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Evaluation of venous thromboembolism risk assessment models for hospital inpatients: the VTEAM evidence synthesis

Daniel Edward Horner, Sarah Davis, Abdullah Pandor, Helen Shulver, Steve Goodacre, Daniel Hind, Saleema Rex, Michael Gillett, Matthew Bursnall, Xavier Griffin, Mark Holland, Beverley Jane Hunt, Kerstin de Wit, Shan Bennett and Robin Pierce-Williams

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Evaluation of venous thromboembolism risk assessment models for hospital inpatients: the VTEAM evidence synthesis

Daniel Edward Horner[1,2,3*] Sarah Davis[3] Abdullah Pandor[3] Helen Shulver[3] Steve Goodacre[3] Daniel Hind[3] Saleema Rex[3] Michael Gillett[3] Matthew Bursnall[3] Xavier Griffin[4] Mark Holland[5] Beverley Jane Hunt[6] Kerstin de Wit[7,8] Shan Bennett[3] and Robin Pierce-Williams[9]

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Investigation Branch. Beverley Hunt, Dan Horner and Xavier Griffin were previously involved in developing relevant National Institute for Health and Care Excellence (NICE) guidance on prevention and management of venous thromboembolic disease.

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Abstract

Evaluation of venous thromboembolism risk assessment models for hospital inpatients: the VTEAM evidence synthesis

Daniel Edward Horner[1,2,3*] Sarah Davis[3] Abdullah Pandor[3] Helen Shulver[3] Steve Goodacre[3] Daniel Hind[3] Saleema Rex[3] Michael Gillett[3] Matthew Bursnall[3] Xavier Griffin[4] Mark Holland[5] Beverley Jane Hunt[6] Kerstin de Wit[7,8] Shan Bennett[3] and Robin Pierce-Williams[9]

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Background: Pharmacological prophylaxis during hospital admission can reduce the risk of acquired blood clots (venous thromboembolism) but may cause complications, such as bleeding. Using a risk assessment model to predict the risk of blood clots could facilitate selection of patients for prophylaxis and optimise the balance of benefits, risks and costs.

Objectives: We aimed to identify validated risk assessment models and estimate their prognostic accuracy, evaluate the cost-effectiveness of different strategies for selecting hospitalised patients for prophylaxis, assess the feasibility of using efficient research methods and estimate key parameters for future research.

Design: We undertook a systematic review, decision-analytic modelling and observational cohort study conducted in accordance with Enhancing the QUAlity and Transparency Of health Research (EQUATOR) guidelines.

Setting: NHS hospitals, with primary data collection at four sites.

Participants: Medical and surgical hospital inpatients, excluding paediatric, critical care and pregnancy-related admissions.

Interventions: Prophylaxis for all patients, none and according to selected risk assessment models.

Main outcome measures: Model accuracy for predicting blood clots, lifetime costs and quality-adjusted life-years associated with alternative strategies, accuracy of efficient methods for identifying key outcomes and proportion of inpatients recommended prophylaxis using different models.

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Results: We identified 24 validated risk assessment models, but low-quality heterogeneous data suggested weak accuracy for prediction of blood clots and generally high risk of bias in all studies. Decision-analytic modelling showed that pharmacological prophylaxis for all eligible is generally more cost-effective than model-based strategies for both medical and surgical inpatients, when valuing a quality-adjusted life-year at £20,000. The findings were more sensitive to uncertainties in the surgical population; strategies using risk assessment models were more cost-effective if the model was assumed to have a very high sensitivity, or the long-term risks of post-thrombotic complications were lower.

Efficient methods using routine data did not accurately identify blood clots or bleeding events and several pre-specified feasibility criteria were not met. Theoretical prophylaxis rates across an inpatient cohort based on existing risk assessment models ranged from 13% to 91%.

Limitations: Existing studies may underestimate the accuracy of risk assessment models, leading to underestimation of their cost-effectiveness. The cost-effectiveness findings do not apply to patients with an increased risk of bleeding. Mechanical thromboprophylaxis options were excluded from the modelling. Primary data collection was predominately retrospective, risking case ascertainment bias.

Conclusions: Thromboprophylaxis for all patients appears to be generally more cost-effective than using a risk assessment model, in hospitalised patients at low risk of bleeding. To be cost-effective, any risk assessment model would need to be highly sensitive. Current evidence on risk assessment models is at high risk of bias and our findings should be interpreted in this context. We were unable to demonstrate the feasibility of using efficient methods to accurately detect relevant outcomes for future research.

Future work: Further research should evaluate routine prophylaxis strategies for all eligible hospitalised patients. Models that could accurately identify individuals at very low risk of blood clots (who could discontinue prophylaxis) warrant further evaluation.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/AWTW6200).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

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Glossary

Cost-effectiveness acceptability curve A way of illustrating cost-effectiveness results by plotting the probability that the intervention is cost-effective (*y*-axis) against the maximum that society is willing to pay for an improvement in health (*x*-axis).

Cost-effectiveness plane A way of illustrating cost-effectiveness results by plotting the mean incremental cost and effectiveness on a four-quadrant graph. Interventions that are more costly and more effective fall in the north-east quadrant.

Deep-vein thrombosis A blood clot that develops within a deep vein in the body, most commonly in the leg.

Hospital-acquired thrombosis Any new episode of venous thromboembolism (deep-vein thrombosis or pulmonary embolism) diagnosed during hospitalisation or within 90 days of discharge following an inpatient stay of at least 24 hours, or following a surgical procedure under general or regional anaesthesia.

Incremental cost-effectiveness ratio The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest.

Major bleeding Serious or fatal bleeding episodes, as defined by the International Society for Thrombosis and Haemostasis.

Clinically relevant non-major bleeding Bleeding episodes which are not major, but require clinical assessment and potential intervention, as defined by the International Society for Thrombosis and Haemostasis.

Post-thrombotic syndrome Pain, swelling, itching, skin discolouration and leg ulcers occurring after a deep-vein thrombosis, caused by damage to the valves in the leg veins that prevent backflow of blood.

Prophylaxis A measure taken to prevent a disease.

Pulmonary embolism A blood clot that breaks off from the deep veins and travels around the circulation to block the pulmonary arteries (arteries in the lung). Most deaths arising from deep-vein thrombosis are caused by pulmonary embolism.

Quality-adjusted life-year A measure of the benefit of healthcare that combines the impact of both the expected length of life and quality of life.

Risk assessment models A set of criteria that aims to estimate the risk of a particular condition/complication and often used by clinicians to inform individual patient decisions on medical interventions.

Thromboprophylaxis A measure taken to reduce the risk of thrombosis; prophylaxis against thrombosis. This measure can be undertaken using drugs (pharmacological thromboprophylaxis) or using compression devices (mechanical thromboprophylaxis).

Venous thromboembolism Thrombosis is the blocking of a blood vessel by a blood clot. This clot may be dislodged fully or partly from its site of origin and travel downstream to lodge in a vital organ, a process described as embolisation. Clots formed in the deep veins of the legs are known as deep-vein thromboses and when fragments break off they travel through the body to block pulmonary arteries. This process is termed pulmonary embolism. Venous thromboembolism is a composite term to describe all the above, including both deep-vein thrombosis and pulmonary embolism.

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List of abbreviations

AES	antiembolism stockings
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CRNMB	clinically relevant non-major bleeding
CRF	case report form
CrI	credible interval
CTEPH	chronic thromboembolic pulmonary hypertension
CTRU	Clinical Trials Research Unit
DOAC	direct oral anticoagulant
DVT	deep-vein thrombosis
EHR	electronic health record
EVPI	expected value of perfect information
EVPPI	expected value of partial perfect information
EQUATOR	Enhancing the QUAlity and Transparency Of health Research
GI	gastrointestinal
GTAC	Gene Therapy Advisory Committee
HAT	hospital-acquired thrombosis
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly, Drugs/alcohol concomitantly
HES	hospital episodes statistics
HIT	heparin-induced thrombocytopenia
HRA	Health Research Authority
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICD-10	International Classification of Diseases, Tenth Revision
ICH	intracranial haemorrhage
IQR	interquartile range
IMPROVE	International Medical Prevention Registry on Venous Thromboembolism
LMWH	low-molecular-weight heparin
NICE	National Institute for Health and Care Excellence
NLP	natural language processing
NMA	network meta-analysis
NSQIP	National Surgical Quality Improvement Programme
NYHA	New York Heart Association
OXVASC	Oxford Vascular Study
PE	pulmonary embolism
PMG	project management group
PPI	patient and public involvement
PSA	probabilistic sensitivity analysis
PREFER-VTE	Prevention of Thromboembolic Events – European Registry in Venous Thromboembolisma
PRISMA	Preferred Reporting Items for Systematic Review and Meta-analyses
PROBAST	prediction model risk of bias assessment tool
PROSPERO	Prospective Register of Systematic Reviews
PTS	post-thrombotic syndrome

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QALYs	quality-adjusted life-years
RAM	risk assessment model
RCT	randomised controlled trial
REC	Research Ethics Committee
RIETE	Computerized Registry of Patients with Venous Thromboembolism
ROC	receiver operating characteristic
SD	standard deviation
SECF	Sheffield Emergency Care Forum
SMR	standardised mortality ratio
SNOMED	Systematised Nomenclature of Medicine
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TESS	Trauma Embolic Scoring System
VKA	vitamin K antagonist
VTE	venous thromboembolism
VTEAM	Venous ThromboEmbolism Assessment Methods
XAMOS	Xarelto® in the prophylaxis of post-surgical venous thromboembolism after elective major orthopedic surgery of hip or knee

Plain language summary

People who are admitted to hospital are at risk of blood clots that can cause serious illness or death. Patients are often given low doses of blood-thinning drugs to reduce this risk. However, these drugs can cause side effects, such as bleeding.

Hospitals currently use complex risk assessment models (risk scores, which usually include patient, disease, mobility and intervention factors) to determine the individual risk of blood clots and identify people most likely to benefit from blood-thinning drugs. There are a lot of different risk scores and we do not know which one is best. We also do not know how these scores compare to each other or whether using scores to decide who should get blood-thinning drugs provides good value for money to the NHS.

We reviewed all previous studies of risk scores. We found that they did not predict blood clots very well and we could not recommend one score over another. We then created a mathematical model to simulate the use of blood-thinning drugs in people admitted to hospital. The model suggested that giving blood-thinning drugs to everyone who could have them would probably provide the best value for money, in medical patients. Our findings were the same, but less certain, for surgical patients.

We also collected information from four NHS hospitals to explore possibilities for future research. Our work showed that routinely collected electronic data on blood clots and bleeding events is not very accurate and that using different scores could result in variable use of blood-thinning medications.

Our findings suggest that it may be better value to the NHS and better for patients if we were to offer blood-thinning medications to everyone on admission to hospital, without using any risk score. However, this approach needs further research to ensure it is safe and effective. Such research would not be able to rely on routine electronic data to identify blood clots or bleeding events, in isolation.

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Scientific summary

Background

Venous thromboembolism (VTE) is a composite diagnosis including deep-vein thrombosis (DVT) and pulmonary embolism (PE). The condition is a global health burden, affecting over 1:1000 adults worldwide, every year. Previous epidemiological studies have shown more than half of all VTE events to be hospital-associated (or acquired) thrombosis (HAT), occurring during admission or within 90 days of discharge.

Current evidence suggests that many HAT events are potentially preventable. Pharmacological prophylaxis in medical and surgical inpatients has been shown to be clinically effective in several large studies and meta-analyses. However, although prophylaxis reduces the risk of VTE for hospital inpatients, it also incurs costs and potentially increases the risk of bleeding. As such, international guidelines recommend a process of individualised VTE risk assessment at the point of hospital admission. Several risk assessment models (RAMs) have been developed to aid this process. The accuracy and cost-effectiveness of these models are uncertain.

Further prospective studies in this area are challenging due to national guidance, contract standards and high rates of routine prescribing (> 70%). We sought to assess the clinical and cost-effectiveness of VTE RAMs through secondary research methods, by conducting a systematic review of RAM accuracy and subsequent decision-analytic modelling. In addition, we sought to evaluate the accuracy of routine data sources to identify core VTE and bleeding outcomes and estimate key clinical parameters for any future implementation study.

Objectives

The prespecified and combined project objectives were as follows:

1. Update existing systematic reviews to identify VTE RAMs for hospital inpatients and determine their comparative accuracy for predicting the risk of VTE.
2. Undertake decision-analytic modelling to determine the cost-effectiveness of pharmacological prophylaxis guided by a RAM, compared to prophylaxis for all and prophylaxis for none.
3. Use the decision-analytic model to identify key areas of uncertainty and determine the value of gathering additional information to reduce uncertainty.
4. Pilot the use and evaluate the accuracy of efficient methods to measure core clinical VTE and bleeding outcomes.
5. Estimate key parameters for planning a future implementation study.

Methods

Workstream 1 used a systematic review and economic analysis to address objectives 1, 2 and 3. We extended and updated overlapping systematic reviews of available RAMs, performed quality assessment of relevant studies and synthesised performance measures (e.g. sensitivity, specificity and concordance (*C*) statistics) to evaluate the prognostic accuracy of individual RAMs. We subsequently used this information to inform decision-analytic modelling. The target population for the conceptual model was hospital inpatients, including medical, surgical and trauma patients but excluding critical care patients, children and women admitted to hospital for pregnancy-related reasons. Patients at increased risk of bleeding were assumed not to receive pharmacological prophylaxis under any strategy and were

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excluded from the model. We compared strategies of using no pharmacological prophylaxis, pharmacological prophylaxis for all and pharmacological prophylaxis given in accordance with validated RAMs. The use of mechanical prophylaxis was considered out of scope for the modelling. We used a lifetime horizon and reported primary outcomes of costs and quality-adjusted life-years (QALYs). Multiple scenario and sensitivity analyses were conducted by subgroup.

Workstream two used primary research to address objectives four and five. We conducted a multicentre observational cohort study across four hospitals to compare prespecified methods of efficient data collection to formal case note review. We identified a target population hospitalised during 2019 and extracted data from prospectively completed VTE risk assessments, when available. Research assistants undertook further retrospective case note review for each patient episode. We used electronic health records to evaluate additional risk characteristics and record all relevant clinical outcomes, including the subsequent diagnosis of HAT, major bleeding and clinically relevant non-major bleeding events. We then collated multiple routine data sources for each patient episode to determine the accuracy of these methods in identifying relevant clinical outcomes, compared to a gold standard of case note review. The primary outcome measures for workstream two were contingency tables with sensitivity, specificity and predictive values. Feasibility criteria for any future study using efficient data methods were set a priori. We also estimated the potential variation in prescribing recommendations using multiple validated RAMs and estimated key parameters for any future implementation study.

The Venous ThromboEmbolism Assessment Methods study received a favourable opinion from the Proportionate Review Sub-committee of the London – West London & Gene Therapy Advisory Committee (GTAC) Research Ethics Committee and approval from the Health Research Authority (HRA) and Care Research Wales (HCRW) on 18 September 2019 (reference 19/LO/1303, IRAS project ID 262220).

Results

Workstream 1

Our updated systematic review included 51 studies, comprising 24 unique validated RAMs. The vast majority of studies evaluated VTE RAMs in medical (n = 21), surgical (n = 15) or mixed (n = 4) cohorts of hospital inpatients. The most widely evaluated models were the Caprini RAM (22 studies), the Padua prediction score (16 studies), the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) models (8 studies), the Geneva Risk Score (4 studies) and the Kucher Score (4 studies). All studies had a high or unclear risk of bias, with the main issues related to patient selection, outcome and analysis factors. *C*-statistics varied markedly between these studies and between models, with no RAM performing obviously better than other models. Similarly, estimates for sensitivity and specificity were highly variable.

In the decision analytic modelling, we estimate that in medical inpatients, prophylaxis reduces serious adverse outcomes [fatal PEs, fatal bleeding and non-fatal intracranial haemorrhage (ICH)] from 53 per 10,000 to 42 per 10,000, with a reduction in symptomatic DVTs and non-fatal PEs that is higher than the increase in other bleeds. In the long-term outcomes at 5 years, there is a large reduction in the number of patients experiencing post-thrombotic syndrome (PTS) following prophylaxis from 787 per 10,000 to 385 per 10,000, but minimal difference in overall survival. Modelling showed that thromboprophylaxis for all has a high probability (> 99%) of being the most cost-effective strategy (£20,000 per QALY threshold) based on the performance of existing RAMs in cohorts of medical inpatients. This finding was generally robust under the scenario and sensitivity analyses with one exception; targeting thromboprophylaxis using a Padua score ≥ 3 (84% of cohort) had a 76.6% probability of being the most cost-effective strategy when assuming higher RAM performance (sensitivity 99.9%; specificity 23.7%).

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 due to the high probability that prophylaxis for all is the optimal strategy. However, the EVPI would be £2.42 per person per year if a more accurate RAM could be developed for medical inpatients.

In surgical inpatients, the risk of a serious adverse outcome (as above) 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 form 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. Modelling showed that giving prophylaxis to all surgical inpatients 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. These findings were sensitive to some uncertainties explored in the scenario and sensitivity analyses. In particular, prophylaxis for all may no longer be the optimal strategy for surgical inpatients when the risk of PTS is lower, when using an extended duration of prophylaxis or where a RAM is assumed to have a very high sensitivity.

The overall EVPI associated with all parameters included in the PSA when valuing a QALY at £20,000 was £16.35 per person. This does not include the uncertainty of considering which RAM to use as the EVPI and 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 [expected value of partial perfect information (EVPPI)], the relative risk of VTE for patients having thromboprophylaxis compared to patients not having thromboprophylaxis was the parameter with the largest EVPPI.

In specific surgical populations requiring longer durations of prophylaxis, we found that pharmacological prophylaxis for all eligible patients remained optimal in those having elective knee replacement. Offering prophylaxis at a Pannucci score of ≥ 3 (sensitivity of 84% and specificity of 49%) was optimal when prescribing 28 days of low-molecular-weight heparin (LMWH) to patients having elective hip replacement. These conclusions were sensitive to prophylaxis strategy; using direct oral anticoagulants (DOACs) rather than LMWH resulted in prophylaxis for all as the optimal strategy for both hip and knee patients.

Workstream 2

The observational cohort study was conducted across all four sites, enrolling 2115 patient hospitalisation episodes, with 2008 eligible for analysis. Medical and surgical cases were evenly balanced, but with more emergency (73.7%) than elective (25.8%) admissions. The sensitivity of routine coding data for detection of HAT and major bleeding events was 62% [95% confidence interval (CI) 54 to 69] and 38% (95% CI 27 to 50), respectively. Local VTE data sets performed better, with sensitivity of 81% (95% CI 75 to 87). The specificity of routine coding data for VTE and bleeding was 98% (95% CI 97 to 99) and 95% (95% CI 94 to 96), respectively, and the specificity of local VTE data sets was 100% (95% CI 99 to 100). We were unable to demonstrate overall feasibility of using efficient outcome measures and did not meet several prespecified criteria.

In a smaller subgroup of patients with prospectively collected data, we evaluated potential variation in pharmacological prophylaxis using different RAMs. We identified 543 hospital episodes with VTE risk assessment performed during 2019, with 254 episodes suitable for inclusion, data extraction and comparative analysis. Overall recommendations for pharmacological prophylaxis varied substantially between seven RAMs, ranging from 13% of admitted patients for the IMPROVE associative score (95% CI 9.4 to 17.7) to 91% (95% CI 86.3 to 93.6) for the Department of Health (now Department of Health and Social Care) VTE risk assessment tool. The latter tool resulted in an absolute increase of 28% for prophylaxis recommendation, compared to other RAMs.

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Within this multicentre cohort of hospitalised inpatients, the HAT event rate was 1.6% (95% CI 1.0 to 2.2) and the major bleeding event rate was 2.5% (95% CI 1.8 to 3.2).

Conclusions

We updated prior systematic reviews to conclude that that the available evidence has significant methodological limitations and demonstrates current RAMs to have weak predictive accuracy.

Decision-analytic modelling showed that the balance of VTE or major bleeding risks, combined with the RAM performance in medical cohorts, means that thromboprophylaxis for all is the optimal strategy within our model for medical inpatients. These findings were robust to multiple scenarios and sensitivity analyses. The optimal strategy for surgical inpatients is to offer thromboprophylaxis to all. However, the scenario analyses for surgical inpatients found that the optimal strategy was sensitive to many of the individual model inputs and assumptions tested. In addition, the optimal strategy for surgical patients receiving extended duration thromboprophylaxis appeared dependent on duration of therapy and prophylaxis strategy.

The findings from our cohort study suggest that efficient methods for identifying 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 did not reach several predefined feasibility metrics. We also found limitations in the ability of efficient methods to identify individual risk variables and facilitate RAM comparison in future work. The majority of our sites did not collect contemporaneous data on risk assessment in a digital, or easily accessible format.

Implications for policy-makers

If, despite drug costs and potential harms, pharmacological prophylaxis for all is the most cost-effective strategy, use of unvalidated RAMs may be suboptimal. 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 routinely offered pharmacological prophylaxis on hospital admission without complex risk assessment. In this circumstance, patients who are ineligible for pharmacological prophylaxis due to high bleeding risk, specific contraindications or personal choice could opt out, but still utilise evidence-based mechanical thromboprophylaxis strategies.

The findings from our cohort study have implications for funders looking to support further work in this area. These data suggest large studies entirely reliant on routine data collection methods for complex time-dependent outcome measures (such as HAT or major bleeding) are likely to be inaccurate.

Recommendations for future research

Further research should evaluate the following themes in this area of clinical care:

1. Evaluation of routine pharmacological prophylaxis for all eligible medical and surgical patients on hospital admission, compared to current practice of risk assessment using a RAM. Such work would need to be conducted at scale and could not rely on efficient methods for outcome measurement in isolation.
2. Development and validation of RAMs to identify individuals receiving prophylaxis at very low risk of blood clots, who could therefore potentially discontinue pharmacological prophylaxis early during hospital stay.

3. Our analysis was inevitably limited in scope and did not examine the use of RAMs to identify accurate prediction of bleeding risk, the use of mechanical prophylaxis in medical patients with increased bleeding risk (or contraindications to pharmacological prophylaxis) or patients at risk of thromboprophylaxis failure. These issues could be priorities for future research.

Study registration

This study is registered as Research Registry 5216, PROSPERO CRD42020165778.

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Chapter 1 Introduction

The problem – preventing hospital-acquired venous thromboembolism

Venous thromboembolism (VTE) remains a major worldwide health burden, with an annual incidence of between 0.75 and 2.69 per 1000 individuals in the population.[1] At least half of all VTE occurs during hospitalisation, or up to 90 days following discharge; such cases are described as hospital-associated VTE or hospital-acquired thrombosis (HAT).[2] Many HAT cases are potentially preventable, through the use of thromboprophylaxis during the initial hospital stay and patient education.[3–5] Despite the widespread availability of evidence-based prevention strategies, HAT has been described as the number one patient safety issue for individuals requiring hospital admission, worldwide.[6] Previous evidence suggests that HAT accounts for more deaths and disability than nosocomial pneumonia, catheter-related bloodstream infections or adverse drug events in low- and middle-income countries.[7]

Both pharmacological and mechanical thromboprophylaxis can reduce the risk of VTE. However, pharmacological thromboprophylaxis potentially increases the risk of bleeding and exposes patients to iatrogenic adverse events. Therefore, the decision to provide thromboprophylaxis involves consideration of the risks of VTE and bleeding, along with the costs of providing thromboprophylaxis and treating the consequences of VTE and bleeding.

VTE risk assessment models (RAMs) are used to estimate the risk of VTE and hence the benefit of providing thromboprophylaxis. Using a VTE RAM to target those with higher risk should improve cost-effectiveness. However, this cannot be assumed. If thromboprophylaxis is very effective, then it may be cost-effective to treat everyone rather than treating only those at higher risk. If it is not very effective, then it may not be cost-effective to treat anyone.

The cost-effectiveness of VTE risk assessment tools: uncertainty and evidence deficit

Many VTE RAMs have been developed and some have been validated by estimating the prognostic accuracy for VTE. Systematic reviews have examined VTE RAMs for acutely ill medical patients (11 studies), hospitalised non-surgical patients (11 studies) and all hospitalised populations (22 studies).[8–10] The reviews identified many RAMs but with limited evaluation. The primary studies had important methodological limitations and were generally judged as low quality. There was substantial variation between the primary studies in terms of populations, methods and outcomes used, which precluded meta-analysis and limited comparison between RAMs. Overall, the studies suggested that the identified RAMs had modest prognostic value with most reporting *C*-statistics around 0.6–0.7. Sensitivity and specificity depended upon the threshold used but high sensitivity could only be achieved by substantial loss of specificity. An ideal RAM could not be recommended by any of the reviews. However, further primary research has been published since these systematic reviews were undertaken, so there may be some benefit from updating these reviews.

To date, limited research has explored the trade-off between the risks of VTE and thromboprophylaxis. This trade-off is essential in determining whether a RAM will be cost-effective and, if so, the threshold of risk or balance of sensitivity and specificity that should be used in decision-making. Le *et al.* used decision-analytic modelling to estimate a risk threshold for prophylaxis in hospitalised medical patients.[11] Undertaken from a US health system perspective with a willingness to pay threshold of $100,000 per quality-adjusted life-year (QALY) gained, the analysis showed that pharmacological thromboprophylaxis was cost-effective for an average medical patient with a VTE risk exceeding 1.0%. Decision-analytic

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modelling undertaken from a NHS perspective using thresholds advised by the National Institute for Health and Care Excellence (NICE) could inform NHS use of VTE prophylaxis.

There has been very little primary research into VTE RAMS in the NHS. Ideally, the preferred approach in this situation would be to derive and validate VTE RAMs in a typical setting. However, the established effectiveness of VTE prophylaxis in hospital inpatients presents a substantial challenge for studies estimating the accuracy of VTE RAMs. Given our current understanding, it would be unethical to withhold prophylaxis from patients who are at risk of VTE. The fundamental aim of risk assessment is to identify patients where VTE could be prevented by thromboprophylaxis. Over 70% of medical patients in the UK receive thromboprophylaxis when the Department of Health (now Department of Health and Social Care) risk assessment tool is used (NICE 2018).[8] In this situation, around half of all VTE will have been prevented and any prognostic model derived from observational data will largely be predicting VTE that would not be prevented with thromboprophylaxis.[4,12] Any prognostic model derived in this setting would, therefore, be based on factors that predict non-preventable VTE while underestimating (or missing) those that predict preventable VTE. A RAM that predicted non-preventable VTE while failing to predict preventable VTE would be of no clinical benefit and could potentially increase harm.

These uncertainties are highlighted in recent NICE guidance within a UK setting, which now advocates use of any RAM published by a national UK body, professional network or peer-reviewed journal.[8] Australasian guidance is similar.[13] However, North American guidelines offer variable messaging on risk assessment. The American Society of Haematology guidelines avoid any recommendations on RAM use, but advise that clinicians 'integrate VTE and bleeding risk assessments into clinical decision-making processes'.[14] Alternatively, the American College of Chest Physician guidelines dichotomise non-surgical patients into low and high risk within their recommendations, basing assessment on a specific RAM (the Padua prediction score).[15,16] All guidelines highlight the limitations within the evidence base for RAMs. Such disparity in recommendations invites variation in practice and ongoing uncertainty for clinicians and patients.

Chapter 2 Rationale and objectives

Rationale

Recent systematic reviews have shown the limited evaluation of VTE RAMs to date and we have highlighted the challenge of obtaining robust primary data.[8–10] However, it would be worth updating recent systematic reviews to avoid research waste and ensure that further research is based on the best currently available data. Decision-analytic modelling of the published evidence can also be used to estimate the cost-effectiveness of VTE RAMs for hospital inpatients. It can determine whether risk assessment has the potential to be cost-effective compared with thromboprophylaxis for all and, if so, what threshold of risk should be used for providing thromboprophylaxis and what trade-off between sensitivity and specificity would be optimal. It can, therefore, increase the insights available from the existing evidence and identify areas of uncertainty that require further research. This is particularly valuable when ethical considerations limit the design of primary research.

Given that the widespread use of VTE prophylaxis limits the potential to undertake prognostic accuracy studies of VTE RAMs, future primary research may need to evaluate the comparative effectiveness and cost-effectiveness of implementing alternative approaches to risk assessment. This research could involve individual patient or cluster randomised interventional trial designs, quasi-randomised methods or observational methods. These methods could all benefit from using an efficient design, in which routine data sources are used to measure VTE and bleeding outcomes, and potentially also to record or implement RAMs as part of an evaluation. Efficient methods could increase the available sample size for future primary research and support a study comparing different risk-assessment methods. This could increase the potential range of feasible study designs and the information generated by future primary research. However, research is required to determine whether efficient methods are feasible for comparative evaluation of VTE RAMs. Specifically:

1. In order to be used in future research designs, routine data sources need to accurately record VTE and bleeding outcomes.
2. Efficient methods for recording or implementing RAMs should build upon existing methods of delivering risk assessment within a hospital setting.
3. Future research comparing RAMS would need to ensure that different patients (and different proportions of patients) received prophylaxis, otherwise any differences in outcome would be difficult to attribute to the RAM used.

Objectives

We aimed to evaluate the cost-effectiveness of VTE RAMs in hospital inpatients, determine the optimal approach to providing thromboprophylaxis and determine how changing the risk threshold for prophylaxis affects cost-effectiveness. We also sought to evaluate the potential performance of different RAMs in an NHS setting, assess the use of efficient methods to capture data on risk characteristics and to determine the accuracy of efficient methods to capture relevant outcomes in a future trial. Our specific objectives were as follows:

1. Update recent systematic reviews to identify VTE RAMs for hospital inpatients and estimate prognostic accuracy.
2. Undertake decision-analytic modelling to determine the cost-effectiveness of VTE risk assessment compared to thromboprophylaxis for all and thromboprophylaxis for none, specifically determining the risk threshold that optimises effectiveness (QALYs) and cost-effectiveness (i.e. maximises net benefit assuming willingness to pay according to NICE thresholds).
3. Use the decision-analytic model to identify key areas of uncertainty and determine the value of gathering additional information to reduce uncertainty.

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4. Pilot the use of efficient methods alongside routine practice to determine the feasibility of a future implementation study of VTE risk assessment tools in hospital inpatients.
5. Estimate key parameters for planning a future implementation study.

Objectives 1, 2 and 3 are addressed by workstream 1 (systematic review and economic modelling). Objectives 4 and 5 are addressed by workstream 2 (cohort study).

Chapter 3 Workstream 1 – systematic review

A systematic review of the literature was undertaken to determine the comparative accuracy of individual RAMs for predicting the risk of developing VTE in hospital inpatients. Sections of this chapter have been reproduced from Pandor *et al.* under licence CC BY 4.0.[17]

This review was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[18] and was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020165778).

Methods

Eligibility criteria

We sought studies evaluating RAMs which could be applied to a general inpatient population (medical, surgical or trauma), rather than disease-specific models. All primary validation studies (as derivation studies may give an overoptimistic assessment of model performance measures) that evaluated the accuracy (e.g. sensitivity, specificity, concordance statistic) of a multivariable RAM (or scoring system) for predicting the risk of developing VTE were eligible for inclusion. We selected studies that included validation of the model in a group of patients that were not involved in model derivation. This involved either splitting the study cohort (internal) or using a new cohort (external). The study could have reported derivation of the model, but we only used the validation data to estimate accuracy. The study population consisted of hospital inpatients including those who required medical care, undergoing any surgery (excluding day surgery) or received care following an injury. Studies that primarily focused on children (aged under 16 years), women admitted to hospital for pregnancy-related reasons and any patient admitted to a level 2 or above critical care environment (e.g. patients requiring more detailed observation or intervention including support for a single failing organ system or postoperative care and those 'stepping down' from higher levels of care) were excluded. These patient groups have VTE risk profiles that differ markedly from the general inpatient population, making the use of a generic model inappropriate.

Data sources and searches

Potentially relevant studies were identified by searching the following electronic databases and research registers:

- Ovid MEDLINE® Epub Ahead of Print, In-process and Other Non-indexed Citations, Ovid MEDLINE® Daily, MEDLINE and Versions® (OvidSP) 1946 to February 2021
- EMBASE (OvidSP) 1974 to February 2021
- Cochrane Database of Systematic Reviews (www.cochranelibrary.com/) 1996 to February 2021
- Cochrane Central Register of Controlled Trials (www.cochranelibrary.com/) 1898 to April 2017
- ClinicalTrials.gov (US NIH) 2000 to February 2021
- International Clinical Trials Registry Platform (WHO) 1990 to February 2021

The search strategy used free text and thesaurus terms and combined synonyms relating to the condition (e.g. VTE in medical inpatients) with risk prediction modelling terms. No language restrictions were used. However, as the current review updated three previous systematic reviews,[8,9,10] searches were limited by date from 2017 (last search date from earlier reviews)[8] to February 2021. Searches were supplemented by hand-searching the reference lists of all relevant studies (including existing systematic reviews); forward citation searching of included studies (using the Web of Science Citation Index Expanded and Conference Proceedings Citation Index – Science) to identify articles that cite the relevant articles; contacting key experts in the field; and undertaking targeted searches of the World

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Wide Web using the Google search engine. Further details on the search strategy can be found in *Appendix 1*.

All identified citations from the electronic searches and other resources were imported into and managed using the EndNote bibliographic software (version X8; Clarivate Analytics, Philadelphia, PA, USA).

Study selection process

The inclusion of potentially relevant articles was undertaken using a two-step process. First, all titles were examined for inclusion by one reviewer Katie Sworn (KS) and any citations that clearly did not meet the inclusion criteria (e.g. non-human, unrelated to VTE inpatients) were excluded. Second, all abstracts and full-text articles were then examined independently by two reviewers (KS and AP). Any disagreements in the selection process were resolved through discussion or if necessary, arbitration by a third reviewer (SG) and included by consensus.

Data abstraction and quality assessment strategy

Data relating to study design, methodological quality and outcomes were extracted by one reviewer (KS) into a standardised data extraction form and independently checked for accuracy by a second [AP or Michael Tonkins (MT)]. Any discrepancies were resolved through discussion or if necessary, arbitration by a third reviewer (SG) and included by consensus. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

The methodological quality of each included study was assessed using PROBAST (Prediction model Risk Of Bias Assessment Tool).[19,20] This instrument evaluates four key domains: patient selection, predictors, outcome and analysis. Each domain is assessed in terms of risk of bias and the concern regarding applicability to the review (first three domains only). To guide the overall domain-level judgement about whether a study is at high, low or an unclear (in the event of insufficient data in the publication to answer the corresponding question) risk of bias, subdomains within each domain include a number of signalling questions to help judge with bias and applicability concerns. An overall risk of bias for each individual study was defined as low risk when all domains were judged as low; and high risk of bias when one or more domains were considered as high. Studies were assigned an unclear risk of bias if one or more domains were unclear and all other domains were low. Further details on the PROBAST tool can be found in *Appendix 1*, *Table 20*.

The methodological quality of each included study was independently evaluated by two reviewers (KS and AP). Any discrepancies were resolved through discussion or if necessary, with involvement of a third reviewer (MT). Blinding of the quality assessor to author, institution or journal was not considered necessary.

Data synthesis and analysis

We were unable to perform meta-analysis due to significant levels of heterogeneity between studies (participants, inclusion criteria, clinical condition) and variable reporting of items. As a result, a pre-specified narrative synthesis approach[21,22] was undertaken, with data being summarised in tables with accompanying narrative summaries that included a description of the included variables, statistical methods and performance measures [e.g. sensitivity, specificity and *C*-statistic (a value between 0.7–0.8 and > 0.8 indicated good and excellent discrimination, respectively; and values < 0.7 were considered weak[23])], where applicable. All analyses were conducted using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA).

Patient and public involvement

Patients and the public were not involved in the design of this systematic review. However, all patient representatives reviewed the most widely validated risk models identified, to comment on

the appropriateness of criteria, acceptability and potential for face-to-face and remote (patient-led) completion.

