The University Of Sheffield.

Salford Royal NHS Foundation Trust

VTEAM

The Venous Thromboembolism Assessment Model study

The cost-effectiveness of venous thromboembolism risk assessment tools for hospital in patients

RESEARCH PROTOCOL
(Version 2.2) 9th January 2020

Sheffield CTRU	**157401**
IRAS	**262220**
REC	**19/LO/1303**
Registry	**researchregistry5216**
Authorised by:	**Professor Steve Goodacre**

Sheffield Clinical Trials Research Unit (CTRU)

VTEAM: The Venous Thromboembolism Assessment Model study

This document describes the VTEAM study, and provides information about procedures throughout the study.

Contents

Abbreviations

CAG	Confidentiality Advisory Group
CRF	Case Report Form
CTRU	Clinical Trials Research Unit
DVT	Deep vein thrombosis
EVPPI	Expected value of partial perfect information
EVSI	Expected value of sample information
HES	Hospital Episodes Statistics
HTA	Health Technology Assessment
ONS	Office for National Statistics
PSA	Probabilistic sensitivity analysis
PMG	Project Management Group
SSC	Study Steering Committee
PE	Pulmonary embolism
PPI	Patient and Public Involvement
QALYs	Quality-adjusted life-years
RAM	Risk Assessment Model
REC	Research Ethics Committee
ROC	Receiver Operating Characteristic
ScHARR	School of Health and Related Research
SECF	Sheffield Emergency Care Forum
SOP	Standard Operating Procedures
VTE	Venous thromboembolism

General Information

Sponsor

The University of Sheffield
Regent Court
30 Regent Street
Sheffield
S1 4DA

Sponsor Representative: Dr Jennifer Burr
Email: j.a.burr@sheffield.ac.uk
Tel: (+44) (0)114 222 0792

Co-chief Investigator

Professor Steve Goodacre
Professor of Emergency Medicine
School of Health and Related Research (ScHARR)
The University of Sheffield
Regent Court
Sheffield
S1 4DA
Email: s.goodacre@sheffield.ac.uk
Tel: (+44) (0)114 222 0842

Co-chief Investigator

Professor Daniel Horner
Professor of the Royal College of Emergency Medicine
& Consultant in Emergency and Intensive Care
Emergency Department
Salford Royal NHS Foundation Trust
Salford
M6 8HD
Email: daniel.horner@srft.nhs.nuk

Co-applicants

Dr Daniel Hind
Reader in Complex Interventions and Assistant Director CTRU
University of Sheffield

Ms Sarah Davis
Senior Lecturer in Health Economics
University of Sheffield

Mr Mike Bradburn
Senior Medical Statistician
University of Sheffield

Associate Professor Kerstin Hogg
Assistant Professor
McMaster University

Mr Abdullah Pandor
Senior Research Fellow
University of Sheffield

Associate Professor Xavier Luke Griffin
Associate Professor of Trauma Surgery
University of Oxford

Professor Beverly Hunt
Consultant and Honorary Senior Lecturer

Dr Mark Holland
Consultant Acute Physician

Guy's and St Thomas' NHS Foundation Trust	Salford Royal NHS Foundation Trust
Mrs Shan Bennett PPI representative Sheffield Emergency Care Forum	Mr Robin Pierce-Williams PPI representative Thrombosis UK

Protocol amendments since Version 1.0

Section 5.1 Selection of participants (page 17)
Inclusion criteria updated to include age range
Section 7.0 Data handling and record keeping (page 19 and 20)
Addition of archiving details and retention period

Protocol amendments since Version 2.0

Title page
Addition of acronym and logo
Section 5.1 Data collection
Amendment of 12 months to 11 months

Protocol amendments since Version 2.1

Section 5.1 Selection of participants (page 17)
Inclusion/exclusion criteria updated from age 18 to age 16
Section 7.0 Data Handling and record keeping (page 19).
Removal of paragraph 2 (page 20) relating to data-management
Section 11.0 Ethics (page 21)
Paragraph 3. (Page 22) Minor clarification of data collection process with reference to Hospital Episode Statistics

Summary of Research

Research question
What is the optimal risk-assessment strategy for providing venous thromboembolism (VTE) prophylaxis to hospital inpatients and how does changing the risk threshold for prophylaxis affect cost-effectiveness?

Background
Prophylaxis reduces the risk of VTE for inpatients but incurs costs and increases the risk of bleeding. VTE risk assessment tools can select higher risk inpatients for prophylaxis. A prognostic accuracy study of VTE risk assessment tools in the NHS will not yield useful results due to the widespread use of VTE prophylaxis.

Aims and objectives
We aim to determine the cost-effectiveness of inpatient VTE risk assessment tools and the direction of further research. Our specific objectives are to:

1. Update systematic reviews of inpatient VTE risk assessment tools
2. Use decision-analysis modelling to determine the cost-effectiveness of VTE risk assessment tools and risk threshold that optimises effectiveness and cost-effectiveness
3. Determine the value of information provided by future research
4. Determine the feasibility of using efficient methods in a future implementation study of VTE risk assessment tools

Methods
We plan to undertake evidence synthesis and piloting of efficient primary research methods. 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. The health technologies being assessed are risk assessment tools that use clinical information to select patients with an increased risk of VTE for prophylaxis. The outcomes of interest are VTE (deep vein thrombosis (DVT) and pulmonary embolism (PE)) and bleeding events.

Work stream 1 (evidence synthesis) will update existing systematic reviews to identify risk-assessment tools and estimate their prognostic accuracy. Decision-analytic modelling will then simulate the management of a cohort of hospital inpatients and compare strategies using risk-based prophylaxis to prophylaxis for all or prophylaxis for none. We will estimate VTE events, bleeding events, quality-adjusted life-years (QALYs) and costs associated with each strategy and then estimate the incremental cost per QALY gained by each strategy compared to the next most effective alternative on the efficiency frontier. We will then estimate the expected value of information of further primary research.

Work stream 2 (feasibility study) will involve an observational study of 3000 inpatients across four NHS hospitals to develop efficient methods for a future implementation study. We will not attempt to change practice or implement any risk-assessment methods. We will pilot the collection of standardised VTE risk-assessment data in routine clinical practice and the use of linked Hospital Episodes Statistics and Office for National Statistics (ONS) mortality data for outcome measurement. We will then test the completeness of linkage and review case notes of patients to determine the accuracy of routine data.

Timelines for delivery
Year 1: Systematic reviews, decision analysis modelling, value of information analysis; pre-piloting, ethical and regulatory approvals
Year 2: Write-up and dissemination of secondary research; data collection, analysis and reporting of primary research

Anticipated impact and dissemination
Our findings will inform NICE guidance and determine how VTE prophylaxis should be provided across the NHS.

1.0 Introduction

Background and Rationale

What is the problem and how do we intend to address it?
Hospital-associated venous thromboembolism (VTE) has been described as the number one patient safety issue in hospitalised patients (Shojania 2017). Both pharmacological and mechanical prophylaxis can reduce the risk of VTE but pharmacological prophylaxis increases the risk of bleeding. Therefore, the decision to provide prophylaxis involves consideration of the risks of VTE and bleeding, along with the costs of providing prophylaxis and treating the consequences of VTE and bleeding.

