to be around 0.6%. This exploratory analysis suggests that offering 6 weeks of postpartum prophylaxis to women with three antepartum risk factors would only be cost-effective if the absolute risk in this group is at the higher end of the expected range. In addition, offering antepartum prophylaxis from 28 weeks is unlikely to be cost-effective in this group. These findings only apply to women where none of the three risk factors are a prior VTE or another risk factor that currently qualifies the woman for prophylaxis from booking under the RCOG guideline as these women were excluded when calculating the absolute risks.

Summary of key findings

- In high-risk antepartum women, such as those with a prior VTE, prophylaxis with LMWH reduces the risk of both symptomatic VTE and a serious adverse outcome (fatal PE, fatal bleed, ICH). These benefits outweigh the increased risks of other major bleeding even when offering antepartum prophylaxis from booking to all.
- In high-risk antepartum women, there is considerable uncertainty regarding the most cost-effective prophylaxis strategy, and this is largely due to uncertainty in the effectiveness of LMWH for preventing VTE in this population (i.e. the RR of VTE).
- In unselected postpartum women, the risks of VTE are low and the benefits of preventing VTE are not clearly outweighed by the additional risks of major bleeding.
- In unselected postpartum women, none of the prophylaxis strategies compared were likely to be cost-effective compared to offering no prophylaxis, and the choice of optimal prophylaxis strategy is not particularly sensitive to any of the uncertainties in the parameter inputs.
- In the subgroup of obese postpartum women, the uncertainty regarding the optimal prophylaxis strategy is greater than in the unselected group, because the risks of VTE are slightly higher than in the unselected postpartum group and because the RAM developed for obese postpartum women (Ellis-Kahana) performs slightly better than the RAMs available for unselected postpartum women (Sultan, RCOG, SFOG).
- In the subgroup of obese postpartum women, the majority of the uncertainty regarding the most cost-effective prophylaxis strategy is related to the uncertainty in the RR of VTE for LMWH compared to no prophylaxis.
- In postpartum women who have had a caesarean section, the available RAMs with performance data in this population (RCOG and Binstock novel) have poor specificity and the most cost-effective strategy is likely to be prophylaxis for none when considering only those RAMs validated in women having caesarean section.
- If we assume that a RAM can be developed for women who have had caesarean section, which performs similarly to the Sultan RAM in the unselected postpartum population, then there would be significant uncertainty regarding the most cost-effective prophylaxis strategy in women following caesarean section and most of that uncertainty would relate to the RR of VTE.
- The deterministic scenario analyses suggest the impact of PTS on quality of life is fairly important in determining the optimal prophylaxis strategy for both antepartum and postpartum prophylaxis.
- The deterministic scenario analyses also suggest that assumptions regarding the risk of PTS in those with asymptomatic DVT, the cost of risk assessment and the duration of efficacy assumed for 10 days of LMWH are important in the postpartum population.
- For a RAM to be cost-effective for use in an unselected antepartum population, it would need to have high specificity (specificity of 90–95% for sensitivity of 100–53%).
- Offering antepartum prophylaxis from 28 weeks to women with three antepartum clinical risk factors (excluding prior VTE) as per current RCOG guidance is unlikely to be cost-effective.

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Chapter 6 Estimating the expected value of future research

Introduction

The aim of the EVSI analysis was to determine how much additional net monetary benefit could be achieved by further research to reduce uncertainty in those parameters that are associated with significant decision uncertainty, as identified in the EVPPI analysis (see *Chapter 4*). While the EVPPI analysis estimated the maximum net monetary benefit that could be achieved by having perfect information on a particular parameter or set of parameters, the EVSI analysis acknowledges that no future study could realistically obtain perfect information. It, therefore, estimates the maximum net monetary benefit that could be achieved by a study with a particular design and sample size, which is conducted with the intention of providing additional information to reduce the uncertainty in a particular set of parameters.

Methods

The EVPPI analysis (see *Chapter 4*) suggested that the majority of the decision uncertainty was related to uncertainty around the RR of VTE. Therefore, we decided to estimate the EVSI of obtaining sample information on the RR of VTE using a RCT design. As any RCT to determine the risk of VTE would also be likely to record major bleeding episodes as a safety outcome, we assumed that our RCT would update both the RR of VTE and the RR of major bleeding.

In the high-risk antepartum population, we acknowledge that a RCT of LMWH compared to no LMWH was not considered likely to be acceptable or feasible based on the findings of the qualitative research. However, given the high degree of uncertainty in the RR of VTE, and the high EVPPI associated with this parameter, we have decided to estimate the EVSI for a RCT of LMWH versus no LMWH in order to quantify the opportunity cost of not conducting a RCT in this group.

As there was minimal EVPPI in the unselected postpartum population, we decided to focus our EVSI on the subgroups of postpartum women selected according to risk factors (obesity and caesarean section delivery) where the EVPPI was higher. However, for the post-caesarean section population, it should be noted that the calculations assume that a RAM is available in the post-caesarean section population that performs similarly to the Sultan RAM in the unselected population. This is because there was minimal EVPI for individual parameters when considering only the RAMs validated in a post-caesarean section population (RCOG/Binstock).