Results

Quantity and quality of research available

The literature searches identified 6355 citations. Of these, 51 studies[15,24–73] investigating 24 unique RAMs met the inclusion criteria. A flow chart describing the process of identifying relevant literature can be found in *Figure 1*. A total of 60 full-text articles were excluded as they did not meet all the pre-specified inclusion criteria. The majority of the articles were excluded primarily for not using a RAM for predicting the risk of developing VTE, having no useable or relevant outcome data or an inappropriate

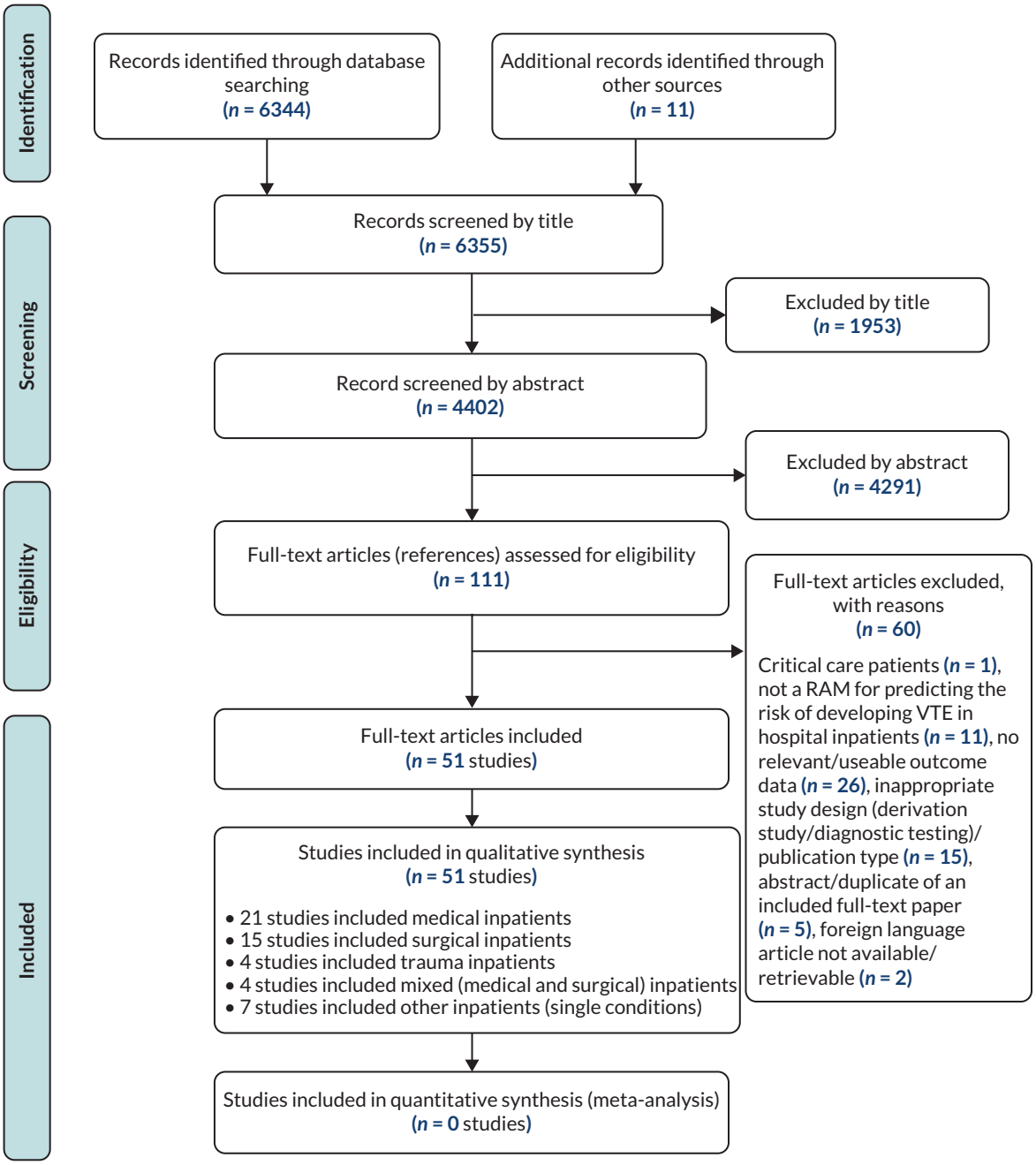

FIGURE 1 Study flow chart (adapted from free online resources hosted by the EQUATOR network https://www.equator-network.org).

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study design (e.g. derivation study, reviews, commentaries or editorials). A full list of excluded studies with reasons for exclusion is presented in *Report Supplementary Material 1*.

Description of included studies (design and patient characteristics)

The design and participant characteristics of the 51 included studies[15,24–73] that provided data on the comparative accuracy of RAMs for predicting VTE in patients admitted to hospital is summarised in *Table 1*. All studies were published between 2003 and 2020 and were undertaken in North America (*n* = 24),[26,27,35–42,45,49,50,54–61,67,70,71] Asia (*n* = 13),[31,32,44,46–48,62–65,69,72,73] Europe (*n* = 9),[15,25,28–30,33,51,53,68] the Middle-East (*n* = 2),[24,65] South America (*n* = 1),[34] Australia (*n* = 1)[43] and one study was intercontinental.[52] Sample sizes ranged from 70[42] to 1,099,093[45] patients in 37 observational cohort studies [11 prospective[15,24,25,30,31,34,46,53,54] (5 of which were multicentre) and 26 retrospective[26–29,35,36,38–43,45,48,51,52,55–57,60,61,64,65,67,70,71] (16 of which were multicentre) in design]. Sample sizes in 14 case–control studies[32,33,37,44,47,49,50,59,62,63,68,69,72,73] (4 of which were multicentre) ranged from 148[63] to 19,217[59] patients.

The vast majority of studies evaluated VTE risk assessment in hospital inpatients who required medical care (*n* = 21),[15,28–30,33,34,38,39,47,49,51,53,59,60,63,68,69,71–73] were undergoing surgery (*n* = 15)[26,27,35,37,40,42,45,48,50,54,58,61,65,67,70] or were a mixed medical and surgical cohort (*n* = 4).[25,31,32,36] The remaining studies focused on patients receiving care for trauma (*n* = 4),[41,43,57,64] cancer (*n* = 4),[24,44,56,62] stroke (*n* = 1),[46] burn injuries (*n* = 1)[55] and sepsis (*n* = 1).[66] The mean age ranged from 45 years[41] to 76 years[52] (not reported in 29 studies)[15,25–27,32,33,35,37,40,42–47,49,50,54,57–60,63,64,67,68,72,73] and the proportion of female subjects ranged from 17%[42] to 81%[61] (not reported in 12 studies).[25–27,35,37,45,50,54,57,58,60,63]

The majority of studies (*n* = 37)[15,24,26,28–34,38,40,42–49,51,54,57–60,62,64–66,68,69,72,73] defined the VTE end point [deep-vein thrombosis (DVT) and or pulmonary embolism (PE)] as being objectively confirmed. Of the remainder, three studies[36,56,71] had no objective confirmation of VTE and 11 studies[25,27,35,37,41,50,55,61,63,67,68] did not report the methods for diagnosis confirmation. In terms of VTE risk period, half of the studies (*n* = 23)[15,24–27,28,30,37–40,42,45,46,49,51–54,58,59,61,71] utilised the RAMs to predict the occurrence of VTE within 3 months of the index hospitalisation. The remaining studies did not report the VTE risk period. The reported incidence of VTE ranged widely from 0.3%[39,70] to 27.9%[48] depending on definition, study design and study participants (e.g. medical, surgical or trauma).

The studies included in this review evaluated 24 validated unique RAMs. The most widely evaluated models were the Caprini RAM (22 studies),[24,26,31–35,37,38,40,42,44,45,47,48,50,51,61,62,65,72,73] Padua Prediction Score (16 studies),[15,29,30,32,33,36,39,47,50,51,65,66,68,69,72,74] International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) models (8 studies),[29,30,33,39,49,51,52,59] the Geneva risk score (4 studies)[28,29,30,33] and the Kucher score (4 studies).[33,39,68,71] A summary of their associated characteristics and composite clinical variables is provided in *Appendix 1*, *Table 21*. Our patient and public involvement (PPI) group reviewed the most widely validated RAMs and identified all as appropriate and acceptable, in the context of face-to-face risk assessment. They did not feel patient-led completion of any RAM in isolation, to be feasible.

Statistical methods varied significantly between studies. Most studies reported the discrimination of the RAMs using a combination of the *C*-statistic and sensitivity or specificity.

Thromboprophylaxis was employed in about half (*n* = 25) of the studies, with the proportion receiving thromboprophylaxis ranging from 3.8% to 100%. It was not employed in three studies, and 23 studies did not report on thromboprophylaxis use. The use of thromboprophylaxis may lead to underestimation of predictive accuracy if a given RAM were to predict VTE events that were subsequently prevented by thromboprophylaxis.

Risk of bias and applicability assessments of included studies

The overall methodological quality of the 51 included studies[15,24–73] is summarised in *Table 2* and *Figures 2* and *3*. The methodological quality of the included studies was variable, with most studies

TABLE 1 Summary of design and patient characteristics

Author, year	Country	Design	Single/ multicentre	Sample size	Population	Mean age (years)	Female	VTE prophylaxis	Risk assessment model	Target condition (risk period)	Incidence
Autar, 2003[25]	UK	P, CS	Single	148	Hospitalised patients from orthopaedic, medical and surgical specialties	NR	NR	50%	Novel (Autar 2003)	DVT, not defined (90 days)	18.9%
Rogers, 2007[58]	USA	P, CS	Multi	91,308	Hospitalised surgical patients (undergoing vascular and general surgery)	NR	NR	NR	Novel (Rogers 2007)	VTE (30 days)	0.6%
Abdel-Razeq, 2010[24]	Jordan	P, CS	Single	606	Hospitalised (> 24 hours) cancer patients aged ≥ 18 years	51	49%	55%	Caprini (modified)	VTE, symptomatic (60 days)	3.5%
Bahl, 2010[26]	USA	R, CS	Multi	8216	Hospitalised surgical patients (undergoing general, vascular and urologic surgery)	NR	NR	NR	Caprini	VTE, (30 days)	1.4%
Barbar, 2010[15]	Italy	P, CS	Single	1180	Hospitalised medical patients	NR	53%	16%	Padua	VTE, symptomatic (90 days)	3.1%
Rothberg, 2011[60]	USA	R, CS	Multi	48,540	Hospitalised (≥ 3 days) medical patients aged ≥ 18 years	NR	NR	30%	Novel (Rothberg 2011)	VTE, hospital-associated (NR)	0.5%
Woller, 2011[71]	USA	R, CS	Multi	46,856	Hospitalised medical patients aged ≥ 18 years	61	54%	NR	Intermountain Kucher	VTE, defined by ICD-9 codes (90 days)	4.5%
Pannucci, 2012[55]	USA and Canada	R, CS	Multi	5761	Hospitalised (> 2 days) patients with a burn injury aged ≥ 18 years	46	31%	NR	Novel (Panunucci 2012)	VTE, not defined (NR)	1.0%
Rogers, 2012[57]	USA	R, CS	Multi	234,032	Hospitalised trauma patients	NR	NR	NR	TESS	VTE (NR)	NR
Bilimoria, 2013[27]	USA	R, CS	Multi	88,053	Hospitalised surgical patients (undergoing colorectal surgery)	NR	NR	NR	ACS NSQIP – Colon-specific ACS NSQIP – Universal	DVT, not defined (30 days)	2.3%

continued

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TABLE 1 Summary of design and patient characteristics (*continued*)

Author, year	Country	Design	Single/ multicentre	Sample size	Population	Mean age (years)	Female	VTE prophylaxis	Risk assessment model	Target condition (risk period)	Incidence
Hegsted, 2013[41]	USA	R, CS	Single	2281	Hospitalised (≥ 2 days) trauma patients aged ≥ 13 years	45	30%	NR	RAP	DVT, not defined or PE (NR)	DVT: 10.5% PE: 1.5%
Vardi, 2013[66]	Israel	P, CS	Single	1080	Hospitalised (≥ 2 days) sepsis patients aged > 18 years	75	48%	18%	Padua	VTE, hospital associated (NR)	1.3%
Ho, 2014[43]	Australia	R, CS	Single	357	Hospitalised major trauma patients	NR	25%	NR	TESS	VTE, symptomatic (NR)	20.7%
Liu, 2014[46]	China	P, CS	Single	287	Hospitalised acute stroke patients aged > 18 years	NR	37%	22%	Post-stroke DVT Prediction System	DVT (14 ± 3 days)	10.5%
Mahan, 2014[49]	USA	CC	Multi	417	Hospitalised (≥ 3 days) medical patients aged ≥ 18 years	NR	51%	NR	IMPROVE (7-factor)	VTE, hospital-associated (92 days)	NA
Nendaz, 2014[53]	Switzerland	P, CS	Multi	1478	Hospitalised (> 24 hours) medical patients aged ≥ 18 years	65	47%	57%	Geneva Padua	VTE, symptomatic including PE or DVT (90 days)	2.0%
Pannucci, 2014[54]	USA	P, CS	Multi	3576	Hospitalised surgical patients aged ≥ 18 years	NR	NR	66%	Novel (Panunucci, 2014)	VTE (90 days)	1.4%
Rosenberg, 2014[59]	USA	CC	Multi	19,217	Hospitalised (≥ 3 days) medical patients aged ≥ 18 years	NR	53%	43%	IMPROVE (7-factor)	VTE, defined by ICD-9 codes (90 days)	NA
Zhou 2014[73]	China	CC	Single	998	Hospitalised (≥ 2 days) medical patients aged > 18 years	NR	42%	15%	Caprini Padua	VTE, defined by ICD-10 codes (NR)	NA
Hewes, 2015[42]	USA	R, CS	Single	70	Hospitalised cancer patients (undergoing oesophagectomy)	NR	17%	96%	Caprini (modified)	VTE (60 days)	14.3%
de Bastos, 2016[34]	Brazil	P, CS	Single	11,091	Hospitalised medical patients aged > 18 years	50	39%	0%	Caprini	VTE, symptomatic (NR)	0.3%

TABLE 1 Summary of design and patient characteristics (*continued*)

Author, year	Country	Design	Single/ multicentre	Sample size	Population	Mean age (years)	Female	VTE prophylaxis	Risk assessment model	Target condition (risk period)	Incidence
Grant, 2016[38]	USA	R, CS	Multi	63,548	Hospitalised (≥ 2 days) medical patients aged ≥ 18 years	66	55%	61%	Caprini	VTE, hospital associated (90 days)	1.1%
Greene, 2016[39]	USA	R, CS	Multi	63,548	Acutely ill, hospitalised (≥ 2 days) medical patients aged ≥ 18 years	66	55%	61%	IMPROVE (4-factor) Intermountain Kucher Padua	VTE, hospital associated (90 days)	1.1%
Hachey, 2016[40]	USA	R, CS	Single	232	Hospitalised surgical patients (undergoing segmentectomy, lobectomy or pneumonectomy for lung cancer)	NR	57%	92%	Caprini	VTE (60 days)	5.2%
Lui, 2016[47]	China	CC	Single	640	Hospitalised (> 2 days) medical patients aged ≥ 18 years	NR	48%	NR	Caprini Padua	VTE (NR)	N/A
Lobastov, 2016[48]	Russia	R, CS[a]	Multi	140	Hospitalised high-risk emergency surgery patients (undergoing general and neurosurgery)	69	51%	100%	Caprini	DVT or PE, new (NR)	27.9%
Shaikh, 2016[61]	USA	R, CS	Multi	1598	Hospitalised surgical patients (undergoing plastic surgery)	50	81%	34%	Caprini	VTE, not defined (30 days)	1.5%
Elias, 2017[36]	USA	R, CS	Single	30,726	Hospitalised (> 2 days) medical and surgical patients	NR	56%	21%	Padua	VTE, defined by ICD-9 codes (NR)	0.8%
Frankel, 2017 (abstract)[37]	USA	CC	NR	149	Hospitalised surgical patients aged ≥ 18 years (undergoing robotic-assisted laparoscopic prostatectomy)	NR	NR	NR	Caprini	VTE, not defined (90 days)	NA
Krasnow, 2017 (abstract)[45]	USA	R, CS	Multi	1,099,093	Hospitalised surgical patients (major urological cancer surgery)	NR	NR	NR	Caprini	VTE, symptomatic (90 days)	1.2%

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TABLE 1 Summary of design and patient characteristics (*continued*)

Author, year	Country	Design	Single/ multicentre	Sample size	Population	Mean age (years)	Female	VTE prophylaxis	Risk assessment model	Target condition (risk period)	Incidence
Patell, 2017[56]	USA	R, CS	Single	2780	Hospitalised (> 24 hours) cancer patients aged > 18 years	62 (median)	44%	65%	Khorana	VTE, defined by ICD-9 codes (NR)	3.8%
Winoker, 2017[70]	USA	R, CS	Multi	300	Hospitalised surgical patients (undergoing urological surgery using robot-assisted partial nephrectomy)	61 (median)	38%	NR	ACS NSQIP – Universal	VTE, not defined (NR)	0.3%
Blondon, 2018[30]	Switzerland	P, CS	Multi	1478	Hospitalised (> 24h) medical patients aged ≥ 18 years	65	47%	59%	IMPROVE (7-factor) Geneva[b] Padua[b]	VTE, symptomatic including PE or DVT (90 days)	2.0%
Chen, 2018[32]	China	CC	Single	390	Hospitalised (> 2 days) patients aged ≥ 18 years with and without DVT	NR	49%	41%	Caprini Padua	DVT (NR)	NA
Dornbus, 2018 (abstract)[35]	USA	R, CS	NR	2830	Hospitalised surgical patients (undergoing neurosurgery)	NR	NR	NR	Caprini	VTE, not defined (NR)	NR
Vaziri, 2018[67]	USA	R, CS	Single	1006	Hospitalised surgical patients (undergoing neurosurgery)	NR	54%	NR	ACS NSQIP – Universal	VTE, not defined (NR)	1.3%
Vincentelli, 2018[68]	Italy	CC	Multi	1215	Acutely ill, hospitalised medical patients aged > 18 years	NR	56%	NR	Chopard Kucher Padua	VTE (NR)	NA
Zhou, 2018[72]	China	CC	Single	1804	Hospitalised (≥ 2 days) medical patients aged > 18 years	NR	41%	5%	Caprini Padua	VTE, defined by ICD-10 codes (NR)	NA
Blondon, 2019a[3]	Italy	R, CS[a]	Single	1180	Hospitalised medical patients	72	53%	20%	Geneva (simplified)	VTE, symptomatic (90 days)	3.1%
Blondon, 2019b (abstract)[29]	Switzerland	R, CS[a]	Multi	991	Hospitalised elderly medical patients	75	45%	NR	Geneva (simplified) IMPROVE (NR) Padua	VTE, symptomatic (NR)	15.0%

TABLE 1 Summary of design and patient characteristics (*continued*)

Author, year	Country	Design	Single/ multicentre	Sample size	Population	Mean age (years)	Female	VTE prophylaxis	Risk assessment model	Target condition (risk period)	Incidence
Cobben, 2019[33]	Netherlands	CC	Multi	556	Hospitalised (> 24 hours) medical patients	NR	48%	NR	Caprini Geneva IMPROVE (4-factor) IMPROVE (7-factor) Intermountain Kucher Lecumberri NAVAL NICE Guideline Padua PRETEMED Guideline Zakai *et al.* (model 2)	VTE (NR)	NA
Tachino, 2019[64]	Japan	R, CS	Multi	859	Hospitalised (> 24 hours) trauma patients aged ≥ 18 years	NR	36%	NR	RAP Quick RAP	VTE (NR)	3.0%
Tian, 2019[65]	China	R, CS	Single	533	Hospitalised surgical patients (undergoing thoracic surgery)	53	47%	0%	Caprini Khorana Padua Novel (Rogers, 2007)	VTE (NR)	8.4%
Bo, 2020[31]	China	P, CS	Multi	24,524	Hospitalised (≥ 2 days) patients from medical and surgical specialties aged ≥ 18 years	57	43%	NR	Caprini	DVT (NR)	0.9%
Hu, 2020[44]	China	CC	Single	442	Hospitalised (≥ 2 days) cancer patients aged ≥ 18 years	NR	38%	3.8	Caprini Khorana	VTE, defined by ICD-10 codes (NR)	NA
Mlaver, 2020[50]	USA	CC	Single	189	Hospitalised surgical patients (undergoing hepatobiliary, colorectal, endocrine, plastic, transplant or general surgery)	NR	NR	NR	Caprini Padua	VTE, not defined (NR)	NA

continued

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TABLE 1 Summary of design and patient characteristics (*continued*)

Author, year	Country	Design	Single/ multicentre	Sample size	Population	Mean age (years)	Female	VTE prophylaxis	Risk assessment model	Target condition (risk period)	Incidence
Moumneh, 2020[51]	France	R, CS[a]	Multi	14,660	Acutely ill, hospitalised (≥ 2 days) medical patients aged ≥ 40 years	73	50%	46.1	Caprini Padua IMPROVE (7 factor)	VTE, symptomatic including PE or DVT (90 days)	1.8%
Nafee, 2020[52]	35 countries	R, CS[a]	Multi	6459	Hospitalised medical patients	76	55%	100	IMPROVE (NR) Novel (Nafee, 2020a) Novel (Nafee, 2020b)	VTE (77 days)	6.3%
Shang, 2020[62]	China	CC	Single	2878	Hospitalised (≥ 2 days) cancer patients aged ≥ 18 years	56	53%	NR	Caprini (2009) Caprini (2013)	VTE, (NR)	NA
Shen, 2020[63]	China	CC	Single	148	Hospitalised (≥ 2 days) medical patients aged ≥ 18 years	NR	NR	0	Novel (Shen 2020)	VTE, not defined (NR)	NA
Wang, 2020[69]	China	CC	Single	1579	Hospitalised (≥ 3 days) medical patients aged ≥ 18 years	53	43%	NR	Padua	VTE (NR)	NA

ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program; CC, case–control; CS, cohort study; NA, not applicable; NR, not reported; P, prospective; R, retrospective; RAP, risk assessment profile; TESS, Trauma Embolic Scoring System.

a Prospective cohort study with retrospective analysis, thus classified as retrospective cohort study.

b Data overlap with Nendaz, 2014.[54]

TABLE 2 Summary of each study's risk of bias and applicability concern using the PROBAST tool – review authors' judgements

	Risk of bias				Concern regarding applicability			Overall judgement	
Author, year	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	Risk of bias	Applicability
Abdel-Razeq, 2010[24]	High	High	High	High	High	High	High	High	High
Autar, 2003[25]	High	High	High	High	High	High	High	High	High
Bahl, 2010[26]	High	High	High	High	Unclear	Unclear	Unclear	High	Unclear
Barbar, 2010[15]	Low	Unclear	Unclear	High	Low	Unclear	Unclear	High	Unclear
Bilimoria, 2013[27]	Low	Low	Low	High	Low	Low	Low	High	Low
Blondon, 2019a[28]	Low	Unclear	High	High	Low	Low	Low	High	Low
Blondon, 2019b (abstract)[29]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Blondon, 2018[30]	Low	Unclear	Unclear	High	Unclear	Low	Unclear	High	Unclear
Bo, 2020[31]	Low	Unclear	Unclear	Unclear	High	Low	Low	Unclear	High
Chen, 2018[32]	High	High	High	High	Unclear	High	High	High	High
Cobben, 2019[33]	Unclear	Unclear	High	High	Unclear	Low	Unclear	High	Unclear
de Bastos, 2016[34]	High	Low	High	High	High	Low	Low	High	High
Dornbus, 2018 (abstract)[35]	High	Unclear	High	Unclear	Unclear	Unclear	Unclear	High	Unclear
Elias, 2017[36]	High	Unclear	High	High	Low	Low	High	High	High
Frankel, 2017 (abstract)[37]	High	Unclear	Unclear	High	High	Unclear	Unclear	High	High
Grant, 2016[37]	High	Unclear	Unclear	Unclear	Low	Low	Low	High	Low
Greene, 2016[39]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear	Low
Hachey, 2016[38]	High	Unclear	Unclear	High	High	Low	High	High	High
Hegsted, 2013[41]	High	Unclear	High	High	High	Low	Unclear	High	High
Hewes, 2015[42]	High	Unclear	Unclear	High	High	Unclear	Low	High	High
Ho, 2014[43]	Unclear	Unclear	Unclear	High	High	Unclear	Unclear	High	High

continued

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TABLE 2 Summary of each study's risk of bias and applicability concern using the PROBAST tool – review authors' judgements (*continued*)

	Risk of bias				Concern regarding applicability			Overall judgement	
Author, year	**Participants**	**Predictors**	**Outcome**	**Analysis**	**Participants**	**Predictors**	**Outcome**	**Risk of bias**	**Applicability**
Hu, 2020[44]	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	High
Krasnow, 2017 (abstract)[45]	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	High
Liu, 2014[46]	Low	Low	Unclear	Unclear	High	High	High	Unclear	High
Liu, 2016[47]	High	Unclear	High	High	High	Low	Low	High	High
Lobastov, 2016[48]	Unclear	Unclear	Unclear	High	High	Low	High	High	High
Mahan, 2014[49]	Low	Unclear	Unclear	Unclear	High	Low	Unclear	Unclear	High
Mlaver, 2020[50]	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	High
Moumneh, 2020[51]	High	Unclear	Unclear	Low	High	Low	Low	High	High
Nafee, 2020[52]	Unclear	Low	Low	Low	Unclear	Low	Low	Unclear	Unclear
Nendaz, 2014[53]	Low	Unclear	Low	High	Low	Unclear	Low	High	Unclear
Pannucci, 2012[55]	High	Unclear	Unclear	High	High	High	Unclear	High	High
Pannucci, 2014[54]	Low	Unclear	High	High	High	Low	Low	High	High
Patell, 2017[56]	High	Unclear	Unclear	High	High	Unclear	Unclear	High	High
Rogers, 2007[58]	Unclear	Unclear	Unclear	High	Low	Unclear	Unclear	High	Unclear
Rogers, 2012[57]	High	High	Unclear	High	High	High	Unclear	High	High
Rosenberg, 2014[59]	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Rothberg, 2011[60]	High	Unclear	Unclear	High	Low	Unclear	Unclear	High	Unclear
Shaikh, 2016[61]	High	Unclear	High	High	High	Unclear	High	High	High
Shang, 2020[62]	Low	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	High
Shen, 2020[63]	Unclear	High	Unclear	Unclear	High	Unclear	Unclear	High	High
Tachino, 2019[64]	High	Unclear	Unclear	High	High	Unclear	Unclear	High	High
Tian, 2019[65]	High	Unclear	High	High	High	High	High	High	High

TABLE 2 Summary of each study's risk of bias and applicability concern using the PROBAST tool – review authors' judgements (*continued*)

	Risk of bias				Concern regarding applicability			Overall judgement	
Author, year	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	Risk of bias	Applicability
Vardi, 2013[66]	Unclear	Low	Low	High	High	Low	Low	High	High
Vaziri, 2018[67]	Unclear	Unclear	Unclear	High	High	Unclear	Unclear	High	High
Vincentelli, 2018[68]	High	Low	Unclear	High	High	Low	Unclear	High	High
Wang, 2020[69]	Low	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	High
Winoker, 2017[70]	High	Unclear	Unclear	High	High	High	High	High	High
Woller, 2011[71]	High	High	Unclear	High	Unclear	Unclear	Unclear	High	Unclear
Zhou 2014[73]	Unclear	Unclear	Unclear	High	High	Unclear	Unclear	High	High
Zhou, 2018[72]	Low	High	High	High	High	Unclear	Unclear	High	High

Green shading = favourable result, yellow shading = unclear results, red shading = unfavourable result.

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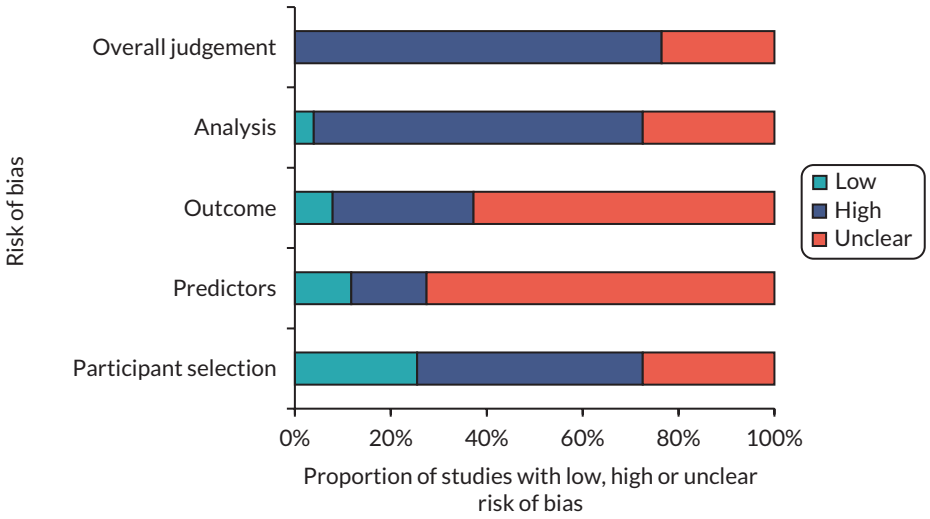

FIGURE 2 PROBAST assessment summary graph – review authors' judgements on risk of bias.

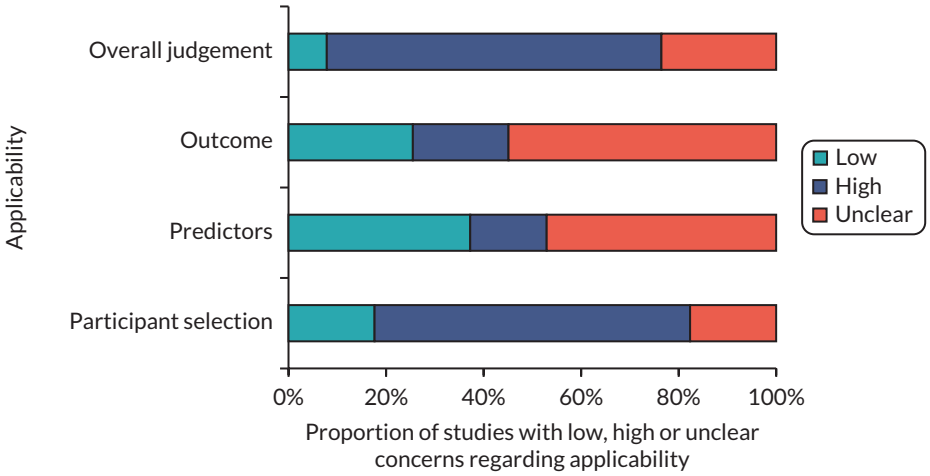

FIGURE 3 PROBAST assessment summary graph – review authors' judgements on applicability.

having high or unclear risk of bias in at least one item of the PROBAST tool. The main sources of potential bias were related to the following domains: (1) patient selection factors, such as retrospective data collection, incomplete patient enrolment or unclear criteria for patients receiving VTE prophylaxis; (2) predictor and outcome bias arising from inappropriate inclusion of predictors within RAMs, unclear methods of outcome definition, low event rates and missing predictor or outcome data; (3) analysis factors, such as small sample sizes, inappropriate handling of missing data and failure in reporting relevant performance measures such as calibration.

Assessment of applicability to the review question led to the majority of studies being classed either as high (n = 35)[24,25,31,32,34,36,37,40–51,54–57,61–70,72,73] or unclear (n = 12)[15,26,29,30,33,35,52,53,58,60,71] risk of inapplicability. These assessments were generally related to patient selection (highly selected study populations, e.g. single pathologies, single site settings), predictors (inconsistency in definition, assessment or timing of predictors) and outcome determination.