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

Many VTE risk assessment tools have been developed and some have been validated by estimating the prognostic accuracy for VTE, albeit with significant methodological limitations (see below *Existing Literature*). To date, limited research has explored the trade-off between the risks of VTE and prophylaxis. This trade-off is essential to determining whether a risk assessment tool will be cost-effective and, if so, the threshold of risk or balance of sensitivity and specificity that should be used in decision-making.

We have carefully considered but decided against proposing a prospective cohort study of the predictive accuracy of risk assessment tools because this design would have an insurmountable flaw if undertaken alongside current NHS practice. The fundamental aim of risk assessment is to predict patients whose VTE will be prevented by prophylaxis. Over 70% of medical patients in the UK receive prophylaxis when the Department of Health risk assessment tool has been used (NICE 2018). In this situation, around half of the VTE that could have been prevented by prophylaxis will have been prevented and the prognostic model will largely be predicting VTE that were not prevented by currently-used prophylaxis. Any prognostic model derived in this setting would therefore be based on factors that predict non-preventable VTE whilst under-estimating (or missing) those that predict preventable VTE. A risk assessment tool that predicted non-preventable VTE while failing to predict preventable VTE would potentially be worse than useless.

In accordance with the commissioning brief, we propose and provide justification for an alternative efficient study design to estimate the cost-effectiveness of VTE risk assessment tools for hospital inpatients. We will use decision-analysis modelling of published evidence to determine how the cost-effectiveness of prophylaxis varies for different thresholds of risk.

This will determine whether risk assessment has the potential to be cost-effective compared with prophylaxis for all and, if so, what threshold of risk should be used for providing prophylaxis and what trade-off between sensitivity and specificity would be optimal for a risk assessment tool. We used this approach in our evaluation of risk assessment tools for prophylaxis for people with lower limb immobilisation due to injury (HTA15/187/06), showing that a risk assessment tool with sensitivity around 90% and specificity around 50% would be optimal, assuming an appropriate trade-off on the receiver operating characteristic (ROC) curve.

Decision-analysis modelling may identify an approach to prophylaxis that is clearly optimal and can be recommended for practice. However, it is likely that uncertainties around implementation of a potentially optimal strategy (or strategies) will mean that primary research evaluating implementation in practice will be required before a clear recommendation can be made. A prognostic accuracy study would not be informative, for the reason outlined above. Instead, an implementation study is likely to be needed to determine how risk assessment tools are followed in practice, the impact of risk assessment on the use of prophylaxis and the safety of withholding prophylaxis from low risk patients (determined by the VTE rate in those not receiving prophylaxis).

The exact design of an implementation study will depend upon the findings of evidence synthesis but would be likely to involve cluster randomisation of hospitals or wards to alternative risk-assessment strategies or an observational study in which hospitals using different risk-assessment strategies were selected and compared. An efficient design would be required, in which standardised risk-prediction data is collected and linked to routinely available outcome data. This would overcome barriers of individual patient recruitment to achieve a comprehensive cohort with sufficient power to detect low event rates in specific sub groups. However, it is not currently clear whether this design is achievable within ethical, regulatory and practical constraints. It will also only become clear, with the findings of the evidence synthesis, whether alternative strategies require comparison and what these alternative strategies should be. In view of these fundamental uncertainties around the design of an implementation study we propose a stand-alone feasibility study to determine whether an efficient design is feasible and estimate key parameters for a future implementation study.

Existing literature

We undertook a scoping search of VTE risk assessment tools from inception to May 2018 by adapting the search strategy we used in our systematic review of risk assessment tools in lower limb immobilisation (Pandor 2018). This identified 5662 potentially relevant citations. Initial screening identified recent systematic reviews of VTE risk assessment models (RAMs) in acutely ill medical patients (Stuck 2017) and hospitalised non-surgical patients (Huang 2013), along with nine recent relevant primary studies not included in these reviews (Grant 2016, Liu 2016, Rafizadeh 2016, Greene 2016, Elias 2017, de Bastos 2016, Blondon 2018, Zhou 2018, Depietri 2018, Hostler 2018). We also examined the review of RAMs undertaken for NICE guidance (NICE 2018).

Stuck et al identified 11 studies reporting eight RAMs: the 4-Element RAM, Caprini RAM, Woller full logistic model, Geneva risk score, IMPROVE tool, Kucher score, Rothberg multivariable model and Padua Prediction Score. Huang et al identified 11 studies reporting RAMs, six derived from primary data and five based on expert opinion. The NICE review identified 22 studies evaluating 13 RAMs, including the Caprini RAM, Kucher score, Geneva risk score, IMPROVE tool, Intermountain RAM, Khorana Score, Padua Prediction Score and Trauma Embolic Scoring System.

There was substantial variation between the primary studies in terms of populations, methods and outcomes used, which precluded meta-analysis and limited comparisons

between RAMs. Overall, the studies suggested that the RAMs had modest prognostic value with most reporting c-statistics around 0.6 to 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 but this does not mean that risk assessment has no value. Risk assessment based on modest prognostic accuracy could still be useful, as any targeting of prophylaxis may be an improvement on untargeted treatment.

The primary studies had important limitations and were generally judged as low quality. Reporting of the use of prophylaxis was variable and, where reported, it appeared that a substantial proportion of the study population had received prophylaxis. Many of the limitations, including inability to control for the use of prophylaxis, are not readily remediable. This suggests that, although further studies of risk assessment tools are in progress, they are unlikely to provide robust evidence to guide decision-making.

We identified one previous study that used decision-analysis modelling to estimate a risk threshold for prophylaxis in hospitalised medical patients (Le 2017). Undertaken from a United States health system perspective with a willingness to pay threshold of $100,000 per quality-adjusted life year (QALY) gained, the analysis showed that prophylaxis was cost-effective for an average medical patient with a VTE risk exceeding 1.0%. This model has a number of similarities to our model of VTE risk assessment in lower limb immobilisation but also some key differences (other than the population studied), and to inform NHS practice modelling would need to be undertaken from a NHS perspective using NICE thresholds. However, it shows how decision-analysis modelling can be used to guide selection of an appropriate risk assessment tool and thus guide practice.

2.0 Aims and objectives

We aim to evaluate the cost-effectiveness of VTE risk assessment tools in hospital inpatients, determine the optimal approach to providing VTE prophylaxis and determine how changing the risk threshold for prophylaxis affects cost-effectiveness. Our specific objectives are to:

1. Update recent systematic reviews (Huang 2013, Stuck 2017, NICE 2018) to identify tools for VTE risk assessment in hospital inpatients and estimate prognostic accuracy
2. Undertake decision-analysis modelling to determine the cost-effectiveness of VTE risk assessment compared to prophylaxis for all and prophylaxis 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-analysis model to identify key areas of uncertainty and determine the value of gathering additional information to reduce uncertainty
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

The PICO terms for the main research question are:

Population:	NHS hospital inpatients
Intervention:	VTE prophylaxis (pharmacological or mechanical) based on a risk assessment tool
Comparator:	VTE prophylaxis for all patients or none
Outcomes:	VTE and bleeding events, QALYs, incremental cost per QALY gained, incremental net monetary benefit

3.0 Research Plan

3.1 Design

We plan to undertake two parallel streams of work over two years:

1. Evidence synthesis, involving systematic review, decision analysis modelling and value of information analysis;
2. Feasibility study, involving piloting of efficient research methods for an implementation study of VTE risk-assessment tools.

