Estimating the value of future research to improve guidelines on thromboprophylaxis for women during pregnancy and after delivery

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Study acronym (tbc) [PregDVT used as temporary placeholder]

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

Contents

Abbreviations

ACOG	American Congress of Obstetricians and Gynaecologists
BMI	Body-mass index
DVT	Deep vein thrombosis
CTEPH	Chronic thromboembolic pulmonary hypertension
DiPEP	Diagnosis of PE in Pregnancy
EVPPI	Expected value of partial perfect information
EVSI	Expected value of sample information
HTA	Health Technology Assessment
ICH	Intracranial haemorrhage
ICTRP	International Clinical Trials Registry Platform
ISTH	International Society on Thrombosis and Haemostasis
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PE	Pulmonary embolism
PMG	Project management group
PPI	Patient and Public Involvement
PSA	Probabilistic sensitivity analysis
PSC	Project Steering Committee
PTS	Post thrombotic syndrome
QALYs	Quality-adjusted life-years
RAM	Risk Assessment Model
RCT	Randomised controlled trial
REC	Research Ethics Committee
RCOG	Royal College of Obstetricians and Gynaecologists
ROC	Receiver Operating Characteristic
ScHARR	School of Health and Related Research
TiLLI	Thromboprophylaxis in Lower Limb Immobilisation
VTE	Venous thromboembolism
WHO	World Health Organisation

General Information

Sponsor

This project is not a health/social care study so does not require a Research Governance Sponsor.

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Copyright statement

Protocol amendments since Version 1.0

None

Summary of Research

Research question
What is the value of undertaking a study to determine the clinical and cost-effectiveness of risk stratification tools for the prediction of venous thromboembolism (VTE) and appropriate provision of thromboprophylaxis for women in pregnancy and after delivery?

Background
Pharmacological prophylaxis to prevent VTE is currently recommended for women who are deemed to be at high risk of VTE during pregnancy or in the 6 weeks after delivery. The decision to provide prophylaxis involves weighing the benefits, harms and costs, which will vary according to the individual's VTE risk. It is unclear whether the current risk stratification approach could be improved by further research.

Aims and objectives
The aim of the research project is to determine whether further primary research is worthwhile to inform NHS practice on the use of risk stratification tools for the prediction of VTE and appropriate provision of thromboprophylaxis for women in pregnancy and in the puerperium. The specific objectives will be;

1) To estimate the expected costs, health benefits (quality-adjusted life-years) and incremental net monetary benefit of providing thromboprophylaxis using current and alternative risk stratification tools and to quantify the uncertainty around those estimates, given current evidence
2) To determine which factors are the most important drivers of uncertainty when trying to determine the optimal risk-based thromboprophylaxis strategy in this population
3) To identify one or more potential future studies to gather additional evidence that would reduce the current decision uncertainty, whilst being feasible and acceptable to patients and clinicians.
4) To evaluate the value of the potential future research studies in terms of the net health benefits to patients and the cost of the research.

Methods
A decision analytic model will be developed which will be informed by reviews of the existing literature. This model will be used to determine which factors are the most important drivers of uncertainty using expected value of perfect information analysis. Qualitative research, in the form of workshops with patients and a survey of clinicians, will then be undertaken to identify one or more potential future studies that could be conducted to gather additional evidence to reduce the current decision uncertainty. Expected value of sample information analysis will then be used to evaluate the value of the potential future research studies in terms of the net health benefits to patients and the cost of the research.

Timelines for delivery
The project will take place over 15 months with cost-effectiveness modelling (including rapid reviews of parameters) and expected value of perfect information analysis in months 1 to 7, qualitative work to inform potential study designs in months 8 to 10, expected value of sample information analysis in months 11 to 12 and write up and dissemination in months 13 to 15.

Anticipated impact and dissemination

We anticipate that this project will inform the funding of future research studies and may also inform clinical guideline updates. We will share our findings and research recommendations with UK research funders and guideline developers. We will also disseminate professional and plain language summaries to relevant clinical, public and patient representative organisations so they are able to make an evidence-based case for further research or changes to current clinical practice.

1.0 Introduction

Background and Rationale

What is the problem and how do we intend to address it?

In the UK, pharmacological prophylaxis to prevent VTE in pregnancy is usually with low molecular weight heparin. It is currently recommended in pregnancy and for 10 days to 6 weeks postpartum for women deemed to be at high risk of VTE [1]. However, there is no high quality evidence to support this approach [2]. International guidelines therefore rely on expert opinions, which vary with regard to the threshold of risk for recommending low molecular weight heparin [3]. Furthermore the number needed to treat to prevent one episode of VTE is high (ranging from 667 to 10018 postnatally depending on time since birth and risk factors [4]), with significant costs (£223.70 over 6 weeks [5]) and a substantial treatment burden for the women, who usually self-inject daily (oral anticoagulants are not used in pregnancy). VTE remains the leading cause of direct maternal death in the UK [6], despite the introduction of Royal College of Obstetricians and Gynaecologists (RCOG) recommendations for thromboprophylaxis resulting in 41% of postnatal women and 7% of antenatal women qualifying for thromboprophylaxis [7].