Quantitative data synthesis (summary of results)

As there were a reasonable number of studies to compare, a summary of the *C*-statistics for studies involving medical, surgical and trauma patients, respectively, is presented in *Figure 4*, with the results grouped by RAM. Results of other hospital inpatients are presented in *Appendix 1*, *Table 22*. *C*-statistics

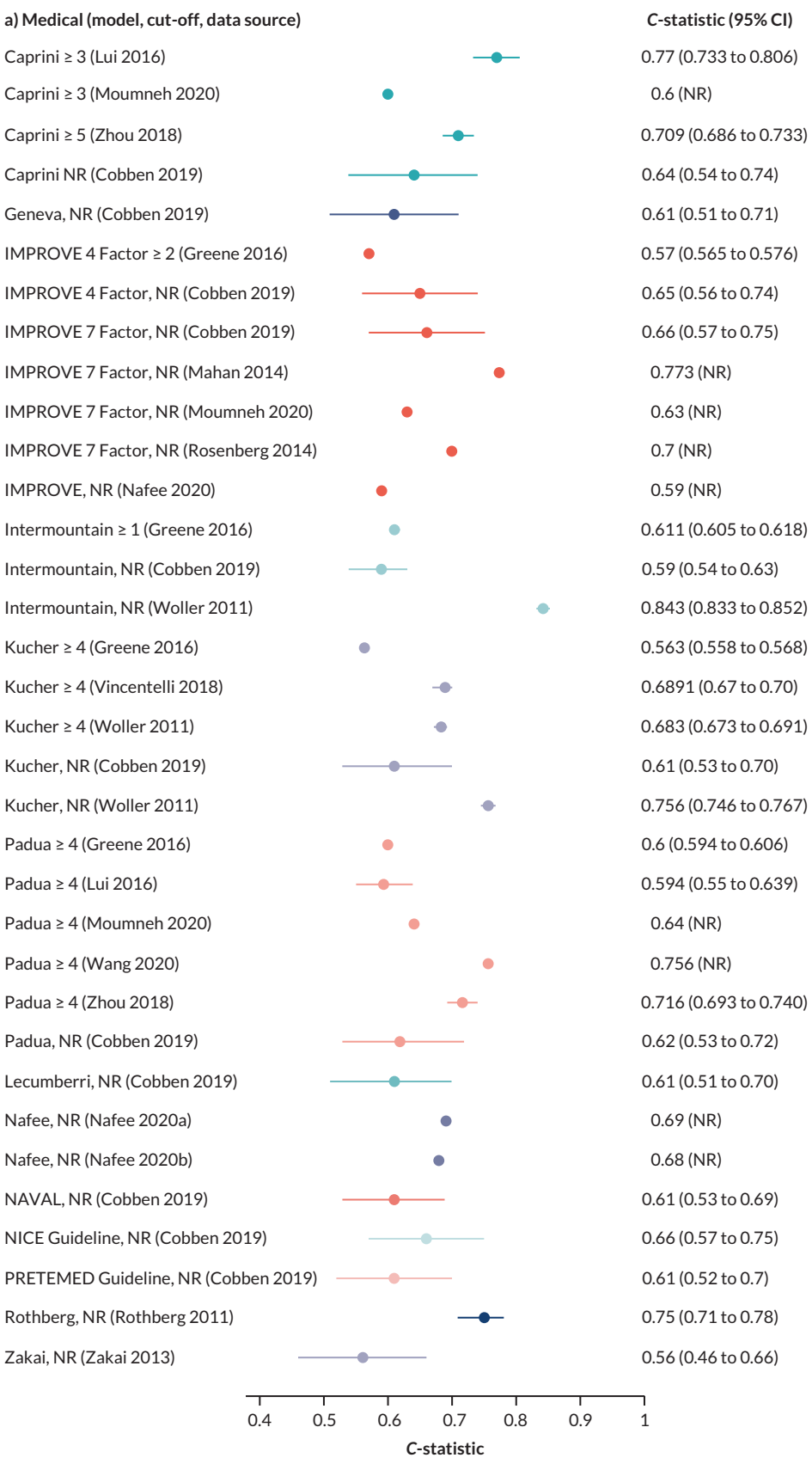

FIGURE 4 *C*-statistics by model for studies involving (a) medical, (b) surgical and (c) trauma inpatients. ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program; CI, confidence interval; NR, not reported; RAP, risk assessment profile. (*continued*)

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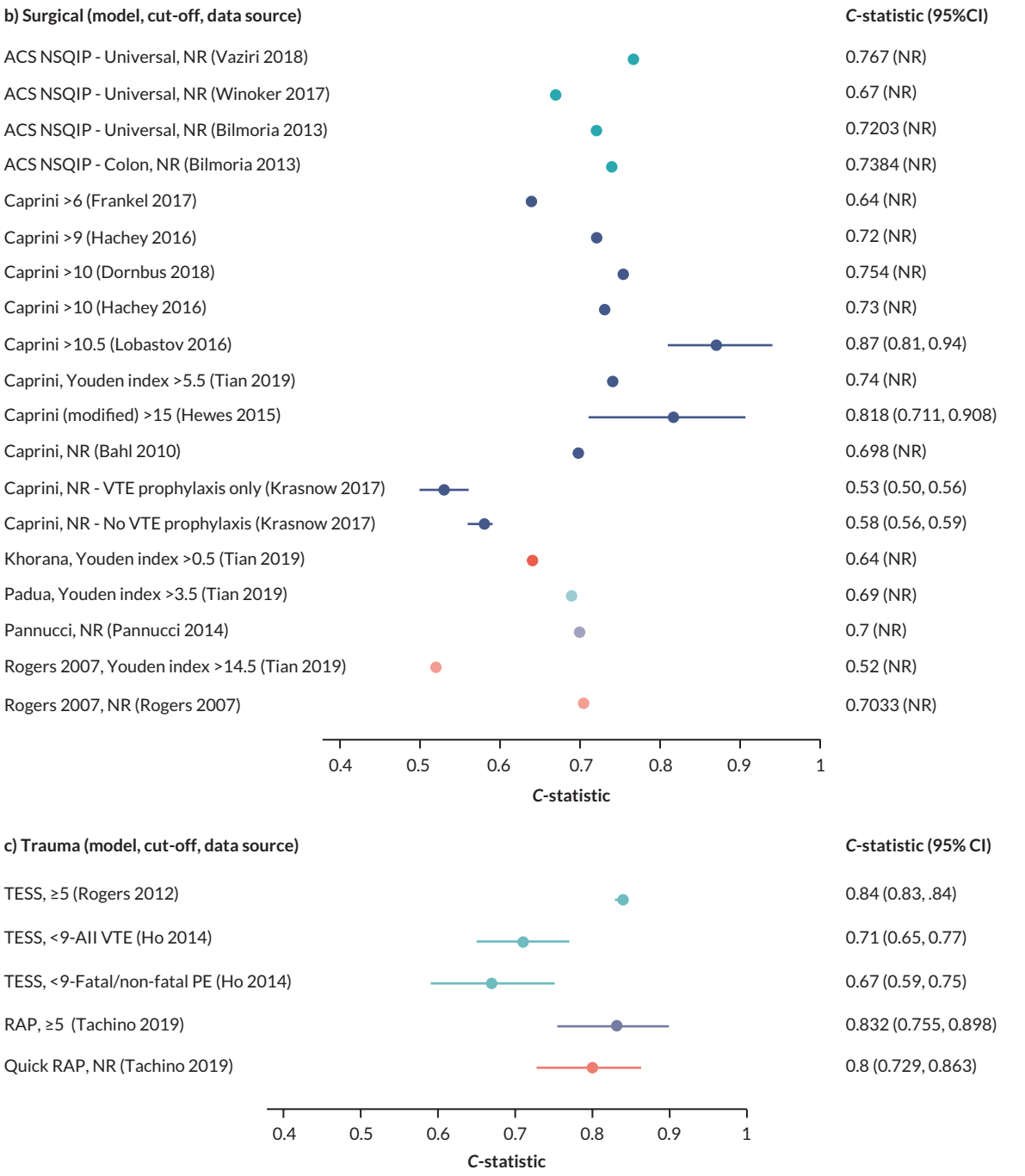

FIGURE 4 C-statistics by model for studies involving (a) medical, (b) surgical and (c) trauma inpatients.
ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program; CI, confidence interval; NR, not reported; RAP, risk assessment profile.

varied markedly between these studies and between models, with no RAM performing obviously better than other models. In studies evaluating a single model, *C*-statistics[23] were sometimes weak (< 0.7; 10 studies with 17 data points), often good (0.7–0.8; 17 studies with 20 data points) and a few were excellent (> 0.8; 5 studies with 5 data points). There was marked heterogeneity between multiple studies evaluating the same model. Studies evaluating multiple (more than 3) models[33,39] tended to report weak accuracy across all the models (*C*-statistic < 0.7; 2 studies with 16 data points).

Table 3 shows the sensitivity and specificity at various thresholds for studies involving medical, surgical and trauma patients, respectively, with the results grouped by RAM. Interpretation was again limited by marked heterogeneity, which was exacerbated when different thresholds were reported by different studies evaluating the same model. Model accuracy was generally poor, with high sensitivity usually reflecting a threshold effect, as evidenced by corresponding low specificity (and vice versa).

Summary of key findings

- A number of RAMs have been evaluated for potential VTE risk stratification of hospitalised adult patients.
- In general, external validation studies have poor designs and limited generalisability.
- Available data suggest that RAMs have generally weak predictive accuracy for VTE.
- Use of VTE prophylaxis varied across the study populations and was not reported for many studies.
- There is insufficient evidence and too much heterogeneity to recommend the use of any particular RAM for predicting the risk of developing VTE in hospital inpatients.

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TABLE 3 Sensitivity and specificity for studies involving medical, surgical and trauma inpatients

Risk assessment models	Threshold or cut-off	End point	Data source	Sensitivity (95% CI)	Specificity (95% CI)
Medical inpatients					
Caprini (7 studies)	Risk score ≥ 3	VTE	Lui 2016[47]	70.9% (NR)	73.4% (NR)
	Risk score ≥ 3	VTE	Moumneh 2020[51]	98.1% (95.6 to 99.4)	7.5% (7.1 to 8.0)
	Risk score ≥ 3	VTE	Zhou 2014[73]	82.3% (NR)	60.4% (NR)
	Risk score ≥ 3	VTE	Zhou 2018[72]	84.3% (NR)	33.5% (NR)
	Risk score ≥ 5	VTE	Zhou 2018[72]	57.1% (NR)	75.4% (NR)
	Risk score ≥ 5	VTE	Grant 2016[38]	69.7% (NR)	50.28% (NR)
	Risk score ≥ 7	VTE	Grant 2016[38]	42.69% (NR)	74.71% (NR)
	Risk score ≥ 9	VTE	Grant 2016[38]	18.51% (NR)	89.03% (NR)
	NR[a]	VTE	de Bastos 2016[34]	86.5% (NR)	47.0% (NR)
	NR	VTE	Cobben 2019[33]	88.6% (NR)	21.4% (NR)
Chopard (1 study)	Risk score ≥ 3	VTE	Vincentelli 2018[68]	64.2% (38.4 to 81.9)	57.7% (63.9 to 79.4)
Geneva models (4 studies)	Risk score ≥ 3	VTE	Blondon 2018;[30] Nendaz 2014[53]	All patients: 90.0% (73.5 to 97.9)	All patients: 35.3% (32.8 to 37.8)
				No prophylaxis: 85% (NR)	No prophylaxis: NR
	NR	VTE	Cobben 2019[33]	75.0% (NR)	34.1% (NR)
	Simplified model: Risk score ≥ 3	VTE	Blondon 2019a[28]	95.0% (NR)	44.0% (NR)
	Simplified model: NR	VTE	Blondon 2019b (abstract)[29]	86.4% (NR)	NR
IMPROVE models (4 studies)	4-factor model: NR	VTE	Cobben 2019[33]	27.9% (NR)	85.4% (NR)
	7-factor model: Risk score ≥ 2	VTE	Moumneh 2020[51]	73.8% (68.0 to 79.0)	47.1% (46.3 to 47.9)

TABLE 3 Sensitivity and specificity for studies involving medical, surgical and trauma inpatients (*continued*)

Risk assessment models	Threshold or cut-off	End point	Data source	Sensitivity (95% CI)	Specificity (95% CI)
	7-factor model: Risk score 2–3	VTE	Blondon 2018;[30] Nendaz 2014[53]	All patients: 87% (NR)	All patients: NR
				No prophylaxis: 85% (NR)	No prophylaxis: NR
	7-factor model: Risk score ≥ 3	VTE	Blondon 2018;[30] Nendaz 2014[53]	All patients: 73% (NR)	All patients: NR
				No prophylaxis: 54% (NR)	No prophylaxis: NR
	7-factor model: Risk score ≥ 4	VTE	Moumneh 2020[51]	24.7% (19.6 to 30.4)	85.5% (84.9, 86.1)
	7-factor model: NR	VTE	Cobben 2019[33]	63.3% (NR)	70.7% (NR)
	NR	VTE	Blondon 2019b (abstract)[29]	57.6% (NR)	NR
Intermountain (1 study)	NR	VTE	Cobben 2019[33]	26.4% (NR)	90.2% (NR)
Kucher (2 studies)	Risk score ≥ 4	VTE	Vincentelli 2018[68]	25.1% (17.0 to 55.1)	92.9% (81.0, 95.4)
	NR	VTE	Cobben 2019[33]	28.0% (NR)	85.7% (NR)
Lecumberri (1 study)	NR	VTE	Cobben 2019[33]	61.6% (NR)	46.3% (NR)
NAVAL (1 study)	NR	VTE	Cobben 2019[33]	19.0% (NR)	92.7% (NR)
NICE Guidelines (1 study)	NR	VTE	Cobben 2019[33]	77.6% (NR)	39.0% (NR)
Padua (10 studies)	Risk score ≥ 4	VTE	Barbar 2010[15]	94.6% (NR)	62.0% (NR)
	Risk score ≥ 4	VTE	Blondon 2018;[30] Nendaz 2014[53]	All patients: 73.3% (54.1 to 87.7)	All patients: 51.9% (49.3, 54.5)
				No prophylaxis: 62% (NR)	No prophylaxis: NR
	Risk score ≥ 4	VTE	Lui 2016[47]	23.4% (NR)	85.6% (NR)
	Risk score ≥ 4	VTE	Moumneh 2020[51]	91.6% (87.6 to 94.7)	25.6% (24.9, 26.3)

continued

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TABLE 3 Sensitivity and specificity for studies involving medical, surgical and trauma inpatients (*continued*)

Risk assessment models	Threshold or cut-off	End point	Data source	Sensitivity (95% CI)	Specificity (95% CI)
	Risk score ≥ 4	VTE	Zhou 2014[73]	30.1% (NR)	12.7% (NR)
	Risk score ≥ 4	VTE	Zhou 2018[72]	49.1% (NR)	83.8% (NR)
	Risk score ≥ 4	VTE	Vincentelli 2018[68]	52.4% (38.4 to 81.9)	72.3% (63.9, 79.4)
	Risk score ≥ 4	VTE	Wang 2020[69]	76.2% (NR)	61.6% (NR)
	NR	VTE	Blondon 2019b (abstract)[29]	72.7% (NR)	NR
	NR	VTE	Cobben 2019[33]	61.8% (NR)	48.8% (NR)
PRETEMED Guidelines (1 study)	NR	VTE	Cobben 2019[33]	81.6% (NR)	24.4% (NR)
Shen 2020 (1 study)	NR	VTE	Shen 2020[63]	77.8% (NR)	84.7% (NR)
Zakai 2013 (1 study)	Model 2: NR	VTE	Cobben 2019[33]	63.8% (NR)	31.7% (NR)
Surgical inpatients					
Caprini (8 studies)	Risk score > 5	VTE	Hachey 2016[40]	100% (100 to 100)	7.2% (4.1, 11.0)
	Risk score ≥ 5	VTE	Mlaver 2020[50]	88.9% (NR)	32.7% (NR)
	Risk score > 5	VTE	Shaikh 2016[61]	70.8% (48.9 to 87.4)	39.39% (37.0, 41.9)
	Youden index > 5.5	VTE	Tian 2019[65]	76.0% (NR)	64.0% (NR)
	Risk score > 6	VTE	Frankel 2017 (abstract)[37]	61.5% (NR)	59.8% (NR)
	Risk score > 6	VTE	Shaikh 2016[61]	58.3% (36.6 to 77.9)	60.1% (57.6, 62.5)
	Risk score > 7	VTE	Hachey 2016[40]	100% (100 to 100)	31.4% (25, 37.3)
	Risk score > 9	VTE	Hachey 2016[40]	83.3% (58.3 to 100)	60.5% (54.4, 67.3)
	Risk score > 9	VTE	Shaikh 2016[61]	16.7% (NR)	93.3% (NR)
	Risk score > 10	VTE	Hachey 2016[40]	75.0% (50 to 100)	69.6% (64.6, 76.4)
	Risk score > 10	VTE	Dornbus 2018 (abstract)[24]	78.9% (NR)	60.9% (NR)
	Risk score > 10.5	DVT or PE	Lobastov 2016[48]	95.0% (NR)	73.0% (NR)
	Risk score > 15[b]	VTE	Hewes 2015[42]	100% (100 to 100)	66.7% (55.0, 78.3)

TABLE 3 Sensitivity and specificity for studies involving medical, surgical and trauma inpatients (*continued*)

Risk assessment models	Threshold or cut-off	End point	Data source	Sensitivity (95% CI)	Specificity (95% CI)
Khorana (1 study)	Youden index > 0.5	VTE	Tian 2019[65]	78.0% (NR)	48.0% (NR)
Padua (2 studies)	Risk score ≥ 4	VTE	Mlaver 2020[50]	61.1% (NR)	47.4% (NR)
	Youden index > 3.5	VTE	Tian 2019[65]	36.0% (NR)	93.0% (NR)
Rogers 2007 (1 study)	Youden index > 14.5	VTE	Tian 2019[65]	53.0% (NR)	54.0% (NR)
Trauma patients					
RAP (2 studies)	Risk score ≥ 5	VTE	Tachino 2019[64]	100% (86.8 to 100)	37.9% (34.6, 41.3)
	Risk score 5 to ≤ 14	DVT or PE	Hegsted 2013[41]	DVT: 82.0% (77 to 87) PE: 71.0% (55 to 86)	DVT: 57.0% (55, 59) PE: 53.0% (51, 56)
	Risk score > 14	DVT or PE	Hegsted 2013[41]	DVT: 15.0% (11 to 20) PE: 12.0% (1 to 23)	DVT: 97.0% (97, 98) PE: 96.0% (95, 97)
TESS (2 studies)	Risk score ≥ 5	VTE	Rogers 2012[57]	77.4% (NR)	75.6% (NR)
	Risk score < 9	VTE	Ho 2014[43]	All VTE: 97.0% (91 to 99)	All VTE: 27.0% (22, 32)
	Risk score < 9	VTE	Ho 2014[43]	Fatal and non-fatal PE: 97.0% (87 to 99)	Fatal and non-fatal PE: 24.0% (20, 29)
	Risk score < 9	VTE	Ho 2014[43]	Fatal PE only: 100% (81 to 100)	Fatal PE only: 20.0% (13, 28)

CI, Confidence interval; NR, not reported; RAP, risk assessment profile; TESS, Trauma Embolic Scoring System.
a Paper states 'moderate and high risk'.
b Modified Caprini model.

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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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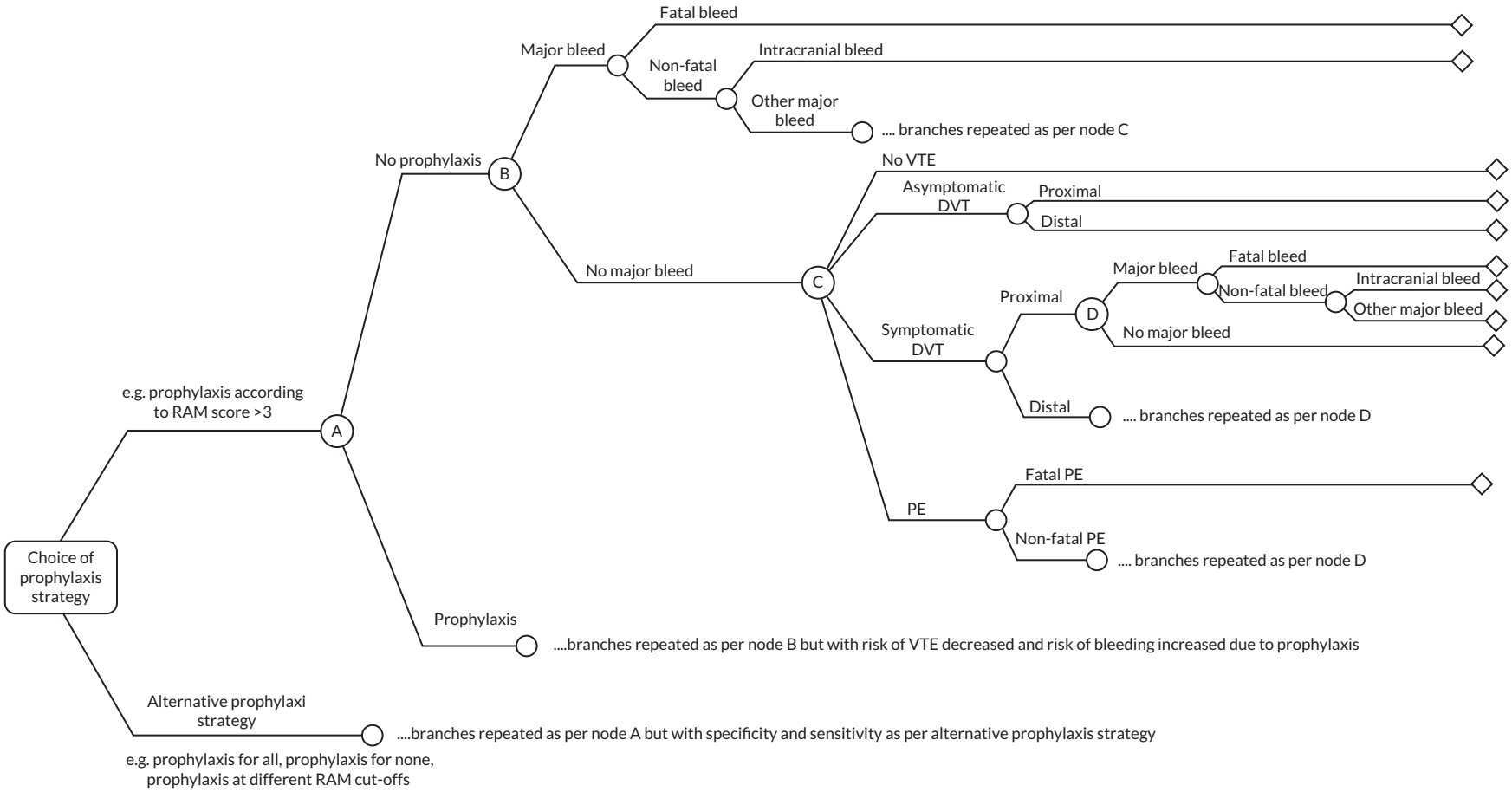

FIGURE 5 Short-term (6-month) decision tree model structure.

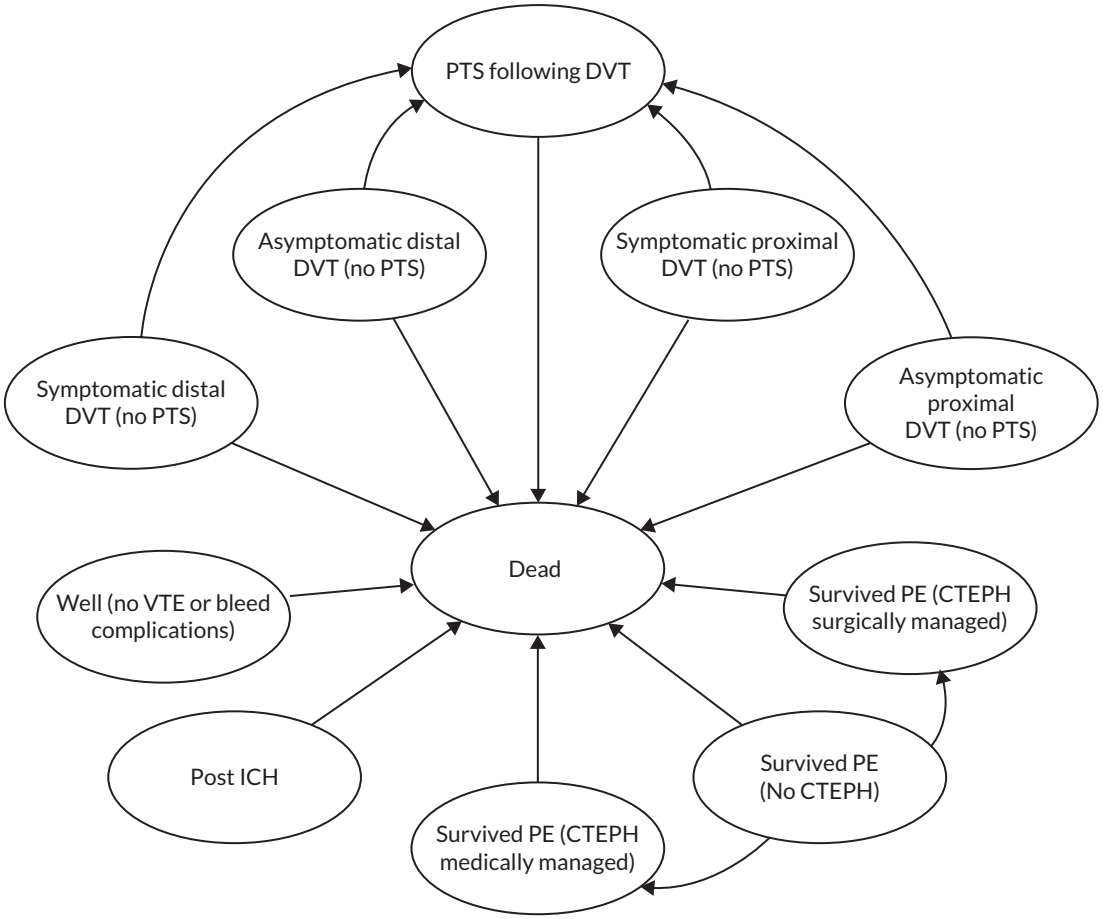

FIGURE 6 Long-term Markov model.

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.

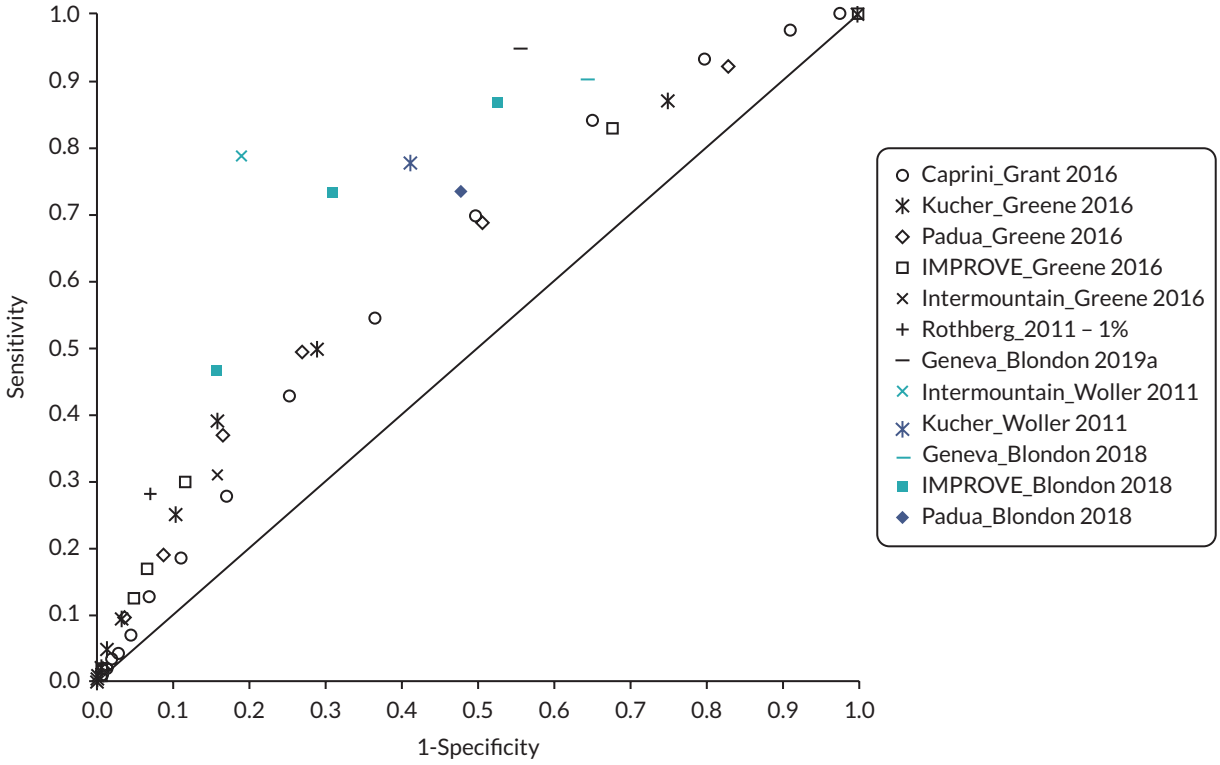

FIGURE 7 ROC curve for multiple risk assessment models evaluated in cohorts of medical inpatients.

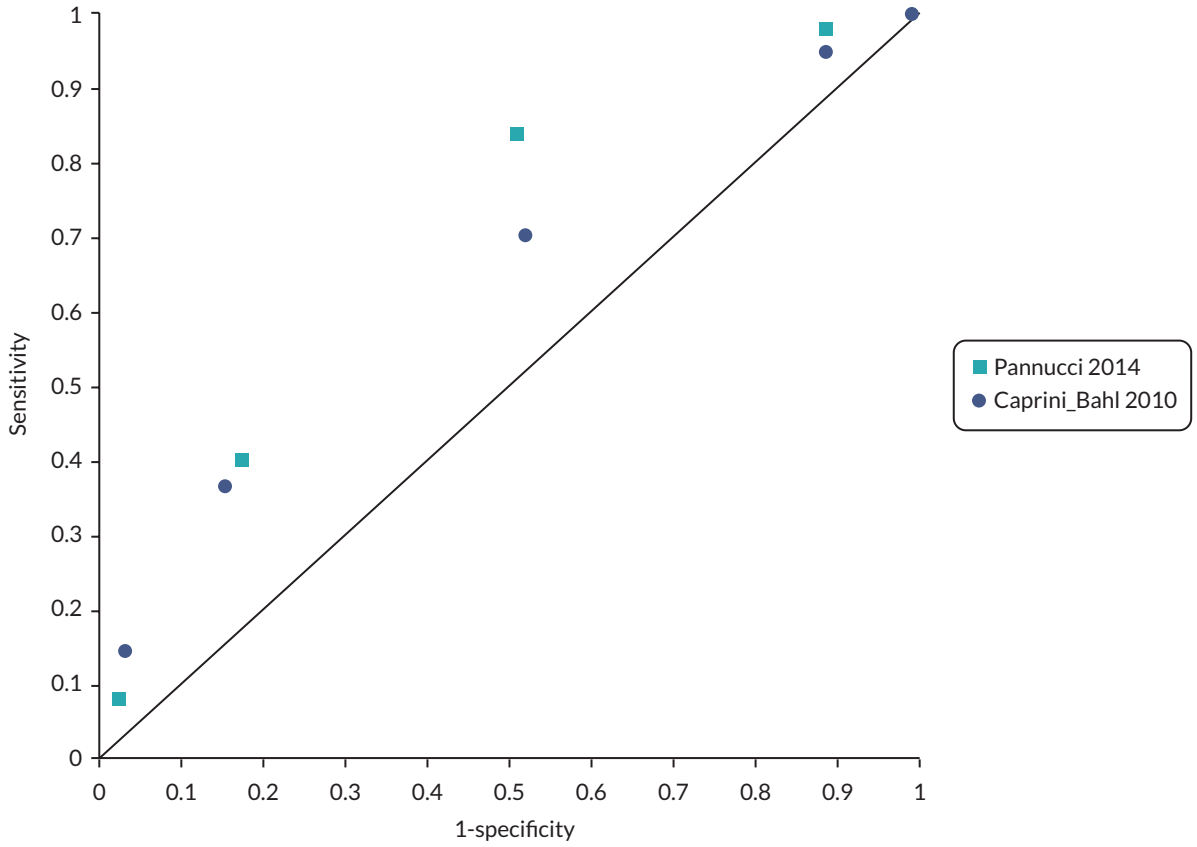

FIGURE 8 ROC curve for multiple risk assessment models evaluated in cohorts of surgical inpatients.

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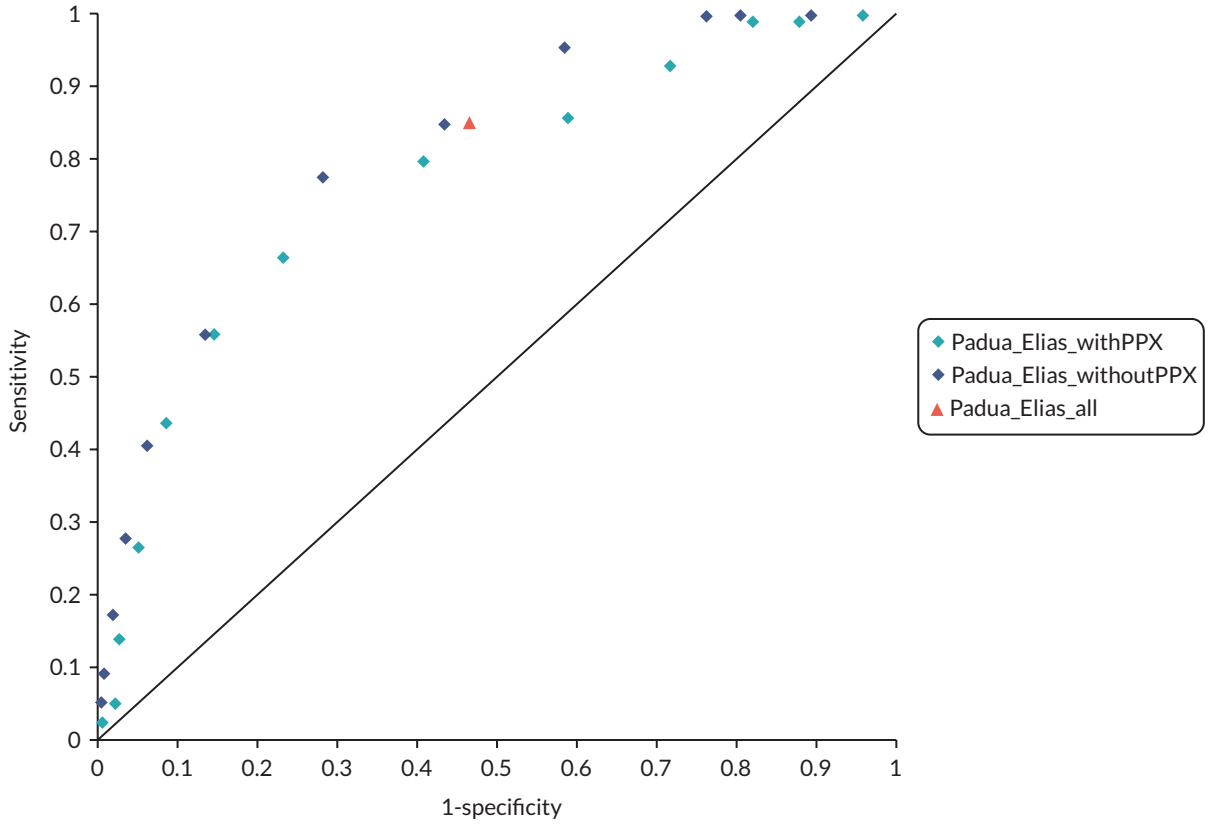

FIGURE 9 ROC curve for the Padua RAM in a mixed cohort of medical and surgical patients reported by Elias *et al.*[36] [with/without prophylaxis (PPX) and all].

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

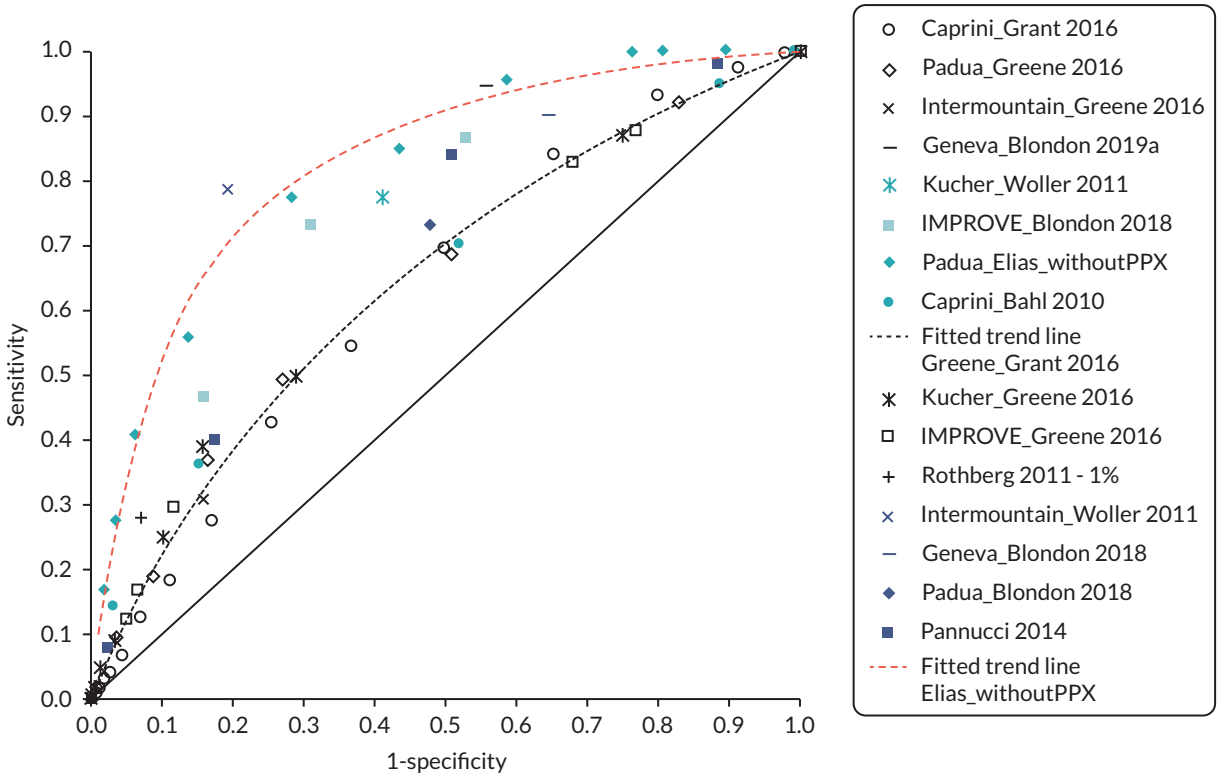

FIGURE 10 ROC curve for all studies (surgical, medical and mixed) with trend lines fitted.