The EVSI was calculated using the regression-based approach described by Strong *et al.*[122] This approach was implemented using the online SAVI tool.[116,122] In this method, for each set of parameter samples used in the PSA, it is necessary to simulate the summary statistics we would expect in a future trial.[122] In this case, we used a binominal distribution to sample the expected number of patients having VTE in each arm conditional on the sampled absolute risk in patients having no LMWH and conditional on the sampled RR of VTE for LMWH compared to no LMWH. The proportion of patients having events in each arm was then used to estimate the RR for a trial with those VTE outcomes. A similar approach was used for the risk of major bleeding but conditional on the absolute risk of major bleeding for those having LMWH and the RR of major bleeding for LMWH compared to no LMWH. Due to the similarity between the EVPPI calculation and the EVSI calculation, the SAVI tool can be used to provide an estimate of the EVSI, by including these sampled estimates of the RRs expected from future trials as

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two additional sets of parameters, and then using the SAVI tool to calculate the EVPPI for these two additional parameters.[116] This process was repeated for trials of different sizes.

To provide some context as to whether the research benefits are likely to outweigh the research, an informal review of National Institute for Health and Care Research (NIHR)-funded projects was conducted to identify clinical trials of pharmacological interventions in women who are pregnant or who have recently given birth (see *Appendix 9*). Twenty relevant studies were identified with numbers recruited ranging from 200 to 11,020. The median cost was £1.4 million with an interquartile range (IQR) of £1.1–2.0 million.

Results

Antepartum women with a prior venous thromboembolism

The overall EVPI was £1454 per patient in high-risk antepartum women, and this is therefore the most EVSI per patient that can be obtained from any study design. *Figure 26* presents the EVSI per patient for a RCT of LMWH versus no LMWH, which updates both the RR of VTE and the RR of major bleeding for various trial sizes [assuming the same number of participants (*N*) per arm]. It can be seen that the EVSI increases as the size of the proposed trial increases but with diminishing returns rising from £874 per patient for a trial with 30 patients per arm to £1318 per patient for a trial with 500 patients per arm. The population-level EVSI over 5 years of births is estimated to be £13.1 million for a RCT with 30 patients per arm, rising to £19.7 million for a trial with 500 patients per arm.

It should be noted that from a frequentist hypothesis test-based perspective, to detect a difference of 3.83% in VTE risk, with 80% power and a two-sided significance level of 5%, a RCT would need to recruit 616 patients per arm. (This calculation assumes both arms are given postpartum LMWH and uses the incidences of VTE predicted by the economic model; 4.14% for antepartum LMWH from booking followed by postpartum LMWH, 7.94% for no antepartum prophylaxis followed by postpartum LMWH.)

Obese postpartum women

In the obese postpartum subgroup, the patient EVPI was £22.35. The results of the EVSI analysis are summarised in *Figure 27*. The EVSI analysis found that a RCT which updated the RR of VTE and the RR

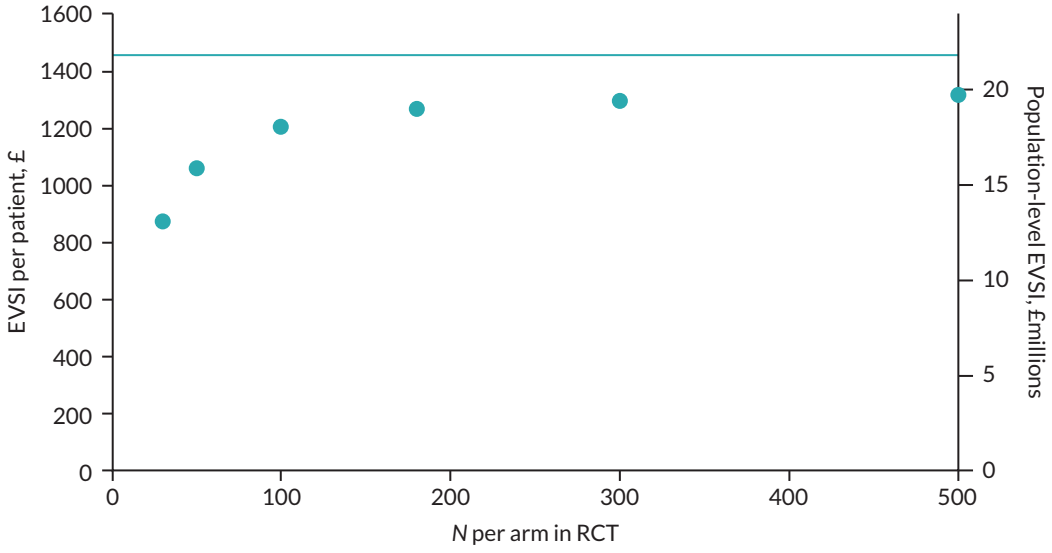

FIGURE 26 Patient-level and population-level EVSI for a RCT of LMWH vs. no prophylaxis in high-risk antepartum women.