The evidence synthesis study will address the main research question and objectives 1-3. Systematic reviews will identify risk-assessment tools and use available data to estimate the accuracy of existing tools for predicting VTE in hospital inpatients. We will then develop a decision-analysis model to simulate the management of hospital inpatients according to strategies for VTE prophylaxis including prophylaxis for all, prophylaxis for none and prophylaxis according to risk-assessment tools identified in the systematic reviews. Modelling will be used to estimate the cost-effectiveness of each strategy compared to the next most effective alternative and determine the risk threshold that optimises effectiveness (QALYs) and cost-effectiveness (maximises net benefit assuming willingness to pay according to NICE thresholds). Modelling will also be used to identify key areas of uncertainty and determine the value of information required to reduce uncertainty.

The feasibility study will address objective 4. We anticipate that the design of an implementation study to evaluate the clinical effectiveness and cost-effectiveness of a risk-assessment tool in routine NHS practice will be based on the population, health technologies and outcomes outlined below, and will involve either allocation of hospitals or wards to alternative risk-assessment methods or selection of hospitals with different risk-assessment methods. The precise design and risk-assessment methods evaluated in an implementation study will depend on the results of evidence synthesis.

The primary outcome of an implementation study is likely to be the rate of symptomatic VTE. This is relatively low so a large study with an efficient design will be required to have adequate power to detect important differences in key patient groups. The feasibility study will therefore determine whether key outcomes can be reliably measured using routine data sources, such as Hospital Episodes Statistics (HES).

The feasibility study will also determine whether standardised risk-assessment data can be prospectively recorded and collected in an efficient manner along with data showing whether prophylaxis is prescribed and administered. This is not essential to a fully pragmatic implementation study but would provide very valuable insights into the process of implementing risk-based VTE prophylaxis and would allow evaluation of alternative risk-assessment strategies. It will also allow us to determine the proportion of patients who would receive VTE prophylaxis with different risk-assessment tools, and will thus inform the modelling and the design of any future implementation study. Feasibility work will include estimating user acceptability and clinician time involved in risk-assessment.

We will use the following definitions of the health technology, study population, setting and outcomes across both elements of the study.

3.2 Health technology being assessed

Risk assessment tools use clinical information from the patient's history and examination to identify patients with an increased risk of VTE who could be selected for prophylaxis. Tools may take the form of rules, that simply categorise patients according to whether they need prophylaxis, or scores that estimate the risk of VTE but leave the decision to provide prophylaxis in the hands of the user. The latter tools may also include assessment of the risk

of bleeding, to be weighed against the benefits of reducing VTE risk. Existing tools use either a flowchart or checklist to guide the user through the process of risk assessment and lead to a decision regarding VTE prophylaxis. They may be paper-based or electronic. The latter can potentially facilitate more complex risk assessment based upon weighting of risk factors, if appropriate data are available to support such weighting.

3.3 Target population
Hospital inpatients, including medical, surgical and trauma patients but excluding children, women admitted to hospital for pregnancy-related reasons and any patient admitted to a level 2 or above critical care environment.

3.4 Inclusion/Exclusion Criteria
We will include all patients who should be assessed for VTE risk. Pregnant/postpartum women and children have a different risk/benefit profile as a result of specific physiology differences and anatomical variance, so are excluded. Patients admitted to a critical care environment are considered at high risk of subsequent VTE, with incidence rates during thromboprophylaxis trials in control arm groups of between 13-31%. As such, NICE guidance (NG89) strongly recommends pharmacological thromboprophylaxs for this group, in the absence of contraindications. In addition, these patients are often complex; decisions on the risk/benefit profile of thromboprophylaxis are influenced by site and type of any recent surgical procedure, ongoing bleeding risk, coagulopathy, goals of care and degree of organ failure.

3.5 Setting
Hospital wards managing medical, surgical and trauma patients.

3.6 Outcomes
DVT: a filling defect identified by ultrasound or venography or CT scan, or a positive image on MR direct thrombus imaging, within the inferior vena cava, common iliac, internal iliac, external iliac, common femoral, superficial femoral, popliteal trifurcation, posterior tibial, peroneal, gastrocnemius or soleal veins of the leg.
Clinically detected DVT: a DVT with symptoms of leg pain, swelling or discolouration that is identified during routine patient care.
Screening-detected DVT: a DVT, with or without symptoms, that is not identified during routine patient care but is detected if radiological screening is undertaken.
PE: a filling defect reported to be pulmonary embolism found on CT pulmonary angiography or digital subtraction angiography in a branch of the pulmonary artery. Or else a high probability perfusion or ventilation-perfusion scan.
Major bleeding: as defined by the International Society of Thrombosis and Haemostasis (Schulman 2005).
Clinically relevant non-major bleeding: as defined by International Society of Thrombosis and Haemostasis (Schulman 2005).

4.0 Work stream 1: Evidence synthesis

4.1 Systematic reviews
Systematic reviews will be undertaken in accordance with guidelines published by the Centre for Reviews and Dissemination (Centre for Reviews and Dissemination 2008) and the protocol will be registered with the PROSPERO register (National Institute for Health Research, PROSPERO 2012). We will adapt the search strategy we used in HTA15/187/06 and existing reviews (Huang 2013, Stuck 2017, NICE 2018) to identify prognostic accuracy

studies of risk assessment tools for VTE in hospital inpatients and data sources for the decision-analytic model.

Relevant studies will be identified through electronic searches of key electronic databases including MEDLINE, EMBASE and all databases in the Cochrane Library (including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials and NHS Economic Evaluations Database). References will also be located through review of reference lists for relevant articles and through use of citation search facilities through the Web of Knowledge. In addition, systematic searches of trial registries and the Internet using the Google search engine will be used to identify unpublished materials and work in progress. Key authors and professional and academic research groups will also be contacted and asked for unpublished material.

Studies will be included if they report VTE outcomes (clinically detected, screening-detected DVT, PE or mortality) for hospital inpatients according to a VTE risk-assessment tool. The inclusion of potentially relevant articles will be undertaken using a two-step process:

1. All titles will be examined for inclusion by one reviewer. Any citations that clearly do not meet the inclusion criteria (i.e. non-human, unrelated to VTE) will be excluded.
2. All abstracts and full text articles will be examined independently by two reviewers. Any disagreements in the selection process will be resolved through discussion and arbitration by a third reviewer if necessary. The decisions will be coded and recorded on a reference management database by the Project Manager.

Data will be extracted independently by one reviewer using a standardised data extraction form and independently checked for accuracy by a second. Uncertainties will be resolved by discussion. Those that cannot be resolved will be referred to the rest of the project team. Where multiple publications of the same study are identified, data will be extracted and reported as a single study. The following standardised data will be extracted from each eligible study: date, setting, population characteristics (age, sex, diagnosis), risk-assessment tool characteristics, VTE outcome definitions and results according to risk strata. If appropriate, the authors of the primary studies will be contacted for missing data.

Methodological quality will be assessed using a generic list of features recommended by Altman (Altman 2001) and Moons (Moons 2014) for prediction modelling studies and used in HTA15/187/06.