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

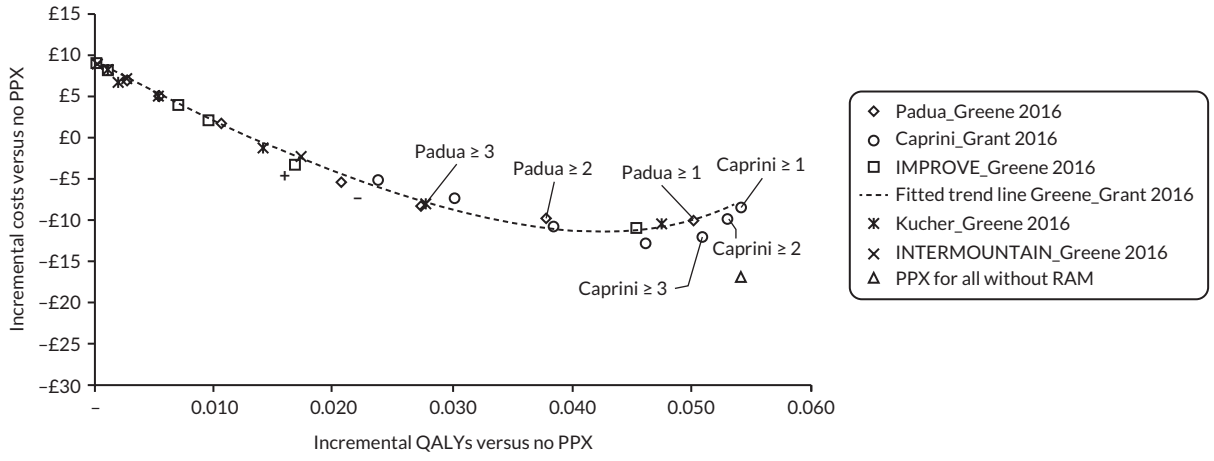

FIGURE 13 Deterministic base-case results for medical inpatients when using RAMs evaluated in a single cohort of patients (Greene *et al.*[39] and Grant *et al.*[38]).

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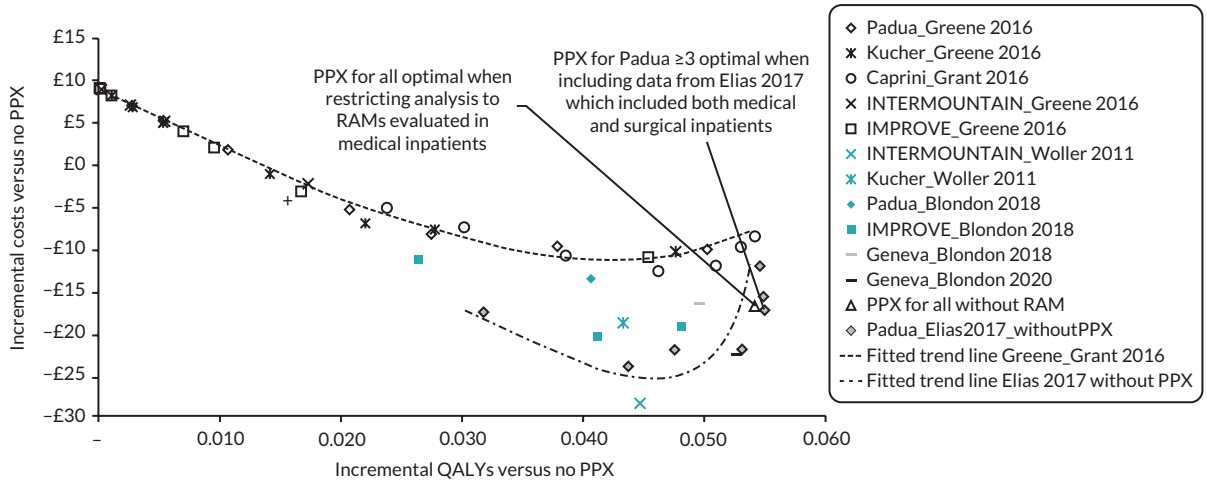

FIGURE 14 Deterministic base-case results for medical inpatients when using RAMs evaluated by Greene *et al.*[39] and Grant *et al.*[38] and RAMs evaluated in other cohorts (including the mixed cohort of surgical and medical patients reported by Elias *et al.*[36]).

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

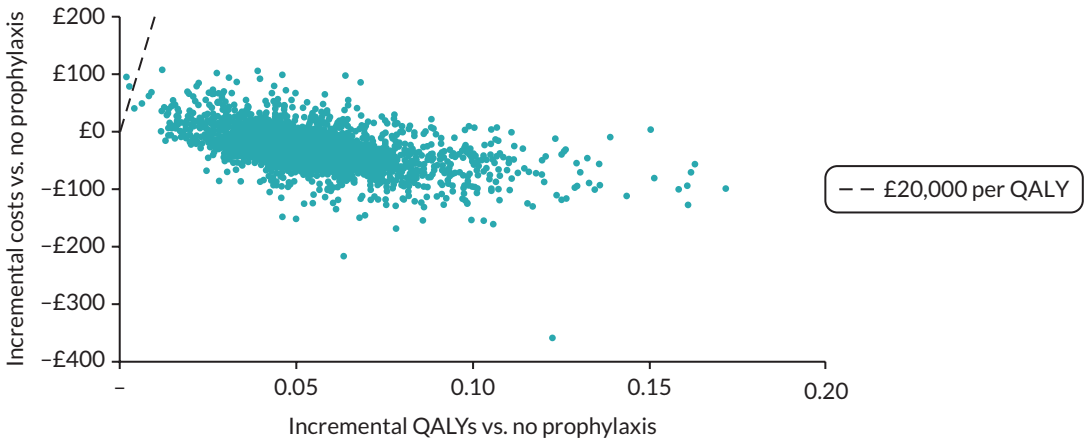

FIGURE 15 Cost-effectiveness plane for prophylaxis for all versus prophylaxis for none in medical inpatients.

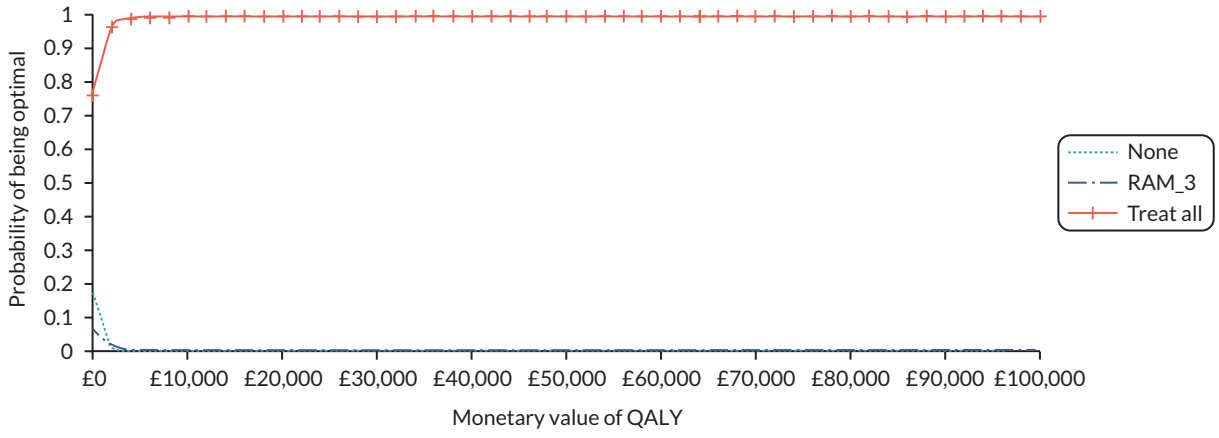

FIGURE 16 Cost-effectiveness acceptability curve (CEAC) for medical inpatients (applying performance of Padua RAM from Greene *et al.*[39]). Strategies with < 1% probability across all values of a QALY are not plotted.

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

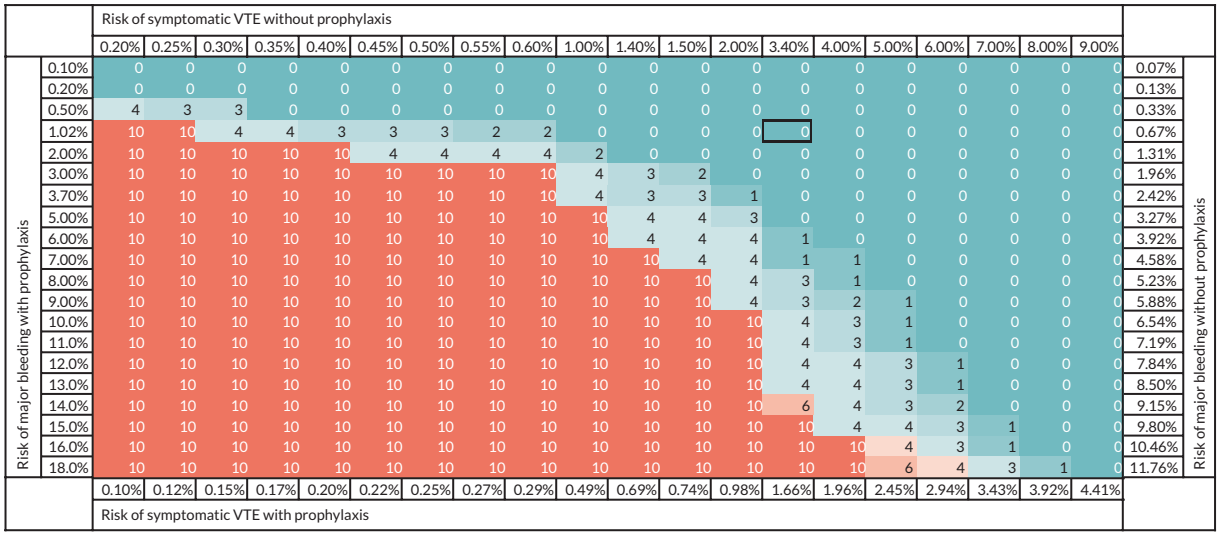

FIGURE 17 Optimal risk assessment strategy for cohorts of medical inpatients with varying levels of baseline risks (box indicates base-case scenario). It should be noted that the rows and columns do not represent equal steps in risk; red (10) indicates prophylaxis for none is optimal and blue (0) indicates 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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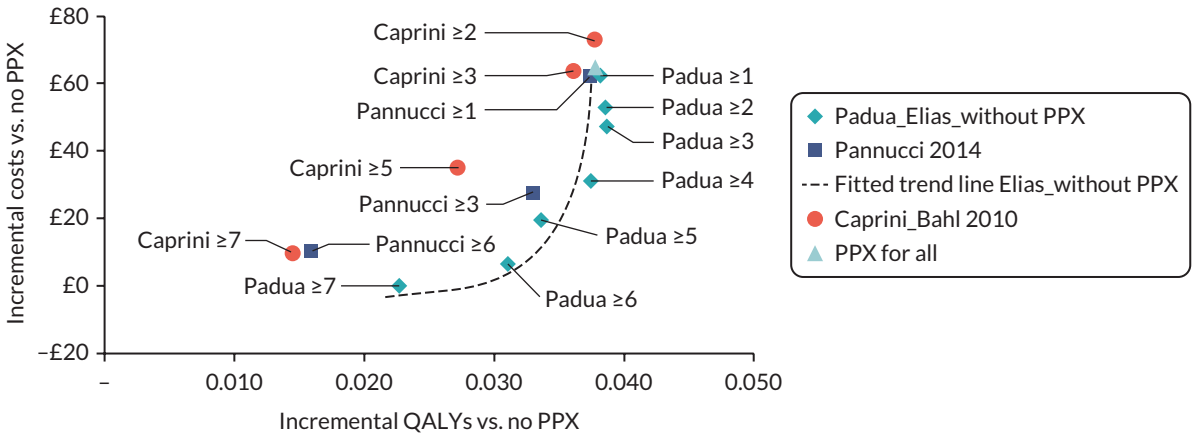

FIGURE 18 Deterministic base-case results for surgical inpatients when using RAMS evaluated in either surgical populations (Pannucci *et al.* 2014[54], Bahl *et al.* 2010[26]) or mixed populations of both surgical and medical inpatients [Elias without prophylaxis (PPX)].

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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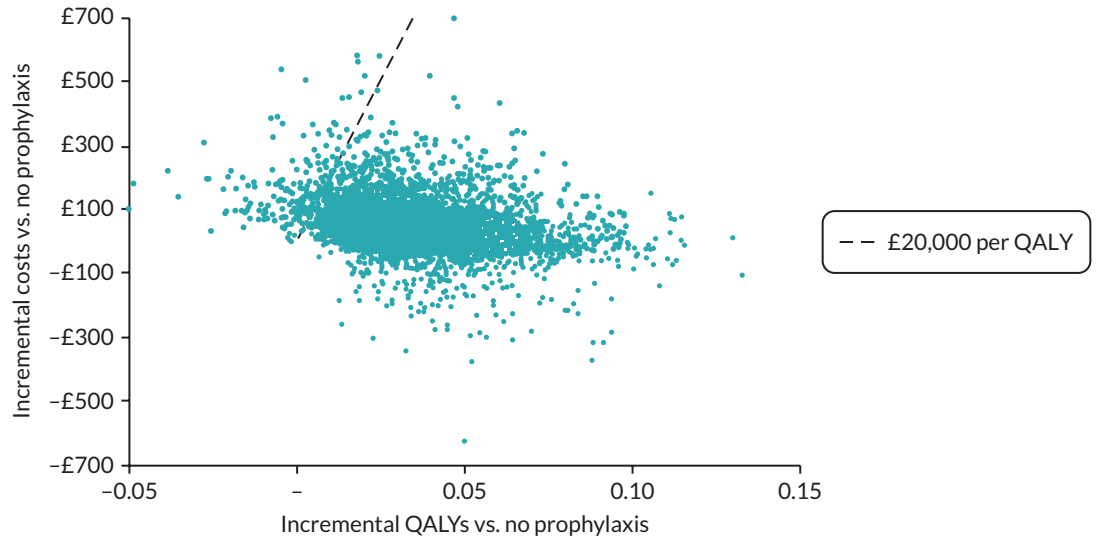

FIGURE 19 Cost-effectiveness plane for prophylaxis for all versus prophylaxis for none in surgical inpatients.

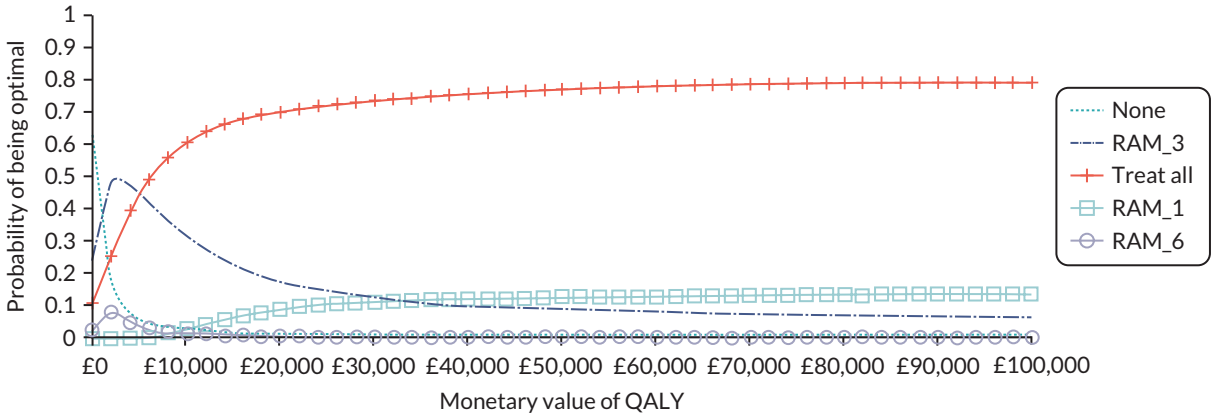

FIGURE 20 CEAC for surgical inpatients (assuming the RAM used is Pannucci).

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.

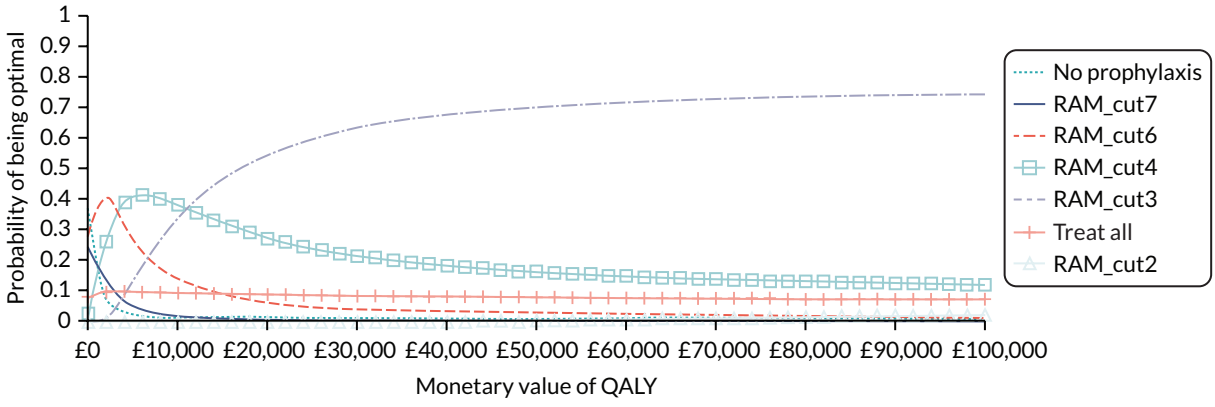

FIGURE 21 CEAC for surgical inpatients (assuming the RAM used is Padua from Ellias *et al.*[36]).

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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.

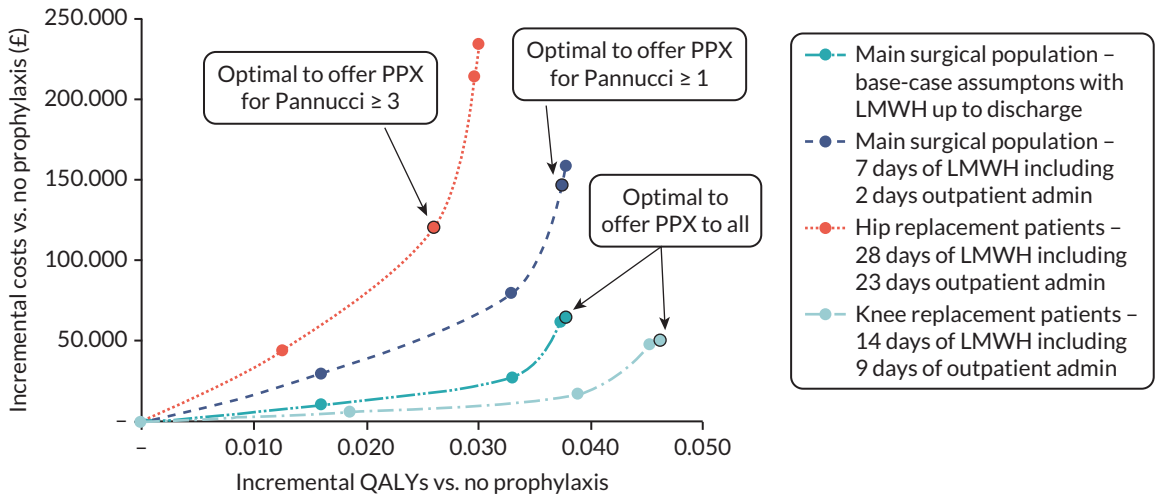

FIGURE 23 Incremental costs and QALYs versus no prophylaxis for various RAM cut-off points (Pannucci ≥ 6, Pannucci ≥ 3, Pannucci ≥ 1, PPX for all) for populations requiring PPX after discharge.

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 5 Workstream 2 – assessing the feasibility of efficient data methods for use in future implementation research

The accuracy of clinical outcome data on VTE events and bleeding is key to any future study of RAM performance and/or validation. However, any such studies are likely to require a large sample size, given the potential for low event rates and small absolute risk impact. The practical challenges and costs of individual patient contact and routine follow-up in such large studies may be prohibitive.

In this study, we sought to pilot the use of efficient methods alongside routine practice to determine the feasibility of a future implementation study of VTE risk assessment tools in hospital inpatients. Our main aim was to compare the accuracy and completeness of available coding data, local registry data and efficient data collection methods to determine clinically relevant VTE and bleeding outcomes against case note review by trained research assistants. We also collated further information on delivery methods for VTE risk assessment during routine care and the potential for granular data collection on individual risk variables, which could allow efficient RAM comparison in future work. Finally, we explored the ethical and regulatory acceptability of a data-enabled approach to any future potential implementation study.

We conducted this study in accordance with international in accordance with Enhancing the QUAlity and Transparency Of health Research (EQUATOR) guidelines. A completed STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) reporting checklist was used throughout to inform design, conduct and analysis of this observational cohort study and has been submitted with the report.

Methods

A multicentre observational, cohort study with prespecified feasibility criteria. We approached four sites to participate in this study: Salford Royal NHS Foundation Trust, Manchester University Hospitals NHS Foundation Trust, the Northern General Hospital in Sheffield and St Thomas' NHS Foundation Trust. All sites agreed to participate, approve and deliver this feasibility study over a 12-month period from August 2020 to 2021 inclusive.

Population

We identified a consecutive, unselected cohort of general medical and surgical patients requiring hospitalisation at each site during the calendar year from 1 January to 31 December 2019. We chose 2019 because of concern that patients admitted during the COVID-19 pandemic might have been assessed for use of thromboprophylaxis differently to prior guidelines. We collated data on all risk assessments performed prospectively at the point of hospital admission, then scrambled episodes into randomly assorted batches of 50 ('A' batches) to ensure diversity in speciality presentation and mitigate seasonal bias. We excluded paediatric patients (age < 16), anyone requiring critical care admission (defined as level 2 care or above) and pregnant/post-partum patients due to differential risk, as outlined in the wider study protocol.

Study design

For each patient episode in each batch, we extracted basic speciality data using business intelligence and VTE risk assessments completed prospectively by clinical teams during the provision of routine care. Risk assessments were captured differently at each site, including the use of paper proformas, dichotomous output on electronic prescribing record, or through a detailed structured note within the electronic healthcare record. Example images/screenshots for each site can be found in *Appendix 3*,

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Figure 28. All four sites recommended the Department of Health tool in local guidelines, to facilitate initial VTE risk assessment.

Research assistants at each site were subsequently employed to undertake retrospective case note review for each patient episode through shared primary and secondary care electronic health records (EHRs). We extracted descriptive data on relevant clinical outcomes such as the subsequent diagnosis of HAT, major bleeding and CRNMB events as per internationally agreed definitions.[79,80] Data extractors were trained in identification of these variables/outcomes and followed a detailed workflow diagram (see *Appendix 3*, *Figure 29*). Data abstractors were blinded to batch allocation, International Classification of Disease, Tenth Revision (ICD-10) coding/HAT database entries and the final analysis plan.

Following case note review, we collated multiple routine data sources for each patient episode to determine the accuracy of these methods in identifying relevant clinical outcomes, identified by research assistants. Data sources for interrogation were identified a priori and included the following: ICD-10 diagnostic codes judged relevant to thrombosis or bleeding by the project management group (PMG) (see *Appendix 3*, *Table 30*); Emergency Care Data Set/Systematised Nomenclature of Medicine (SNOMED) codes relevant to thrombosis or bleeding; and local HAT database entries. HAT database entries are co-ordinated by local thrombosis committees and include a contemporary register of all patients diagnosed with acute VTE (using radiology/pathology data), who are subsequently identified as HAT following local root cause analysis. All data sources were interrogated for the duration of hospital stay and up to 90 days post discharge, for each patient episode. Data sources were obtained through routine local business intelligence requests or direct approach to local coding teams. HAT database entries were obtained through local thrombosis committees, where feasible.

Given the potential for very low numbers of outcome events in the wider study population, we augmented the sample with likely positive thrombosis and bleeding cases. We obtained positive cases through ICD-10 coding identification for VTE events (V batches) and bleeding events (B batches) in accordance with the previously selected code list (see *Appendix 3*, *Table 30*) and local HAT database entries (H batches) within the relevant study period. Positive cases were scrambled, batched and reviewed in accordance with the general protocol.

The following feasibility criteria were proposed within our original protocol to determine success and accuracy of efficient data methods to identify relevant clinical outcomes:

1. ethical and regulatory approval for proposed methods
2. proportion of outcome events identified by routine data sources that are confirmed by record review (target 100%)
3. proportion of cases with no outcome event identified by routine data sources that have an event identified on record review (target 0%)
4. proportion of each RAM and individual risk variables collectible using efficient data methods (target 90%)
5. proportion of inpatients with data collected (target 90%).

In addition, we proposed using this sample of patients to estimate key parameters for any future implementation study, including the primary outcome event rates for HAT and major bleeding.

Statistical analysis

The accuracy of routinely recorded HAT and bleeding events was compared against direct case note review data for the cohort. Case note review determination of events was assumed to be the gold standard. Data are presented in contingency tables with sensitivity, specificity, positive and negative predictive values along with confidence intervals calculated using the Wilson score method.[139]

The primary analysis included patients identified from all sources (A, V, B or H batches) with bleeding and HAT assumed to have not occurred unless coded as such in the relevant data, or detected following case note review. In addition, two pre-planned sensitivity analyses were undertaken:

1. Inclusion was limited to cases identified in routine case review (i.e. 'A batch patients' only), with exclusion of all augmented sample cases.
2. Inclusion limited to participants for whom bleeding or HAT was definitively recorded.

We used case note review identification of HAT and bleeding events as the reference standard and report contingency tables for diagnostic test characteristics of all preidentified efficient data sources. We took a conservative approach and interpreted missing or unknown end points as 'no event'.

The proposed sample size was reliant on an initial iterative developmental phase, including database refinement, user acceptability testing and site trial. We originally planned to identify 3000 inpatients across 4 hospitals during a 12-month study period within the 2-year project plan, dependent on appointment of research assistants and time required for outcome ascertainment. This sample size was designed to allow key parameters to be estimated with a high degree of precision across the whole cohort (standard error < 1%).

Ethical aspects

The study received a favourable opinion from the Proportionate Review Sub-committee of the London – West London & Gene Therapy Advisory Committee (GTAC) Research Ethics Committee (REC) and approval from the HRA and Care Research Wales (HCRW) on 18 September 2019 (reference 19/LO/1303, IRAS project ID 262220).

Participating sites identified members of the clinical care team (research nurses or assistants predominately) to access patient records and extract clinical data using a predesigned and protected Microsoft Excel database with embedded macro function, hosted at site. All data subsequently underwent local de-identification following completion and were exported to an independent team of statisticians at the Clinical Trials Research Unit (CTRU) in Sheffield, for collation and analysis. The REC approved this process and, as researchers outside the clinical care team only used anonymised data, Clinical Advisory Group approval was not required. We were able to access HES through the sites, and we were, therefore, able to undertake the original proposed analysis without involving NHS Digital.

All aspects of the data collection process, export, analysis and oversight were regularly reviewed by the internal PMG including CTRU representation, and an external Trial Steering Committee (TSC), throughout the duration of the project.

Patient and public involvement

Representatives of two PPI groups, Thrombosis UK and Sheffield Emergency Care Forum (SECF) joined the research team and were involved in developing the initial proposal and undertaking the wider study.

The SECF is a patient and public representative group with an interest in emergency care research. The forum has provided PPI for many emergency care research projects over the last 10 years.[140] Thrombosis UK is a charity that aims to identify, inform and partner with the NHS, healthcare providers and individuals to work to improve prevention of VTE and the management and care of VTE events (see https://www.thrombosisuk.org/).

The PPI members were involved in determining the study design and ensuring that the proposal addressed the needs of patients and the NHS, while respecting the needs of potential participants. Their input regarding the importance of providing thromboprophylaxis for potential participants of any prospective cohort study and the need for such a study to yield reliable findings was instrumental in determining our approach to answering the research question. The PPI members also provided input at

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project management meetings and, where required, in day-to-day running of the project. The members used meetings and surveys of their wider PPI groups to enhance PPI in the project.

In relation to this particular substudy, the PPI members had specific roles in ensuring the acceptability of methods explored in the feasibility study. The efficient methods required to deliver an implementation study involve use of patient data without consent. We planned our methods so that they are compatible with ethical principles and data protection regulation, and would be acceptable to our PPI representatives. However, the feasibility study involved piloting these methods and the potential to adapt the methods to ensure efficiency. The PPI representatives were involved in project management, monitoring of data collection and specifically considered the acceptability of any proposed changes to the methodology throughout the project.

Results

Baseline sampling and augmentation

Over the 12-month feasibility study period we successfully set up and delivered the project across four sites. Patients (2115) were identified and selected for analysis with an original hospital admission occurring in the calendar year 2019. Of these, 107 patient episodes were ineligible due to being pregnant or post-partum women (*n* = 49); admitted to a critical care environment of level 2 or above (*n* = 38); children aged under 16 (*n* = 13) or for unrecorded reasons (*n* = 7) leaving 2008 episodes for analysis. All episodes were suitable for data extraction and comparison to routine data sources. Ethical and regulatory approvals were secured for all sites. All sites failed to meet their sample target of 750 for reasons mainly related to the SARS-CoV-2 pandemic, including redeployment of research staff to clinical care, delayed local approvals secondary to prioritised pandemic research and a longer than anticipated time for individual outcome ascertainment per case review. Data were missing or the outcome unknown for fewer than 2% of participants for each outcome/site.

Patient episodes showed an even balance of medical and surgical cases, but with a focus on emergency (73.7%) rather than elective (25.8%) admissions. A broad range of subspeciality interests were represented within the cohort. Median length of stay was 3 days [interquartile range (IQR) 3–8] and mean length of stay 7.75 days [standard deviation (SD) 16.5]. Speciality groups with frequencies and percentages are shown in *Table 13*. The vast majority of patient episodes (1809, 90.1%) were taken from 'A' batches, through patients identified as having a VTE risk assessment. The total sample was augmented by 45 (2.2%) patients with potential bleeding events (one B batch) and 154 (7.7%) patients with potential VTE events (one V and two H batches). Sites contributed evenly to the sample with the exception of Manchester; numbers at this site reflect a significant delay to institutional approval during the pandemic, with this research deprioritised. Site and batch numbers are shown in *Table 14*.

Accuracy of efficient data methods compared to case note review for ascertainment of key clinical outcomes

The accuracy of routine data sources for HAT and major bleeding events compared to case note review are shown in *Table 15*. The proportion of outcome events identified by routine data sources that were confirmed by case note review was 71% (95% CI 63% to 79%). The proportion of cases with no HAT outcome event identified by routine data sources that had an event identified on record review (target 0%) was 3% (95% CI 2 to 4) for ICD-10/SNOMED coding and 2% (95% CI 1 to 2) for local HAT database entries.

The sensitivity was 62% (95% CI 54% to 69%) for the use of ICD-10/SNOMED coding data to detect HAT events and 81% (95% CI 75% to 87%) for local HAT database entries. Sensitivity by individual site ranged from 45% (95% CI 28% to 63%) to 72% (95% CI 61% to 82%) using ICD-10/SNOMED coding and 68% (95% CI 51% to 84%) to 94% (95% CI 87% to 100%) using local HAT database entries. The sensitivity of ICD-10/SNOMED coding to detect major bleeding events identified by case note review

TABLE 13 Clinical category and admission type, with frequency and percentage contribution

	Frequency	Percentage
Admission type		
Missing	1	0.05
Elective	518	25.80
Emergency	1480	73.71
Unknown	9	0.45
Total	2008	100
Speciality group		
Missing	9	0.45
Medical	902	44.92
Surgical	951	47.36
Tertiary speciality	146	7.27
Total	2008	100
Clinical category		
Missing	9	0.45
Acute medicine	340	16.93
Ageing and complex medicine	133	6.62
Cardiology	41	2.04
Cardiothoracic surgery	87	4.33
Dermatology	2	0.1
Emergency medicine	87	4.33
Gastroenterology	61	3.04
General surgery	285	14.19
Medical: other	169	8.42
Neurology	10	0.5
Neurorehabilitation	2	0.1
Neurosurgery	39	1.94
Gynaecology	57	2.84
Renal medicine	26	1.29
Respiratory	63	3.14
Rheumatology	2	0.1
Trauma and orthopaedics	158	7.87
Upper GI surgery	13	0.65
Urology	107	5.33
Surgery: other	170	8.47
Tertiary speciality: other	147	7.32
Total	2008	100

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TABLE 14 Number of cases submitted by site and batch type

	Batch				
	A	B	H	V	Total
GSTT	504	0	21	0	525
Manchester	241	0	0	0	241
Salford	570	45	44	46	705
Sheffield	494	0	43	0	537
Total	1809	45	108	46	2008

TABLE 15 Contingency tables for main outcomes

		HAT from case note review		
		Yes	No	
HAT from ICD-10/SNOMED codes	Yes	95 (A)	39 (B)	PPV 71% (95% CI 63% to 79%)
	No	59 (C)	1815 (D)	NPV 96.9% (95% CI 96% to 97%)
		Sensitivity 62% (95% CI 54% to 69%)	Specificity 98% (95% CI 97% to 99%)	(*N* = 2008)
		Yes	No	
HAT from HAT RCA database	Yes	122 (A)	0 (B)	PPV 100% (95% CI 97% to 100%)
	No	29 (C)	1616 (D)	NPV 98% (95% CI 98% to 99%)
		Sensitivity 81% (95% CI 75% to 87%)	Specificity 100% (95% CI 99.8% to 100%)	(*N* = 1767)
		Major bleed from case note review		
		Yes	No	
Major bleed from ICD-10/SNOMED codes	Yes	25 (A)	98 (B)	PPV 20% (95% CI 13% to 27%)
	No	40 (C)	1845 (D)	NPV 98% (95% CI 97% to 98%)
		Sensitivity 38% (95% CI 27% to 50%)	Specificity 95% (95% CI 94% to 96%)	(*N* = 2008)

NPV, negative predictive value; PPV., positive predictive value.

was 38% (95% CI 27% to 50%). Sensitivity by individual site ranged from 22% (95% CI 0% to 49%) to 56% (95% CI 37% to 75%).

These sensitivity values imply moderate rates of missed HAT and major bleeding events through the use of efficient data methods in isolation. Specificity values were > 90% for both outcomes at all sites, implying reasonable accuracy when an event was identified by efficient data methods.

Sensitivity analyses and estimation of key parameters for future implementation work

A sensitivity analysis was conducted using only patient episodes obtained through 'A' batches, to remove augmentation of the sample and mitigate bias. The sensitivity of efficient data methods to detect key outcomes identified at case note review remained poor. These results are summarised in *Table 16*. This analysis also facilitated estimation of key parameters for any future implementation study. We found the HAT event rate on case note review to be 29/1809 (1.6%, 95% CI 1.0 to 2.2) and the major bleeding event rate to be 45/1809 (2.5%, 95% CI 1.8 to 3.2) within this large cohort of hospitalised patients receiving risk assessment and thromboprophylaxis in the context of routine care.

Key feasibility outcomes

Regarding key feasibility outcomes, we achieved ethical and regulatory approvals and the design of the study was acceptable to all sites. The proportion of HAT events identified by routine data sources that were confirmed by record review (target 100%) was 71% (95% CI 63% to 79%) for ICD-10/SNOMED coding and 100% (95% CI 97% to 100%) for local HAT database entries. The proportion of cases with no HAT outcome event identified by routine data sources that had an event identified on record review (target 0%) was 3% (95% CI 2% to 4%) for ICD-10/SNOMED coding and 2% (95% CI 1% to 2%) for local HAT database entries. The proportion of outcome major bleeding events identified by routine data sources that were confirmed by record review (target 100%) was 20% (95% CI 13% to 27%) for ICD-10/SNOMED coding. The proportion of cases with no major bleeding outcome event identified by routine data sources that have an event identified on record review (target 0%) was 2% (95% CI 1% to 3%) for ICD-10/SNOMED coding.

TABLE 16 Sensitivity analysis using only case note review (A batch) patients

		HAT from case note review		
		Yes	No	
HAT from ICD-10/SNOMED codes	Yes	18 (A)	18 (B)	PPV 50% (95% CI 34% to 66%)
	No	11 (C)	1762 (D)	NPV 99% (95% CI 99% to 100%)
		Sensitivity 62% (95% CI 44% to 80%)	Specificity 99% (95% CI 99% to 99%)	(*N* = 1809)
		Yes	No	
HAT from HAT RCA database	Yes	7 (A)	0 (B)	PPV 100% (95% CI 100% to 100%)
	No	19 (C)	1542 (D)	NPV 99% (95% CI 99% to 99%)
		Sensitivity 27% (95% CI 12% to 48%)	Specificity 100% (95% CI 100% to 100%)	(*N* = 1568)
		Major bleed from case note review		
		Yes	No	
Bleed from ICD-10/SNOMED codes	Yes	14 (A)	68 (B)	PPV 17% (95% CI 11% to 25%)
	No	31 (C)	1696 (D)	NPV 98% (95% CI 98% to 99%)
		Sensitivity 31% (95% CI 18% to 47%)	Specificity 96% (95% CI 95% to 97%)	(*N* = 1809)

NPV, negative predictive value; PPV, positive predictive value.
N = 1809 following removal of H/B/V batch patients.