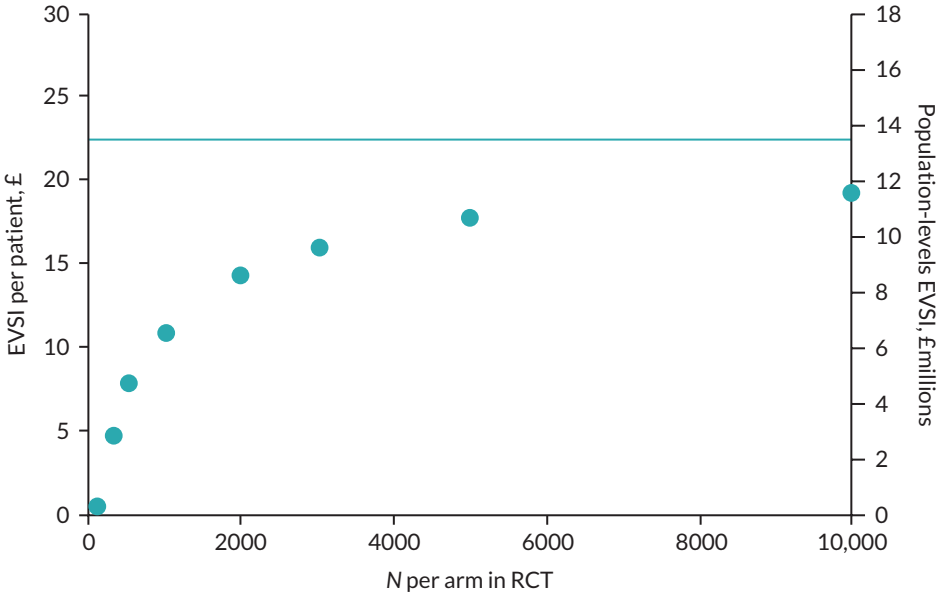

FIGURE 27 Patient-level and population-level EVSI for a RCT of LMWH vs. no prophylaxis in obese postpartum women.

of major bleeding would result in EVSI of £4.73 per patient for 300 patients per arm, rising to £19.33 per patient for a RCT with 10,000 patients per arm. This corresponds with a population-level EVSI of £2.8 million over 5 years of births for a RCT of 300 patients per arm, rising to £11.6 million over 5 years of births for a RCT of 10,000 patients per arm.

It should be noted that from a frequentist hypothesis test-based perspective, to detect a difference in VTE risk of 0.07%, with 80% power and a two-sided significance level of 5%, a RCT would need to recruit 36,798 patients per arm. (NB: This calculation uses the incidences of VTE predicted by the economic model; 0.08% for postpartum LMWH, 0.15% for no prophylaxis.)

Postpartum women following caesarean section

The EVSI analysis in postpartum women following caesarean section assumes that a RAM with similar performance to the Sultan RAM is available for women following caesarean section. This is because there was minimal EVPPI associated with the decision regarding the optimal prophylaxis strategy when assuming that the only RAMs available were the ones validated in cohorts of women who have had a caesarean section (i.e. the RCOG RAM and novel Binstock RAM). These findings should therefore be considered to be exploratory.

It can be seen from *Figure 28* that the EVSI rises sharply from £0.62 per patient for a trial with 1000 patients per arm, to £2.20 per patient for a RCT of 3000 patients per arm. However, it only reaches 49% of the overall EVPI, even when the *N* per arm is increased to 10,000 patients. The population EVSI over 5 years of births is £1.1 million for a RCT of 2000 patients per arm, rising to £2.2 million for a RCT of 5000 patients per arm.

It should be noted that from a frequentist hypothesis test-based perspective, to detect a difference of 0.08% in VTE risk, with 80% power and a two-sided significance level of 5%, a RCT would need to recruit 24,502 patients per arm when comparing LMWH with no prophylaxis in postpartum women following caesarean section. (NB: This calculation uses the incidences of VTE predicted by the economic model; 0.06% for postpartum LMWH, 0.14% for no prophylaxis.)

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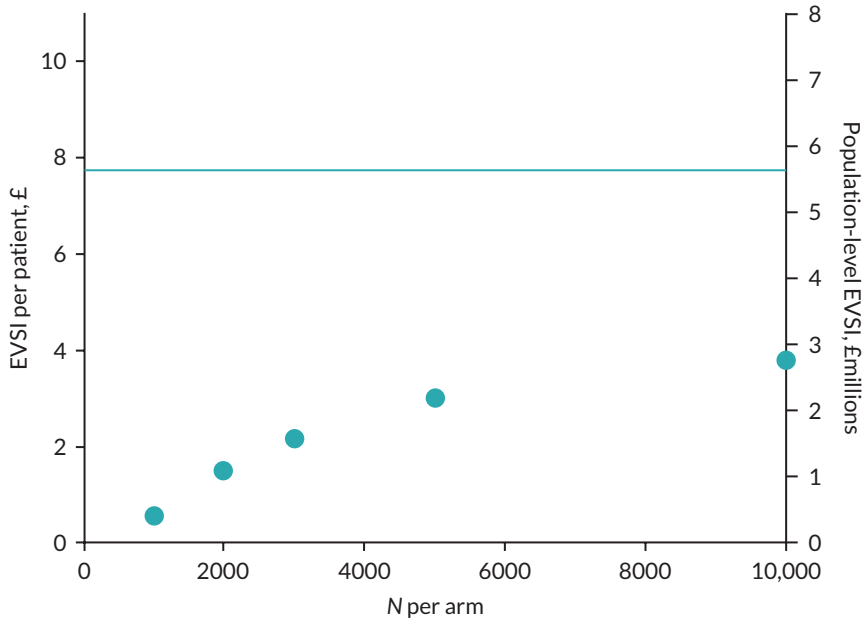

FIGURE 28 Patient-level and population-level EVSI for a RCT of LMWH vs. no prophylaxis in women recruited following caesarean section.

Summary of key findings

- The per patient EVSI is high in high-risk antepartum women leading to a high population-level EVSI despite the fact that only 0.5% of births occur in women with a history of prior VTE.
- A small RCT of only 30 high-risk antepartum women per arm would be sufficient to generate a substantial population-level EVSI of £13.1 million.
- In the obese postpartum population, the per patient EVSI is much lower but a RCT of 300 patients per arm would generate a population-level EVSI of £2.8 million over 5 years of births as around 128,000 pregnancies per annum are in people with high BMI (> 30 kg/m^2).
- In the post-caesarean section population, a larger RCT of 5000 patients per arm would be required to generate a population-level EVSI of £2.2 million over 5 years of births, but this level of EVSI would only be achieved if a RAM was available for the post-caesarean section population which performed similarly to how the Sultan RAM performed in unselected postpartum women.
- Trials designs comparing LMWH with no prophylaxis which are underpowered from a frequentist hypothesis-testing perspective, would still have substantial value compared to the typical cost of trials in these populations which is £1.1–2.0 million.