The decision to provide thromboprophylaxis involves weighing the benefits, harms and costs for an individual, which will vary according to the individual's perceived VTE risk and therefore accurate risk assessment tools are needed which target thromboprophylaxis at those most likely to benefit.

The use of appropriate risk assessment tools to select patients is clearly important as the balance of risks and harms varies according to whether the woman is at high or low risk of a VTE. In addition, guidelines used in different countries have been shown to result in significantly different numbers of patients being eligible for low molecular weight heparin [8,9] which will result in significantly different costs for preventing VTE.

The current National Institute for Health and Care Excellence (NICE) Guideline (NG89) on the prevention of VTE in hospitalised women who are pregnant or who are in the puerperium recommends that clinicians use a tool published by a national UK body, professional network or peer-reviewed journal [10]. Although the NICE Guideline (NG89) states that the most commonly used tool is the RCOG guideline, the All-Wales maternity risk assessment tool, has also been used as an alternative to the RCOG guideline in Wales [11].

Starting with the information provided in the background document for this call, we undertook a rapid scoping review which was supplemented by findings from a systematic search of the following databases for prospective studies of VTE events in pregnant women: MEDLINE, EMBASE, CINAL and AMED from inception to July 2019. This search was conducted as part

of a systematic review and meta-analysis of incidence rates of VTE events in pregnant women worldwide, which is currently under peer review [12]. The search helped to identify additional primary studies utilizing a risk assessment tool, either existing or novel. From these sources we identified a number of alternative risk assessment tools and international guidelines including: St Etienne Score [13], Lyon Score [14], Schoenbeck Score [15], Italian pregnancy healthcare program [16], American Society of Hematology [17], American Congress of Obstetricians and Gynaecologists [ACOG] [18] , American College of Chest Physicians [CHEST] [19], Thrombocalc [20], STRATHEGE [21].

In addition, Sultan et al. have published research describing the development of a tool to estimate the absolute risk of VTE in postpartum women according to their individual risk factor combinations [22]. Such a tool would avoid the need to assume that all risk factors have equal weight and would allow the threshold for intervention to be set according to the absolute risk in the individual. Sultan et al. report that the current RCOG guideline would result in 35% of postpartum women qualifying for thromboprophylaxis but using their risk prediction to select the same proportion of women for thromboprophylaxis would mean treating those with an absolute risk of 6 in 10,000 and would have a slightly higher sensitivity than current RCOG guidance at 68%. The NICE Guideline (NG89) concluded that the tool described by Sultan et al. showed poor sensitivity compared to their pre-specified target of 90% sensitivity. However, this high level of sensitivity may not be realistic because there is evidence that only 70% of women having antenatal pulmonary embolism had any identifiable classic risk factors suggesting that sensitivity rates above 70% may not be achievable [23]. In addition, a high sensitivity rate is usually associated with a lower specificity rate and the overall balance of benefits and harms may be undesirable if that means exposing a high proportion of women to thromboprophylaxis. The paper by Sultan et al. provides information on the sensitivity and specificity of using their risk prediction tool to select patients for thromboprophylaxis at different levels of absolute risk of VTE. These data could be used within a decision analytic model to explore the optimal trade-off between sensitivity and specificity in postpartum women. These target levels of sensitivity and specificity could then be used to determine whether existing published tools are sufficiently accurate rather than relying on arbitrary cut-offs that may be unrealistic or may result in a poor balance of benefits and harms. Therefore, although the NICE Guideline (NG89) recommends that further research should be done to determine the accuracy of risk assessment tools, it is important that we first use the existing research currently available to determine how accurate risk assessment tools need to be to provide a positive balance of risks and harms.

The cost-effectiveness of using VTE risk assessment tools to identify patients for thromboprophylaxis is also dependent on the effectiveness of prophylaxis in this population. A 2014 Cochrane systematic review concluded that there is no high quality randomised controlled trial evidence quantifying the benefits of pharmacological thromboprophylaxis during pregnancy and up to 6 weeks post-partum. [2]. It also concluded that large scale high-quality randomised controlled trials (RCT) of currently used interventions are warranted [2]. However, several pilot studies have been unable to recruit sufficient high risk patients to such trials [24,25,26]. This highlights the need to assess the benefits of thromboprophylaxis in a manner acceptable to patients. Although the RCOG guideline acknowledges the lack of RCT evidence in this population, it makes recommendations for thromboprophylaxis in higher risk women because there is indirect evidence from medical and surgical patients that thromboprophylaxis reduces the risk of VTE by 60 and 70% respectively [1].