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We were unable to use efficient data methods to collect individual risk variables in three out of four sites, due to use of either paper proformas or dichotomous risk assessment without granular data. As such we did not meet the feasibility target of using routine data to collect individual variables for 90% of patients. We were able to collect outcome data in 1745/2008 (87%) of inpatients (target 90%). This was mainly due to inability at the Manchester site to access the local HAT database. Excluding this issue, the other three sites all managed to collect relevant outcome data in > 98% of patient episodes.

Summary and key findings

- In this multicentre cohort study, routine and efficient data methods used to identify HAT events and major bleeding events performed poorly when compared to direct case note review by trained research staff.
- We were able to demonstrate ethical and regulatory approvals for our chosen design across four NHS sites.
- We were unable to demonstrate overall feasibility of an efficient design and did not meet several prespecified criteria set out in the original research proposal:
  - Proportion of outcome events identified by routine data sources that are confirmed by record review (target 100%); VTE 71%, bleeding 20%: **Criteria not met.**
  - Proportion of cases with no outcome event identified by routine data sources that have an event identified on record review (target 0%); VTE 3%, bleeding 2%: **Criteria not met.**
  - Proportion of inpatients with data collected (target 90%); 87% across all sites, 98% across three sites: **Partially met.**
  - Proportion of each predictor variable recorded (target 90%); only routinely recorded at one site: **Criteria not met.**
  - Proportion of each risk assessment tool completed using available data (target 90%); only routinely recorded at one site: **Criteria not met.**
- These findings suggest a future data-enabled study using efficient methods would significantly under-report events, leading to inaccurate RAM evaluation.
- In this multicentre cohort of hospitalised inpatients, the HAT event rate was 1.6% (95% CI 1.0% to 2.2%) and the major bleeding event rate was 2.5% (95% CI 1.8% to 3.2%).

Chapter 6 Workstream 2 – estimating key parameters for future implementation research

In a further substudy, we sought to compare the proportion of hospital patients recommended for pharmacological thromboprophylaxis using multiple RAMs identified by our systematic review in workstream one, alongside current practice. We included RAMs with attempted external validation for this comparison. We specifically aimed to determine the following parameters for a potential future implementation study:

1. The current proportion of hospital inpatients receiving pharmacological prophylaxis in a UK NHS setting after local risk assessment, using the Department of Health tool.
2. The variable proportion of patients who would potentially receive prophylaxis if alternative RAMs were used.

We conducted this substudy in accordance with international EQUATOR guidelines. A completed STROBE reporting checklist was used throughout to inform design, conduct and analysis of this observational cohort study and has been submitted with the report.

Methods

We approached four sites engaging with the wider Venous ThromboEmbolism Assessment Methods (VTEAM) project to participate in this substudy. We originally intended to explore methods of efficient data collection for risk factors across two sites through an iterative process, then further pilot a final data collection tool across all sites. However, only one site maintained an EHR with prospective capture of individual VTE risk characteristics following clinical assessment. Other sites lacked the IT infrastructure to support efficient data collection, using either paper proformas to record risk assessment or dichotomous electronic methods [recording only the capture of a risk assessment (yes/no) and the prescribing intention, as shown in *Appendix 3*, *Figure 28*].

We considered adaptive design during the project and developing a paper case note review process, but encountered multiple barriers to delivery of workstream 2 during the project timeline; access to clinical settings was limited by infection control measures during the pandemic; redeployment of clinically trained research staff limited our available resources; pandemic research was rightly prioritised by local research teams; and NHS service pressures impacted on the project. In addition, working from home guidance further limited the ability to retrieve paper case notes or develop an efficient data collection tool. As such, we focused efforts on data capture from a single site which used a comprehensive EHR with contemporaneous data collection on risk factors at the point of assessment.

Population

We identified a consecutive cohort of general medical and surgical patients requiring hospitalisation during the calendar year from 1 January to 31 December 2019. We chose 2019 because of concern that patients admitted during the COVID-19 pandemic might have been assessed for VTE prophylaxis differently to prior guidelines.[141] We collated data on all risk assessments performed prospectively at the point of hospital admission, then scrambled episodes into randomly assorted batches of 50 to ensure diversity in speciality presentation and mitigate potential seasonal bias. We excluded all patients with an index presentation of suspected VTE, anticoagulated patients and patients with a hospital stay < 24 hours as they were unlikely to require risk assessment or thromboprophylaxis. We also excluded patients requiring critical care admission, children (< 16) and pregnant/post-partum patients due to differential risk, in keeping with the wider study protocol.

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Study design

A single-centre observational cohort study, conducted at Salford Royal NHS Foundation Trust. We extracted initial clinical data on patient episodes using hospital admission records and VTE risk assessments completed prospectively by clinical teams during the provision of routine care. All risk assessments were captured through a structured note within the electronic healthcare record, with granular data capture accessible through business intelligence. The structured note mirrors the Department of Health VTE Risk assessment tool (see *Appendix 3*, *Figure 28*).

We identified additional necessary variables a priori to enable further completion and comparison of 6 prespecified RAMs for each patient episode, in addition to the Department of Health tool. These variables are listed in *Table 17*. We subsequently undertook case note review for each patient episode through shared primary and secondary care EHRs up to 90 days following hospital discharge. We extracted data points necessary to facilitate retrospective completion of the Padua, Caprini, Geneva, Kucher, IMPROVE predictive and IMPROVE associative RAMs. We also extracted descriptive data on relevant clinical outcomes, such as the real-world use of pharmacological thromboprophylaxis, subsequent diagnosis of HAT, length of stay and survival to hospital discharge. Data were also extracted on episodes of major and CRNMB as per internationally agreed definitions.[79,80] Data extractors were trained in identification of these variables/outcomes and followed a detailed workflow diagram (see *Appendix 3*, *Figure 29*). Data abstractors were blinded to the analysis plan.

Statistical analysis methods

The primary analysis was a comparison of the proportion of patients within the cohort in whom pharmacological thromboprophylaxis would be recommended during hospitalisation, by each RAM. We applied conventional prescribing thresholds for each RAM to the cohort in order to estimate the proportion of patients who would require medication, prior to any assessment of bleeding risk. Prescribing thresholds were taken from author recommendations, international guidelines and nationally endorsed summary tools for practical use.[8,15,16,28,34,49,53,59,142–149] We used ordinal scores to create distribution plots, clustered histograms and to facilitate descriptive analysis. We used dichotomous prescribing thresholds (as above) to calculate proportions with 95% confidence intervals and allow head-to-head RAM comparison. We used the Wilson method to estimate confidence intervals around a proportion, adapted by Newcombe.[139]

Missing data were assumed to be negative (risk factor not present) for the primary analysis. A sensitivity analysis was planned with best-case-worse-case imputation for missing data when calculating the percentage of patients who would meet the criteria for prescribing thromboprophylaxis. We estimated that 80% of admitted patients would be classified as eligible for pharmacological thromboprophylaxis, according to the Department of Health VTE risk assessment tool.[8,145] A sample of 250 patients would, therefore, be sufficient to provide estimates of prescribing with a confidence interval range approaching 10%. We proposed a data review following completion of at least 500 case episodes (10 batches).

Ethical aspects

The study received a favourable opinion from the Proportionate Review Sub-committee of the London – West London & GTAC REC and approval from the HRA and Care Research Wales (HCRW) on 18 September 2019 (reference 19/LO/1303, IRAS project ID 262220).

Patient and public involvement

Representatives of two PPI groups, Thrombosis UK and SECF joined the research team and were involved in developing the proposal and undertaking the study.

The SECF is a patient and public representative group with an interest in emergency care research. The forum has provided PPI for many emergency care research projects over the last 10 years (see https://secf.org.uk/ and https://emj.bmj.com/content/33/9/665). Thrombosis UK is a charity that aims

TABLE 17 Individual extra variables collected from case note review required for completion of alternate RAMs, in addition to variables collected to enable completion of the Department of Health risk assessment tool

DOH RAM	Padua RAM	IMPROVE Associative RAM	Geneva RAM	Caprini RAM	Kucher RAM	IMPROVE Predictive RAM
Age	Cardiac failure	Paralysis of the lower extremities	Myeloproliferative syndrome	Sex	Nil additional	Nil additional
Active cancer	Respiratory failure	Immobilisation > 7 days	Nephrotic syndrome	Acute pneumonia (< 1/12)		
Dehydration	Acute myocardial infarction (< 1/12)		Recent travel > 6 hours	Immobilising plaster cast		
Obesity	Acute ischaemic stroke (< 3/12)		Chronic venous insufficiency	Multiple trauma (< 1/12)		
One or more significant medical comorbidities	Acute infectious disease (< 1/12)			Current swollen legs		
Personal history of first-degree relative with a VTE history	Acute rheumatological disorder (< 1/12)			Current central venous access		
Use of HRT				Inflammatory bowel disease		
Use of oestrogen-containing COCP				Other risk factor		
Varicose veins with phlebitis				Major surgery (< 1/12)		
Pregnancy or < 6 weeks post-partum				Hip, pelvis or leg fracture (< 1/12)		
Mobility limited > 3/7						
Acute surgical admission						
Critical care admission						
Specific surgical features						

DOH, Department of Health.
Visual examples of several RAMs can be found at the following web pages:
www.mdcalc.com/calc/2023/padua-t-score-risk-vte
www.mdcalc.com/calc/10349/improve-risk-score-venous-thromboembolism-vte
www.mdcalc.com/calc/3970/caprini-score-venous-thromboembolism-2005
www.outcomes-umassmed.org/IMPROVE/

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to identify, inform and partner with the NHS, healthcare providers and individuals to work to improve prevention of VTE and the management and care of VTE events (see www.thrombosisuk.org/).

The PPI members were involved in determining the study design and ensuring that the proposal addressed the needs of patients and the NHS, while respecting the needs of potential participants. Their input regarding the importance of providing VTE prophylaxis for potential participants of any prospective cohort study and the need for such a study to yield reliable findings was instrumental in determining our approach to answering the research question. The PPI members also provided PPI at project management meetings and, where required, in day-to-day running of the project. The members used meetings and surveys of their wider PPI groups to enhance PPI in the project.

Results

Comparative risk assessment and prescribing outcomes

We analysed 543 hospital episodes with VTE risk assessment performed during 2019. Two-hundred and eighty-nine episodes met exclusion criteria, leaving 254 episodes suitable for data extraction and comparative analysis.

Distribution plots of ordinal scoring for each RAM are shown in *Figure 24*. The Caprini and Department of Health RAMs appeared to be normally distributed, with the former showing the widest dispersion. All others were skewed to the left, indicating a higher attribution of low risk.

Overall recommendations for prescribing varied substantially between RAMs, ranging from 13% for the IMPROVE associative score to 91% for the Department of Health VTE risk assessment tool. Variation persisted throughout medical (15–92%) and surgical subgroups (10–88%). Key results and estimates of recommended prescribing by speciality (with 95% CIs) are shown in *Table 18*. Of note, all RAMs recommended higher rates of prescribing in medically unwell patients within this patient cohort. A bar and dot chart of prescribing recommendations with comparative 95% confidence intervals is shown in *Figure 25*. The Department of Health VTE risk assessment tool was an outlier within this cohort, recommending pharmacological thromboprophylaxis for over 90% of patients with a confidence interval that did not overlap those of any other RAM.

On descriptive analysis, the variables used by the Department of Health tool with the highest prevalence within our cohort were as follows: one or more significant medical co-morbidities (76%); age > 60 (57%); dehydration (38%); significantly reduced mobility (29%); obesity (20%). These 5 variables were responsible for > 90% cumulative prescribing decisions within the cohort, with negligible addition from the other 14 variables.

All tools were subject by missing data with up to 12% of patients being partly scored, largely due to BMI being unavailable in 22 (9%) of patients. This affected all scores other than the two IMPROVE scores which were scored in all bar four (2%) patients. The impact of this was minimal in terms of the percentage of patients that would be recommended for thromboprophylaxis, since the missing data generally could not overturn a 'do not recommend' into 'recommend'. For the Padua score, a further seven patients would meet the cut-off of 4 points if all missing data were assumed to be abnormal, taking the percentage from recommended from 30% to 33%. The equivalent assumption on other tools led to increases of less than 2%.

Temporary reference list for *Figures 24* and *25* and *Table 18*:

1. Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, *et al.* A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost* 2010;**8**:2450–7. https://doi.org/10.1111/j.1538-7836.2010.04044.x **(PADUA)**

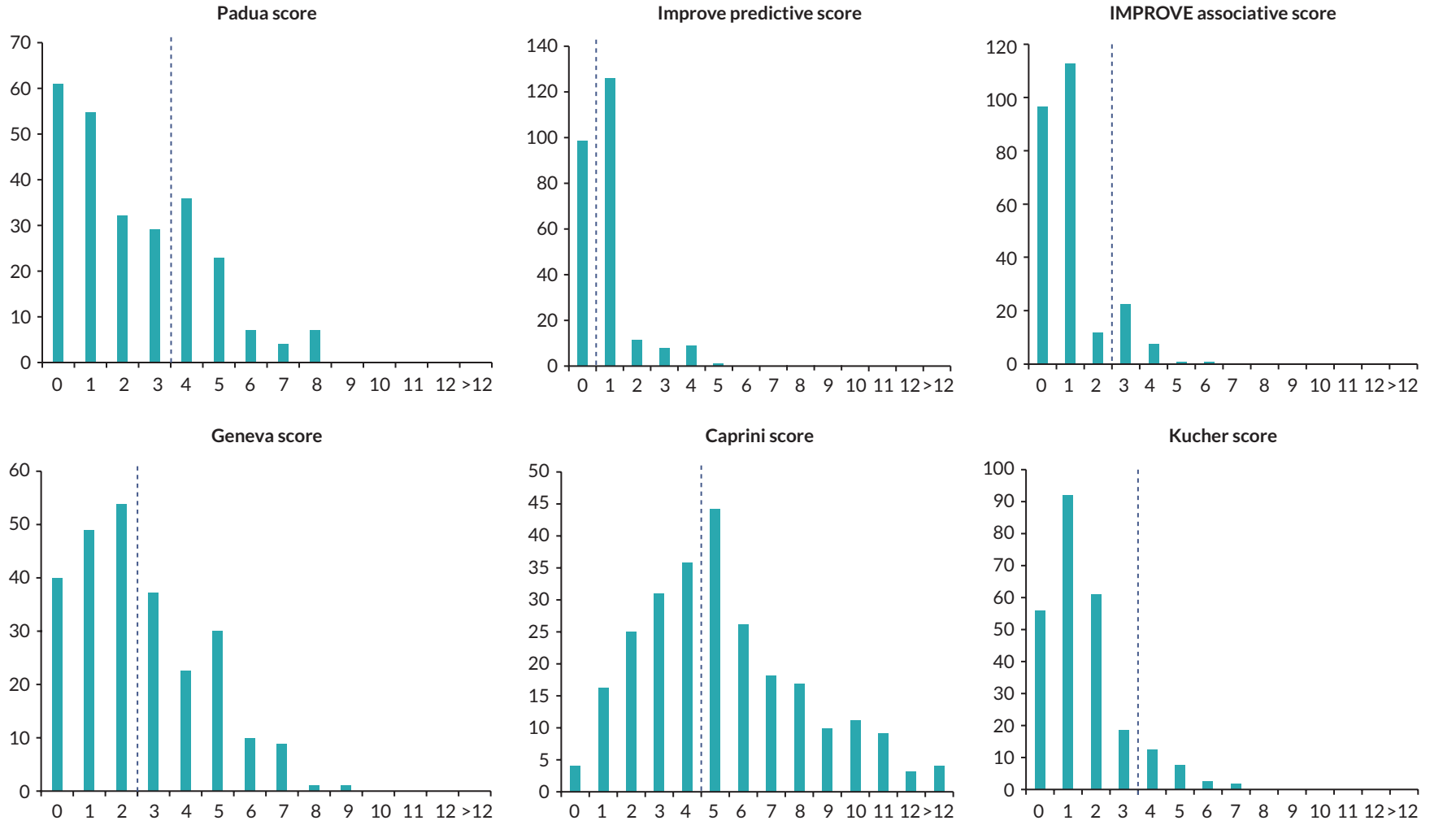

FIGURE 24 Histograms for ordinal score (*x*-axis) by RAM using patient numbers (*y*-axis), with recommended prescribing thresholds (dashed blue lines). Source: National Institute for Health and Care Excellence[8]; Barbar *et al.*[15]; Blondon *et al.*[28]; Caprini *et al.*[142]; Chopard *et al.*[143]; Kucher *et al.*[146]; Spyropoulos *et al.*[148] (*continued*)

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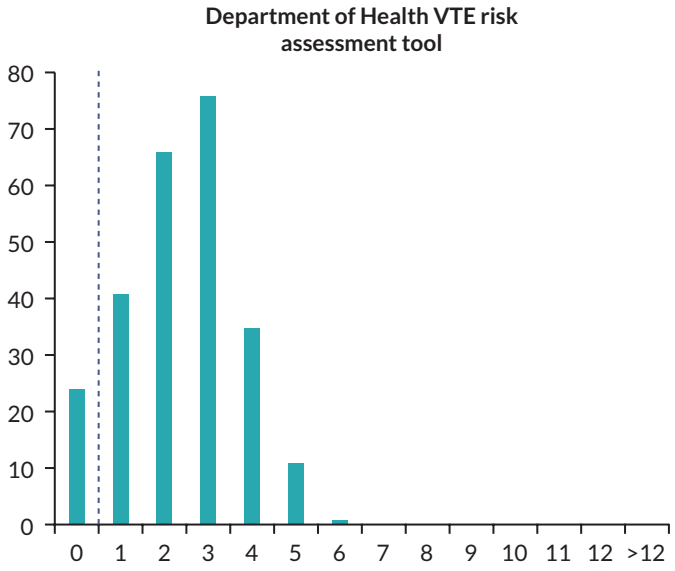

FIGURE 24 Histograms for ordinal score (*x*-axis) by RAM using patient numbers (*y*-axis), with recommended prescribing thresholds (dashed red lines). Source: National Institute for Health and Care Excellence[8]; Barbar *et al.*[15]; Blondon *et al.*[28]; Caprini *et al.*[142]; Chopard *et al.*[143]; Kucher *et al.*[146]; Spyropoulos *et al.*[148]

TABLE 18 Proportional prescribing recommendations using established dichotomised cut points for validated RAMs

RAM and published prescribing threshold	All patients (*n* = 254)	Medical admissions (*n* = 143)	Surgical admissions (*n* = 111)
Department of Health VTE risk assessment tool			
Median value (IQR)	2 (1–3)	3 (2–4)	2 (1–3)
Prescribing threshold (score ≥ 1)[a]	230 (91%, 95% CI 86.3 to 93.6)	132 (92%, 95% CI 86.8 to 95.7)	98 (88%, 95% CI 81.0 to 93.0)
Padua score			
Median value (IQR)	2 (1–4)	3 (1–4)	1 (0–3)
Prescribing threshold (score ≥ 4)	77 (30%, 95% CI 25.0 to 36.2)	56 (39%, 95% CI 31.5 to 47.3)	21 (19%, 95% CI 12.7 to 27.2)
Caprini score			
Median value (IQR)	5 (3–7)	6 (4–8)	4 (2–5)
Prescribing threshold (score ≥ 5)	(56%, 95% CI 49.8 to 61.9)	96 (67%, 95% CI 59.1 to 74.3)	46 (41%, 95% CI 32.7 to 50.7)
Geneva risk score			
Median value (IQR)	2 (1–4)	3 (2–5)	2 (0–3)
Prescribing threshold (score ≥ 3)	111 (44%, 95% CI 37.7 to 49.9)	81 (57%, 95% CI 48.5 to 64.5)	30 (27%, 95% CI 19.6 to 36.0)
Kucher score			
Median value (IQR)	1 (1–2)	1 (1–2)	1 (0–2)
Prescribing threshold (score ≥ 4)	26 (10%, 95% CI 7.1 to 14.6)	16 (11%, 95% CI 7.0 to 17.4)	10 (9%, 95% CI 5.0 to 15.8)
IMPROVE predictive score			
Median value (IQR)	1 (0–1)	1 (0.5–1)	0 (0–1)
Prescribing threshold (score ≥ 1)	155 (61%, 95% CI 54.9 to 66.8)	107 (75%, 95% CI 67.1 to 81.2)	48 (43%, 95% CI 34.4 to 52.5)
IMPROVE associative score			
Median value (IQR)	1 (0–1)	1 (1–1)	0 (0–1)
Prescribing threshold (score ≥ 3)	32 (13%, 95% CI 9.1 to 17.2)	21 (15%, 95% CI 9.8 to 21.4)	11 (10%, 95% CI 5.6 to 16.9)

a The prescribing threshold for this RAM is narrative, described as any thrombosis risk factor noted within a population of surgical patients, or medical patients with significantly reduced mobility.

Source: National Institute for Health and Care Excellence[8]; Barbar *et al.*[15]; Blondon *et al.*[28]; Caprini *et al.*[142]; Chopard *et al.*[143]; Kucher *et al.*[146]; Spyropoulos *et al.*[148]

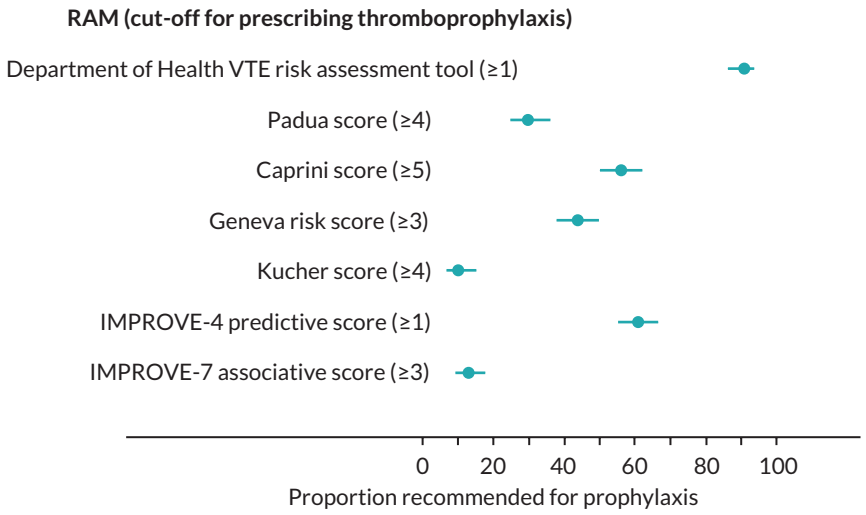

FIGURE 25 A visual comparison of prescribing proportions per RAM, with 95% CIs. Source: National Institute for Health and Care Excellence[8]; Barbar *et al.*[15]; Blondon *et al.*[28]; Caprini *et al.*[142]; Chopard *et al.*[143]; Kucher *et al.*[146]; Spyropoulos *et al.*[148]

2. Blondon M, Righini M, Nendaz M, Glauser F, Robert-Ebadi H, Prandoni P, *et al.* External validation of the simplified Geneva risk assessment model for hospital-associated venous thromboembolism in the Padua cohort. *J Thromb Haemost* 2020;**18**:676–80. https://doi.org/10.1111/jth.14688 **(GENEVA)**
3. Caprini JA, Arcelus JI, Hasty JH, Tamhane AC, Fabrega F. Clinical assessment of venous thromboembolic risk in surgical patients. *Semin Thromb Hemost* 1991;**17 Suppl 3**:304–12. **(CAPRINI)**
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We found no cases where an alternate RAM recommended thromboprophylaxis but the Department of Health tool did not, in keeping with the low threshold (≥ 1 risk factor) of the latter tool. Results for each alternate RAM compared against the Department of Health tool are shown in *Appendix 3*, *Figure 30*.

Estimation of other key parameters for future implementation research

Baseline demographics and relevant clinical outcomes for the final cohort of patients are shown in *Table 19*, by speciality. In this cohort, surgical patients appeared to be younger with lower rates of medical comorbidity and lower rates of significant mobility reduction than medical patients.

We found six cases of HAT within this cohort, with a subsequent overall event rate of 2.4% (95% CI 1.1% to 5.1%). All six of the HAT cases in this cohort were diagnosed in patients who were prescribed thromboprophylaxis during hospital admission in line with an initial assessment using the Department of Health tool. It is, therefore, impossible to estimate whether application of other RAMs would have affected relevant clinical outcomes; all patients were receiving thromboprophylaxis.

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TABLE 19 Baseline demographics and relevant clinical outcomes for all included patients

	All patients (*n* = 254)	Medical admissions (*n* = 143)	Surgical admissions (*n* = 111)
Demographics			
Age	62.6 (22.3)[a]	70.4 (20.7)[a]	52.7 (20.3)[a]
Female sex	139 (54.7)	82 (57.3)	57 (51.4)
BMI	25.7 (6.5)[a]	24.4 (7.0)[a]	27.3 (5.5)[a]
Active cancer	15 (5.9)	9 (6.3)	6 (5.4)
Significant medical comorbidity	192 (75.6)	127 (88.8)	65 (58.6)
Personal history of VTE	16 (6.3)	8 (5.6)	8 (7.2)
Family history of VTE	0 (0)	0 (0)	0 (0)
Significantly reduced mobility for > 3 days	74 (29.1)	55 (38.5)	19 (17.1)
Active bleeding on admission	12 (4.7)	1 (0.7)	11 (9.9)
Emergency admission	251 (98.8)	143 (100)	108 (97.3)
Clinical outcomes			
Pharmacological prophylaxis	219 (86.2)	115 (80.4)	104 (93.7)
Hospital length of stay	5 (2–11)[b]	6 (1–16)[b]	4 (2–6)[b]
Hospital-acquired thrombosis	6	4	2
(HAT) event rate	(2.4, 1.1–5.1)	(2.8, 1.1–7.0)	(1.8, 0.5–6.3)
PE	1 (0.4)	0 (0)	1 (0.9)
Proximal DVT	4 (1.6)	3 (2.1)	1 (0.9)
Distal DVT	1 (0.4)	1 (0.7)	0 (0)
Major bleeding event rate	3	1	2
	(1.2, 0.4–3.4)	(0.7, 0.1–3.9)	(1.8, 0.5–6.3)
Fall in Hb > 2 g/dl	1 (0.4)	0 (0)	1 (0.9)
Critical site	1 (0.4)	1 (0.7)	0 (0)
Requiring surgical intervention	1 (0.4)	0 (0)	1 (0.9)
Clinically relevant non-major bleeding event rate	36	18	18
	(14.2, 10.4–19.0)	(12.6, 8.1–19.0)	(16.2, 10.5–24.2)
Requiring medical intervention by a professional	3 (1.2)	1 (0.7)	2 (1.8)
Leading to hospitalisation or increased level of care	5 (2.0)	2 (1.4)	3 (2.7)
Prompting face-to-face assessment	28 (11.0)	15 (10.5)	13 (11.7)
Alive at hospital discharge	244 (96.5)	135 (94.4)	109 (98.2)

a All data as numerical values with SD.
b IQR or percentage in brackets as appropriate.

Note
Clinical event rates are shown in numbers and percentage with 95% confidence intervals.

Summary and key findings

- The majority of sites approached within this substudy had no mechanism for accessing individual variables recorded at VTE risk assessment, other than case note review of written notes. Only one site recorded risk variables electronically. This raises significant challenges for future implementation research looking to compare RAMs using routine data or through retrospective methodology.
- In this single-centre cohort of predominately emergency admissions, the proportion of patients receiving thromboprophylaxis in current practice was 86.2% (95% CI 81.2% to 90.1%). Over 90% of surgical inpatients received prophylaxis in the context of routine care.
- Prior to evaluation of bleeding risk, existing RAMs produce highly variable rates of recommended pharmacological prophylaxis when applied to the same cohort of medical and surgical hospital inpatients, ranging from 13% (95% CI 9.1% to 17.2%) to 91% (95% CI 86.3% to 93.6%).
- The national UK Department of Health VTE risk assessment tool conferred higher rates of potential prescribing in this cohort than any other RAM, by > 25%.

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Chapter 7 Workstream 2 – national survey of VTE leads regarding current practice and willingness to participate in future implementation research

During this period of research, a number of external topic experts delivered a concurrent national survey of VTE leads, endorsed and supported by the 'Getting it Right First Time (GIRFT)' national project team. This survey has since been published as an online report and quantifies many aspects of current practice relevant to the VTEAM study.[150]

Our PMG chose not to repeat this work, due to the scale and credibility of the GIRFT project and likelihood of survey fatigue in the relevant clinical population. We opted instead to supplement GIRFT data through a further abbreviated national survey of VTE leads at acute NHS hospitals across the UK, focused on practicalities of risk assessment and future research proposals. In particular, we sought to determine (1) local methods used to record VTE risk-assessment data and (2) willingness to participate in an implementation study of risk-assessment tools, in line with our original protocol.

Methods

A national cross-sectional online survey reported using the consensus-based Checklist for Reporting of Survey Studies (CROSS).[151]

Population

We identified local VTE leads through the National Nursing and Midwifery Network, VTE exemplar centre network and the collated list utilised by the recently published GIRFT project. VTE leads represented a range of clinical disciplines, including anticoagulation pharmacists, specialist nurses, doctors and ward managers.

Survey design and dissemination

We designed the survey using Smartsurvey.co.uk. We utilised the VTEAM PMG to refine the questions through iterative development. The final survey included free text answers, radio button responses and multiselect options. Regarding VTE risk assessment, we included questions on positive characteristics (recording the definitive presence of a risk factor) and negative characteristics (recording the definitive absence of a risk factor). The survey was trialled on three members of the PMG prior to circulation, with incorporated feedback. A copy of the survey is available in *Appendix 4*.

We used single-stage sampling over a four-week period, from 20 October 2021 to 17 November 2021 inclusive. We disseminated the survey by personal e-mail, with facilitated access through a weblink, QR code and direct web address. We sent weekly reminders to all potential participants throughout the survey duration. We asked for trust identification to guard against multiple participant responses. Given the time frame, need for site identification and direct personal contact through an established list of VTE leads, we did not add security measures to the survey. We did not seek specific ethical approval for this survey work and assumed implied consent from clinicians for participation in the survey.

Statistical analysis

We did not perform a sample size calculation for this survey. All analyses were proportional or descriptive. No weighting was applied to any variables.

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Results

We received 65 total responses to the survey, with 25 full completions. The survey was sent originally to 105 potential participants, representing a partial response rate of 61.9% and a total response rate of 23.8%. A summary of responding sites is included in *Appendix 4*.

Methods of VTE risk assessment and data capture

The majority of respondents (48%) reported using EHR to conduct VTE risk assessment within an NHS setting, although 20% respondents reported using a hybrid approach (paper prof orma and EHR) at site dependent on ward environment. A large proportion of sites (32%) reported use of a paper pro forma only.

The majority of respondents noted their site method of risk assessment to report positive VTE characteristics (57% for paper pro forma, 73% for EHR) and the final decision on thromboprophylaxis (57% for paper pro forma, 64% for EHR). Routine capture of negative risk characteristics was lower overall, with only 19% of sites using paper pro forma and 32% of sites reporting capture.

The majority of sites (52%) responding reported that they were uncertain as to whether they could access granular data from VTE risk assessments conducted within routine care, through local business intelligence requests.

Willingness to participate in future research

Enthusiasm appeared higher for participation in future research overall. More respondents were willing to participate in future observational research on VTE risk assessment (100%) compared to interventional research, including randomisation to different models of assessment (72%). When further questioned on potential methodologies for future interventional research, most respondents favoured either allocation of the whole trust site or certain wards to intervention/control within the context of a wider national cluster RCT, above a longitudinal step wedge design or individual patient randomisation. This preference continued through scenarios involving comparison of RAMs, higher dosing strategies for higher-risk patients and opt-out strategies for default prescribing. Pie chart summaries of proportional response are shown in *Figure 26* below.

Thematic analysis of free text responses

We received 21 free text responses, listed in *Appendix 4*. Themes of response included support for potential study designs evaluating opt-out strategies for prophylaxis/mandatory prescribing, higher dosing strategies for higher-risk patients and further refinement of bleeding risk scores. Several responses highlighted support for cluster or broad implementation study designs in this area, citing the existing challenges of standardisation and the potential for individual randomisation strategies to increase confusion. In particular, several respondents referred to the 'tick box' nature of VTE risk assessment and highlighted the increasing medical scrutiny on the value of complex risk assessment.

Several respondents highlighted areas of VTE risk assessment they felt required further specific research: exclusion of medical patients at 'baseline' mobility; better clarification of dehydration and other subjective risks; evidence that routine care follows national guidance on assessment and prescribing; validity of the Department of Health risk assessment tool; defining higher-risk categories.

Concerns were highlighted regarding the variation in care by speciality group, and the potential for more nuanced risk assessment to benefit certain elective surgical groups. In addition, several responders highlighted the potential delays in adapting EHRs as a concern for future research designs looking to change the manner/standard of risk assessment. Finally, several respondents noted concern about an opt-out strategy as moving away from current evidence themes on individualisation of approach.

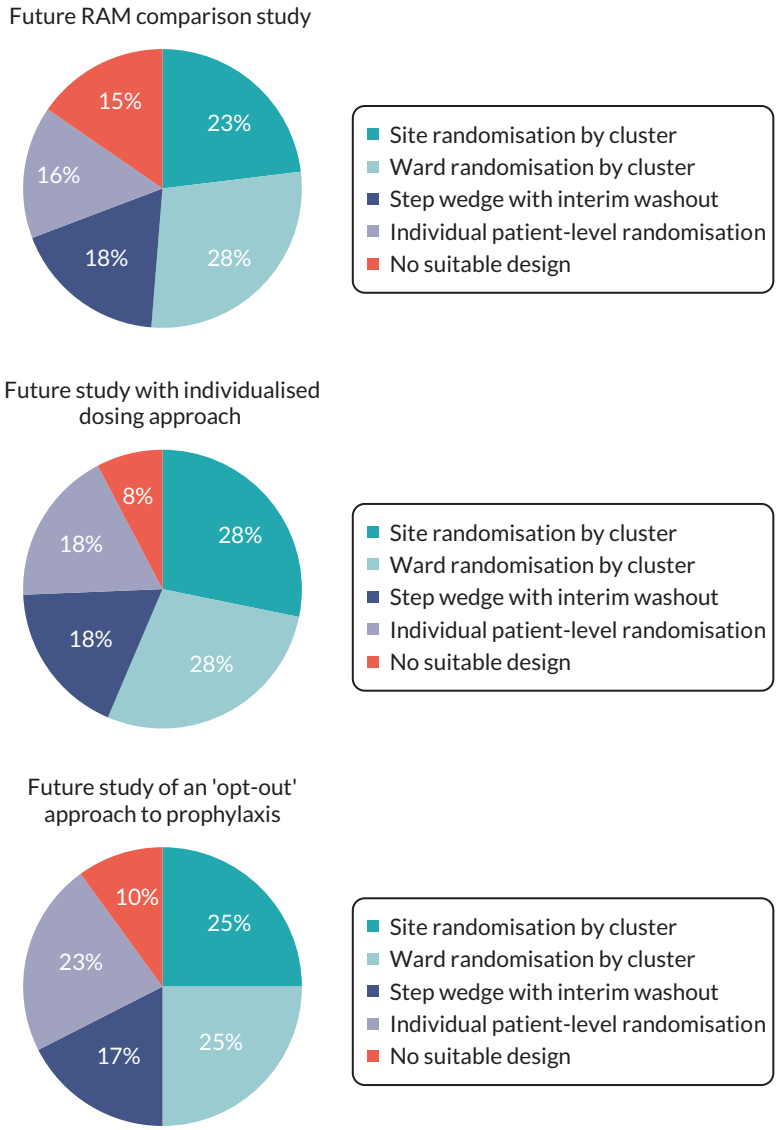

FIGURE 26 Proportional summary preferences for research design methods on future prophylaxis studies.