Chapter 7 Discussion

Statement of principal findings

Systematic review of risk assessment models

The systematic review identified 19 externally validated RAMs (and one internally validated risk model) that aimed to predict the risk of VTE in pregnant and postpartum women and who could be selected for thromboprophylaxis. Although various risk models (based on a variety of predictor variables) are being used, most of these lacked rigorous development and evaluation. The predictive accuracy of the RAMs was highly variable, and the substantial risk of bias concerns and the general lack of methodological clarity and unclear applicability make meaningful comparisons of the evidence difficult.

Cost-effectiveness and value of perfect information

In high-risk antepartum women, such as those with a prior VTE or thrombophilia, there is considerable uncertainty regarding the cost effectiveness of using RAMs to select women for antepartum prophylaxis, with none of the strategies having more than a 36% probability of being optimal (when valuing a QALY at £30,000). The overall EVPI is £1454 per patient with 94% of this attributable to the uncertainty in the RR of VTE for LMWH compared to no prophylaxis. This conclusion was fairly robust in the sensitivity and scenario analyses, although the optimal strategy varied when assuming a lower utility loss attributable to PTS and when assuming that the average patient has a BMI of 36 kg/m^2 instead of 27 kg/m^2.

In unselected postpartum women, the combination of poor RAM performance and low absolute risks of VTE meant that a strategy of offering no prophylaxis had a high probability (89%) of being optimal (when valuing a QALY at £30,000) compared to RAM-based prophylaxis strategies. This conclusion was fairly robust in the sensitivity and scenario analyses, although using the Sultan RAM to offer prophylaxis to 5% of patients with the highest VTE risk would be optimal if the risk of VTE was double that assumed in the base case or if the RAM could be administered for zero cost.

In the subgroup of obese postpartum women, the uncertainty regarding the optimal prophylaxis strategy is greater than in the unselected group, because the risks of VTE are slightly higher than in the unselected postpartum group and because the RAM developed for obese postpartum women (Ellis-Kahana) performs slightly better than the RAMs available for unselected postpartum women (Sultan, RCOG, SFOG). Using the Ellis-Kahana RAM to select obese postpartum women for prophylaxis has a 64% probability of being the optimal strategy, when valuing a QALY at £30,000. The EVPI is £22.35 per patient, with 99% of this attributable to uncertainty regarding the RR of VTE for LMWH compared to no prophylaxis.

In postpartum women who have had a caesarean section, the available RAMs with performance data in this population (RCOG and Binstock novel) have poor specificity, and a strategy of no prophylaxis has a high probability of being optimal (93%) when considering only those RAMs validated in women having caesarean section (and when valuing a QALY at £30,000). However, if we assume that a RAM can be developed for women who have had a caesarean section, which performs similarly to the Sultan RAM in the unselected postpartum population, then the probability of no prophylaxis being optimal would reduce to 57%. In this scenario, the EVPI would be £7.74 per patient, with 68% of that related to the RR of VTE.

The exploratory analyses suggest that for a RAM to be cost-effective for use in an unselected antepartum population, it would need to have high specificity (90–95% for sensitivity of 100–53%). In addition, offering antepartum prophylaxis from 28 weeks to women with three antepartum clinical risk factors (excluding prior VTE) as per current RCOG guidance is unlikely to be cost-effective.

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Workshops

The workshops indicated that a study randomising women to LMWH or placebo would be less acceptable to women who have had a prior VTE or thrombophilia than for other groups of women. Workshop participants reported receiving limited information about VTE or risks and benefits of thromboprophylaxis during pregnancy and the puerperium and those without prior VTE often did not understand why they had received treatment. However, women with experience of a prior VTE felt that it would not be ethical to randomise women to placebo given the perceived risk of VTE and the perceived effectiveness of LMWH in this group. The workshop participants generally favoured using a cluster randomisation approach over individual randomisation, to allocate women to LMWH or no LMWH in future trials, as they perceived that providing consistency in care across a hospital would have benefits, although some expressed concerns that cluster randomisation may lead to differences in care in different geographic locations.

Survey

Healthcare professionals surveyed most commonly reported using the RCOG guidelines to support decision-making and reported lower clinical equipoise for women with prior VTE, thrombophilia, or BMI > 40 kg/m^2. Healthcare professionals who would be responsible for recruiting women into the study felt that randomisation to a RCT of LMWH or placebo would be less acceptable to women who have had prior VTE or thrombophilia than for other groups of women. The survey also suggests that healthcare professionals have greater clinical equipoise for a study determining the effectiveness of thromboprophylaxis in antepartum women with three clinical risk factors (other than prior VTE or thrombophilia) who are currently eligible for prophylaxis from 28 weeks. The survey results also suggest that in postpartum women there is greater clinical equipoise in women whose risk factors are an elective caesarean section combined with either age over 35 years or obesity, and women whose only clinical risk factors are age and a BMI between 30 and 40 kg/m^2. The majority of healthcare professionals surveyed felt that, in a future trial of LMWH compared to placebo in women who are pregnant or who have recently given birth, it would only be acceptable to allocate treatment at an individual level, as opposed to using cluster randomisation at the hospital or NHS trust level.