None of the publications describing alternative VTE risk assessment tools which we identified have assessed the net impact on patients' health in terms of the overall quality-adjusted life-years (QALYs) gained, from using an alternative risk assessment tool to guide thromboprophylaxis instead of the current RCOG guidelines. Neither have they assessed whether the overall balance of costs, benefits and harms would support a change in clinical

practice. There is therefore a need to assess the incremental cost-effectiveness of using the current RCOG guidelines and alternative published VTE risk assessment tools to guide thromboprophylaxis in this population.

Our proposed research would address this need by using decision analytic modelling to extrapolate the expected costs and the expected health outcomes for different alternative VTE risk assessment tools, which use different cut-offs for thromboprophylaxis intervention. This will allow us to explore the optimal cut-off for thromboprophylaxis intervention in terms of the balance of risks, benefits and costs. So for example, a higher threshold for providing thromboprophylaxis may result in more pregnancy associated VTE, with an associated increase in long-term morbidity and mortality, but this must be balanced against the benefits of exposing fewer women to the risk of major bleeding during thromboprophylaxis which can itself have significant ongoing morbidity. In addition, fewer women receiving thromboprophylaxis will result in lower thromboprophylaxis costs and lower costs for managing thromboprophylaxis related major bleeding. These may somewhat off-set the additional costs of short- and long-term VTE management from any increase in pregnancy related VTE. The decision analytic modelling will therefore be able to assess whether the current approach to thromboprophylaxis based on the RCOG guidelines is effective and cost-effective compared to the use of alternative risk scoring assessment tools, all of which will have a different balance or benefits, harms and costs.

Furthermore, our scoping review suggests that further primary research will be needed to address gaps in the current evidence base. Expected value of perfect information analysis is a form of decision analysis that provides a framework for synthesising the best available evidence at the current time to assess not only the optimal strategy given the current evidence, but the areas of uncertainty where further research would be worthwhile [27]. Expected value of sample information analysis allows researchers to determine the value of conducting different research studies in the future, by simulating the potential outcomes of those studies [28]. It also allows researchers to assess the impact of varying aspects of the study design to determine the optimal study design [29]. Our proposed research will include the use of expected value of perfect information and expected value of sample information analysis to identify where further research would be beneficial to better define which women should be receiving thromboprophylaxis. We will ensure that the study designs examined in the expected value of sample information analysis are informed by patient views and are considered feasible by clinicians by conducting qualitative work in the form of patient workshops and a survey of clinicians.

Research into improving risk assessment for VTE in pregnancy and postpartum is important and timely because despite successive iterations of National (RCOG) guidelines that have advocated for low molecular weight heparin in increasing proportions of women deemed to be at intermediate and high risk of VTE, the absolute risk of VTE in pregnancy or post-partum has not reduced and VTE remains the leading direct cause of maternal mortality. Several explanations for this are possible: the risk assessment tools are inadequate, the application of these tools is incomplete or inaccurate, the demographics of the pregnant population (increasing age, BMI and comorbidities) are changing making the background risk without thromboprophylaxis higher. The persistent finding of VTE as a leading cause of death and morbidity in the UK is despite deaths from other direct causes, notably pre-eclampsia and anaesthesia reducing.

This research is also particularly timely because there are now a number of published risk assessment tools available, and it is unclear whether offering thromboprophylaxis according to these tools would be more cost-effective than the current practice of using the RCOG guidelines. In particular, a retrospective analysis comparing the All-Wales maternity risk assessment to the RCOG guidelines suggests that there may be scope for reducing the

numbers receiving thromboprophylaxis without increasing preventable VTE events, although the authors recommend that a prospective study should be conducted including a cost-effectiveness analysis. This reflects the lack of studies explicitly comparing the balance of costs, benefits and harms when using different risk assessment methods to direct thromboprophylaxis in this population. Furthermore, the fact that there is significant variation in the numbers who would be eligible for thromboprophylaxis under guidelines used in different jurisdictions internationally suggests that there may be scope for improving current UK practice. However, this variation in guidelines is somewhat driven by a lack of primary research quantifying the benefits and harms of thromboprophylaxis specifically in women who are pregnant or who have recently delivered. This is separate to the issue of whether risk assessment tools are sufficiently accurate at predicting those at risk of VTE. Therefore, research needs to go beyond estimating the best option based on current evidence and expected value of sample information analysis is needed to estimate the value of different potential future research studies to address the different evidence gaps that make it difficult to determine the optimal strategy at this time.

2.0 Aims and objectives

The aim of the research project is to determine whether further primary research is worthwhile to inform NHS practice on the use of risk stratification tools for the prediction of VTE and appropriate provision of thromboprophylaxis for women in pregnancy and in the puerperium. The specific objectives will be;

1) To estimate the expected costs, health benefits (QALYs) and incremental net monetary benefit for providing thromboprophylaxis using current and alternative risk stratification tools and to quantify the uncertainty around those estimates, given current evidence

2) To determine which factors are the most important drivers of uncertainty when trying to determine the optimal risk stratification and thromboprophylaxis treatment strategy in this population

3) To identify one or more potential future studies to gather additional evidence that would reduce the current decision uncertainty, whilst being acceptable to patients and clinicians.