Limitations in the data available and marked heterogeneity between primary studies identified in our scoping review mean that meta-analysis is unlikely to be possible. We therefore plan to present descriptive estimates of key parameters from each study. If adequate data are identified, we will draw upon extensive experience from previous projects to undertake appropriate meta-analysis.

Literature searches for key parameters in the model will be developed as the project progresses, in response to the needs of the model. We anticipate that many of the parameters required will be similar to those used to populate our existing model on the cost-effectiveness of VTE prophylaxis for people with lower limb immobilisation due to injury (HTA15/187/06) and therefore literature searches will focus on updating reviews conducted to inform our previous model and replacing any data sources that are specific to patients with lower limb injury and not generalizable to hospital inpatients.

4.2 Decision analysis modelling

We will build a decision-analytic model to simulate the management of a hypothetical cohort of hospital inpatients. We will develop the decision analysis model we used for HTA15/187/06, adapting it for hospital inpatients and drawing upon the recently published

analysis by Le et al (2017). The model will take a health and social care perspective and a time horizon of the lifetime of the patient.

The model will consist of two phases:

1. From hospital admission to 90 days after discharge, during which time VTE and bleeding events will be assumed to occur
2. From 90 days after discharge to death, during which time the long-terms costs and effects of VTE and bleeding events will accrue

The study population will be defined as outlined in the Target Population section above. The characteristics of the population (age, sex, diagnosis, risk factors for VTE, co-morbidities) will be estimated from studies identified in the literature searches, audits and routine NHS data sources.

The model will simulate the management of the cohort according to a range of strategies that could be used to select patients for VTE prophylaxis, including prophylaxis for all, prophylaxis for none and prophylaxis based on VTE risk-assessment tools. A group of clinical experts will be convened and asked to review the outputs of the systematic review and select VTE risk-assessment tools for inclusion in the analysis on the basis of (1) study quality and thus reliability of estimates of sensitivity and specificity, (2) applicability to routine NHS practice, and (3) providing a range of trade-offs between sensitivity and specificity, if possible.

In the primary analysis we will assume that patients with a bleeding risk, such as those identified on the Department of Health risk-assessment tool (https://www.nice.org.uk/guidance/ng89/resources/department-of-health-vte-risk-assessment-tool-pdf-4787149213) do not receive prophylaxis under any strategy and are excluded from the model. In a secondary analysis we will explore the impact of using the IMPROVE bleeding risk score alongside VTE risk assessment to determine whether prophylaxis is given (Decousus 2011, Depietri 2018, Hostler 2016).

We will use existing literature to estimate the risks of VTE and bleeding outcomes (as defined above) for the cohort if no prophylaxis is given and then use relative risk estimates from existing systematic reviews of VTE prophylaxis for relevant inpatient populations to estimate the VTE and bleeding risks with prophylaxis (NICE 2018, Kahn 2018). Alternatively, if more reliable event rate estimates are available for inpatients receiving prophylaxis, we will use the inverse of the relative risks to estimate the risks in those not receiving prophylaxis. We will explore using different risk estimates for different inpatient populations, depending upon the data available.

The proportion of patients having VTE prophylaxis for each strategy is determined by the risk of VTE in the population and the sensitivity and specificity of the strategy for identifying patients who go on to have VTE. The proportion having VTE and / or bleeding events is then calculated for those receiving or not receiving prophylaxis which is dependent on the factors above plus the effectiveness and safety of prophylaxis. In the secondary analysis the risk of bleeding events will also depend upon the sensitivity and specificity of the IMPROVE bleeding risk score for predicting bleeding events.

The sensitivity and specificity of each risk-assessment tool for predicting VTE will be estimated using data from the systematic review, with the clinical expert group being used to judge the appropriateness of estimates and select between studies if more than one estimate exists for any tool.

We will also undertake the following threshold analyses:

1. Theoretical risk-assessment tools will be examined with sensitivity and specificity varying across a credible ROC curve, to determine the balance of sensitivity and specificity at which effectiveness (QALYs) and cost-effectiveness (net benefit assuming willingness to pay £20,000/QALY or £30,000/QALY) is optimised
2. A one-way sensitivity analysis will vary the baseline risk of VTE in a comparison between prophylaxis for all and prophylaxis for none, to determine the thresholds of baseline risk at which prophylaxis for all is more effective and cost-effective than prophylaxis for none (i.e. the threshold at which the benefits of prophylaxis outweigh the risks and the threshold at which the benefits outweigh the risks and costs)

At the end of phase 1 of the model each patient will be characterised according to whether or not they have suffered VTE or bleeding events. They will then enter phase 2 of the model, which will determine the lifetime costs and QALYs accrued by each patient. This phase will incorporate any long term consequences of both VTE and major bleeds.

Each patient in the cohort will accrue costs and outcomes determined by whether they receive prophylaxis or not, whether they developed clinically significant VTE, and whether they suffer any bleeding events. We will use parameter estimates and a model structure developed for our recent study of the cost-effectiveness of VTE prophylaxis for lower limb immobilisation due to injury (HTA15/187/06).

The total costs and QALYs accrued across the cohort will be calculated and a fully incremental analysis will be undertaken. Costs will be evaluated from an NHS and personal social services perspective. Future costs and benefits will be discounted at 3.5% in line with current best practice, as defined by NICE (NICE 2013).

Uncertainty about parameters that are subjected to formal evidence synthesis will be characterised by drawing samples from their appropriate joint posterior distributions. For parameters where the studies yield no or minimal relevant information with which to populate the model, elicitation sessions with experts, and scenario analyses will be considered. These sources of evidence will be combined to produce estimates of model parameters and define the associated probability distributions.

Differences in resource use between the different VTE prophylaxis strategies, including medications, clinical time to implement risk assessment, and management of VTE and bleeding-related adverse events, will be valued by applying Department of Health reference costs (Department of Health 2014) or PSSRU unit costs (Curtis 2015) for episodes of care and BNF list prices for medications (British National Formulary 2016).

Analyses will be undertaken to identify the key parameters determining the cost-effectiveness of the different strategies with the objective of identifying how secure the conclusions of the economic analyses are, given the available evidence. Uncertainty with respect to model parameters will be explored with a probabilistic sensitivity analysis (PSA). The information derived from PSA will be summarised graphically (within a cost-effectiveness acceptability curve). The probability that the cost-effectiveness of the intervention is within the £20,000-£30,000 per QALY range, reflecting the thresholds typically used by NICE (NICE, 2013) in appraising health technologies will be explicitly reported.

If there is evidence that the tools perform differently in different subgroups, then we would explore this in the economic model to determine whether these differences translated into different estimates of cost-effectiveness.

The decision analytic model will be used to estimate the value of information of further primary research and determine the optimal direction of future research, whilst taking into account restrictions placed on potential research by widespread use of VTE prophylaxis. The

expected value of partial perfect information (EVPPI) will be estimated for groups of parameters. This will be done using the Sheffield Accelerated Value of Information application which calculates EVPPI directly from the PSA results avoiding the need for computationally expensive nested double loop simulations (Strong 2014). If the EVPPI estimates suggest that further primary research may be valuable to reduce the uncertainty around specific groups of parameters, then expected value of sample information (EVSI) analysis will be performed to inform decisions regarding future primary research (Strong 2015).