Expected value of future research

The EVSI analysis found that a RCT of 30 patients per arm comparing LMWH with no prophylaxis would have a value of £13.1 million over 5 years of births, rising to £19.7 million for a RCT of 500 patients per arm. This suggests that further research would have substantial benefits relative to the typical costs for an NIHR-funded RCT in this population which are estimated to be £1.1–2.0 million. The EVSI analysis found that a RCT of LMWH versus no prophylaxis in obese postpartum women would have a value of £2.8 million, over 5 years of births, if it enrolled 300 patients per arm, rising to £11.6 million if enrolling 10,000 patients per arm. In the post-caesarean section group, a RCT of 2000 patients per arm would be needed to generate an EVSI of £1.1 million over 5 years of births, when assuming that a RAM which performs similarly to the Sultan RAM is available. Trials designs which are underpowered from a frequentist hypothesis-testing perspective would still have substantial value compared to the typical cost of trials in these populations, which is £1.1–2.0 million, assuming that decision-makers are willing to use the estimates of efficacy obtained, to make better informed decisions about prophylaxis in this population, without requiring them to meet a formal hypothesis test.

Strengths and limitations

Systematic review of risk assessment models

Our systematic review work has a number of strengths. This is the first systematic review to evaluate RAMs for predicting the risk of developing VTE in women during pregnancy and in the puerperium period. It was conducted with robust methodology in accordance with the PRISMA statement[20] and the protocol was registered with the PROSPERO register. Clinical experts, in addition to the core review

team, were involved and consulted throughout as advisors and to assess the validity and applicability of research findings during the review processes.

The main limitations of this study related to the observational nature of the studies reviewed and their own limitations. Most of the included risk prediction studies were retrospective cohorts. Retrospective cohort studies of large health database registries are limited by poor data quality and failure to accurately ascertain outcomes and case-control designs are prone to bias including uncontrolled confounding, temporal and selection bias.[123] Conversely, better-quality data may be obtained with prospective cohorts, but smaller sample sizes will lack statistical power. In addition, most of the external validation studies evaluated predictive performance of risk models that were not statistically derived (i.e. without model development and internal validation). This process is vital, as risk models with only external validation may be subject to overfitting and optimism.[42] Similarly, the absence of model performance measures such as calibration or discrimination hinders the full appraisal of models.[43]

Due to the high levels of heterogeneity between studies, we were unable to undertake any meta-analysis or statistical examination of the causes of heterogeneity due to the small number of external validation studies per risk model. Potential sources of heterogeneity include variation in study design, the study population, risk model implementation, outcome definition and measurement and the use of thromboprophylaxis. As a result, we reported descriptive statistics to provide a better understanding of the evidence base applicable to the subject matter, and shortcomings regarding reliability and validity of the data. Finally, assessments on study relevance, information gathering and validity of articles were unblinded and could potentially have been influenced by pre-formed opinions. However, masking is resource-intensive with uncertain benefits in protecting against bias decisions.[124]

Cost-effectiveness and value of perfect information

A strength of the decision-analytic modelling is that we have been able bring together the available evidence to explore whether prophylaxis is cost-effective in different groups of women at differing levels of VTE risk and to identify which factors are associated with significant decision uncertainty when trying to determine the optimal prophylaxis strategy. This is important because much of the current guidance on prophylaxis in women who are pregnant or who have recently given birth is based on expert consensus that the effectiveness would be similar to that seen in other populations: medical and surgical patients who are not pregnant or in the puerperium. This is because there is minimal RCT evidence to quantify the safety and efficacy of LMWH in women who are pregnant or who have recently given birth. Assuming that the effectiveness of thromboprophylaxis is similar in pregnant and non-pregnant populations did not seem clinically reasonable given the pro-thrombotic physiological changes during pregnancy. Therefore, rather than relying on the assumption that efficacy is equivalent to that seen in other populations, we have instead been able to explore the decision uncertainty associated with having broad CIs around the estimates of treatment efficacy. This led to the conclusion that there would be substantial net benefits (cost savings or QALY gains) from having better information on the efficacy of LMWH in pregnant women and women who have recently given birth.

The main limitations in the analysis relate to areas where data were lacking entirely. For example, we were unable to assess the cost effectiveness of using the RCOG RAM in an unselected antepartum population due to an absence of studies reporting both sensitivity and specificity for RCOG in this population. In addition, for some parameters, we had to rely on data that had been estimated in non-pregnant populations. In many cases, such as the risk of fatal bleeding during VTE treatment and the costs of major bleeding, these factors were not found to be significant drivers of decision uncertainty in the scenario analyses. However, for some parameters, the optimal prophylaxis strategy was different when plausible alternatives were explored, such as when assuming that PTS is associated with a 2% decrement in utility instead of a 10% decrement in utility. Another limitation is that we used a cohort-level modelling approach which assumes that everyone in the model has average characteristics. We found that this may have affected the choice of optimal strategy but only in the high-risk antepartum

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population where it adds to the decision uncertainty between offering antepartum prophylaxis using EThIG and offering only postpartum prophylaxis. In addition, the results for the Lyon RAM should be interpreted with some caution as we have assumed in the base case that patients identified as requiring antepartum prophylaxis using the Lyon score will have prophylaxis from booking, whereas, in fact, some will have prophylaxis delayed until 28 weeks gestation if their Lyon score is between 3 and 6. This is likely to have overestimated the cost effectiveness of using the Lyon score, as delaying prophylaxis until 28 weeks reduces the incremental QALYs more than it reduces the incremental costs.