4) To evaluate the value of the potential future research studies in terms of the net health benefits to patients and the cost of the research.

PICO definition of the research question

Population: Women who are pregnant or in the puerperium (within six weeks post delivery) receiving care in both hospital and primary care settings. The antenatal and postnatal populations will be considered as separate subgroups.

Intervention: Pharmacological thromboprophylaxis provision in pregnancy and postnatally based on alternative risk stratification tools for the prediction of VTE.

Comparators: Thromboprophylaxis provision in pregnancy and postnatally based on the risk assessment tool used in current UK practice (the RCOG guideline) and a hypothetical strategy of no thromboprophylaxis.

Outcomes: Incremental analysis of cost per QALY gained for each alternative thromboprophylaxis strategy. An estimate of the gain in incremental net monetary benefit that could be achieved by obtaining perfect information on model parameters. An estimate of the expected value of one or more potential primary research studies in reducing current uncertainty around the optimal use of thromboprophylaxis in pregnancy and postnatally

Additional study outputs: Information about the optimal design and sample size for a future primary research study taking into account the views of patients and clinicians regarding the acceptability and feasibility of such a study

3.0 Research Plan

3.1 Design

Decision analytic modelling is a tool for bringing together existing evidence from published literature to determine what the likely impact would be of making alternative health care decisions. The most common form of decision analytic modelling in a healthcare setting is cost-effectiveness analysis. This determines the impact of alternative health technologies in terms of both costs to the healthcare system and benefits or harms to patients. Benefits and harms are usually brought together in an overall estimate of QALYs gained. In the UK, technologies that increase QALYs at a cost of under £20,000 per QALY are generally considered to be cost-effective by NICE. Cost-effectiveness analysis can therefore be used to determine the most cost-effective treatment strategy given current evidence. Expected value of perfect information analysis is a form of decision analysis that provides a framework for synthesising the best available evidence at the current time to assess not only the optimal strategy given the current evidence, but also the areas of uncertainty where further research would be worthwhile [27]. Expected value of sample information analysis allows researchers to determine the value of conducting different research studies in the future, by simulating the potential outcomes of those studies [28]. It also allows researchers to assess the impact of varying aspects of the study design to determine the optimal study design [29]. In situations where data are lacking to inform the decision analytic modelling, estimates can be elicited from relevant experts and those estimates and the uncertainty around them can be included in the modelling. This allows the decision analytic modelling framework to be used to estimate the value of further research to provide data where it is currently lacking.

In this case, a decision analytic model will be developed to assess the costs and benefits of using alternative risk assessment tools to determine thromboprophylaxis in women during pregnancy and the puerperium and to determine the optimal strategy for thromboprophylaxis given current evidence. This model will be informed by reviews of the existing literature. The decision analytic model will then be used to determine which factors are the most important drivers of uncertainty using expected value of perfect information analysis. Qualitative workshops with patients and a survey of clinicians, will then be undertaken to identify one or more potential future studies that could be conducted to gather additional evidence to reduce the current decision uncertainty. Expected value of sample information analysis will then be used to evaluate the value of the potential future research studies in terms of the net health benefits to patients and the cost of the research

The research will draw upon our previous experience of undertaking a recent similar evidence synthesis (HTA15/187/06) aimed at determining the effectiveness and cost-effectiveness of thromboprophylaxis in lower limb immobilisation (TiLLI)[5]. In TiLLI we used decision-analysis modelling to determine the effectiveness and cost-effectiveness of

providing thromboprophylaxis based on a risk assessment tool compared to thromboprophylaxis for all and thromboprophylaxis for none. This included an expected value of perfect information analysis to identify the key sources of decision uncertainty.

We will further draw on our current experience from an on-going project to determine the optimal risk assessment tool for providing VTE thromboprophylaxis to hospital patients (excluding women admitted to hospital for pregnancy related reasons) which will also use cost-effectiveness modelling and expected value of perfect/sample information analysis to inform the design of future primary research (NIHR127454).

The proposed study here will use similar methods to these two previous projects but applied to a different population, i.e. women during pregnancy and the puerperium, rather than hospitalised patients or outpatients having lower limb immobilisation.

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 thromboprophylaxis. Tools may take the form of rules, that simply categorise patients according to whether they need thromboprophylaxis or scores that estimate the risk of VTE but leave the decision to provide thromboprophylaxis in the hands of the user.

3.3 Target population

Women who are pregnant or in the puerperium (within six weeks post delivery) receiving care in both hospital and primary care settings. The antenatal and postnatal populations will be considered as separate subgroups.

3.4 Inclusion/Exclusion Criteria

All women who are pregnant or in the puerperium are recommended to have risk assessment for VTE under the current RCOG guidelines and therefore all these women are included in the target population.