The output of the EVPI analysis is an estimate of the opportunity cost (measured in either pounds that could be spent elsewhere in the NHS or health gains that could be achieved elsewhere in the NHS) of making a decision based on the current imperfect information when compared with making a decision based on perfect information regarding all parameters. This tells us the maximum that it is worth spending on further research to eliminate decision uncertainty. The EVPPI tells us the maximum it is worth spending on specific parameters or groups of parameters (e.g. efficacy, utility values, complication rates) to achieve perfect information on those specific parameters without gaining perfect information on all parameters. This therefore tells us the maximum that could be justifiably spent on research to gain more information for those specific parameters. It would help us prioritise future research based on whether it would reduce uncertainty in those parameters that most influence the decision. The EVSI tells us whether specific future trial designs, such as an RCT to better determine efficacy, a cohort study to better determine complication rates or a quality of life study to better determine health utility, are worthwhile given the cost of the research, how much it is expected to reduce the uncertainty and the opportunity cost of making the decision with the current information (the EVPPI)."

5.0 Work stream 2: Feasibility study

The feasibility study will pilot efficient research methods for an implementation study of VTE risk-assessment tools and estimate key parameters for study design. The implementation study design will be determined by the findings of the evidence synthesis but is likely to involve either a cluster design in which wards or hospitals are allocated to alternative risk-assessment strategies or an observational design in which hospitals using different strategies are compared. The study population, setting, health technologies being assessed and outcomes are likely to be those defined above, with the primary outcome being any clinically-relevant VTE. The feasibility of such a study will depend upon our ability to undertake efficient intervention and outcome data collection from a large study population.

The feasibility study will involve an iterative process of developing and testing data collection methods but ultimately aims to determine the feasibility of (1) using routine administrative data to measure VTE and bleeding outcomes, and (2) collecting standardised VTE risk assessment data as part of routine practice. The feasibility study will be an observational study. We will not attempt to change practice or implement any risk-assessment methods. The target population, health technology and outcomes of interest are as defined in the overview of the research plan above.

Objective 1 will be addressed by determining whether routine administrative data sources correctly code VTE or bleeding events, verified by review of hospital records. The reference standard for this assessment will be based on expert review of identified cases, using the outcome definitions provided above.

Objective 2 will be addressed by determining the proportion of cases in which each key risk predictor is routinely recorded in a standardised risk assessment. The key risk predictors will be selected and defined by an expert panel drawing upon items used in existing risk-

assessment tools and their expert clinical knowledge. The PPI members of the research team will work with representative groups to review the acceptability of using each risk predictor to determine whether prophylaxis is given.

5.1 Selection of participants

The study will be undertaken initially in Salford Royal Hospital and a second NHS hospital acting as a pilot site. We will select wards at each hospital covering medical, surgical and trauma admissions. The participants will be all inpatients requiring assessment for VTE risk and will be entered into the study base on the following criteria:

Inclusion criteria

1. Hospital inpatients, including medical, surgical and trauma patients, requiring assessment for VTE risk
2. Patients aged 16 and over

Exclusion criteria

1. Pregnant/postpartum women
2. Children under the age of 16 years
3. Patients admitted to a critical care environment defined as level 2 or above

The study will not change patient care and only members of the clinical team will access personal data, so we will not seek individual patient consent to participate.

We will subsequently identify two additional hospitals to determine whether the data collection methods developed in the two initial sites can be applied elsewhere and ensure that findings are more generalizable.

Initially we will seek Research Ethics Committee (REC) approval to only use anonymised data, so that only members of the clinical team (including research nurses) are able to access personal data. During the study we will explore whether and how this restriction limits our ability to collect and link the necessary risk-assessment and outcome data. If we are limited to the extent that a case can be made for using personal data without consent, we will apply to the Confidentiality Advisory Group (CAG) of the Health Research Authority for appropriate approval and/or to test the case for approval in a definitive study. Throughout this process we will work with our PPI representatives to consult PPI groups (SECF, Thrombosis UK and hospital-based PPI groups) to determine patient and public views on the acceptability of using data in this way for research.

We will also undertake a national survey of VTE leads at acute NHS hospitals across the UK to determine (1) current practice regarding VTE risk-assessment and use of prophylaxis at their hospital, (2) methods used to record VTE risk-assessment data, and (3) willingness to participate in an implementation study of risk-assessment tools. Current practice will be determined by asking respondents to provide hospital VTE prophylaxis guidance and any other relevant information. Willingness to participate will be explored through survey questions asking whether they consider the hospital would be able to take part in an observational study or a cluster randomised study, in which the whole hospital or individual wards would be randomised.

5.2 Data collection

Piloting of data collection methods will take place over 11 months but this will initially be an intermittent and iterative process, during which data collection methods will be developed, tested, reviewed and revised at two sites, and then introduced at two additional sites. This will culminate in a 2-month period of continuous data collection across four hospitals, during which the developed process will be formally tested.

Routine practice requires recording of VTE predictors for all inpatients. We will identify how data are recorded and what items are recorded, and then compare this to data requirements for existing risk-assessment tools and any other potentially important VTE risk predictors.

We will explore whether augmenting or standardising routine data recording can improve the scope and quality of data recorded, using electronic methods wherever possible. We will also explore whether VTE risk factors are recorded through hospital information systems, either for VTE risk-assessment or for general data collection. If so, we will explore processes for extracting and linking relevant data items. We will therefore determine and optimise the scope of risk-assessment variables that can be routinely recorded in a standardised manner.

In the final 2-month period we will pilot the methods we have developed to test the completeness of recording of predictor variables and our ability to calculate existing risk assessment scores from the collected data.

The main outcome measures are defined in the overview of the research plan. The primary outcome for any future implementation study will be clinically important VTE, defined as diagnostic coding of any VTE event during hospital attendance or admission, or recording of VTE as a cause of death, up to 90 days after initial risk assessment.

An implementation study of risk-assessment tools will need to link risk-assessment data collected at hospital admission to routinely collected outcome data, such as HES. These data can be accessed through the hospital providing the data or through NHS Digital. Both routes require personal details, such as a hospital number or NHS number, to allow accurate linkage to risk-assessment data. Research nurses can access data through the hospital but this approach may miss events occurring after discharge and presenting to another hospital. Accessing data through NHS Digital using personal details would require CAG approval.

To determine the validity of efficient methods for identifying outcomes we will undertake case note review of all events identified through routine data sources and a sample of cases with no event identified. Research nurses will review hospital records and record details of any outcome events up to 90 days and enter the data on to a standardised Case Report Form (CRF). Two independent experts will then review anonymised data collected on the outcome events and determine whether they are classified as outcomes according to definitions determined by an independent adjudication panel. Discordant judgements will be resolved through discussion and, if appropriate, independent assessment by a third reviewer.

5.3 Data analysis

The following criteria will be used to determine success:

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 inpatients with data collected (target 90%)
5. Proportion of each predictor variable recorded (target 90%)
6. Proportion of each risk assessment tool completed using available data (target 90%)

We will also estimate key parameters for any future implementation study:

1. The primary outcome event rate
2. Event rates for other outcomes
3. The proportion receiving prophylaxis in current practice
4. The proportion who would receive prophylaxis if alternative risk assessment tools were used

Descriptive analysis will report proportions, with a 95% confidence interval, from the 2-month pilot phase.