The EVPI and EVSI analyses use a regression-based approach with a generalised additive model (GAM) and therefore examination of the residuals is useful for assessing the robustness of the regression assumptions. While checking the regression assumptions, we noted that there was some heteroskedasticity in the plot of residuals against fitted values, but no structure (e.g. a U-shaped or S-shaped pattern) which would suggest any bias in the fitted values. In addition, the normal Q–Q plot had tails showing deviation from the assumption of normality at extreme values. As the calculation of EVPI/EVSI using the GAM regression approach only requires an estimate of the posterior mean net benefits, the calculation of the EVPI/EVSI is not biased by unequal variance of errors.[122] However, the estimation of the standard error of the EVPI/EVSI does rely on the net benefits having approximately equal variance and approximate normality.[122] Therefore, the standard errors for the EVPPI estimates provided in *Appendix 5* should be treated with caution.

Furthermore, although the EVPI and EVSI analyses capture the CIs around various parameters that inform the model, these CIs mainly reflect uncertainty related to the sample size in the study and they may not adequately capture uncertainty related to study quality. Where possible, we have used sensitivity analyses to explore the uncertainties in the evidence base and any assumptions made in the model due to a lack of evidence. We have also highlighted where the conclusions rely on evidence from studies where there are quality issues, such the lack of an external validation study for the Ellis-Kahana RAM.

Workshops

Workshops were designed to understand potential perspectives of future trial engagement and were not intended as consensus events or to provide in-depth qualitative analysis of patient experience. However, they did highlight aspects of the patient experience that had potentially hitherto been underestimated and that would likely have an impact on future trial recruitment and retention.

Many of our findings were reflected in wider studies exploring the patient perspective of randomisation to clinical trials during pregnancy. We identified that women appear to have a high level of trust in treatment decisions made on their behalf during pregnancy and the puerperium and were involved in limited discussions of risks and benefits of treatment. Smyth *et al*. reported that high levels of trust in clinicians made pregnant women more likely to take part in trials, which suggests that clinicians may have a key role in information provision and influencing decisions about whether to take part in trials.[125]

Questions about pregnant women's decisional capacities have been highlighted in previous studies.[126,127] Women in our study reported concerns about their ability to make informed choices immediately after birth, but not during pregnancy and were strongly in favour of antepartum recruitment to non-emergency trials. Smyth *et al*. found that women reported recruitment to clinical trials to be better earlier in pregnancy, although some expressed concerns that being aware of potential complications in pregnancy may create anxiety.[125]

We reported that participants saw RCTs as an opportunity to access improved care and information, as well as improving care for others and emphasised the need to protect their baby in treatment decisions. In a review of factors influencing recruitment to maternal and perinatal trials, Tooher *et al*. identified that women will prioritise their responsibility to the unborn child over their own health or altruistic reasons for participation.[128] van der Zande *et al*. similarly reported that pregnant women would be more likely

to participate in research if they perceived there to be 'collateral benefits' such as access to additional services and enhanced maternity care.[119] They similarly identified that barriers to research included discomfort due to tests such as needle pricks, which reflects the findings from our study that suggested that the impact of injections may affect recruitment or retention to a trial.

Although we tried to include a range of participants, particularly those who had different educational backgrounds, our sample was disproportionately highly educated. Participants were, by definition, interested in taking part in research and so may not offer a view about participation in research that was representative of the general population. Respondents for the high-risk workshop were principally identified via an advert circulated via Thrombosis UK and could therefore be considered to be a selected group of patients with a higher level of health literacy and engagement.

Similarly, due to non-dominant ethnic groups being under-represented in health studies and due to the clear ethnic disparities in maternity outcomes,[1,129] we were keen to include women from different ethnic backgrounds. We selected diverse organisations with access to a range of under-represented populations to help with the recruitment, as well as specifying that we wanted to speak to people from ethnic minority groups in some of our recruitment materials. However, none of the respondents who provided demographic details identified themselves as black or mixed/multiple ethnic groups and only two participants were Asian/Asian British with the rest being white/Caucasian. We offered payment at a rate of double minimum wage, which has been suggested as a potential enabler to encouraging diversity of engagement.[129,130] However, our approaches were entirely impersonal (partly due to the COVID-19 pandemic) and materials were not made available in other languages, with workshops conducted in English, which have been highlighted as potential barriers to successful recruitment for minority ethnic groups.[130] Given that communication of risk and paucity of information was highlighted as a significant issue in understanding clinical equipoise and potential future trial involvement by the mainly white/Caucasian research participants, it is likely that these perceptions would be amplified in a more diverse population.[129,130]

Survey

We were unable to calculate a survey response rate for the online survey due to the lack of denominator; survey respondents were recruited via professional organisations' research networks and social media pages. The survey response rate was low and should not be used to indicate sample size for potential future trials (i.e. results may not be representative of the broader clinical population). However, although survey response numbers overall were low, they provided an indication of clinician perspectives on the evidence base for thromboprophylaxis in pregnancy and thereby likely support for recruitment to future RCTs in this population.