3.5 Setting

Any primary or secondary care setting providing care to the target population including within community settings

3.6 Outcomes

The overall outcome is an estimate of the expected value of further research. This will be estimated from the expected costs and benefits of thromboprophylaxis given according to alternative risk assessment strategies determined by the economic modelling. Benefits will be measured in QALYs which will be valued at £20,000.

The benefits will be driven by differences in clinical outcomes including the following;
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 and meets the criteria above.
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 [30].
Clinically relevant non-major bleeding: as defined by International Society of Thrombosis and Haemostasis [30].
Additional relevant clinical outcomes may be included in the economic modelling with the final set of clinical outcomes included in the economic model to be informed by discussion with clinicians and patient and public involvement (PPI) representatives

4.0 Work stream 1: Evidence synthesis

4.1 Decision-analytic modelling

Decision-analytic modelling will simulate the management of VTE risk in pregnant women and the management of VTE risk in the 6 weeks post-delivery. The model will compare using thromboprophylaxis based on alternative VTE risk assessment tools to current practice, which is the use of thromboprophylaxis based on the RCOG guidelines. The costs and QALYs for these alternative strategies will be estimated relative to a hypothetical strategy of no thromboprophylaxis. A fully incremental analysis will be undertaken to determine the optimal thromboprophylaxis strategy given current evidence. The alternative risk assessment tools included in the incremental analysis will be selected from those identified in the rapid review. Risk assessment tools used in other international jurisdictions will be included in the model provided data exist to estimate outcomes relative to either no thromboprophylaxis, the RCOG guideline or another published tool. In addition, clinical and patient experts will be asked to consider whether any of the risk assessment tools would not be acceptable to patients and the public or could not be feasibly implemented within a UK NHS setting. Consideration will then be given as to whether these tools should be excluded from the analysis or whether they would need adapting to make them acceptable or feasible in a UK setting. However, any decision to adapt a risk assessment tool in a future study would always need to be balanced against the impact this would have on its ability to predict risk. Where data exist on the sensitivity and specificity of providing thromboprophylaxis at different thresholds of risk, such as those provided by Sultan et al.,[22] these will be explored to determine the optimal trade-off between sensitivity and specificity, using an approach similar to that undertaken in our previous work aimed at determining the effectiveness and cost-effectiveness of thromboprophylaxis in lower limb immobilisation (TiLLI - HTA15/187/06). 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 [31].

We will employ the same basic model structure as used in the TiLLI decision analysis model (HTA15/187/06), but the model inputs and assumptions will be reviewed and adapted to be relevant to women during and after pregnancy. The overall design of the existing TiLLI model is a decision-tree combined with a state-transition model (sometimes referred to as a Markov model). The TiLLI model uses a 6 month decision tree to capture the short-term risk of venous thromboembolism (VTE) events (symptomatic and asymptomatic deep vein thrombosis [DVT] and fatal and non-fatal pulmonary embolism [PE]) during the period of immobilisation (6 weeks). It also captures the three month period of anticoagulant treatment used in the treatment of symptomatic VTE. The decision tree also captures the risk of major bleeds (fatal bleeds, non-fatal intracranial haemorrhage [ICH] and other major bleeds), which are increased both by thromboprophylaxis and by anticoagulants used in the treatment of VTEs. The long-term state-transition part of the model captures the ongoing costs and morbidity associated with ICH and complications diagnosed following VTE, such as post thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH).

The long-term model also allows us to extrapolate the life-years lost due to fatal bleeds and fatal PEs occurring during the decision-tree phase and the impact of ICH and CTEPH on life expectancy.

The basic structure of this existing TiLLI model will be retained for the proposed research but all the parameters will be reviewed to ensure that they are applicable to the target population for this project, i.e. women who are pregnant or who have recently delivered. In addition, we will review the structural assumptions and adapt the model to include any additional outcomes that are considered relevant to this population based on the advice from clinical and patient experts. For example, wound breakdown and wound infection will be added as relevant outcomes post-delivery. In the TiLLI decision analysis, we found that the main factors driving decision uncertainty were the efficacy estimates for thromboprophylaxis, the extent to which daily injections reduced quality of life and the potential for complications of VTE to have a long-term impact on quality of life. As DVT was the most common adverse outcome following lower limb immobilisation, the incidence and quality of life reductions attributable to PTS were particularly important. In the model for the Diagnosis of PE in Pregnancy (DiPEP) study (HTA13/21/01), which used decision analysis modelling to determine optimal diagnostic testing strategies for pregnant women with suspected PE, the impact of long-term adverse outcomes was again an important driver of decision uncertainty [32]. However, in this case the risk of CTEPH and its impact on life-expectancy was found to be a key area of decision uncertainty. In both cases, these long-term consequences were uncertain and were subject to scenario analyses. Some of the data sources included in the TiLLI model, such as the incidence, costs and QALY losses associated with PTS, CTEPH and ICH, are likely to be equally applicable to this population. However, other parameters, such as the incidence of DVT and PE, are likely to need source data which are specific to the population considered here. These will be identified from the published evidence by undertaking rapid literature reviews. In some cases, we may need to use evidence from broader populations e.g. risks of bleeding from post-operative patients, where data from our target population are lacking. In particular, we anticipate from our scoping review that there will be no high quality data sources that are directly relevant to pregnant and postpartum women for the estimate of thromboprophylaxis effectiveness. We may therefore need to use estimates from other indirect populations. In the TiLLI model, the RCTs included in our systematic effectiveness review reported very few incidences of major bleeding as an adverse event and therefore we used data from the systematic review of thromboprophylaxis in hospitalised patients from the NICE Guideline (NG89) instead. Clinical experts will be used to determine whether any indirect data sources identified are sufficiently relevant to the population being considered. For example pregnant and postpartum women are likely to be younger than the average patient at risk of VTE due to hospitalisation and they will have a lower prevalence of comorbidities.