Summary and key findings

- Recently published GIRFT data suggest that the vast majority of UK sites (87%) continue to use the Department of Health VTE risk assessment tool to guide pharmacological prophylaxis decisions on admission to hospital. A high proportion (80%) of these sites also use weight-adjusted prescribing strategies.
- Less than half of respondents to our survey report consistent use of an EHR to facilitate and record VTE risk assessment. Less than a third of sites record the absence of VTE risk characteristics. Half of our respondents were uncertain as to whether they could access granular data on risk characteristics through local business intelligence/information technology support services. This implies future studies using routinely collected data on individual VTE risk characteristics at admission are likely to be untenable.
- VTE leads appear enthusiastic for further research in this area. Regarding interventional research, respondents appeared to prefer implementation designs (whole clinical areas randomised to a new intervention) rather than an individual patient randomised design.

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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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Abdullah Pandor (https://orcid.org/0000-0003-2552-5260) (Information Specialist) led the systematic review in workstream 1 and critically revised the work for important intellectual content.

Helen Shulver (https://orcid.org/0000-0001-7152-4125) (Study Manager) contributed to the design of the study, contributed to the Project Management Group throughout the study and provided project leadership for a substantial portion of the project.

Steve Goodacre (https://orcid.org/0000-0003-0803-8444) (Emergency Medicine) contributed to the design of the study, led workstream 1 as co-chief investigator and critically revised the work for important intellectual content.

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Shan Bennett (patient representative) contributed to the design of the study, contributed to the project management group throughout the study and provided patient and public involvement throughout the study.

Robin Pierce-Williams (patient representative) contributed to the design of the study, contributed to the project management group throughout the study and provided patient and public involvement throughout the study.

All authors were involved in the final approval of the version to be published.

All authors agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Publications

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Horner D, Rex S, Reynard C, *et al*. Accuracy of efficient data methods to determine the incidence of hospital-acquired thrombosis and major bleeding in medical and surgical inpatients: a multicentre observational cohort study in four UK hospitals. *BMJ Open* 2023;**13**:e069244. https://doi.org/10.1136/bmjopen-2022-069244

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Davis S, Goodacre S, Horner D *et al*. Effectiveness and cost effectiveness of pharmacological thromboprophylaxis for medical inpatients: decision analysis modelling study. *BMJ Medicine* 2024;**3**:e000408. https://doi.org/10.1136/bmjmed-2022-000408

Acknowledging the use of patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are

used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

Data-sharing statement

All data requests regarding primary research within this project should be submitted to ctru@sheffield.ac.uk for consideration. Access to anonymised data may be granted following review. Requests for access to data regarding secondary research within this project should be addressed to the corresponding author or to the data custodian (if known).

Ethics statement

Full HRA and ethical approval was granted for the Venous ThromboEmbolism Assessment Methods (VTEAM) study (Rec Ref: 19/LO/1303). The protocol for the full study is available online. Completed EQUATOR checklists have been submitted for each chapter as relevant.

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Appendix 1 Literature search strategy and additional materials for the systematic review of RAMs for VTE in hospital inpatients

Database searched:	Ovid MEDLINE® Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Ovid MEDLINE® Daily, Ovid MEDLINE and Versions®
Platform or provider used:	Ovid SP
Date of coverage:	1946 to February 2021
Search undertaken:	February 2021

1 pulmonary embolism/ or thromboembolism/ or venous thromboembolism/ or venous thrombosis/ or upper extremity deep vein thrombosis/
2 (((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj3 (embolism or emboli or embolus or emboliz* or thromboembolism))).ti,ab.
3 1 or 2
4 letter/ or editorial/ or news/ or exp historical article/ or anecdotes as topic/ or comment/ or case report/ or (letter or comment).ti.
5 randomized controlled trial/ or random*.ti,ab.
6 4 not 5
7 animals/ not humans/
8 exp animals, laboratory/
9 exp animal experimentation/
10 exp models, animal/
11 exp rodentia/
12 (rat or rats or mouse or mice).ti.
13 6 or 7 or 8 or 9 or 10 or 11 or 12
14 3 not 13
15 (risk* adj2 assess*).ti,ab.
16 ((score* or scoring) adj2 (tool* or system*)).ti,ab.
17 ((risk* or predict* or prognos*) adj4 (tool* or rule* or index* or indices or score* or scoring or scale* or model* or system* or algorithm* or stratif* or criteria or calculat*)).ti,ab.
18 (vienna adj5 cats).ti,ab.
19 (vienna cancer and thrombosis study).ti,ab.
20 trauma embolic scoring.ti,ab.
21 tess.ti,ab.
22 (roger* or caprini* or kucher* or cohen* or padua* or khorana* or autar).ti,ab.
23 (well* adj2 (score* or scoring)).ti,ab.
24 department of health.ti,ab,au.
25 or/15-24
26 14 and 25
27 limit 26 to yr='2017 -Current'

Databases searched:	EMBASE
Platform or provider used:	Ovid SP
Date of coverage:	1974 to February 2021
Search undertaken:	February 2021

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1 thromboembolism/ or venous thromboembolism/ or vein thrombosis/ or deep veinthrombosis/ or leg thrombosis/ or lower extremity deep vein thrombosis/ or postoperativethrombosis/ or lung embolism/ or upper extremity deep vein thrombosis/
2 (((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj3 (embolism or emboli or embolus or emboliz* or thromboembolism))).ti,ab.
3 1 or 2
4 letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.
5 randomized controlled trial/ or random*.ti,ab.
6 4 not 5
7 animal/ not human/
8 nonhuman/
9 exp animal experiment/ or exp experimental animal/
10 animal model/
11 exp rodent/
12 (rat or rats or mouse or mice).ti.
13 6 or 7 or 8 or 9 or 10 or 11 or 12
14 3 not 13
15 (risk* adj2 assess*).ti,ab.
16 ((score* or scoring) adj2 (tool* or system*)).ti,ab.
17 ((risk* or predict* or prognos*) adj4 (tool* or rule* or index* or indices or score* or scoring or scale* or model* or system* or algorithm* or stratif* or criteria or calculat*)).ti,ab.
18 (vienna adj5 cats).ti,ab.
19 (vienna cancer and thrombosis study).ti,ab.
20 trauma embolic scoring.ti,ab.
21 tess.ti,ab.
22 (roger* or caprini* or kucher* or cohen* or padua* or khorana* or autar).ti,ab.
23 (well* adj2 (score* or scoring)).ti,ab.
24 department of health.ti,ab,au.
25 or/15-24
26 14 and 25
27 limit 26 to yr='2017 -Current'

Databases searched:	Cochrane CENTRAL Register of Randomised Controlled Trials & Cochrane Database of Systematic Reviews
Platform or provider used:	www.thecochranelibrary.com
Date of coverage:	Inception to February 2021
Search undertaken:	February 2021

#1. MeSH descriptor: [venous thromboembolism] this term only
#2. MeSH descriptor: [pulmonary embolism] this term only
#3. MeSH descriptor: [venous thrombosis] this term only
#4. MeSH descriptor: [thromboembolism] this term only
#5. MeSH descriptor: [upper extremity deep vein thrombosis] this term only
#6. ((*venous or *vein) next (thrombosis or thromboses or thrombus or thromboembolism) or dvt or vte or (pulmonary or lung) near/3 (embolism or emboli or embolus or emboliz* or thromboembolism)):ti,ab
#7. #1 or #2 or #3 or #4 or #6
#8. (risk* near/2 assess*):ti,ab

#9. ((score* or scoring) near/2 (tool* or system*)):ti,ab
#10. ((risk* or predict* or prognos*) near/4 (tool* or rule* or index* or indices or score* or scoring or scale* or model* or system* or algorithm* or stratif* or criteria or calculat*)):ti,ab
#11. (vienna near/5 cats):ti,ab
#12. (vienna cancer and thrombosis study):ti,ab
#13. trauma embolic scoring:ti,ab
#14. tess:ti,ab
#15. (roger* or caprini* or kucher* or cohen* or padua* or khorana* or autar):ti,ab
#16. (well* near/2 (score* or scoring)):ti,ab
#17. (department of health):ti,ab
#18. (or #8-#17)
#19.

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TABLE 20 PROBAST tool – the domains and signalling questions for the assessment of risk of bias and applicability

Domains			
Patient selection	**Predictors**	**Outcome**	**Analysis**
Signalling questions			
1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case–control study data?	2.1 Were predictors defined and assessed in a similar way for all participants?	3.1 Was the outcome determined appropriately?	4.1 Were there a reasonable number of participants with the outcome?
1.2 Were all inclusions and exclusions of participants appropriate?	2.2 Were predictor assessments made without knowledge of outcome data?	3.2 Was a pre-specified or standard outcome definition used?	4.2 Were continuous and categorical predictors handled appropriately?
–	2.3 Are all predictors available at the time the model is intended to be used?	3.3 Were predictors excluded from the outcome definition?	4.3 Were all enrolled participants included in the analysis?
–	–	3.4 Was the outcome defined and determined in a similar way for all participants?	4.4 Were participants with missing data handled appropriately?
–	–	3.5 Was the outcome determined without knowledge of predictor information?	*Development studies only* 4.5 Was selection of predictors based on univariable analysis avoided?
–	–	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of controls) accounted for appropriately?
–	–	–	4.7 Were relevant model performance measures evaluated appropriately?
–	–	–	*Development studies only* 4.8 Was model overfitting, underfitting and optimism in model performance accounted for?
–	–	–	*Development studies only* 4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?

TABLE 20 PROBAST tool – the domains and signalling questions for the assessment of risk of bias and applicability (adapted) (*continued*)

Domains			
Patient selection	**Predictors**	**Outcome**	**Analysis**
RISK OF BIAS[a]			
Could the selection of participants have introduced bias?	Could the selection of predictors or their assessments have introduced bias?	Could the selection of outcomes or its determination have introduced bias?	Could the statistical analysis have introduced bias?
APPLICABILITY			
Is there concern that the included participants and setting do not match the review question?	Is there concern that the definition, assessment, or timing of predictors in the model does not match the review question?	Is there concern that the outcome, its definition, timing, or determination does not match the review question?	–

a Signalling questions response options (rating of reporting by authors): yes (Y); no (N); probably yes (PY); probably no (PN); no information (NI).
b Risk of bias response options (in general): If all signalling questions were answered as: Y or PY, this domain was considered as 'low' risk of bias; N or PN on one or more questions, this was judged as 'high' risk of bias; and NI on one or more questions and it was low risk for all other domains, this was judged as 'unclear' risk of bias.
c Applicability response options: The degree of applicability was rated as 'low', 'high' or 'unclear' concern. The 'unclear' category was used only when the reported information was insufficient.
Source: Adapted from free online resources hosted by the protest group at https://www.probast.org

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TABLE 21 Widely evaluated generic RAMs, their associated characteristics and composite clinical variables

Characteristics	Name of VTE risk assessment model					
	Caprini score	Padua prediction score	IMPROVE predictive score	IMPROVE associative score	Geneva risk score	Kucher score
General						
Author, year	Caprini 2005[142]	Barbar 2010[15]	Tapson 2007[149]	Spyropoulos 2011[148]	Chopard 2006[143]	Kucher 2005[146]
Applicable cohort	Surgical and medical	Medical	Medical	Medical	Medical	Surgical and medical
Design	Ordinal with cumulative score	Dichotomous variables with cumulative score	Dichotomous variables with VTE probability estimate	Dichotomous variables with VTE probability estimate	Dichotomous variables with cumulative score	Dichotomous variables with cumulative score
Number of VTE risk variables	31	11	4	7	19	8
C-statistic (range) across medical, surgical and trauma cohorts	0.53–0.87 (12 studies)	0.594–0.756 (7 studies)	0.57–0.65 (2 studies)	0.63–0.7731 (4 studies)	0.61 (1 study)	0.563–0.756 (4 studies)
When is pharmacological thromboprophylaxis recommended?	Score ≥ 5	Score ≥ 4	No specific threshold Identified	No specific threshold identified	Score ≥ 3	Score ≥ 4
Clinical variables						
Patient related						
Active cancer	Yes	Yes	Yes	Yes	Yes	Yes (major risk)
Age	Yes	Yes (≥ 70)	Yes (≥ 60)	Yes (≥ 60)	Yes (≥ 60)	Yes (≥ 70 minor risk)
Dehydration	No	No	No	No	Yes	No
Thrombophilia	Yes (generic and named conditions)	Yes (generic)	Yes (generic)	Yes (generic)	Yes (generic)	Yes (major risk)
Obesity	Yes (≥ 25 kg/m^2)	Yes (≥ 30 kg/m^2)	No	No	Yes (≥ 30 kg/m^2)	Yes (≥ 30 kg/m^2 minor risk)

TABLE 21 Widely evaluated generic RAMs, their associated characteristics and composite clinical variables (*continued*)

Characteristics	Name of VTE risk assessment model					
	Caprini score	Padua prediction score	IMPROVE predictive score	IMPROVE associative score	Geneva risk score	Kucher score
Comorbidity	Yes (1–5 points for individual comorbidities)	Yes (1 point each for several individual comorbidities)	No	No	Yes (2 points each for several individual comorbidities)	No
Prior VTE	Yes	Yes	Yes	Yes	Yes	Yes (major risk)
Family history of VTE	Yes	No	No	No	No	No
Use of HRT	Yes	Yes	No	No	Yes	Yes (minor risk)
Use of oestrogen-containing contraceptive therapy	Yes	Yes	No	No	Yes	Yes (minor risk)
Varicose veins	Yes	No	No	No	No	No
Pregnancy or post-partum period	No	No	No	No	Yes	No
Unexplained stillbirth or spontaneous abortions	Yes (≥ 3 spontaneous abortions)	No	No	No	No	No
Current swollen legs	Yes	No	No	No	Yes	No
Current central venous access	Yes	No	No	No	No	No
Recent major surgery	Yes (< 1 month)	Yes (< 1 month)	No	No	No	No
Recent use of plaster cast immobilisation	Yes (< 1 month)	No	No	No	No	No
Lower limb paralysis	Yes	No	No	Yes	No	No
Travel related	No	No	No	No	Yes (> 6 hours)	No
Admission related						
Reduced mobility	Yes (variable points)	Yes	No	Yes (≥ 7 days)	Yes (≥ 3 days)	Yes (minor risk)

continued

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TABLE 21 Widely evaluated generic RAMs, their associated characteristics and composite clinical variables (*continued*)

Characteristics	Name of VTE risk assessment model					
	Caprini score	Padua prediction score	IMPROVE predictive score	IMPROVE associative score	Geneva risk score	Kucher score
Arthroplasty surgery	Yes	No	No	No	No	No
Hip fracture	Yes	No	No	No	No	No
Pelvic or lower limb surgery	Yes (arthroscopic)	No	No	No	No	No
Total anaesthetic and surgical time	Yes (≥ 45 minutes)	No	No	No	No	Yes (≥ 60 minutes intermediate risk)
Acute surgical admission	No	No	No	No	No	No
Acute infection	No	Yes	No	No	Yes	No
Acute rheumatological disorder	No	Yes	No	No	Yes	No
Critical care admission	No	No	No	Yes	No	No
Surgery leading to reduced mobility	Yes	No	No	No	No	No
Other						
'Other risk factors'	Yes	No	No	No	No	No

HRT, hormone replacement therapy.

TABLE 22 Summary of predictive performance for studies involving hospital inpatients who required care for cancer, stroke, burn injuries and sepsis or were a mixed medical/surgical cohort

Data source (Author, year)	End point	Incidence	Risk assessment model	Threshold or cut-off	Predictive performance		
					C-statistic (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Mixed inpatients							
Autar 2003[25]	DVT	18.9%	Novel (Autar 2003[26])	Risk score ≤ 6	NR	100% (NR)	100% (NR)
			Novel (Autar 2003[26])	Risk score 7–10	NR	86.0% (NR)	68.0% (NR)
			Novel (Autar 2003[26])	Risk score 11–14	NR	68.0% (NR)	31.0% (NR)
			Novel (Autar 2003[26])	Risk score ≥ 15	NR	25.0% (NR)	10.0% (NR)
Elias 2017[36]	VTE	0.8%	Padua (automated)	Risk score ≥ 5	0.81 (0.79 to 0.83)	85.4% (NR)	53.3% (NR)
Chen 2018[32]	DVT	NA	Caprini	Risk score ≥ 4	NR	73.8% (NR)	64.7% (NR)
			Caprini	Risk score ≥ 5	NR	62.8% (NR)	82.6% (NR)
			Padua	Risk score ≥ 3	NR	53.5% (NR)	82.1% (NR)
			Padua	Risk score ≥ 4	NR	42.1% (NR)	92.5% (NR)
Bo 2020[31]	DVT	0.9%	Caprini	Risk score ≥ 3.5	0.74 (0.71 to 0.77)	75.0% (NR)	62.0% (NR)
Cancer inpatients							
Abdel-Razeq 2010[24]	VTE	3.5%	Caprini (modified)	Risk score ≥ 3	NR	100% (NR)	9.2% (NR)
			Caprini (modified)	Risk score ≥ 5	NR	57.1% (NR)	53.2% (NR)
Patell 2017[56]	VTE	3.8%	Khorana	Risk score ≥ 3	NR	18.9% (NR)	87.2% (NR)
Hu 2020[44]	VTE	NA	Caprini	Risk score ≥ 5	0.71 (0.66 to 0.75)	82.4% (NR)	46.2% (NR)
			Khorana	Risk score ≥ 2	0.58 (0.53 to 0.63)	35.3% (NR)	78.7% (NR)
Shang 2020[62]	VTE	NA	Caprini 2009	Risk score ≥ 3	0.72 (0.70 to 0.74)	83.5% (NR)	52.7% (NR)
			Caprini 2013	Risk score ≥ 5	0.80 (0.78 to 0.82)	80.9% (NR)	65.9% (NR)

continued

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TABLE 22 Summary of predictive performance for studies involving hospital inpatients who required care for cancer, stroke, burn injuries and sepsis or were a mixed medical/surgical cohort (*continued*)

Data source (Author, year)	End point	Incidence	Risk assessment model	Threshold or cut-off	Predictive performance		
					C-statistic (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Burns inpatients							
Pannucci 2012[55]	VTE	1.0%	Novel (Pannucci 2012[56])	NR	0.75	NR	NR
Post-stroke inpatients							
Liu 2014[46]	DVT	10.5%	Post-stroke DVT Prediction System	NR	0.65 (0.59 to 0.70)	NR	NR
Sepsis inpatients							
Vardi 2013[66]	VTE	1.3%	Padua	NR	All patients 0.58 (0.43 to 0.73)	All patients NR	All patients NR
			Padua	NR	No prophylaxis 0.54 (0.37 to 0.71)	No prophylaxis NR	No prophylaxis NR

NA, not applicable; NR, not reported.

Appendix 2 Supplementary material from the economic evaluation

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TABLE 23 Clinical parameters (including probabilistic distributions)

Parameter description	Midpoint value	Uncertainty measure	Distribution	Source
Sensitivity of decision tools	See *Figure 6*	Not reported – assumed fixed in PSA	Not applicable	Systematic review of RAMs
Specificity of decision tools	See *Figure 6*	Not reported – assumed fixed	Not applicable	Systematic review of RAMs
Probability of PE in medical inpatients	1.38%	95% CI 0.7% to 2.2%	Beta (13, 929)	Barbar *et al.*[15]
Probability of symptomatic DVT in medical inpatients	2.02%	95% CI 1.2% to 3.0%	Beta (19, 923)	Barbar *et al.*[15]
Probability of PE in (elective) surgical inpatients	0.62%	95% CI 0.45% to 0.82%	Beta (42, 6726)	Pannucci *et al.*[54]
Probability of symptomatic DVT in (elective) surgical inpatients	0.78%	95% CI 0.59% to 1.01%	Beta (53, 6715)	Pannucci *et al.*[54]
Proportion of all DVTs that are symptomatic	6.21%	95% CI 4.4% to 8.2%	Beta (40, 604)	CG92 [This results in an incidence of asymptomatic DVT of 12.2% (95% CI 7.9% to 18.%) in medical inpatients and 31.4% (95% CI 16.9% to 51.9%) in surgical inpatients]
Proportion of DVTs that are distal (same proportion applied for symptomatic and asymptomatic DVTs)	69%	95% CI 67% to 71%	=1-Beta (1991, 32,713)/ Beta (6467, 28,789)	CG92 reports that 31% of all DVTs were proximal as estimated from the RCTs in their review that reported the incidence of both: (1991/34,704)/ (6467/35,256) = (6%/18%) = 31%
Effectiveness of prophylaxis in acutely ill medical inpatients – Risk ratio (RR) for VTE	0.49	95% CI 0.37 to 0.67	Lognormal (−0.40, 0.15)	Meta-analysis of VTE events in the three RCTs included in NG89 for LMWH (standard dose/standard duration) vs. placebo in acutely ill medical patients
Effectiveness of prophylaxis in surgical inpatients – Risk ratio (OR) for VTE	0.26	95% CI 0.09 to 0.87	Lognormal (−1.34, 0.58)	Network meta-analysis by Wade *et al.*[98] – estimate for heparin vs. no heparin
Risk of major bleeding for PPX in medical inpatients	1.02%	95 CI 0.65% to 1.47%	Beta (23, 2236)	Incidence of bleeding across the LMWH arms of three RCTs which reported bleeding risk in the systematic review of LMWH vs. placebo for acutely ill medical inpatients reported in NG89
Risk of major bleeding for PPX in inpatients having elective surgery	3.70%	95 CI 1.87% to 6.13%	Beta (11, 286)	Incidence of bleeding across the LMWH arms of five RCTs which reported bleeding risk in the systematic review of LMWH vs. placebo/mechanical prophylaxis for abdominal surgery in NG89

TABLE 23 Clinical parameters (including probabilistic distributions) (*continued*)

Parameter description	Midpoint value	Uncertainty measure	Distribution	Source
Proportion of major bleeding during PPX that is fatal for medical inpatients	14%	95% CI 8% to 23%	Beta (12, 71)	Bleeds occurring within 14 days of hospitalisation for medical inpatient (minimum length of stay of 3 days) from IMPROVE registry – average across cohort regardless of use of PPX or not (Decousus *et al.*[100])
Proportion of major bleeding during PPX that is fatal for surgical inpatients	0.9%	95% CI 0.02% to 3.36%	Beta (1, 108)	Proportion of major bleeds that were fatal in cohort of patients having elective hip or knee replacements receiving standard care of which 81.7% received LMWH (Turpie *et al.*[110])
Proportion of non-fatal major bleeding during PPX that is ICH for medical inpatients	10%	95% CI 4% to 18%	Beta (7, 64)	Bleeds occurring within 14 days of hospitalisation for medical inpatient (minimum length of stay of 3 days) from IMPROVE registry – average across cohort regardless of use of PPX or not (Decousus *et al.*[100])
Proportion of non-fatal major bleeding during PPX that is ICH for surgical inpatients	1.9%	95% CI 0.23% to 5.10%	Beta (2, 106)	Proportion of non-fatal major bleeds that were ICH in cohort of patients having elective hip or knee replacements receiving standard care of which 81.7% received LMWH (Turpie *et al.*[110])
RR of bleeding for prophylaxis vs. none in medical inpatients – HR	1.53	95% CI 0.90 to 2.53	Lognormal (0.43, 0.33)	Meta-analysis of VTE events in the three RCTs included in NG89 for LMWH (standard dose/standard duration) vs. placebo in acutely ill medical patients
RR of bleeding for prophylaxis vs. none in elective surgical inpatients – HR	2.98	95% CI 0.88 to 14.80	Lognormal (1.01, 0.72)	Network meta-analysis of major bleeding for LMWH (standard dose/standard duration) vs. placebo/ mechanical prophylaxis in patients having abdominal surgery from NG89
Risk of bleeding during 3-month anticoagulant treatment for VTE	0.8%	95% CI 0.2% to 2.0%	Beta (3, 352)	6-month incidence pooled across patients with HAS-BLED score of 0 or 1 from Kooiman *et al.*[104]
Proportion of major bleeds during VTE treatment that are fatal	25%	95% CI 21% to 28%	Beta (135, 411)	Based on case-fatality rates for major bleeds within the RIETE registry (Nieto *et al.*)[106]
Proportion of non-fatal major bleeds during VTE treatment that are ICH	9%	95% CI 6.5% to 11.9%	Beta (37, 374)	Based on proportion of major non-fatal bleeds within RIETE registry that were ICH (Nieto *et al.*)[106]
All-cause (non-VTE related) mortality for general population not in hospital	Varies by age	Assumed fixed	Not applicable	ONS lifetables 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 23 Clinical parameters (including probabilistic distributions) (*continued*)

Parameter description	Midpoint value	Uncertainty measure	Distribution	Source
SMR for deaths in emergency medical inpatients in year after admission compared with deaths in age- and sex-matched general population	9.43	Ratio of two sampled death rates 11.7 (95% CI 11.6 to 11.8) in general population 108 (95% CI 104.4 to 116.5) in hospitalised medical patients	Norm (11.7, 0.05) Norm (108, 3.09)	Moore *et al.*[90]
Mortality in year after admission for surgical inpatients compared to medical inpatients – HR	1.9	95% CI 1.7 to 2.0	Lognormal (0.64, 0.04)	Clark *et al.*[85]
SMR for patients surviving ICH compared with general population				SMR from Fogelholm *et al.*[119] applied for years 2 to 6 and then assumed no increased mortality risk Increased risk in year after ICH is assumed to be the same as for all hospital inpatients as the SMR for ICH is lower than for the SMR for all medical and surgical inpatients Confidence intervals around SMR not reported so have assumed ± 20% on the log scale
– Year 1 after ICH	NA	Same as for all hospitalised patients		
– Years 2–6 after ICH	2.2	95% CI 1.8 to 2.7	Log (SMR) = Norm (0.8, 0.1)	
Probability of PE being fatal in general medical inpatients	26.8%	95% CI 11.3% to 33.1%	Beta (11, 30)	Average case-fatality rate across five RCTs reporting both PE and fatal PE incidence in NG89 (Samama *et al.*,[97] Leizorovicz *et al.*,[95] Hull *et al.*,[123] Harenberg *et al.*,[122] Kleber *et al.*[124])
Probability of PE being fatal in general surgical inpatients	6.0%	95% CI 5.3% to 13.4%	Beta (11, 173)	Average case-fatality rate across RCTs of surgical patients included in reviews in CG92
Cumulative risk of PTS for treated symptomatic DVT at 3 years				Cumulative incidence at 3 years based on the TULIPA PLUS registry reported by Hach-Wunderle *et al.*[110] Distribution of risk across years 1–3 based on van Dongen *et al.*[111] Zero risk assumed from year 4 onwards
Proximal	32.4%	95% CI 22.1% to 43.6%	Beta (23, 48)	
Distal	15.6%	95% CI 7.9% to 25.3%	Beta (10, 54)	
OR for PTS in asymptomatic untreated proximal DVT vs. treated proximal DVT	2.71	95% CI 1.44 to 5.1	Log (OR) = Norm (0.99, 0.32)	OR from van Dongen *et al.*[111] OR applied to risk for treated asymptomatic DVT to get incidence at 3 years of 56.6% for proximal [This gives a PTS risk of 56.5% (95%CI 29.0% to 79.8%) in asymptomatic untreated proximal DVT]
OR for PTS in asymptomatic distal DVT	1	Fixed	Not applicable	Assumed no increased risk for asymptomatic in distal DVT.

TABLE 23 Clinical parameters (including probabilistic distributions) (*continued*)

Parameter description	Midpoint value	Uncertainty measure	Distribution	Source
Incidence of CTEPH at 2 years (converted to annual risk of 1.6%)	3.2%	95% CI 2.0 % to 4.4%	Beta (32, 967)	Ende-Verhaar *et al.*[108] based on incidence in those surviving the initial treatment period of 3–6 months Assumed no risk beyond 2 years based on Pengo *et al.*[109]
Proportion of CTEPH treated surgically	59.5%	95% CI 55.8% to 63.2%	Beta (404, 275)	Delcroix *et al.*[120]
Proportion of CTEPH that are surgically treated who also received bridging medical care	30.0%	95% CI 24.6% to 33.5%	Beta (117, 287)	Delcroix *et al.*[120]
Mean hazard for exponential survival curve in medically treated patients with CTEPH	0.1168	SE = 0.0123	Norm (0.1168, 0.0123)	Original data from Delcroix *et al.*[120] but curves taken from Goodacre *et al.*[178] (If the death hazard falls below general population values, then general population values apply)
Mean and SD for lognormal survival curve in surgically treated patients with CTEPH	Mean = 5.08 SD = 3.34	SE of mean = 0.574 SE of SD = 0.399	Multivariate normal	Original data from Delcroix *et al.*[120] but curves taken from Goodacre *et al.*[178] (If the death hazard falls below general population values, then general population values apply) Variance–covariance matrix
				Mean log: Mean log 0.017708; SD log −0.05572
				SD log: Mean log −0.05572; SD log 0.230935
Age	−0.0001728	SE = 0.0003737	Multivariate normal	
Age × Age	−0.000034	SE = 3.96×10^{-6}		
Constant	0.9584588	SE = 0.0077431		

CG, clinical guideline; CODA, convergence diagnostics and output analysis; ONS, Office for National Statistics; OR, odds ratio; PSA, probabilistic sensitivity analysis; 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.

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TABLE 24 Summary of cost parameters

Parameter description	Mean value	95% CI[a]	Source	Notes
Application of RAM to patient	£9.08	Fixed	Curtis *et al.*[178]	Cost for 5 minutes of hospital consultant time
Prophylaxis for medical/surgical inpatients 5 days of LMWH (Dalteparin) administered by hospital nurse	£23.91	NA	Admin costs from Curtis *et al.*[178] Drug costs based on Drug Tariff	Dalteparin is lowest-cost formulation of LMWH based on current Drug Tariff prices.
Treatment of symptomatic proximal DVT	£763.12	£748.04 to £795.10	NHS reference costs Drug tariff	Clinical expert discussion regarding likelihood resource use, combined with NHS reference cost data for healthcare contacts and drug tariff costs for treatments (see *Table 30* for more detailed costing breakdown)
Treatment of symptomatic distal DVT	£642.95	£621.76 to £668.61	NHS reference costs[180] Drug tariff[181]	Clinical expert discussion regarding likelihood resource use, combined with NHS reference cost data for healthcare contacts and drug tariff costs for treatments (see *Table 30* for more detailed costing breakdown)
Treatment of non-fatal PE	£1848.75	£1816.98 to £1884.53	NHS reference costs[180] Drug tariff[181]	Clinical expert discussion regarding likelihood resource use, combined with NHS reference cost data for healthcare contacts and drug tariff costs for treatments (see *Table 30* for more detailed costing breakdown)
Fatal PE	£1517.13	£1491.37 to £1542.99	NHS reference costs[180]	As per non-fatal minus drug therapy for PE
Fatal bleed	£1865.51	£678.86 to £3698.12	Luengo-Fernandez *et al.*[124]	Costs of fatal haemorrhagic stroke from OXVASC subgroup with atrial fibrillation. Uplifted to current prices using inflation indices[179]
Non-fatal non-ICH bleed	£1209.75	£1199.79 to £1220.07	NHS reference costs 2015–2016[180]	Weighted average of reference costs for gastrointestinal bleed (HRG codes FZ38G – FZ38P)
Post non-fatal ICH – first 90 days	£21,987.80	£17,413.48 to £27,302.45	Luengo-Fernandez *et al.*[124]	Weighted average of costs for non-fatal haemorrhagic strokes Uplifted to current prices using inflation indices[179]
Post non-fatal ICH – post acute (beyond 90 days) costs per annum	£8292.83	£5,57.42 to £11,613.69	Luengo-Fernandez *et al.*[124]	Average costs across all stroke types (haemorrhagic not reported separately). Includes GP and ED costs and long-term care cost Uplifted to current prices using inflation indices[179]
PTS cost per annum – year 1 Mild/moderate Severe	£293.16 in year 1	£279.90 to £306.40	NHS reference costs 2015–2016[180]	One first and one follow-up vascular surgery outpatient appointments 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)

TABLE 24 Summary of cost parameters (*continued*)

Parameter description	Mean value	95% CI[a]	Source	Notes
PTS cost per annum – year 2 Mild/moderate Severe	£78.00 in each subsequent year	Fixed	Curtis *et al.*[179]	2 × GP surgery consultations with qualification costs including direct care staff costs at £37 per appointment
CTEPH cost per annum Medically managed	£18,569.53 each year	Fixed	NICE CG92[182]	Cost in CG92 was £1219 per 4 weeks in 2008–09 prices.[182] This was uplifted to 2016–17 prices using inflation indices.[181] Assume treatment lifelong
CTEPH cost per annum Surgically managed	£10,236.60 in year 1 and zero in Y2 onwards	£9932.52 to £10,557.20	NHS reference costs 2015–2016[180]	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; ED, emergency department; 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; LTRiP (cast), Leiden–Thrombosis Risk Prediction for patients with cast immobilisation score; NICE, National Institute for Health and Care Excellence; ONS, Office for National Statistics; OR, odds ratio; OXVASC, Oxford Vascular Study; RIETE, The Computerized Registry of Patients with Venous Thromboembolism; SMR, standardised mortality ratio; TULIPA, Thrombosis and Pulmonary Embolism in Out-Patients; SE, standard error.
a Except where stated otherwise, e.g. SD or SE.

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TABLE 25 Drug costs for treating DVT and PE

Drug	Dosing and delivery	Product and cost	Drug cost per course	Monitoring/ administration cost	Proportion using treatment
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 days) treatment period	Apixaban 5 mg = £53.20 for 56 tablets (cost per tablet is same for 28 tablet pack size)	£186.20	£73[a]	20% (half of the 40% using DOACs)
Rivaroxaban	Initially 15 mg twice daily for 21 days, to be taken orally with food. Followed by 20 mg once daily, to be taken orally with food for the remainder of the 3-month (91 days) treatment period	Rivaroxaban 20 mg = £50.40 for 28 tablets (cost per tablet is same for 15 mg and larger and smaller pack sizes)	£201.60	£73[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 if assuming weight of 80 kg	Clexane Forte 120 mg/0.8 ml solution (Sanofi) – £87.93 for 10 pre-filled syringes Prescription only medicine assumed for other drugs	£61.55	£72.71[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 (Pfizer Ltd/Ennogen Healthcare Ltd/JM McGill Ltd) – £42.34 for five pre-filled syringes	£59.28	£72.71[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 80 kg	Innohep 14,000 units/0.7ml solution (LEO Pharma) – £83.30 for 10 pre-filled syringes	£58.31	£72.71[b]	6% (20% of heparin use)
Warfarin	5 mg once daily orally for 3 months (91 days)	Warfarin sodium 5mg (various suppliers) = £0.70 for 28 tablets	£3.22	£238.84[c]	60%
Average across those using DOACs and those using LMWH/VKA			£115.55	£216.07	**Total: £331.63**

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 need for ongoing treatment.
b Based on the costs estimated by Menakaya *et al.*[121] with the number of district nurse administrations reduced to reflect shorter duration of treatment (7 days vs. 6 weeks).
c Based on HRG costs for nine face-to-face visits at 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 need for ongoing treatment.