We did not try to understand clinicians' views of recruitment to clinical trials in depth, but to understand which patient groups they would be most likely to be willing to recruit. Our findings suggested that clinicians would be risk averse in recruiting groups of women who may currently be considered high risk according to existing guidelines. Other recent studies have reported that clinicians are protective advocates for pregnant women and play a strong gatekeeping role in recruitment to clinical trials.[126,127] Hanrahan *et al.* identified that clinicians were uncomfortable recruiting for trials that 'moved them away established clinical practice'[127] and that intervention needs to align with their professional opinion,[131] suggesting that clinicians are unlikely to recruit without altering their perceptions of clinical equipoise. Similarly, Tooher *et al.* identified that doctors with strong preference for one or other of the trial options are less likely to recruit to clinical trials.[128]

Expected value of future research

The EVSI analysis suggests that substantial net benefits (cost savings or QALY gains) could be generated by conducting further research and using this to make better decisions on when to offer prophylaxis to women who are at risk of VTE during pregnancy or in the puerperium. Overall, the EVSI analysis is supportive of further research to estimate the RR of VTE for LMWH compared to no LMWH.

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However, this information should not be acted on in isolation, but must also take into account the acceptability and feasibility of randomising women to receive no LMWH, particularly in the high-risk antepartum population.

The EVSI analysis in the post-caesarean section population should be interpreted with caution because the analysis assumes that a RAM is available that performs better than the available RAMs with performance data in this population (RCOG/novel Binstock). In addition, the EVSI analysis for the obese subgroup uses performance data from the Ellis-Kahana RAM which has not yet been evaluated in an external cohort.

The EVSI analysis does not rely on estimating the size of trial that would be required to meet a formal hypothesis test of whether there is a difference in VTE risk between LMWH and no prophylaxis. Instead, it simulates the expected outcomes from trials of various sizes and estimates the net benefits (cost savings or QALY gains) that would be achieved from using that additional evidence to make better informed decisions about prophylaxis in this population. Therefore, a trial would not need to be adequately powered from a frequentist hypothesis-testing perspective to provide valuable information. However, for the value of the future research studies estimated by the EVSI analysis to be realised in practice, there would need to be a willingness to use the updated estimates of efficacy obtained, to make better informed decisions about prophylaxis in this population, without requiring them to meet a formal hypothesis test.

Equality, diversity and inclusion

Participant representation

We specifically developed our recruitment strategy for the workshops to obtain a diverse sample of participants, seeking in particular to recruit participants from ethnic minority backgrounds. We selected diverse organisations with access to a range of under-represented populations to help with the recruitment, as well as specifying that we wanted to speak to people from ethnic minority groups in some of our recruitment materials. However, despite offering payment, we were unable to recruit a diverse sample of participants (see *Workshops* for details). Recruitment was affected by the ongoing COVID-19 pandemic, which meant that we were unable to offer face-to-face workshops and undertook recruitment entirely remotely.

For the clinician survey, we were unable to state whether our sample was representative of the wider population of clinicians as we did not have data about non-respondents. We reported the characteristics of respondents in terms of gender, ethnicity and length of experience.

Research team

The research team was mixed in terms of gender and ethnicity and the project provided a development opportunity for several project team members.

Patient and public involvement

The project team included a PPI representative (RC), from Thrombosis UK, who has relevant personal experience of VTE. She contributed to the design of the study at the application stage. She attended all project management group meetings and contributed to key decisions such as ensuring that the economic model captured outcomes important to women at risk of VTE during pregnancy or in the puerperium. She was instrumental in developing the questions for the workshop and in leading the recruitment strategy for patients with prior VTE. She also contributed to the interpretation and dissemination of the study findings including the lay summary. We recruited two PPI members to join the study steering committee but struggled to maintain engagement from these members after the first meeting.

Chapter 8 Conclusions

Implications for patients, clinicians and policy-makers

The absolute risk of VTE across unselected antepartum patients is low (34 in 10,000). Therefore, any RAM being used in an unselected antepartum population would need to have a high specificity (90–95% for a sensitivity of 100–53%) in order to be used to target prophylaxis in a cost-effective manner. Performance data from studies in unselected antepartum women were limited and no data were available on the performance of the current RCOG guidance across an unselected group of antepartum women. However, exploratory analyses found that offering antepartum prophylaxis from 28 weeks to women who have three clinical risk factors (none of which would qualify them for earlier prophylaxis) as per current RCOG guidance is unlikely to be cost-effective. The survey of clinicians suggests that there is reasonable clinical equipoise about the value of antepartum prophylaxis in women who currently qualify for antepartum prophylaxis from 28 weeks because of a combination of age, BMI and parity (number of previous births).

The absolute risk of VTE in women who have had a prior VTE is 5.81% in the antepartum period and 6.85% in the 6 weeks after delivery. Two RAMs developed specifically for high-risk antepartum women, such as those with a prior VTE or known thrombophilia were identified (Lyon and EThIG). No data were identified on how these performed compared to the RCOG guidelines. However, there is an ongoing study comparing the Lyon RAM with current local practice, which in the UK would be the RCOG guideline. The decision analysis in high-risk antepartum women suggests that offering postpartum prophylaxis for 6 weeks after delivery is likely to be cost-effective compared to no prophylaxis, because the majority of the costs of postpartum prophylaxis are offset by the cost savings of avoiding postpartum VTE. However, the cost-effectiveness of offering antepartum prophylaxis, in those already receiving postpartum prophylaxis, is less certain. This is because the majority of the VTE risk in high-risk women falls in the postpartum period, but the costs of offering antepartum prophylaxis from booking are much higher than the costs of 6 weeks of postpartum prophylaxis.