Differences in resource use between the different VTE thromboprophylaxis 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 [33] or PSSRU unit costs [34] for episodes of care and BNF list prices for medications [35].

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. For example, we may need to use an estimate of the effectiveness of low molecular weight heparin in preventing VTE from an indirect population. However, when including this estimate in the model we will need to incorporate the additional uncertainty that comes from using evidence from an indirect population and not

simply apply the parameter uncertainty associated with the use of thromboprophylaxis in the indirect population.

We will estimate the incremental cost per QALY gained by each thromboprophylaxis strategy compared to the next most effective alternative on the efficiency frontier to determine the optimal strategy given current evidence. Analyses will be undertaken to identify the key parameters determining the cost-effectiveness of the different strategies with the objective of identifying how robust 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 [31] in appraising health technologies will be explicitly reported.
We will use expected value of perfect information analysis to determine which model inputs are important drivers of decision uncertainty and therefore which uncertain parameters should be the focus of future research. 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 [36]
We will then estimate the expected value of sample information of further primary research. This will involve selecting a set of potential future study designs and using expected value of sample information analysis to simulate the possible findings of those studies to determine the likelihood that future research will allow a more optimal thromboprophylaxis strategy to be identified. The expected value of sample information analysis will be able to explore aspects of the study design and the impact these factors have on the sample size required. For example, the model could explore the sample size required when using a surrogate outcome, such as screening detected VTE, versus the more clinically relevant outcome of symptomatic VTE. Efficient methods for calculating expected value of sample information from the PSA results, using a process similar to that used for EVPPI, are now available making this step more computationally efficient and less time consuming [37].

Although the candidate study designs will be informed by the uncertainties identified by the decision analytic modelling, we anticipate that these could include; 1) a prognostic accuracy study to estimate the accuracy of risk assessment tools, 2) a comparative study to estimate the effectiveness and cost-effectiveness of giving thromboprophylaxis according to several alternative risk assessment tools, 3) a comparative study of thromboprophylaxis versus no thromboprophylaxis in a patient population with intermediate risk where the trade-off between risks and benefits is currently unclear. We note that any prognostic study is likely to be severely limited if the use of thromboprophylaxis according to existing risk assessment tools is already widespread since thromboprophylaxis would presumably be preventing many of the events that a prognostic study was aiming to predict.

The identification of suitable designs for future research studies will also be informed by the qualitative work with clinicians and patients to ensure that they are both feasible and acceptable to patients. For example, if a comparative study is considered then we will consider whether cluster level randomisation, to allow consistent care across a hospital site or NHS trust, is preferable to individual randomisation. The acceptability of using surrogate rather than clinical outcomes could also be explored with both patients and clinicians. Then expected value of sample information analysis will be conducted to determine whether each proposed study design is likely to provide value for money in terms of the trade-off between net health benefits to patients and the cost of the research.

4.2 Literature review

The literature review aspect of the project will focus on identifying suitable parameters for the decision analytic model in a systematic, transparent and efficient manner as a full systematic

review of each parameter may be neither feasible nor necessary. Whilst procedural guidance on identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models is limited, we will take the approach suggested by Kaltenthaler et al.[38,39].

Rapid review methods will be undertaken to identify and select evidence to inform certain model parameters. Depending on the nature of the evidence being sought, a hierarchy of evidence sources, relevance and assessment will be considered for individual parameter estimates [40]. Rapid review approaches are widely accepted by policy makers, in clinical guidelines and health technology assessments [41-42]. There is some evidence to suggest that rapid approaches may provide similar results to more robust methods [43-45]. In addition, not all findings from systematic reviews have been found to be robust [46,47].