5.4 Sample size

The sample size is only estimated for the 2-month pilot phase in which we test the data collection methods. The initial iterative developmental phase will collect data in each cycle until a reasonably reliable conclusion can be drawn regarding the issue of interest. The broad inclusion criteria and lack of requirement for consent means that there are few practical limitations to patient numbers.

We plan to identify 3000 inpatients over 2 months across 4 hospitals. This will allow key parameters to be estimated with a high degree of precision across the whole cohort (standard error <1%) and an acceptable degree of precision in specific patient groups.

6.0 Trial Supervision

The University of Sheffield will act as Sponsor for the trial. A Study Steering Committee (SSC) and a Project Management Group (PMG) will be established to govern the conduct of the study. These committees will function in accordance with Sheffield CTRU standard operating procedures.

6.1 Project Management Group

SG will take overall responsibility for delivering the study. DHo will lead the feasibility study. A project management group consisting of the co-applicants and study researchers will meet in person or by teleconference at least bi-monthly to oversee day-to-day management of the study. Core groups for the evidence synthesis (SG, DHo, AP, SD) and feasibility study (DHo, SG, DHi, MB) will meet more frequently to deliver these elements of the study. The evidence synthesis work stream will be undertaken in the section of Health Economics and Decision Science in the School of Health and Related Research (ScHARR). The feasibility study work stream will be coordinated by the Sheffield Clinical Trials Research Unit (CTRU) and undertaken in Salford Royal Hospital (led by DHo) and a second NHS hospital who had the capacity and capability to deliver the study.

PPI will be coordinated by RPW, working with Thrombosis UK, and SB, working with SECF, who will both attend project management meetings, if required.

6.2 Study Steering Committee

A Study Steering Committee will provide independent oversight to the study. This will consist of an independent chair, independent experts in VTE, orthopaedics and internal medicine, independent PPI representatives, along with SG and DHo from the study team. Independent members will be recommended to the HTA programme by the lead applicant. The SSC will primarily be responsible for providing independent oversight of the feasibility study but will also provide advice and expert input, as required, to the evidence synthesis. The SSC will meet at regular intervals as outlined in the SSC terms of reference. The SSC can prematurely close the trial following advice from the sponsor, funder or PMG.

7.0 Data handling and record keeping

Participant confidentiality will be respected at all times and no patient identifiable data will be accessed by anyone outside of the clinical care team.

The clinical research nurses will be provided with a password-protected database that will be used to store data on an NHS computer. Only they will have access to this database. They will periodically send anonymised data to the University of Sheffield Clinical Trials Research Unit via a secure electronic transfer.

7.1 Archiving

Study records will be stored for a period of 10 years after the completion of the trial before being destroyed.

8.0 Dissemination, outputs and anticipated impact

The main outputs of the study will be:

1. An optimal strategy for providing prophylaxis, based on current evidence
2. Risk thresholds that optimise effectiveness (QALYs) and cost-effectiveness
3. Value of information for future research
4. A proposal for a feasible implementation study

Outputs 1 and 2 will inform policy and practice. We will submit open-access scientific papers reporting these outputs to high impact general medical journals to ensure the widest possible awareness, accessibility and impact. We will present our findings at relevant scientific meetings, especially those attended by clinicians working in haematology, general medicine and orthopaedics. We will send professionals summaries of our findings to relevant professional organisations. We also send professional summaries to VTE leads at acute hospitals.

This study is intended to inform future NICE guidance for reducing the risk of hospital-acquired VTE. We will therefore make contact with the NICE Guideline Development Group and provide professional summaries, published papers and the full HTA report.

We will disseminate plain language summaries of our findings to the public and patients through our collaborating PPI groups (SECF and Thrombosis UK). We will also offer to present our findings at any professional or public meetings organised by SECF or Thrombosis UK.

Outputs 3 and 4 will inform future research priorities. We will provide research recommendations based on our findings that will be fed back to the commissioning arm of the HTA programme to determine what (if any) future research should be commissioned. We will also disseminate professional and plain language summaries, along with the full report, to relevant professional, public and patient representative organisations so they are able to make a fully informed contribution to any future research prioritisation process. Our full findings will be published in the open-access NIHR report. We will use submissions to scientific journals, online academic forums and social media to ensure that the research community is aware of our findings, so that any interested research groups are in a position to draw upon our findings in developing future research proposals.

9.0 Project timetable

The project will take place over 2 years, according to the GANTT chart below. We will provide progress reports covering the following elements of the study at the end of each of six-month phase:

1. Systematic review update; confirmation of set-up and regulatory submissions for the feasibility study
2. Decision-analysis modelling and value of information analysis; pre-piloting for the feasibility study

3. Write-up and dissemination of the evidence synthesis; data collection piloting in the feasibility study
4. Record linkage, analysis and writing-up of feasibility study

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
EVIDENCE SYNTHESIS								
Systematic review								
Decision analysis modelling								
Writing up and dissemination								
FEASIBILITY STUDY								
Ethics & Confidentiality Advisory Group approvals								
Piloting data collection								
Piloting record linkage								
Analysis and write-up								

10.0 Funding and role of the funder

This study has been funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme. The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication.

11.0 Ethics

The evidence synthesis work stream will only use secondary research methods, carries no significant ethical risk and therefore does not require ethical approval. The feasibility study work stream only involves observational methods, with no change to patient care, so ethical risks are low and mainly related to patient confidentiality and data protection.

The main ethical issue relates to using patient data without consent. This is justified, both ethically and with regard to General Data Protection Regulations, on the basis of medical research in the public interest. An implementation study requires a large, unselected patient population that includes all people at risk of VTE. It would therefore not be feasible to seek patient consent to use their data and the ethical risks of causing distress and confusion by seeking consent for secondary data use would outweigh the ethical benefits. We will only use anonymised data in the analysis and will put in place a process to minimise the risks to patient confidentiality.

As outlined in the data collection section, we will explore using standardised, routinely-recorded risk-assessment information. This is collected by the clinical team as part of routine

care and will be extracted by research nurses in the participating hospitals. Only anonymised details will be used by the research team. However, we will need to link risk-assessment data to outcomes recorded in routine clinical coding used to generate Hospital Episodes Statistics and then review hospital records to determine the accuracy of the clinical coding. We will explore whether this can be feasibly done within the hospital or whether personal data need to be used to link with data collected nationally by NHS Digital.

In the first six months of the project we will secure Research Ethics Committee approval and HRA approval to undertake the feasibility study. Initially this will be on the basis of only members of the clinical care team (including research nurses) using personal data. If this does not allow data linkage to support an efficient study, we will seek CAG section 251 approval to use personal data to link hospital data with NHS Digital data.

12.0 Regulatory approval

The study will be submitted to local participating Trusts to confirm Capacity and Capability before any research activity takes place.

13.0 Indemnity / Compensation / Insurance

The University of Sheffield has in place insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this research project.

14.0 Patient and Public Involvement

Representatives of two PPI groups have joined the research team and been involved in developing the proposal. They have been involved in determining the study design and ensuring that the proposal addresses 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 have been instrumental in determining our approach to answering the research question.

The Sheffield Emergency Care Forum (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 then last ten years (see https://secf.org.uk/ and https://emj.bmj.com/content/33/9/665). Shan Bennett (SB) is a member of SECF whose father recently suffered a blood clot. She provided PPI for similar previous projects, including the DiPEP study (Diagnosis of PE in Pregnancy, HTA13/21/01) and the TiLLI study (Thromboprophylaxis in Lower Limb Immobilisation, HTA 15/187/06). SB and the lead applicant (SG) have presented the proposal to a meeting of the SECF and have used their feedback to develop the proposal.