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

TABLE 26 Resource use and costs for patients presenting with PE and symptomatic DVT

	Proportion using resource				
	Non-fatal PE	Symptomatic proximal DVT	Symptomatic distal DVT	Unit cost per patient using this resource	Description
Healthcare contacts/admission					
GP visit	20%	50%	50%	£39	GP cost per surgery consultation with qualification costs including direct care staff costs
Ambulance transfer to Emergency Department	60%	10%	0%	£257	NHS Schedule for Reference Costs 2018–19 'See and treat and convey', code ASS02
Emergency Department visit leading to admission	60%	10%	0%	£279	NHS Schedule for Reference Costs 2018–19 VB05Z Type 01 Admitted (Category 2 investigation with Category 3 treatment)
Emergency Department without admission	40%	90%	100%	£239	NHS Schedule for Reference Costs 2018–19 VB05Z Type 01 Non-admitted (Category 2 investigation with Category 3 treatment)
Short-stay admission for PE	60%	0%	0%	£1410	NHS Schedule for Reference Costs 2018–19 Weighted average cost of non-elective inpatient (short and long stay with excess bed-days) for 'Pulmonary Embolus with Interventions', codes DZ09J to DZ09N & DZ09P and DZ09Q
Short-stay admission for DVT	0%	10%	0%	£904	NHS Schedule for Reference Costs 2018–19 Weighted average cost of non-elective inpatient (short and long-stay with excess bed-days) for 'Deep-Vein Thrombosis' CC score 0–12+, codes YQ51A to YQ51E.
Critical care unit stay	10%	0%	0%	£1028	NHS Schedule for Reference Costs 2018–19 Weighted average cost of adult Critical Care, 0–6 or more organs Supported, codes XC01Z to XC01Z
Subtotal for healthcare contacts	**£1374**	**£379**	**£259**		
Diagnostic costs					
Risk assessment tool (Wells score)	Included in Emergency Department episode so not costed separately				
D-Dimer					
ECG					
Chest X-ray					

continued

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TABLE 26 Resource use and costs for patients presenting with PE and symptomatic DVT (*continued*)

	Proportion using resource				
	Non-fatal PE	Symptomatic proximal DVT	Symptomatic distal DVT	Unit cost per patient using this resource	Description
Proximal leg vein ultrasound	0%	100%	100%	£53	NHS Schedule for Reference Costs 2015–16.[180] RD40Z outpatient ultrasound scan with duration of less than 20 minutes, without contrast £55 [RD47Z may be more relevant for diagnosis of distal DVTs but cost is similar (£58)]
CTPA	90%	0%	0%	£108	NHS Schedule for Reference Costs 2015–16.[180] RD21A outpatient computerised tomography scan of one area, with post contrast only, 19 years and over
V/Q SPECT	5%	0%	0%	£287	NHS Schedule for Reference Costs 2015–16.[180] RN08A outpatient single photon emission computed tomography (SPECT), 19 years and over
V/Q planar	5%	0%	0%	£321	NHS Schedule for Reference Costs 2015–16.[180] RN18A outpatient lung ventilation or perfusion scan, 19 years and over
Echocardiogram	20%	0%	0%	£76	NHS Schedule for Reference Costs 2015–16.[180] RD51A outpatient simple echocardiogram
Subtotal for unbundled diagnostics	£143	£53	£53		
Subtotal for drug treatment	£332	£332	£332		
Total	£1,849[a]	£763	£643		

CC, complication or comorbidity; CTPA, computerised tomography pulmonary angiography; ECG, electrocardiogram; GP, general practitioner; SPECT, single photon emission 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 £1517.

TABLE 27 Utility values applied in short-term decision tree

Absolute utility value	Absolute utility value	Range	Source	Notes
Well/asymptomatic DVT without prophylaxis			Ara and Brazier[137]	Population mean utility values based on average age and sex mix at baseline
Medical inpatients	0.800	0.799–0.801		
Surgical inpatients	0.849	0.847–0.851		
Symptomatic proximal or distal DVT			Monreal *et al.*[113]	3.8% reduction relative to well patients based on comparison of average utility over 6 months for DVT (0.820) vs. PE vs. utility of matched population norms (0.852)
Medical	0.769	0.756–0.779		
Surgical	0.817	0.802–0.828		
Non-fatal PE			Chuang *et al.*[130]	4.0% reduction relative to well patients based on comparison of average utility over 6 months (0.804) for PE vs. utility of matched population norms (0.838)
Medical	0.769	0.756–0.779		
Surgical	0.815	0.803–0.827		
Non-fatal ICH			Luengo-Fernandez *et al.*[123]	Absolute decrement of 0.22 measured at 1 month
Medical	0.580	0.540–0.619		
Surgical	0.629	0.589–0.669		
Non-fatal non-ICH bleed			Chuang *et al.*[130]	Assumed same utility decrement for PE and GI bleeds at 1 month. 14% reduction based on utility for PE at 1 month (0.718) vs. utility of matched population norms (0.838) from Chuang *et al.*[130]
Medical	0.685	0.684–0.686		
Surgical	0.727	0.725–0.729		
Prophylaxis – absolute decrement applied to utility values of well/asymptomatic DVT	0.007	0.000–0.050	Marchetti *et al.*[136]	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	0.000–0.083	Marchetti *et al.*[136]	Patients willing to trade average of 4 days per year to avoid treatment with warfarin
Fatal PE	0	NA	Assumption	

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TABLE 28 Utility multipliers for state-transition phase of the model

Health state(s)	Utility multiplier relative to well	Range	Source	Notes
PE survivor without CTEPH and PE survivor more than 1 year after surgery for CTEPH	1.000	0.998–1.000	Chuang *et al.*[130]	Average over 6–12 months following PE compared to matched general population norms
Any DVT without PTS	1	NA	Assumption	Supported by Lubberts *et al.*[127] systematic review finding no significant HRQoL decrement in nine long-term studies based on SF-36 outcomes
Non-fatal ICH			Luengo-Fernandez *et al.*[123]	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
Medical	0.888	0.837–0.937		
Surgical	0.894	0.847–0.941		
PTS	0.895	0.816–0.952	Enden *et al.*[133]	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	0.629	0.579–0.690	Meads *et al.*[135]	Multiplier calculated based on comparison of utility for CTEPH (0.56) vs. utility for NYHA class I (0.89)
Dead	0		Assumption	

TABLE 29 Probabilistic distributions for cost and utility inputs

Parameter description	Midpoint value	Uncertainty measure	Distribution	Source
Ambulance transfer to ED	£257	SE = £11	Gamma (551, 0.47)	NHS Schedule for Reference Costs 2018–19. HRG code, ASS02 See and treat and convey
ED visit leading to admission	£279	SE = £6	Gamma (2210, 0.15)	NHS Schedule for Reference Costs 2018–19. HRG code: Type 01, leading to admission, VB05Z Emergency Medicine, Category 2 Investigation with Category 3 Treatment
ED visit not leading to admission	£239	SE = £4	Gamma (3204, 0.07)	NHS Schedule for Reference Costs 2018–19. HRG code: Type 01, not leading to admission, VB05Z Emergency Medicine, Category 2 Investigation with Category 3 Treatment
DVT admission – weighted average of following HRG costs:				NHS Schedule for Reference Costs 2018–19. Non-elective inpatient (NEI) and non-elective short stay (NESS) costs for HRG codes covering deep-vein thrombosis with CC scores ranging from 0 to 12+
YQ51A – NEI (*N* = 1377)	£4017	SE = £198	Gamma (412, 9.7)	
YQ51A – NESS (*N* = 492)	£564	SE = £33	Gamma (288, 2.0)	
YQ51B – NEI (*N* = 1183)	£2873	SE = £129	Gamma (495, 5.8)	
YQ51B – NESS (*N* = 895)	£470	SE = £13	Gamma (1237, 0.4)	
YQ51C – NEI (*N* = 1665)	£2433	SE = £78	Gamma (973, 2.5)	
YQ51C – NESS (*N* = 2391)	£418	SE = £11	Gamma (1433, 0.3)	
YQ51D – NEI (*N* = 1686)	£2020	SE = £46	Gamma (1903, 1.1)	
YQ51D – NESS (*N* = 6249)	£384	SE = £9	Gamma (1822, 0.2)	
YQ51E – NEI (*N* = 908)	£1772	SE = £42	Gamma (1814, 1.0)	
YQ51E- NESS (*N* = 11,731)	£320	SE = 9	Gamma (1330, 0.2)	
PE admission – weighted average of following HRG costs:				NHS Schedule for Reference Costs 2018–19. Non-elective inpatient (NEI) costs and non-elective short stay (NESS) costs for HRG codes covering pulmonary embolus with and without interventions with CC score from 0 to 12+
DZ09J – NEI (*N* = 888)	£5450	SE = £277	Gamma (338, 14)	
DZ09J – NESS (*N* = 62)	£1280	SE = £168	Gamma (58, 22)	
DZ09K – NEI (*N* = 585)	£3384	SE = £130	Gamma (676, 5.0)	
DZ09K – NESS (*N* = 65)	£790	SE = £56	Gamma (199, 4.0)	

continued

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TABLE 29 Probabilistic distributions for cost and utility inputs (*continued*)

Parameter description	Midpoint value	Uncertainty measure	Distribution	Source
DZ09L – NEI (*N* = 3160)	£3522	SE = £140	Gamma (663, 5.5)	
DZ09L – NESS (*N* = 1181)	£667	SE = £21	Gamma (1026, 0.7)	
DZ09M – NEI (*N* = 3716)	£2671	SE = £75	Gamma (1255, 2.1)	
DZ09M – NESS (*N* = 2197)	£577	SE = 18	Gamma (1054, 0.6)	
DZ09N – NEI (*N* = 5105)	£2201	SE = £45	Gamma (2358, 0.9)	
DZ09N – NESS (*N* = 4374)	£533	SE = 12	Gamma (2091, 0.3)	
DZ09P – NEI (*N* = 6126)	£1845	SE = £38	Gamma (2417, 0.8)	
DZ09P – NESS (*N* = 8768)	£488	SE = £12	Gamma (1595, 0.3)	
DZ09Q – NEI (*N* = 3226)	£1584	SE = £29	Gamma (2989, 0.5)	
DZ09Q – NESS (*N* = 9048)	£448	SE = 9	Gamma (2376, 0.2)	
Critical care – weighted average of HRG costs for codes:				NHS Schedule for Reference Costs 2018–19. HRG codes for Adult Critical Care for 0–6 organs supported
XC01Z	£1673	*N* = 1	Fixed	
XC02Z	£1574	SE = £152	Gamma (107, 14.7)	
XC03Z	£1655	SE = £114	Gamma (211, 7.9)	
XC04Z	£1640	SE = £67	Gamma (605, 2.7)	
XC05Z	£1450	SE = £49	Gamma (884, 1.7)	
XC06Z	£792	SE = £78	Gamma (104, 7.6)	
XC07Z	£516	SE = £129	Gamma (16.0, 32.2)	
Proximal leg vein ultrasound	£53	SE = £1	Gamma (2135, 0.03)	NHS Schedule for Reference Costs 2018–19
CTPA	£108	SE = £4	Gamma (635, 0.17)	NHS Schedule for Reference Costs 2018–19 RD21A outpatient computerised tomography scan of one area, with post contrast only, 19 years and over
V/Q SPECT	£287	SE = £20	Gamma (202, 1.42)	NHS Schedule for Reference Costs 2018–19 RN08A, outpatient single photon Emission computed tomography (SPECT), 19 years and over

TABLE 29 Probabilistic distributions for cost and utility inputs (*continued*)

Parameter description	Midpoint value	Uncertainty measure	Distribution	Source
V/Q planar	£321	SE = £10	Gamma (1045, 0.31)	NHS Schedule for Reference Costs 2018–19 RN18A outpatient lung ventilation or perfusion scan, 19 years and over
Echocardiogram	£76	SE = £6	Gamma (146, 0.52)	NHS Schedule for Reference Costs 2018–19 RD51A outpatient simple echocardiogram, 19 years and over
Proportion receiving LMWH who need district nurse administration	4%	95% CI 1.3% to 7.8%	Beta (5123)	Menakaya *et al.*[121]
Fatal bleed	£1592	SD = 1886, *N* = 8	Gamma (5.70, 279)	Luengo-Fernandez *et al.*[124] (cost before inflation)
Acute costs for non-fatal ICH (first 90 days) – weighted average of:				Luengo-Fernandez *et al.*[124] (cost before inflation)
Non-disabling non-fatal stroke	£9903	SD = 4510, *N* = 5	Gamma (24, 411)	
Moderately disabling non-fatal stroke	£25,442	SD = 9635, *N* = 3	Gamma (21, 1216)	
Totally disabling non-fatal stroke	£43,036	SD = NA, *N* = 1	Fixed	
Residential costs for non-fatal ICH (first 90 days)	£6880	SD = £15,600, *N* = 136	Gamma (26, 260)	Luengo-Fernandez *et al.*[124] (cost before inflation)
GP costs for non-fatal ICH (first 90 days)	£98	95% CI £27 to £169	Norm (98, 36)	Luengo-Fernandez *et al.*[124] (cost before inflation)
Emergency care costs for non-fatal ICH (first 90 days)	£99	95% CI £56 to £141	Norm (99, 22)	Luengo-Fernandez *et al.*[124] (cost before inflation)
Non-fatal non-ICH bleed (weighted average of HRG costs):				NHS Schedule for Reference Costs 2018–19 HRG codes for GI bleed without interventions, with single interventions and with multiple interventions.
FD03A – NEI (*N* = 1110)	£5377	SE = £201	Gamma (714, 7.5)	
FD03A – NESS (*N* = 30)	£2360	SE = £310	Gamma (58, 41)	
FD03B– NEI (*N* = 885)	£3510	SE = £131	Gamma (722, 4.9)	
FD03B– NSS (*N* = 16)	£2088	SE = £1109	Gamma (3.6, 590)	
FD03C – NEI (*N* = 1642)	£3866	SE = £171	Gamma (514, 7.5)	
FD03C– NSS (*N* = 41)	£1345	SE = £105	Gamma (166, 8.1)	
FD03D – NEI (*N* = 2329)	£2796	SE = £92	Gamma (913, 3.0)	
FD03D– NSS (*N* = 46)	£2360	SE = £156	Gamma (229, 10)	
FD03E – NEI (*N* = 5481)	£2247	SE = £47	Gamma (2331, 1.0)	

continued

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TABLE 29 Probabilistic distributions for cost and utility inputs (*continued*)

Parameter description	Midpoint value	Uncertainty measure	Distribution	Source
FD03E – NEI (*N* = 108)	£1089	SE = £82	Gamma (£178, 6.1)	
FD03F – NEI (*N* = 2891)	£2818	SE = £100	Gamma (792, 3.6)	
FD03F – NEI (*N* = 2213)	£591	SE = £19	Gamma (1000, 0.6)	
FD03G – NEI (*N* = 7278)	£2198	SE = £41	Gamma (2931, 0.8)	
FD03G – NEI (*N* = 8830)	£541	SE = £15	Gamma (1221, 0.4)	
FD03H – NEI (*N* = 16,290)	£1575	SE = £27	Gamma (3523, 0.8)	
FD03H – NEI (*N* = 40,167)	£438	SE = 11	Gamma (1640, 0.3)	
Anticoagulant service face-to-face follow-up consultant led	£53	SE = £5	Norm (53, 5.3) with minimum of zero	NHS Schedule for Reference Costs 2018–19 Service code 324 – WF01A non-admitted
Anticoagulant service face-to-face follow-up non-consultant led	£20	SE = £2	Norm (20, 2.0) with minimum of zero	NHS Schedule for Reference Costs 2018–19 Service code 324 – WF01A non-admitted
Anticoagulant service first face-to-face attendance non-consultant led	£26	SE = £3	Norm (26, 2.6) with minimum of zero	NHS Schedule for Reference Costs 2018–19 Service code 324 – WF01B non-admitted
Anticoagulant service non-face-to-face follow-up non-consultant led	£20	SE = £20	Norm (20, 2.0) with minimum of zero	NHS Schedule for Reference Costs 2018–19 Service code 324 – WF01C non-admitted
Vascular surgery first appointment face to face consultant led	£165	SE = £6	Gamma (759, 0.22)	NHS Schedule for Reference Costs 2018–19 Service code 107 – WF01B non-admitted
Vascular surgery follow-up appointment face-to-face, consultant led	£134	SE = £4	Gamma (942, 0.14)	NHS Schedule for Reference Costs 2018–19 Service code 107 – WF01A non-admitted
Vascular surgery first appointment face-to-face non-consultant led	£132	SE = £11	Gamma (132, 1.0)	NHS Schedule for Reference Costs 2018–19 Service code 107 – WF01B non-admitted
Vascular surgery follow-up appointment face-to-face, non-consultant led	£121	SE = £14	Gamma (79, 1.53)	NHS Schedule for Reference Costs 2018–19 Service code 107 – WF01A non-admitted
Surgical management of CTEPH – average of following HRG costs;				NHS Schedule for Reference Costs 2018–19 HRG codes for complex thoracic procedures, 19 years and over, with CC Score ranging from 0 to 6+
DZ02H	£9782	SE = £363	Gamma (723, 13.5)	
DZ02J	£7500	SE = £300	Gamma (627, 12.0)	
DZ02K	£6506	SE = £270	Gamma (579, 11.2)	

TABLE 29 Probabilistic distributions for cost and utility inputs (*continued*)

Parameter description	Midpoint value	Uncertainty measure	Distribution	Source
Disutility for stroke up to 6 months	−0.22	95% CI −0.26 to −0.18	Norm (−0.22, 0.02)	Luengo-Fernandez *et al.*[123]
Disutility for stroke from 6 months	−0.09	95% CI −0.13 to −0.05	Norm (−0.09, 0.02)	Luengo-Fernandez *et al.*[123]
Utility immediately after DVT	0.72	SE = 0.006	Beta (3977, 1565)	Monreal *et al.*[113]
Utility immediately after PE	0.72	SE = 0.007	Beta (2741, 1080)	Chuang *et al.*[130] (assumed same SD as observed for patients having DVT in Monreal *et al.*[113])
Utility for DVT without PTS	0.86	95% CI 0.823 to 0.903	Beta (248, 40.3)	Enden *et al.*[133]
Disutility for PTS vs. no PTS after DVT	0.09	95% CI 0.03 to 0.15	Beta (7.78, 78.6)	Enden *et al.*[133]
Utility for CTEPH	0.56	SD = 0.29, *N* = 308	Beta (505, 397)	Meads *et al.*[135]
Utility for NYHA class 1	0.86	SD = 0.17, *N* = 35	Beta (105, 12.9)	Meads *et al.*[135]
Utility for LMWH	0.993	SD = 0.016	Beta (27.5, 0.205)	Marchetti *et al.*[136]
Utility for warfarin	0.989	SD = 0.024	Beta (17.6, 0.195)	Marchetti *et al.*[136]
Utility regression for age-related decrement – coefficients for				Ara and Brazier[137]
Age	−0.0001728	SE = 0.0003737	Multivariate normal	Variance–covariance matrix
Age × Age	−0.000034	SE = 3.96×10^{-6}		
Constant	0.9584588	SE = 0.0077431		

	Age	Age × Age	Constant
Age	1.4×10^{-7}		
Age × Age	-1.5×10^{-9}	1.6×10^{-11}	
Constant	-2.80×10^{-6}	2.8×10^{-8}	6×10^{-5}

CC, complications and comorbidities; CG, clinical guideline; CODA, convergence diagnostics and output analysis; CTPA, computerised tomography pulmonary angiography; ED, emergency department; GP, general practitioner; HR, hazard ratio; HRG, healthcare resource group; NA, not applicable; ONS, Office for National Statistics; OR, odds ratio; SE, standard error; SPECT, Single Photon Emission Computed Tomography; V/Q, ventilation – perfusion.

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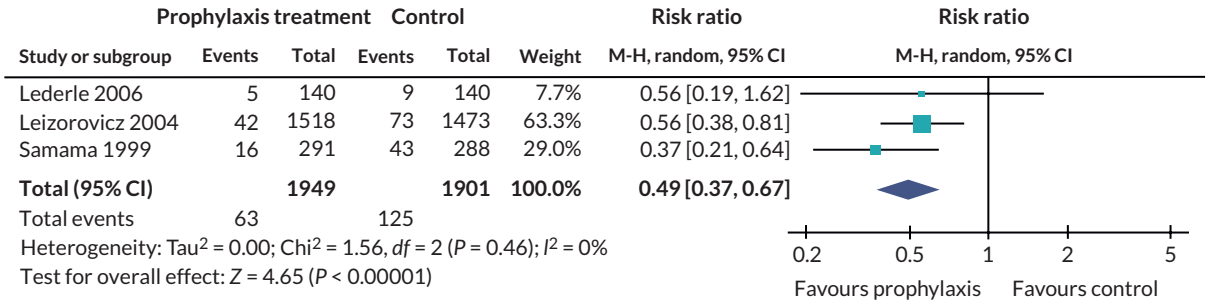

FIGURE 27 Meta-analysis of VTE outcomes in medical inpatients.

1. Lederle FA, Sacks JM, Fiore L, Landefeld CS, Steinberg N, Peters RW, *et al.* The prophylaxis of medical patients for thromboembolism pilot study. *Am J Med* 2006;**119**:54–9. https://doi.org/10.1016/j.amjmed.2005.03.049
2. Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ, *et al.* Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation* 2004;**110**:874–9. https://doi.org/10.1161/01.CIR.0000138928.83266.24
3. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, *et al.* A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med* 1999;**341**:793–800. https://doi.org/10.1056/NEJM199909093411103

Appendix 3 Additional data from the multicentre observational cohort study

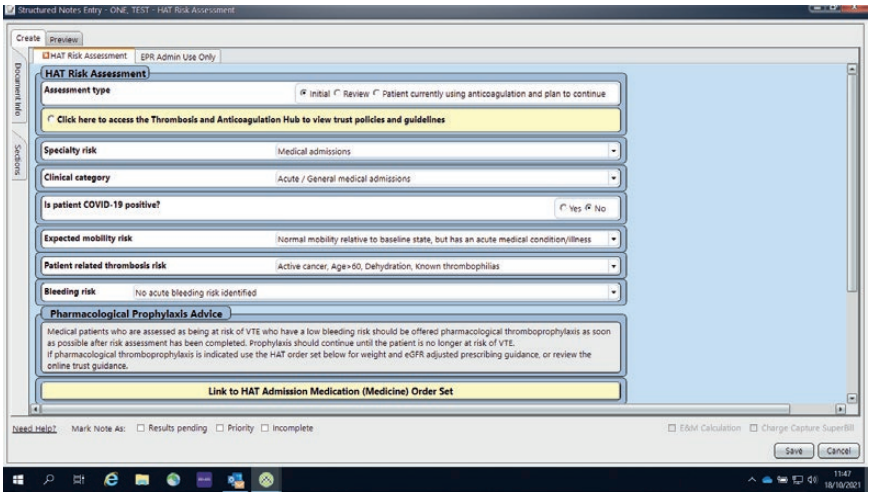

FIGURE 28 Examples of electronic and paper documentation aids for RAM completion.
Site 1 – Structured note completed through Electronic Health Record and designed to aid VTE risk assessment at the point of hospital admission, using the Department of Health RAM (Salford Royal NHS Foundation Trust)
Site 2 – Paper risk assessment proforma with linked prescribing (Manchester NHS Foundation Trust)
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Site 4 – Electronic form within prescribing electronic health record designed to trigger consideration of VTE risk assessment at the point of hospital admission and prompt prescribing in accordance with local guidelines (St Thomas' NHS Foundation Trust). (*continued*)

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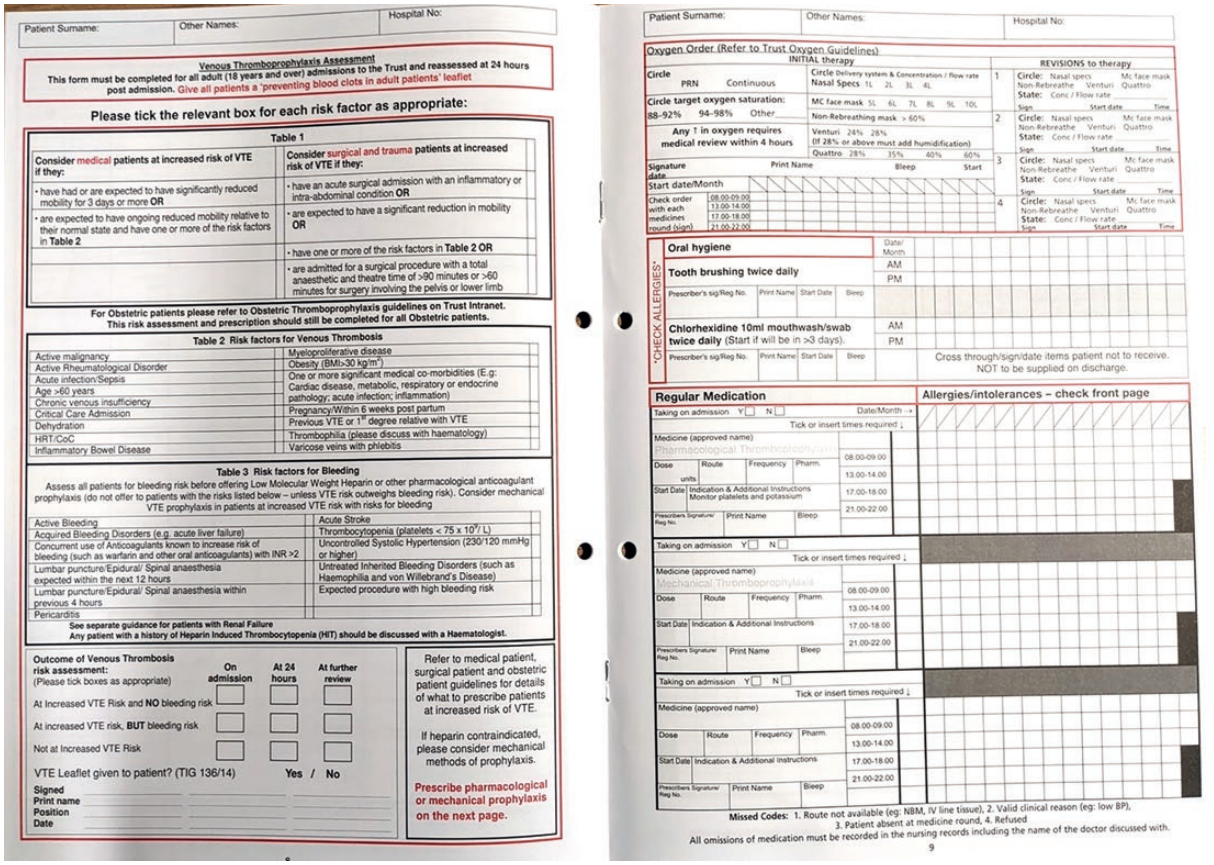

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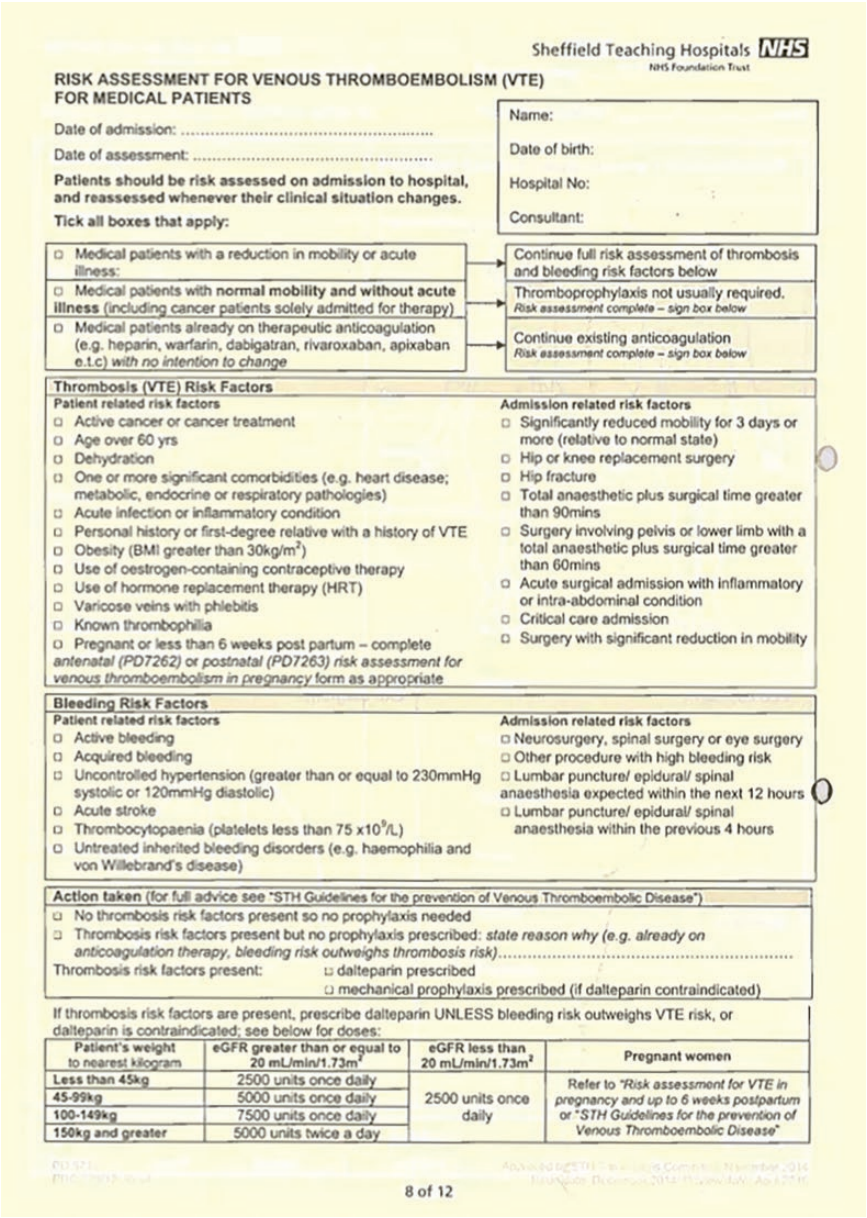

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

RISK ASSESSMENT FOR VENOUS THROMBOEMBOLISM (VTE) FOR MEDICAL PATIENTS

Date of admission: .....

Date of assessment: .....

Patients should be risk assessed on admission to hospital, and reassessed whenever their clinical situation changes.

Tick all boxes that apply:

Name:
Date of birth:
Hospital No:
Consultant:

☐ Medical patients with a reduction in mobility or acute illness:	Continue full risk assessment of thrombosis and bleeding risk factors below
☐ Medical patients with **normal mobility and without acute illness** (including cancer patients solely admitted for therapy)	Thromboprophylaxis not usually required. *Risk assessment complete – sign box below*
☐ Medical patients already on therapeutic anticoagulation (e.g. heparin, warfarin, dabigatran, rivaroxaban, apixaban e.t.c) *with no intention to change*	Continue existing anticoagulation *Risk assessment complete – sign box below*

Thrombosis (VTE) Risk Factors

Patient related risk factors
- ☐ Active cancer or cancer treatment
- ☐ Age over 60 yrs
- ☐ Dehydration
- ☐ One or more significant comorbidities (e.g. heart disease; metabolic, endocrine or respiratory pathologies)
- ☐ Acute infection or inflammatory condition
- ☐ Personal history or first-degree relative with a history of VTE
- ☐ Obesity (BMI greater than 30kg/m^2)
- ☐ Use of oestrogen-containing contraceptive therapy
- ☐ Use of hormone replacement therapy (HRT)
- ☐ Varicose veins with phlebitis
- ☐ Known thrombophilia
- ☐ Pregnant or less than 6 weeks post partum – complete *antenatal (PD7262) or postnatal (PD7263) risk assessment for venous thromboembolism in pregnancy* form as appropriate

Admission related risk factors
- ☐ Significantly reduced mobility for 3 days or more (relative to normal state)
- ☐ Hip or knee replacement surgery
- ☐ Hip fracture
- ☐ Total anaesthetic plus surgical time greater than 90mins
- ☐ Surgery involving pelvis or lower limb with a total anaesthetic plus surgical time greater than 60mins
- ☐ Acute surgical admission with inflammatory or intra-abdominal condition
- ☐ Critical care admission
- ☐ Surgery with significant reduction in mobility

Bleeding Risk Factors

Patient related risk factors
- ☐ Active bleeding
- ☐ Acquired bleeding
- ☐ Uncontrolled hypertension (greater than or equal to 230mmHg systolic or 120mmHg diastolic)
- ☐ Acute stroke
- ☐ Thrombocytopaenia (platelets less than 75 x10^9/L)
- ☐ Untreated inherited bleeding disorders (e.g. haemophilia and von Willebrand's disease)

Admission related risk factors
- ☐ Neurosurgery, spinal surgery or eye surgery
- ☐ Other procedure with high bleeding risk
- ☐ Lumbar puncture/ epidural/ spinal anaesthesia expected within the next 12 hours
- ☐ Lumbar puncture/ epidural/ spinal anaesthesia within the previous 4 hours

Action taken (for full advice see "STH Guidelines for the prevention of Venous Thromboembolic Disease")
- ☐ No thrombosis risk factors present so no prophylaxis needed
- ☐ Thrombosis risk factors present but no prophylaxis prescribed: *state reason why (e.g. already on anticoagulation therapy, bleeding risk outweighs thrombosis risk)*.....

Thrombosis risk factors present:
- ☐ dalteparin prescribed
- ☐ mechanical prophylaxis prescribed (if dalteparin contraindicated)

If thrombosis risk factors are present, prescribe dalteparin UNLESS bleeding risk outweighs VTE risk, or dalteparin is contraindicated; see below for doses:

Patient's weight to nearest kilogram	eGFR greater than or equal to 20 mL/min/1.73m^2	eGFR less than 20 mL/min/1.73m^2	Pregnant women
Less than 45kg	2500 units once daily	2500 units once daily	Refer to *"Risk assessment for VTE in pregnancy and up to 6 weeks postpartum or "STH Guidelines for the prevention of Venous Thromboembolic Disease"*
45-99kg	5000 units once daily		
100-149kg	7500 units once daily		
150kg and greater	5000 units twice a day		

8 of 12

FIGURE 28 Examples of electronic and paper documentation aids for RAM completion.
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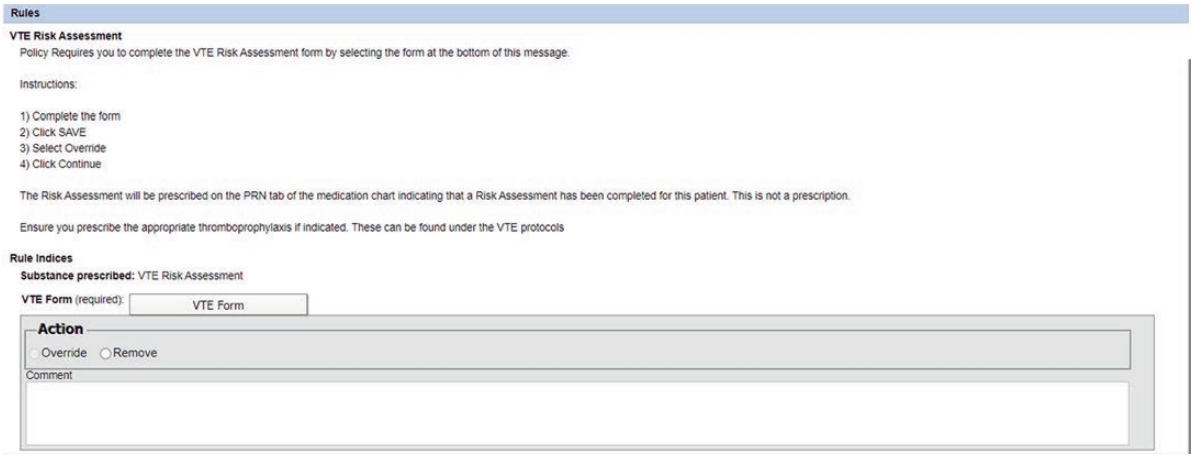


Rules

VTE Risk Assessment

Policy Requires you to complete the VTE Risk Assessment form by selecting the form at the bottom of this message.

Instructions:

1) Complete the form
2) Click SAVE
3) Select Override
4) Click Continue

The Risk Assessment will be prescribed on the PRN tab of the medication chart indicating that a Risk Assessment has been completed for this patient. This is not a prescription.