The key areas likely to be addressed by the rapid literature reviews are;

1) Identification of risk stratification tools in current use in the UK and internationally: This will build on the list of alternative VTE risk assessment tools identified in the commissioning brief and scoping review (RCOG, St Etienne Score, Lyon Score, Schoenbeck Score, Italian pregnancy healthcare program, American Society of Haematology, ACOG, CHEST, Thrombocalc, STRATHEG). Systematic literature searches (of Medline, EMBASE, and the Cochrane Library) will be conducted to identify risk stratification tools currently used for our target population. Searches will combine free text terms and subject headings (MeSH/Emtree) along with filters to identify risk prediction studies based on those developed by the McMaster University HEDGES project [48]. Web of Science will be used to conduct citation searches of included papers to minimise the risk of missing any relevant studies. Where available, data will be extracted on the performance of these risk stratification tools in identifying those patients who go on to have VTE. Where possible, we will record the proportion receiving thromboprophylaxis in the studies identified as the predictive accuracy of the risk assessment tool may be underestimated if those with identifiable risk factors are already receiving thromboprophylaxis.
2) Estimates of efficacy for low molecular weight heparin for preventing VTE in women during pregnancy and up to 6 weeks post-partum: We will conduct further searches of the same sources to identify high quality RCTs of low molecular weight heparin in women during pregnancy and up to 6 weeks post-partum. The aim will be to determine whether the Cochrane systematic review by Bain et al 2013 needs updating and therefore searches will focus on evidence published since 2013. To ensure the most up-to-date coverage, these searches will additionally include the WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov. If the RCT evidence is weak in the direct population of women who are pregnant or in the puerperium, as suggested by our scoping review, we shall also identify published systematic reviews of RCTs in indirect populations, using clinical expert opinion to select relevant indirect populations.
3) Additional ad-hoc searching will be conducted to inform parameters required for the decision analytic model: 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), the model currently being developed for our ongoing project on thromboprophylaxis in hospitalised patients (NIHR127454) or the model for the DiPEP study (HTA13/21/01), which used decision analysis modelling determine optimal diagnostic testing strategies for pregnant women with suspected PE. Therefore literature searches will focus on updating reviews conducted to inform our previous models and replacing any data sources that are not generalizable to women who are pregnant or who have recently delivered.

For the rapid review of VTE risk assessment models for women in pregnancy and after delivery, study selection, data extraction and quality assessment will be undertaken by a single reviewer, and a random subset (minimum 20%) [42,44] checked by a second reviewer. Any disagreements will be resolved through discussion and arbitration by a third reviewer if necessary. The methodological quality of any relevant studies of risk assessment models will be assessed using an appropriate checklist such as PROBAST– a tool to assess the risk of bias and applicability of prediction model studies.[49] The protocol for the rapid review of VTE risk assessment models, has been registered on the PROSPERO database (CRD42020221094).

4.3 Clinical expert input:

Expert elicitation will be used where there is a lack of relevant published literature to inform parameters for the decision analytic modelling. The clinical experts will also be used to validate the model structure and to advise on the relevance of any parameter estimates obtained from the literature including the use of evidence from indirect populations, such as medical and surgical populations, where direct evidence from studies in women who are pregnant or in the puerperium is weak or lacking. Our clinical co-applicants will use their networks, e.g. MacDonald Obstetric Medicine Society, London Obstetric Medicine Group, and Obstetric haematology group of British Society of Haematology to access the opinions of a wider group of clinicians when necessary.

5.0 Work stream 2: Qualitative research

Aim: To identify one or more potential future studies to gather additional evidence that would reduce the current decision uncertainty, whilst being acceptable to patients and clinicians.

Relationship to work stream 1: The qualitative work with workshop participants and clinicians will be informed by the expected value of perfect information modelling to ensure that any proposed research studies discussed with workshop participants and clinicians will address key areas of decision uncertainty. The information obtained in the qualitative work will be used to select and further refine the design of one or more proposed future research studies that will then be assessed using expected value of sample information to determine the overall value of those potential future research studies.

5.1 PPI workshops

Previous studies have struggled to recruit pregnant patients to trials, and there are a number of factors that affect whether pregnant women are willing to participate in research studies, including perceptions of risk, and inconvenience factors. [50-51] We will undertake workshops to obtain the views of women on the acceptability of any potential primary research to ensure that any study design would capture outcomes that are important to women and that the benefits of the research are perceived to outweigh any risks from participation.

5.1.1 Workshop participants

We aim to recruit 20 participants from two broad groups:

- women who have experienced DVT or PE during pregnancy or within six weeks post delivery

- women who have been offered thromboprophylaxis during pregnancy or within six weeks post delivery

We will recruit these women from special interest groups including: Thrombosis UK, National Childcare Trust, the Reproductive Health Research Public Advisory Panel at Sheffield Teaching Hospitals NHS Trust and Katie's Team, which is an East London women's health research patient and public advisory group.

We will seek groups that represent diverse cultural and socio-economic backgrounds to participate in the workshop. The face-to-face workshops will take place in Sheffield or London, depending on which location is accessible to most of our participants.