Thrombosis UK is a charity that aims to identify, inform and partner 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/). Robin Pierce-Williams (RPW) is a patient representative from Thrombosis UK who has personal experience of VTE. He provided PPI for the TiLLI study (HTA 15/187/06). RPW has approval from Jo Jerome, Chief Executive of Thrombosis UK, to undertake surveys and other contacts with members of Thrombosis UK as a means of ensuring wider PPI during the project.

As members of the research team, SB and RPW will provide PPI at project management meetings, if required and in day-to-day running of the project. They will use meetings and surveys of their wider PPI groups to enhance PPI in the project. We will identify additional

PPI representatives from Thrombosis UK with lived experience of VTE and from SECF with lived experience of hospital admission. They will have specific roles in a number of areas:

1. Selection of VTE risk-assessment tools for inclusion in the modelling. The use of VTE risk-assessment needs to be acceptable to patients and the public. If provision of prophylaxis is based upon VTE risk assessment, then patients and the public need to be assured that risk assessment does not appear to be discriminatory or based on assessments that might be insensitive or inappropriate to some patients. Our PPI representatives will review risk assessment tools identified in the systematic review and, in consultation with the wider PPI groups, consider whether the tools and their use for determining prophylaxis are likely to be acceptable to patients and the public.
2. 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 have planned our methods so that they are compatible with ethical principles and data protection regulation, and are acceptable to our PPI representatives. However, the feasibility study will involve piloting these methods and the potential to adapt the methods to ensure efficiency. The PPI representatives will be involved in project management monitoring of data collection and will specifically consider the acceptability of any proposed changes to the methods.
3. Ensuring patient and public values are reflected in the modelling. Decision-analysis modelling inevitably involves making a number of assumptions, especially regarding what costs and outcomes are important and thus need to be included in the model. The PPI representatives will review key assumptions in the model to ensure that they reflect patient and public values. They will draw upon their own and their relative's experiences and will consult with the wider groups when making their judgements. They will help to determine whether certain costs and outcomes are included in the model. For example, in the TiLLI project we decided to include in the model the disutility associated with having to self-administer subcutaneous injections based on PPI advice. This turned out to be an important parameter and highlighted the need for future research to determine whether oral prophylaxis is as effective as subcutaneous prophylaxis.
4. Developing and reviewing outputs from the project so they are relevant and comprehensible to patients and the public. Our dissemination strategy includes developing outputs that inform patients and the public of our findings. The PPI representatives will assist in developing these outputs and will consult with the wider groups to ensure comprehensibility and relevance to patients and the public. SB has had personal experience with a relative of difficulties using long and complex information provided with an agent used in VTE prophylaxis. The development of decision aids and other methods for involving patients in assessing their own risk and determine their preferences regarding prophylaxis is beyond the scope of this project. However, the PPI representatives will consult with their wider groups to determine the acceptability and appropriateness of shared decision-making in this context, and determine how future research should address this issue.

15.0 Research expertise

SG, DHo, AP and SD successfully delivered HTA15/187/06 (https://www.journalslibrary.nihr.ac.uk/programmes/hta/1518706/#/), which used similar methods to those proposed here to determine the effectiveness and cost-effectiveness of VTE prophylaxis for people with lower limb immobilisation. The final report was submitted on time, received positive reviews and has been accepted for publication. SG, MB and BH also undertook the DiPEP study (HTA13/21/01), which used decision analysis modelling to show that a clinical prediction rule for pulmonary embolism in pregnancy was unlikely to be cost-effective compared to scanning for all and therefore that a prospective cohort study would represent poor value for money. SG and DHo will lead the project and deliver the evidence

synthesis with AP and SD, and the primary research with DHi and MB. BH, XG, MH and KdW will provide specialist clinical expertise.

Sheffield CTRU will support the primary research elements of this proposal. DH is Assistant Director for the CTRU and MB is Senior Statistician.

16.0 Success criteria and barriers to proposed work

16.1 Evidence synthesis

The success of the evidence synthesis work stream will be judged by delivery of the key outputs, i.e. an optimal strategy for providing prophylaxis, risk thresholds that optimise effectiveness (QALYs) and cost-effectiveness, and an estimate of the value of information from future research. These outputs are clearly deliverable with the time, expertise and resources outlined in this proposal, but delivery of a definitive answer to the research question will depend upon the primary data available.

The Board feedback asked us to provide reassurance in our application that the parameters used in the model are available and sufficiently robust. We have recently modelled the cost-effectiveness of VTE prophylaxis for people with lower limb immobilisation due to injury (HTA15/187/06), so have identified robust estimates for many key parameters in the model. The main new parameters we need to estimate for our proposed study are those relating to the effectiveness of VTE prophylaxis in hospital inpatients, which have robust estimates from recent systematic reviews (Kahn 2018, NICE 2018), and those relating to the predictive accuracy of risk-assessment tools, which we assume are the focus of the Board's concern.

Our scoping review (see below) has identified a number of studies providing relevant estimates for existing tools but these are limited by poor methodological quality, especially relating to inability to control for use of prophylaxis. As explained in the background, this cannot be addressed by a new prospective cohort study since it will suffer from the same limitation. We therefore share concerns about the quality of predictive accuracy data but contend that modelling provides the most appropriate way of addressing limitations in the current data, thus guiding practice and future research.

We will use the decision-analysis model to (1) explore the potential impact of uncertainty in estimates of predictive accuracy, (2) identify the optimal balance of sensitivity and specificity for a risk-assessment tool, and (3) identify the appropriate risk threshold for providing prophylaxis. The first objective can be undertaken with limited data and the latter two by using theoretical risk-assessment tools with varying prognostic performance. These analyses will help to inform discussions reported in the NICE guideline as to whether 70% of inpatients receiving prophylaxis according to the Department of Health tool or the estimated 40% with the IMPROVE tool is more appropriate. We will also be able to determine which existing risk-assessment tools appear to operate at thresholds for performance likely to be optimal according to our model and, for risk-assessment scores, which score appears to provide an optimal threshold.

The model can therefore provide evidence to indicate whether more liberal or restrictive use of prophylaxis is likely to be appropriate. Ultimately, however, primary research will be required to determine the impact of a risk-adjustment tool (or tools) in practice, hence our concurrent plan to determine the feasibility of efficient methods to evaluate alternative approaches to the use of VTE prophylaxis.

16.2 Feasibility study

The purpose of the feasibility study is to determine the feasibility of a future implementation study. The criteria for determining feasibility are outlined in the data analysis section of the work stream 2 project description.

Barriers to undertaking a useful feasibility study include: difficulties in securing ethical and/or CAG approval due to concerns over data protection, lack of systems to facilitate routine recording of risk-assessment data, and difficulties in linking risk-assessment to outcome data.

We will address data protection and linkage issues by drawing on our extensive experience of working with routine data and undertaking linkage with NHS Digital data. In addition to expertise within the team, there is extensive experience within ScHARR of using and linking ambulance, emergency department and Hospital Episodes Statistics data. We have frequently worked with NHS Digital. ScHARR has well-established information governance procedures to ensure that we are able to use routine data appropriately and with minimal risk.