Ensure you prescribe the appropriate thromboprophylaxis if indicated. These can be found under the VTE protocols

Rule Indices

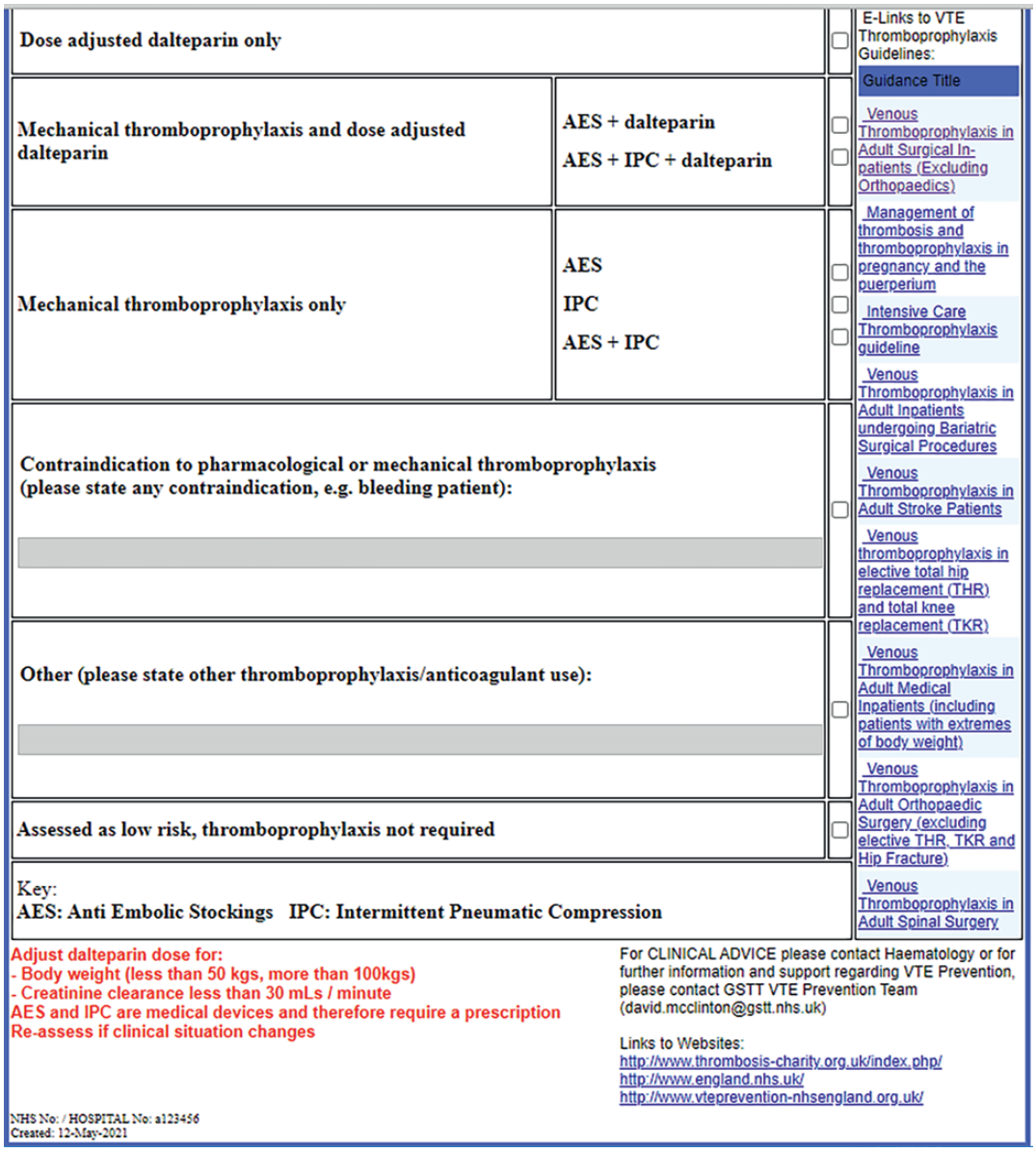
Substance prescribed: VTE Risk Assessment

VTE Form (required): VTE Form

Action

Override Remove

Comment



Dose adjusted dalteparin only		☐
Mechanical thromboprophylaxis and dose adjusted dalteparin	**AES + dalteparin** **AES + IPC + dalteparin**	☐ ☐
Mechanical thromboprophylaxis only	**AES** **IPC** **AES + IPC**	☐ ☐ ☐
Contraindication to pharmacological or mechanical thromboprophylaxis (please state any contraindication, e.g. bleeding patient):		☐
Other (please state other thromboprophylaxis/anticoagulant use):		☐
Assessed as low risk, thromboprophylaxis not required		☐
Key: **AES: Anti Embolic Stockings IPC: Intermittent Pneumatic Compression**		

E-Links to VTE Thromboprophylaxis Guidelines:

Guidance Title
Venous Thromboprophylaxis in Adult Surgical In-patients (Excluding Orthopaedics)
Management of thrombosis and thromboprophylaxis in pregnancy and the puerperium
Intensive Care Thromboprophylaxis guideline
Venous Thromboprophylaxis in Adult Inpatients undergoing Bariatric Surgical Procedures
Venous Thromboprophylaxis in Adult Stroke Patients
Venous thromboprophylaxis in elective total hip replacement (THR) and total knee replacement (TKR)
Venous Thromboprophylaxis in Adult Medical Inpatients (including patients with extremes of body weight)
Venous Thromboprophylaxis in Adult Orthopaedic Surgery (excluding elective THR, TKR and Hip Fracture)
Venous Thromboprophylaxis in Adult Spinal Surgery

Adjust dalteparin dose for:
- Body weight (less than 50 kgs, more than 100kgs)
- Creatinine clearance less than 30 mLs / minute

AES and IPC are medical devices and therefore require a prescription
Re-assess if clinical situation changes

For CLINICAL ADVICE please contact Haematology or for further information and support regarding VTE Prevention, please contact GSTT VTE Prevention Team (david.mcclinton@gstt.nhs.uk)

Links to Websites:
http://www.thrombosis-charity.org.uk/index.php/
http://www.england.nhs.uk/
http://www.vteprevention-nhsengland.org.uk/

NHS No: / HOSPITAL No: a123456
Created: 12-May-2021

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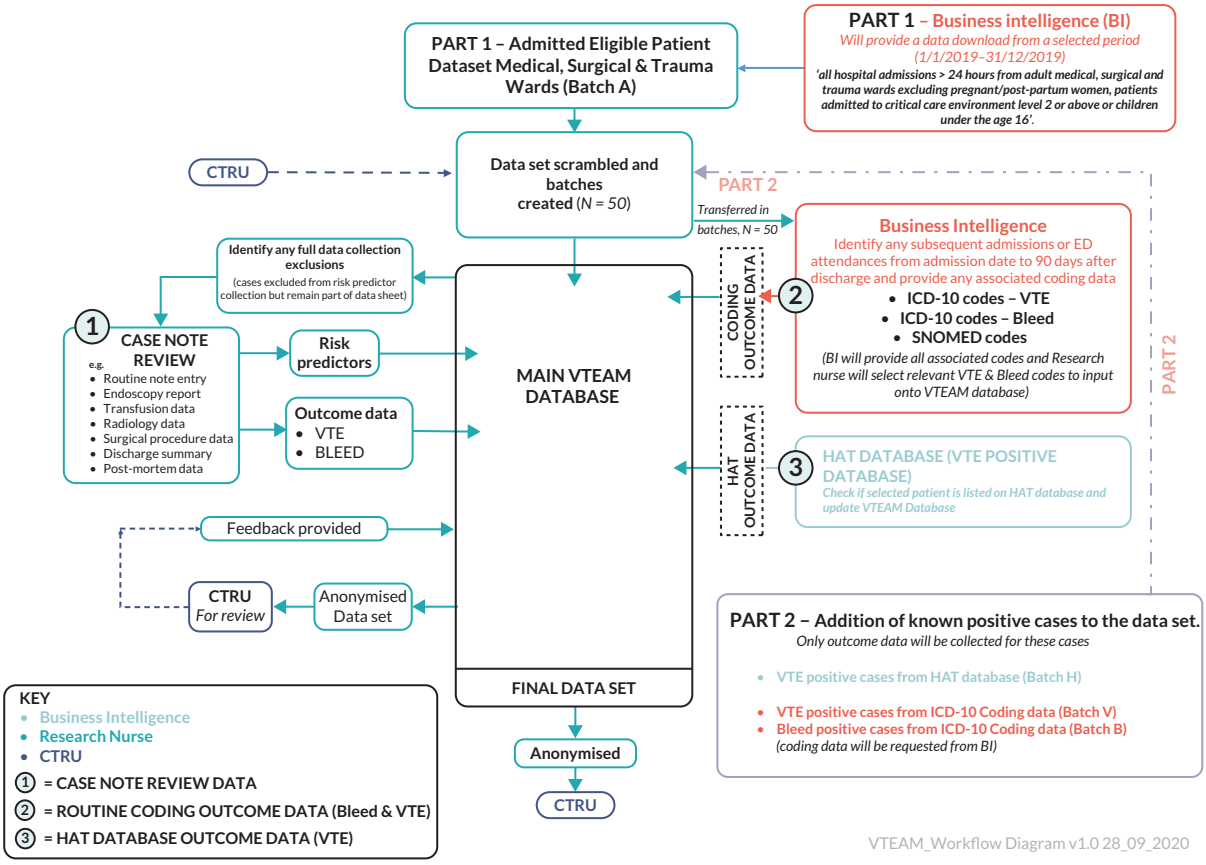

FIGURE 29 Workflow diagram.

Padua

Count	Column labels		
Row labels	Y	N	Grand total
DoH VTE Y	29.9%	60.6%	90.6%
DoH VTE N	0.4%	9.1%	9.4%
Grand total	30.3%	69.7%	100.0%
Inter-model agreement			39.0%

Geneva

Count	Column labels		
Row labels	Y	N	Grand total
DoH VTE Y	42.5%	48.0%	90.6%
DoH VTE N	1.2%	8.3%	9.4%
Grand total	43.7%	56.3%	100.0%
Inter-model agreement			50.8%

Improve 4

Count	Column labels		
Row labels	Y	N	Grand total
DoH VTE Y	59.4%	31.1%	90.6%
DoH VTE N	1.6%	7.9%	9.4%
Grand total	61.0%	39.0%	100.0%
Inter-model agreement			67.3%

Caprini

Count	Column labels		
Row labels	Y	N	Grand total
DoH VTE Y	55.1%	35.4%	90.6%
DoH VTE N	0.8%	8.7%	9.4%
Grand total	55.9%	44.1%	100.0%
Inter-model agreement			63.8%

Improve 7

Count	Column labels		
Row labels	Y	N	Grand total
DoH VTE Y	12.2%	78.3%	90.6%
DoH VTE N	0.4%	9.1%	9.4%
Grand total	12.6%	87.4%	100.0%
Inter-model agreement			21.3%

Kucher

Count	Column labels		
Row labels	Y	N	Grand total
DoH VTE Y	9.8%	80.7%	90.6%
DoH VTE N	0.4%	9.1%	9.4%
Grand total	10.2%	89.8%	100.0%
Inter-model agreement			18.9%

FIGURE 30 Agreement between recommendations using the Department of Health VTE risk assessment tool and other RAMs.

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TABLE 30 Relevant ICD-10 codes for VTE and bleeding agreed by chief investigators and approved by project management group

ICD-10 – 4 digit	Three character description	Four character description	All diagnoses	Main diagnosis	Category	Subcategory	Final selection
I26.0	Pulmonary embolism	Pulmonary embolism with mention of acute cor pulmonale	4031	2353	VTE		Yes
I26.9	Pulmonary embolism	Pulmonary embolism without mention of acute cor pulmonale	108,637	53,273	VTE		Yes
I80.1	Phlebitis and thrombophlebitis	Phlebitis and thrombophlebitis of femoral vein	10,156	4294	VTE		Yes
I80.2	Phlebitis and thrombophlebitis	Phlebitis and thrombophlebitis of other deep vessels of lower extremities	61,647	24,297	VTE		Yes
I80.3	Phlebitis and thrombophlebitis	Phlebitis and thrombophlebitis of lower extremities, unspecified	3971	1876	VTE		Yes
I80.9	Phlebitis and thrombophlebitis	Phlebitis and thrombophlebitis of unspecified site	2906	524	VTE		Yes
I82.2	Other venous embolism and thrombosis	Embolism and thrombosis of vena cava	3891	543	VTE		Yes
I82.8	Other venous embolism and thrombosis	Embolism and thrombosis of other specified veins	10,001	1870	VTE		Yes
I82.9	Other venous embolism and thrombosis	Embolism and thrombosis of unspecified vein	1124	215	VTE		Yes
I60.0	Subarachnoid haemorrhage	Subarachnoid haemorrhage from carotid siphon and bifurcation	226	212	Bleeding	Intracranial bleed	Yes
I60.1	Subarachnoid haemorrhage	Subarachnoid haemorrhage from middle cerebral artery	1125	1014	Bleeding	Intracranial bleed	Yes
I60.2	Subarachnoid haemorrhage	Subarachnoid haemorrhage from anterior communicating artery	1731	1599	Bleeding	Intracranial bleed	Yes
I60.3	Subarachnoid haemorrhage	Subarachnoid haemorrhage from posterior communicating artery	899	838	Bleeding	Intracranial bleed	Yes
I60.4	Subarachnoid haemorrhage	Subarachnoid haemorrhage from basilar artery	384	324	Bleeding	Intracranial bleed	Yes
I60.5	Subarachnoid haemorrhage	Subarachnoid haemorrhage from vertebral artery	101	87	Bleeding	Intracranial bleed	Yes

ICD-10 – 4 digit	Three character description	Four character description	All diagnoses	Main diagnosis	Category	Subcategory	Final selection
I60.6	Subarachnoid haemorrhage	Subarachnoid haemorrhage from other intracranial arteries	564	513	Bleeding	Intracranial bleed	Yes
I60.7	Subarachnoid haemorrhage	Subarachnoid haemorrhage from intracranial artery, unspecified	426	319	Bleeding	Intracranial bleed	Yes
I60.8	Subarachnoid haemorrhage	Other subarachnoid haemorrhage	977	737	Bleeding	Intracranial bleed	Yes
I60.9	Subarachnoid haemorrhage	Subarachnoid haemorrhage, unspecified	7642	4585	Bleeding	Intracranial bleed	Yes
I61.0	Intracerebral haemorrhage	Intracerebral haemorrhage in hemisphere, subcortical	4996	4396	Bleeding	Intracranial bleed	Yes
I61.1	Intracerebral haemorrhage	Intracerebral haemorrhage in hemisphere, cortical	5439	4254	Bleeding	Intracranial bleed	Yes
I61.2	Intracerebral haemorrhage	Intracerebral haemorrhage in hemisphere, unspecified	1431	1157	Bleeding	Intracranial bleed	Yes
I61.3	Intracerebral haemorrhage	Intracerebral haemorrhage in brain stem	1029	866	Bleeding	Intracranial bleed	Yes
I61.4	Intracerebral haemorrhage	Intracerebral haemorrhage in cerebellum	1901	1508	Bleeding	Intracranial bleed	Yes
I61.5	Intracerebral haemorrhage	Intracerebral haemorrhage, intraventricular	3678	1886	Bleeding	Intracranial bleed	Yes
I61.6	Intracerebral haemorrhage	Intracerebral haemorrhage, multiple localised	764	561	Bleeding	Intracranial bleed	Yes
I61.8	Intracerebral haemorrhage	Other intracerebral haemorrhage	3854	3103	Bleeding	Intracranial bleed	Yes
I61.9	Intracerebral haemorrhage	Intracerebral haemorrhage, unspecified	11,863	9028	Bleeding	Intracranial bleed	Yes
I62.0	Other nontraumatic intracranial haemorrhage	Subdural haemorrhage (acute)(nontraumatic)	17,161	8197	Bleeding	Intracranial bleed	Yes
I62.1	Other nontraumatic intracranial haemorrhage	Nontraumatic extradural haemorrhage	318	100	Bleeding	Intracranial bleed	Yes
I62.9	Other nontraumatic intracranial haemorrhage	Intracranial haemorrhage (nontraumatic), unspecified	3230	2383	Bleeding	Intracranial bleed	Yes
I85.0	Oesophageal varices	Oesophageal varices with bleeding	4074	2876	Bleeding	Gastrointestinal	Yes
K22.6	Other diseases of oesophagus	Gastro-oesophageal laceration-haemorrhage syndrome	7232	3237	Bleeding		Yes
K25.0	Gastric ulcer	Gastric ulcer – acute with haemorrhage	2077	1469	Bleeding	Gastrointestinal	Yes

continued

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TABLE 30 Relevant ICD-10 codes for VTE and bleeding agreed by chief investigators and approved by project management group (*continued*)

ICD-10 – 4 digit	Three character description	Four character description	All diagnoses	Main diagnosis	Category	Subcategory	Final selection
K25.2	Gastric ulcer	Gastric ulcer – acute with both haemorrhage and perforation	49	20	Bleeding	Gastrointestinal	Yes
K25.4	Gastric ulcer	Gastric ulcer – chronic or unspecified with haemorrhage	4742	2951	Bleeding	Gastrointestinal	Yes
K25.6	Gastric ulcer	Gastric ulcer – chronic or unspecified with both haemorrhage and perforation	145	74	Bleeding	Gastrointestinal	Yes
K26.0	Duodenal ulcer	Duodenal ulcer – acute with haemorrhage	2955	2161	Bleeding	Gastrointestinal	Yes
K26.2	Duodenal ulcer	Duodenal ulcer – acute with both haemorrhage and perforation	126	96	Bleeding	Gastrointestinal	Yes
K26.4	Duodenal ulcer	Duodenal ulcer – chronic or unspecified with haemorrhage	7607	4972	Bleeding	Gastrointestinal	Yes
K26.6	Duodenal ulcer	Duodenal ulcer – chronic or unspecified with both haemorrhage and perforation	386	263	Bleeding	Gastrointestinal	Yes
K27.0	Peptic ulcer, site unspecified	Peptic ulcer, site unspecified – acute with haemorrhage	78	32	Bleeding	Gastrointestinal	Yes
K27.2	Peptic ulcer, site unspecified	Peptic ulcer, site unspecified – acute with both haemorrhage and perforation	4	1	Bleeding	Gastrointestinal	Yes
K27.4	Peptic ulcer, site unspecified	Peptic ulcer, site unspecified – chronic or unspecified with haemorrhage	231	116	Bleeding	Gastrointestinal	Yes
K27.6	Peptic ulcer, site unspecified	Peptic ulcer, site unspecified – chronic or unspecified with both haemorrhage and perforation	29	9	Bleeding	Gastrointestinal	Yes
K28.0	Gastrojejunal ulcer	Gastrojejunal ulcer – acute with haemorrhage	29	24	Bleeding	Gastrointestinal	Yes
K28.2	Gastrojejunal ulcer	Gastrojejunal ulcer – acute with both haemorrhage and perforation	3	3	Bleeding	Gastrointestinal	Yes
K28.4	Gastrojejunal ulcer	Gastrojejunal ulcer – chronic or unspecified with haemorrhage	149	96	Bleeding	Gastrointestinal	Yes
K28.6	Gastrojejunal ulcer	Gastrojejunal ulcer – chronic or unspecified with both haemorrhage and perforation	11	6	Bleeding	Gastrointestinal	Yes

ICD-10 – 4 digit	Three character description	Four character description	All diagnoses	Main diagnosis	Category	Subcategory	Final selection
K29.0	Gastritis and duodenitis	Acute haemorrhagic gastritis	3340	1365	Bleeding	Gastrointestinal	Yes
K62.5	Other diseases of anus and rectum	Haemorrhage of anus and rectum	37,545	21,106	Bleeding	Gastrointestinal	Yes
K66.1	Other disorders of peritoneum	Haemoperitoneum	3317	642	Bleeding	Gastrointestinal	Yes
K92.0	Other diseases of digestive system	Haematemesis	67,589	27,503	Bleeding	Gastrointestinal	Yes
K92.1	Other diseases of digestive system	Melaena	67,036	22,979	Bleeding	Gastrointestinal	Yes
K92.2	Other diseases of digestive system	Gastrointestinal haemorrhage, unspecified	192,053	97,428	Bleeding	Gastrointestinal	Yes
M25.0	Other joint disorders, not elsewhere classified	Haemarthrosis	3362	1730	Bleeding		Yes
N02.0	Recurrent and persistent haematuria	Recurrent and persistent haematuria – minor glomerular abnormality	48	21	Bleeding		Yes
N02.1	Recurrent and persistent haematuria	Recurrent and persistent haematuria – focal and segmental glomerular lesions	286	76	Bleeding		Yes
N02.2	Recurrent and persistent haematuria	Recurrent and persistent haematuria – diffuse membranous glomerulonephritis	1858	517	Bleeding		Yes
N02.3	Recurrent and persistent haematuria	Recurrent and persistent haematuria – diffuse mesangial proliferative glomerulonephritis	160	49	Bleeding		Yes
N02.4	Recurrent and persistent haematuria	Recurrent and persistent haematuria – diffuse endocapillary proliferative glomerulonephritis	10	4	Bleeding		Yes
N02.5	Recurrent and persistent haematuria	Recurrent and persistent haematuria – diffuse mesangiocapillary glomerulonephritis	47	12	Bleeding		Yes
N02.6	Recurrent and persistent haematuria	Recurrent and persistent haematuria – dense deposit disease	9	1	Bleeding		Yes
N02.7	Recurrent and persistent haematuria	Recurrent and persistent haematuria – diffuse crescentic glomerulonephritis	164	48	Bleeding		Yes

continued

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TABLE 30 Relevant ICD-10 codes for VTE and bleeding agreed by chief investigators and approved by project management group (*continued*)

ICD-10 – 4 digit	Three character description	Four character description	All diagnoses	Main diagnosis	Category	Subcategory	Final selection
N02.8	Recurrent and persistent haematuria	Recurrent and persistent haematuria – other	10,852	1289	Bleeding		Yes
N02.9	Recurrent and persistent haematuria	Recurrent and persistent haematuria – unspecified	2902	1331	Bleeding		Yes
N93.8	Other abnormal uterine and vaginal bleeding	Other specified abnormal uterine and vaginal bleeding	4801	2899	Bleeding	Other bleed	Yes
N93.9	Other abnormal uterine and vaginal bleeding	Abnormal uterine and vaginal bleeding, unspecified	24,423	11,036	Bleeding	Other bleed	Yes
R04.0	Haemorrhage from respiratory passages	Epistaxis	48,741	24,610	Bleeding	Other bleed	Yes
R04.1	Haemorrhage from respiratory passages	Haemorrhage from throat	191	69	Bleeding	Other bleed	Yes
R04.2	Haemorrhage from respiratory passages	Haemoptysis	32,143	12,743	Bleeding	Other bleed	Yes
R04.8	Haemorrhage from respiratory passages	Haemorrhage from other sites in respiratory passages	1332	222	Bleeding	Other bleed	Yes
R04.9	Haemorrhage from respiratory passages	Haemorrhage from respiratory passages, unspecified	83	23	Bleeding	Other bleed	Yes
R23.3	Other skin changes	Spontaneous ecchymoses	10,624	2774	Bleeding		Yes
R58.X	Haemorrhage, not elsewhere classified	Haemorrhage, not elsewhere classified	2747	408	Bleeding		Yes
T81.0	Complications of procedures, not elsewhere classified	Haemorrhage and haematoma complicating a procedure, not elsewhere classified	67,338	28,601	Bleeding		Yes
T81.7	Complications of procedures, not elsewhere classified	Vascular complications following a procedure, not elsewhere classified	1000	201	Bleeding		Yes

Appendix 4 Additional data from the national survey of VTE leads

Survey transcript

VTEAM methodology survey 2021

Introduction

Thank you for clicking the link and considering our survey.

We are writing to you as the project management group of the VTEAM study (NIHR 127454). This project is looking to assess the cost-effectiveness of different venous thromboembolism risk assessment tools for hospitalised inpatients within an NHS care setting.

Our project has several workstreams. Workstream 1 is an evidence synthesis and decision-analytic modelling exercise designed to collate risk assessment models and evaluate clinical effectiveness, then use these data to calculate the comparative cost-effectiveness of different models in practice.

Workstream 2 is a feasibility study, designed to evaluate the use of efficient data methods to collect routine outcome data on VTE and bleeding episodes. Within this workstream we are recording inter- and intra-hospital variation in risk assessment methodology, documentation and information access. Several outputs from the VTEAM study already summarise some of our early findings:

Systematic review of validated VTE risk assessment models – https://bmjopen.bmj.com/content/11/7/e045672

BMJ Uncertainties article; VTE risk assessment for hospitalised patients – www.bmj.com/content/373/bmj.n1106

In this survey, we would like you to provide information on the method of risk assessment used at your trust and how this information is stored locally. We would also like to gauge your opinion as VTE leads about participation in future research evaluating different methods of risk assessment and/or VTE prevention.

There are 10 questions within this survey and completion time is < 10 minutes. Please answer all questions as best you can and provide free text for us at the final question if you have suggestions you feel are within the remit of the project, but not identified within the questions.

Many thanks for your time on this survey, and your leadership in VTE prevention.

Daniel Horner
Steve Goodacre
Beverley Hunt
Kerstin de Wit
Xavier Griffen
Mark Holland

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Local methods of VTE risk assessment and data storage

Which hospital trust, organisation or site are you representing?

How do clinical teams currently conduct a VTE risk assessment for hospitalised inpatients at your trust?

	Paper pro forma
	Within an electronic health record
	A combination of the both within the hospital, dependent on ward environment

If you use a paper pro forma, which of the following fields are recorded?

	Positive VTE risk characteristics
	Negative VTE risk characteristics (do you record the absence of a risk characteristic)
	Final decision on pharmacological thromboprophylaxis
	Not applicable (do not use paper pro forma)

When completing an electronic VTE risk assessment, which of the following fields do you record?

	Positive VTE risk characteristics
	Negative VTE risk characteristics (do you actively record the absence of a VTE risk factor?)
	Final decision regarding pharmacological thromboprophylaxis
	Not applicable (do not use electronic methods of risk assessment)

Would you be able to access granular data from your VTE risk assessments efficiently through a request to local business information/intelligence/data teams, in order to report the presence or absence of risk characteristics in a large cohort of patients?

	Yes
	No
	Uncertain

Potential design preferences and willingness to participate in future studies on VTE risk assessment.

Would you be potentially willing to participate in future observational research on VTE risk assessment methods, collecting data on individual risk characteristics and relevant outcomes up to 90 days post discharge?

	Yes
	No

Would you be potentially willing to participate in future interventional research on VTE risk assessment methods, collecting data on individual risk characteristics and randomising patients to different risk assessment models at hospital admission?

	Yes
	No

Our preliminary findings suggest there is significant uncertainty about the best approach to prophylaxis in patients identified at low risk for VTE events during hospitalisation.

Assuming your trust was properly supported to deliver a trial looking to compare other risk assessment models against current practice, which of the following designs would be acceptable to you as trust VTE lead?

	Potential allocation of your site to a new risk assessment model within the context of a wider national cluster randomised trial for a set study duration
	Potential allocation of certain local wards to a new risk assessment model, within the context of a wider national 'cluster' randomised trial for a set study duration
	Potential allocation of your site to two discrete periods of risk assessment, with an interim washout period, where you were to introduce a new risk assessment model at a certain time period and continue standard practice during the other study period, with ongoing data collection on relevant outcomes
	Individual patient randomisation with fully informed consent
	I do not think any of these designs could be implemented at my trust

Other authors have suggested an individualised approach is likely to be preferably regarding VTE risk assessment and thromboprophylaxis, including higher dosing regimens for patients at higher risk of VTE.

Assuming your trust was properly supported to deliver a trial looking to compare this strategy against current practice, which of the following designs would be acceptable to you as trust VTE lead?

	Potential allocation of your site to a new dosing strategy in higher-risk patients, within the context of a wider national cluster randomised trial for a set study duration
	Potential allocation of certain local wards within your site to a new dosing strategy in higher-risk patients, within the context of a wider national 'cluster' randomised trial for a set study duration
	Potential allocation of your site to two discrete periods of dosing strategy for higher-risk patients, with an interim washout period, where you were to introduce a new dosing strategy for higher-risk patients at a certain time period and continue standard practice during the other study period, with ongoing data collection on relevant outcomes
	Individual patient randomisation with fully informed consent
	I do not think any of these designs could be implemented at my trust

Taking the population as a whole, our preliminary findings suggest it may be most cost-effective to deliver pharmacological thromboprophylaxis as an 'opt out' strategy, unless contraindicated. In this situation, initial assessment would focus primarily on identification of bleeding risks only.

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Assuming your trust was properly supported to deliver a trial looking to compare this strategy against current practice, which of the following designs would be acceptable to you as trust VTE lead?

	Potential allocation of your site to a new 'opt-out' strategy, within the context of a wider national cluster randomised trial for a set study duration
	Potential allocation of certain local wards within your site to a new 'opt-out' strategy, within the context of a wider national 'cluster' randomised trial for a set study duration
	Potential allocation of your site to two discrete periods of VTE risk assessment strategy, with an interim washout period, where you introduce a new opt-out strategy for one period and continue standard practice during the other, with ongoing data collection on relevant outcomes
	Individual patient randomisation with fully informed consent
	I do not think any of these designs could be implemented at my trust

Please also tell us what you think the priority research question should be regarding VTE risk assessment within the current NHS infrastructure. Please also use this opportunity to highlight any issues, queries or uncertainties with regard to the preceding questions and information.

Responding sites

1. St Peters Hospital
2. Sheffield Teaching Hospital NHS Foundation Trust
3. University of Leicester NHS Trust
4. North Bristol Trust
5. Norfolk and Norwich University Hospitals
6. University Hospitals Plymouth NHS Trust
7. Stockport NHS Foundation Trust
8. The Royal Orthopaedic Hospital Birmingham
9. University Hospital of North Midlands
10. Kings College Hospital NHS Foundation Trust
11. Salisbury NHS Healthcare Trust
12. Princess of Wales Hospital, Glamorgan
13. South Tyneside NHS Foundation Trust
14. Royal Cornwall NHS Foundation Trust
15. Princess Alexandra NHS Trust
16. Spire Hospital, Alexandra
17. Oxford University Hospitals NHS Foundation Trust
18. St Georges Hospital
19. Cambridge University Hospital NHS Foundation Trust
20. Ashford and St Peters Hospitals NHS Foundation Trust
21. Salford Royal NHS Foundation Trust

Free text responses

25	As a site we would need adequate support to participate as our current establishment would not support a trial of this scale.	05/11/2021 12:00 PM ID: 178398863
24	n/a	04/11/2021 15:46 PM ID: 178339995
23	Prescribers think VTE risk assessment if a tick box exercise.	04/11/2021 08:37 AM ID: 178291192
22	No question.	02/11/2021 17:39 PM ID: 178174756
21	What would be the criteria for defining 'higher-risk patients?' I am slightly concerned that changing the criteria might cause some confusion.	02/11/2021 17:25 PM ID: 178173203
20	Happy to be involved with any research and discussions around this area.	02/11/2021 11:06 AM ID: 178128769
19	Identifying high-risk patients – benefit of higher dose thromboprophylaxis – validation of current RA tool.	01/11/2021 10:45 AM ID: 178037304
18	We are a low-risk private elective surgery hospital unsure of priority research question.	28/10/2021 11:44 AM ID: 177822796
17	Re Q10 Taking the population as a whole, our preliminary findings suggest it may be most cost-effective to deliver pharmacological thromboprophylaxis as an 'opt out' strategy, unless contraindicated. In this situation, initial assessment would focus primarily on identification of bleeding risks only. I agree the focus should be on the correct identification of bleeding risks.	28/10/2021 09:29 AM ID: 177807213
16	Whether VTE risk assessment actually has any positive impact on VTE prophylaxis prescribing rates and clinical outcomes in regard to HA-VTE.	28/10/2021 09:12 AM ID: 177806366
15	Identifying patients who need prophylaxis (depending upon risk stratification – mechanical or chemical) and duration of prophylaxis, reasons for delay in start of prophylaxis tool to flag daily risk assessment (when clinical condition changes).	28/10/2021 09:02 AM ID: 177805185
14	Is there evidence a VTE RA has been undertaken on admission and appropriate TP prescribed? I am happy to get involved but my biggest problem is I work alone managing a large service and therefore don't always have enough time!	27/10/2021 10:40 AM ID: 177742113
13	Should patients be reviewed prior to stopping VTE prophylaxis, especially if mobility is still restricted?	27/10/2021 10:12 AM ID: 177739844
12	n/a	27/10/2021 09:11 AM ID: 177734851
11	producing a revised risk assessment tool that better identifies medical patients who need thromboprophylaxis.	27/10/2021 08:38 AM ID: 177732485
10	Other authors have suggested an individualised approach is likely to be preferably regarding VTE risk assessment and thromboprophylaxis, including higher dosing regimens for patients at higher risk of VTE.	27/10/2021 07:47 AM ID: 177730926
9	Questions we receive are significance of nil by mouth period and reduced mobility, i.e. is dehydration only risk if bloods demonstrate clinical dehydration. Re-assessment window – latest guidance is time of consultant review or if condition changes. If post-op what would optional time for review?	26/10/2021 21:58 PM ID: 177720950
8	In the current risk assessment, patients (medical) whose mobility is unlikely to be changed during admission are considered as not for further risk assessment. But in my opinion even if they are still mobile, there is a risk of dehydration, less mobile as in the limited space in hospital compared to their own residence, make them more prone to thrombosis. There are patients who are bed-bound and have no change to their mobility since admission, but deficiently are at a high risk for thrombosis as inpatients. Can this be reviewed again?	18/10/2021 10:58 AM ID: 176826830

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7	How we define mobility assumption seems to be if they mobilise to bathroom that counts as mobile.	14/10/2021 16:19 PM ID: 176648271
6	For the three above questions our risk assessment is via an electronic system and it is very difficult to change it or add to it. If this can be overcome, then the options for research with different risk assessments are possible.	14/10/2021 08:52 AM ID: 176598234
5	I think that choosing certain wards for the potential change in assessing and prescribing TP would be best as change is complicated and not often greeted with enthusiasm. In order for a trial to work it must be robust.	13/10/2021 14:54 PM ID: 176551827
4	N/A	13/10/2021 13:16 PM ID: 176539276
3	Priority: Identifying those whose risk of harm associated with chemical thromboprophylaxis outweighs the potential benefits (i.e. refining bleeding scores- elderly, frail, falls risk etc.). Define cohorts at high risk of VTE who would benefit from extended chemical thromboprophylaxis. Study the delivery of thrombosis prevention strategies within organisations. Regarding proposed studies above, they will need to be carefully designed so they can be delivered. If including emergency admissions, with a variety of junior medical staff involved (ED, acute, generalists and specialities) care will need to be taken if to have 'certain wards' allocated to specific treatments. In our organisation, patients can move from ED, to MAU, to speciality wards. Therefore, for 'acute' care, allocation of the site to a specific strategy may work best. BUT for some specialities, (orthopaedic spinal, stroke, cancer surgery), specific guidance will be required. Keen to contribute	13/10/2021 11:30 AM ID: 176520022
2	VTE risk assessment and therefore the prophylaxis is often delayed and in many cases relevant risks are not ticked. I wonder if it would make a difference if it was done during the first doctor's assessment and if highlighting the risks was mandatory. There is also another problem, I find it frustrating when the pharmacists find issues and in many cases, their notes to doctors are not acted on. I agree that research into higher doses of pharmacological prophylaxis for higher-risk patients is needed but also if a patient is in a higher risk category and his weight is at higher end of a specific range, then the dosing could be adjusted, for example: a person weighing 97 kg, could get dosing required for over 100 kg.	13/10/2021 09:59 AM ID: 176510305
1	I think the opt-out question is the most interesting one – happy to participate in a national trial on this, if funded and supported.	12/10/2021 09:31 AM ID: 176411960

EME
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