In postpartum women who have not had a prior VTE, the average absolute risk of VTE in the 6 weeks after delivery is low (7 in 10,000). In women who have had a caesarean delivery, the risks are higher but still low in absolute terms (14 in 10,000). The decision analysis suggests that any RAM used in these groups would need to have high accuracy to provide an appropriate balance of costs, risks and benefits in these groups and would need to perform better than the RAMs identified in the review. This includes the RCOG guideline which is predicted to result in 35% of all postpartum patients receiving prophylaxis for 10 days or more, the proportion being higher (94%) in women who had a caesarean section. The cost effectiveness of RAM-based prophylaxis was more favourable in the subgroup of obese postpartum women (absolute risk of 15 in 10,000), partly because the RAM specifically developed for obese women had a high specificity, meaning that it selected only 10% of obese women for prophylaxis, while achieving a sensitivity of 62%.

Our analysis of the benefits, harms and costs of prophylaxis suggests that it only appears to be cost-effective for selected high-risk groups. However, we acknowledge that decision-making needs to draw upon other factors. For example, the threshold of using prophylaxis to prevent harm in pregnancy may be perceived by some to be lower than the threshold in other clinical areas, such as the use of prophylaxis to prevent hospital-associated VTE. Furthermore, international studies have found that the proportion of women receiving postpartum prophylaxis under the RCOG guideline is higher than when applying equivalent guidance from other countries, suggesting that decision-makers in different countries have come to a different assessment of the balance or benefits, harms and costs.[12,15]

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The stakeholder workshops identified a need for better information for women about the risks and benefits of prophylaxis with LMWH including better information about how to undertake the injections and what side effects to expect.

Suggested research priorities

Having considered both the value of information analysis and the information on the feasibility and acceptability of potential future studies obtained from the workshops and clinician survey, our suggested research priority is:

- A RCT comparing LMWH with no prophylaxis in postpartum women who have not had a previous VTE, but who have other risk factors. Obesity is a highly suitable risk factor to study due to its current high prevalence and easy identification.

The main source of decision uncertainty identified in the value of information analysis was related to uncertainty in the RR of thromboprophylaxis for preventing VTE in women who are pregnant or who have recently given birth. This is because there is minimal RCT evidence to quantify the safety and efficacy of LMWH in this group, with the most directly applicable evidence coming from one small pilot study which recruited eight women per arm. For this reason, much of the current guidance on prophylaxis in women who are pregnant or who have recently given birth is based on expert consensus. The data on effectiveness are extrapolated from other populations, such as medical and surgical patients, who are not pregnant or in the puerperium, and are therefore biologically different. Our analysis has incorporated the uncertainty that comes from this minimal evidence base to estimate the value of further research rather than relying on this assumption of similar efficacy.

The analysis suggests that a future RCT comparing antepartum LMWH with no antepartum prophylaxis in high-risk antepartum women would have substantial value even if it was underpowered from a frequentist hypothesis-testing perspective. This is because it would provide a more precise estimate of the efficacy of LMWH in this group and that has the potential to change the choice of thromboprophylaxis strategy. However, the survey and workshops found that a RCT randomising high-risk antepartum women, with a history of prior VTE or known thrombophilia, to LMWH or placebo is unlikely to be acceptable or feasible. This was because healthcare professionals who would be responsible for recruiting women into the study did not feel that there was clinical equipoise in women who are currently assessed as high risk within the RCOG guidance. Similarly, women with experience of a prior VTE felt that it would not be ethical to randomise women to placebo (i.e. no prophylaxis), given the perceived risk of VTE and the perceived effectiveness of LMWH in this group. For this reason, we consider that any future trial of LMWH versus no prophylaxis should recruit women without a prior VTE, but who have other risk factors for VTE.

There was also substantial decision uncertainty regarding the use of RAMs to select obese postpartum women for postpartum prophylaxis. Again, the main source of decision uncertainty was related to uncertainty in the RR of thromboprophylaxis for preventing VTE. There is a paucity of data on the efficacy of LMWH when used as postpartum prophylaxis and meta-analyses of studies that do exist estimate a higher risk of VTE compared with no LMWH, which is the opposite of what is expected based on data from studies in medical and surgical cohorts. For this reason, the decision analysis incorporated the estimate of efficacy from antepartum women to capture both the clinical expectation that LMWH reduces VTE and the high uncertainty based on current evidence. The analysis suggests that a future RCT comparing LMWH with no prophylaxis in obese postpartum women would have substantial value, even if it was underpowered from a frequentist hypothesis-testing perspective, because it would provide a more precise estimate of the efficacy of LMWH in this group. Therefore, such a study has the potential to change the choice of thromboprophylaxis strategy nationally and wider afield. It would also be relatively easy to do because obesity is easy to identify and measure, no blood tests are required and

it is highly prevalent in the obstetric population. The survey results suggest that in postpartum women there was greater clinical equipoise in women whose risk factors are an elective caesarean section combined with either age over 35 years or obesity, and women whose only clinical risk factors are age over 35 and a BMI between 30 and 40 kg/m^2. However, there was lower support for randomising women with a BMI > 40 kg/m^2 and those having emergency caesarean sections.

The workshop participants felt that recruitment for future trials would be maximised if consent for enrolment was undertaken antenatally. They also generally favoured cluster randomisation over individual randomisation, as they perceived that this would lead to more consistent management within a hospital which would have benefits, although some expressed concerns that cluster randomisation may lead to differences in care in different geographic locations. Clinicians favoured individual randomisation, but there was no clear indication of whether cluster randomisation may be more acceptable if explained more clearly and units were matched appropriately. Clinical equipoise and perceptions of risk may be linked more to current guidelines (notably RCOG) than awareness of underlying evidence. Therefore, in order for future trials to recruit appropriately, a clear explanation of existing evidence, and the risks and benefits of treatment will need to be made available to both clinicians and patients.

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