We will address issues with collecting standardised risk-assessment data by drawing upon clinical academic links with the participating hospitals (SG has an honorary contract with Sheffield Teaching Hospitals, DHo and MH both work at Salford Royal Hospital). We have previous experience of collecting standardised routine data for research purposes in the PAINTED study (Pandemic Influenza Triage in the Emergency Department, HTA11/46/07) and have continued to develop our expertise in using electronic data collection systems.

17.0 References

Altman D. Systematic reviews of evaluations of prognostic variables. BMJ 2001;323:224-8.

Blondon M, Spirk D, Kucher N, Aujesky D, Hayoz D, Beer JH, Husmann M,Frauchiger B, Korte W, Wuillemin WA, Bounameaux H, Righini M, Nendaz M. Comparative Performance of Clinical Risk Assessment Models for Hospital-Acquired Venous Thromboembolism in Medical Patients. Thromb Haemost 2018; 118:82-89.

British National Formulary Online March 2016. British Medical Association and The Royal Pharmaceutical Society.

Centre for Review and Dissemination. CRD's guidance for undertaking reviews in health care. York: University of York; 2008.

Cohen A. Written evidence to the House of Commons Health Committee, 2004. https://publications.parliament.uk/pa/cm200405/cmselect/cmhealth/99/99we07.htm (accessed 03/09/2018)

Curtis L, Burns A. Unit Costs of Health and Social Care 2105. Personal Social Services Research Unit. The University of Kent, UK.

de Bastos M, Barreto SM, Caiafa JS, Boguchi T, Silva JL, Rezende SM. Derivation of a risk assessment model for hospital-acquired venous thrombosis: the NAVAL score. J Thromb Thrombolysis 2016; 41:628-35.

Decousus H, Tapson VF, Bergmann JF, Chong BH, Froehlich JB, Kakkar AK; et al. "Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators.". Chest 2011; 139 (1): 69–79.

Department of Health. NHS reference costs 2013 to 2014. https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014

Depietri L, Marietta M, Scarlini S, Marcacci M, Corradini E, Pietrangelo A, Ventura P. Clinical impact of application of risk assessment models (Padua Prediction Score and Improve Bleeding Score) on venous thromboembolism, major hemorrhage and health expenditure associated with pharmacologic VTE prophylaxis: a "real life" prospective and retrospective observational study on patients hospitalized in a Single Internal Medicine Unit (the STIME study). Intern Emerg Med 2018 Mar 3. doi: 10.1007/s11739-018-1808-z.

Elias P, Khanna R, Dudley A, Davies J, Jacolbia R, McArthur K, Auerbach AD. Automating Venous Thromboembolism Risk Calculation Using Electronic Health Record Data upon Hospital Admission: The Automated Padua Prediction Score. J Hosp Med 2017; 12:231-237.

Grant PJ, Greene MT, Chopra V, Bernstein SJ, Hofer TP. Assessing the Caprini Score for Risk Assessment of Venous Thromboembolism in Hospitalized Medical Patients. Am J Med 2016; 129:528–535.

Greene MT, Spyropoulos AC, Chopra V, Grant PJ, Kaatz S, Bernstein SJ, Flanders SA. Validation of Risk Assessment Models of Venous Thromboembolism in Hospitalized Medical Patients. Am J Med 2016; 129:1001.e9-1001.e28.

Huang W, Anderson FA, Spencer FA, Gallus A, Goldberg RJ. Risk-assessment models for predicting venous thromboembolism among hospitalized non-surgical patients: a systematic review. J Thromb Thrombolysis 2013; 35:67-80.

Hostler DC, Marx ES, Moores LK, Petteys SK, Hostler JM, Mitchell JD, Holley PR, Collen JF, Foster BE, Holley AB. Validation of the International Medical Prevention Registry on Venous Thromboembolism Bleeding Risk Score. Chest 2016; 149:372-9.

Kahn SR, Morrison DR, Diendéré G, Piché A, Filion KB, Klil‐Drori AJ, Douketis JD, Emed J, Roussin A, Tagalakis V, Morris M, Geerts W. Interventions for implementation of thromboprophylaxis in hospitalized patients at risk for venous thromboembolism. Cochrane Database of Systematic Reviews 2018, Issue 4. Art. No.: CD008201. DOI: 10.1002/14651858.CD008201.pub3.

Le P, Martinez KA, Pappas MA, Rothberg MB. A decision model to estimate a risk threshold for venous thromboembolism prophylaxis in hospitalized medical patients. J Thromb Haemost 2017; 15:1132-1141.

Liu X, Liu C, Chen X, Wu W, Lu G. Comparison between Caprini and Padua risk assessment models for hospitalized medical patients at risk for venous thromboembolism: a retrospective study. Interact Cardiovasc Thorac Surg 2016; 23:538-43.

Moons KG, de Groot JA, Bouwmeester W, Vergouwe Y, Mallett S, Altman DG, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. PLoS Medicine 2014;11:e1001744.

National Institute for Health and Care Excellence (NICE). NICE guideline 89 [NG89]: Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. March 2018. https://www.nice.org.uk/guidance/ng89

NICE: Guide to the methods of technology appraisal. The National Institute for Health and Care Excellence. London, UK 2013. https://www.nice.org.uk/article/pmg9/chapter/foreword

National Institute for Health Research. PROSPERO: International Prospective Register of Systematic Reviews, http://www.crd.york.ac.uk/prospero/ (accessed 26/01/2012).

Pandor A, Horner D, Davis S, Goodacre S, Stevens JW, Clowes M, Hunt BJ, Nokes T, Keenan J, Hogg K. Thromboprophylaxis for lower limb immobilisation: Systematic review and economic evaluation. Health Technology Assessment 2018 (in press).

Rafizadeh R, Turgeon RD, Batterink J, Su V, Lau A. Characterization of Venous Thromboembolism Risk in Medical Inpatients Using Different Clinical Risk Assessment Models. Can J Hosp Pharm 2016; 69:454-459.

Shojania,KG, Duncan BW, McDonald KM. (2001). Making Healthcare Safer: A Critical Analysis of Patient Safety Practices. Evidence Report/Technology Assessment No. 43. Agency forHealthcare Research & Quality, Rockville, MD, pp. 332–346.

Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.

Strong M, Oakley JE, Brennan A. Estimating multi-parameter partial Expected Value of Perfect Information from a probabilistic sensitivity analysis sample: a non-parametric regression approach. Medical Decision Making. 2014;34(3):311-26.

Strong M, Oakley JE, Brennan A, Breeze P. Estimating the Expected Value of Sample Information using the Probabilistic Sensitivity Analysis Sample. A Fast Non-Parametric Regression Based Method. Medical Decision Making. 2015;35(5):570-583

Stuck AK, Spirk D, Schaudt J, Kucher N. Risk assessment models for venous thromboembolism in acutely ill medical patients: A systematic review. Thrombosis & Haemostasis 2017; 117:801-808.

Zhou H, Hu Y, Li X, Wang L, Wang M, Xiao J, Yi Q. Assessment of the Risk of Venous Thromboembolism in Medical Inpatients using the Padua Prediction Score and Caprini Risk Assessment Model. J Atheroscler Thromb 2018 Mar 13. doi: 10.5551/jat.43653.