5.1.2. Workshop data collection methods

We will collect qualitative data via workshops involving around 20 participants, split into 2 groups of approximately 10 members per group, with facilitators for each group. Each group will take part in a half-day facilitated workshop lasting 3 hours including a meal break.

Although running both workshops face-to-face is our preferred method, we will have a contingency plan in place to conduct this research via videoconferencing (e.g. MS Teams or Google Hangouts), which we will run as four groups of 5 people. This contingency plan will be implemented in two scenarios; a) should face-to-face workshops not be possible due to public health restrictions, b) should there be difficulties in recruiting sufficient participants who are able to travel to a face-to-face workshop.

The workshops will explore how women feel about taking part in research using scenarios of different trial designs that are identified within the modelling phase. We will explore likely barriers to recruitment and understand how these may be overcome. Workshops will be run by 2 facilitators, with additional researchers undertaking detailed notes of the discussions. Notes will be written up ensuring that participants are not identifiable. We will write up conclusions of the workshops and share these with participants to ensure that we have captured views correctly.

Workshop participants will be reimbursed for travel expenses if the workshops are held face-to-face and workshop participants will receive a voucher for participating (£30).

5.2 Survey of clinicians

It is also important to ensure that proposed research studies are feasible and considered relevant for informing NHS practice by clinicians who will be providing care for this patient group and potentially recruiting into trials.

6.2.1 Survey methods

We will undertake an online Qualtrics survey of clinicians from a range of relevant settings, including academic and non-academic clinicians, and different specialties involved in caring for these women, to understand their perspectives of willingness to recruit into different study designs, how to communicate information to women and how they would use the results of the trials to change practice.

6.2.2 Survey recruitment

We will not identify participants ourselves but will send the invite via relevant institutions (e.g. British Society for Haematology Obstetric Haematology Group, British Maternal Fetal Medicine Society, Royal College of Obstetricians and Gynaecologists, Obstetric Anaesthetists' Association) in order to comply with GDPR. We will seek advice from the study steering committee to ensure we include all relevant organisations to maximise our sample size. Respondents will provide consent within the survey. Invitations will be sent out by institutions, with up to two reminders.

6.0 Study Supervision

The University of Sheffield will act as Sponsor for the project. A Project Steering Committee (PSC) and a Project Management Group (PMG) will be established to govern the conduct of the project including the qualitative research elements.

6.1 Project Management Group

SD will take overall responsibility for delivering the project. SD will also lead on the decision analytic modelling elements of the study, with AP leading on the rapid reviews to support the modelling and FS leading on the qualitative research with patients and clinicians. A project management group consisting of all co-applicants will meet in person or by teleconference a total of 10 times over the 15 month project to oversee day-to-day management of the study. PPI will be co-ordinated by RC, working with Thrombosis UK, who as a co-applicant will attend project management meetings to ensure that PPI is integrated into all key decisions. A project administrator will support not only the day-to-day running of the project but they will also assist in the administrative tasks related to organising the patient workshops.

6.2 Project Steering Committee

A Project Steering Committee will provide independent oversight to the project. This will consist of an independent chair, independent experts in VTE and obstetrics, independent PPI representatives along with SD, CNP and BH from the study team. Independent members will be recommended to the HTA by the lead applicant with advice taken on suitable candidates from other co-applicants. The Project Steering Committee will be responsible for providing independent oversight of the qualitative research in addition to providing expert input as required to the decision analytic modelling.

7.0 Data handling and record keeping

For the PPI workshop, participant confidentiality will be respected at all times and no participant identifiable data will be available to the research team following the workshop. For the survey, we will collate information about the participant's job role (e.g. specialty, grade) but will not collect any personal data.

All researchers have undertaken mandatory information security and information governance training provided by the University of Sheffield. The project will use the University's Shared Network Filestore as their primary data storage which has been designed for the storage of risk bearing data. The University IT department manages regular back up for disaster recovery purposes.

8.0 Dissemination, outputs and anticipated impact

The aims of our dissemination plan are to improve outcomes for women at risk of VTE during or shortly after pregnancy by;

- Providing an evidence-based case for future research studies that address the evidence gaps that contribute most to uncertainty regarding when to offer thromboprophylaxis to women who are pregnant or who have recently delivered
- Ensuring that any future research studies are feasible to conduct and are acceptable to patients, the public and clinicians.
- Providing evidence on the relative cost-effectiveness of current and alternative thromboprophylaxis strategies to allow national guidelines to be updated if our analysis suggests that thromboprophylaxis strategies can be improved in this patient group based on the existing evidence-base.
- Providing accessible summaries for the public, patients and clinicians about the risks and benefits of thromboprophylaxis in women who are pregnant or who have recently delivered so that the reasons behind any changes in national guidelines are understood by those affected.
- Providing accessible information to the public, patients and clinicians about what further research would be most valuable to provide these groups with the information they need to support the case for further research in this area.

The key output of this project will be 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. Relevant groups would include Thrombosis UK, the RCOG network and the International Society on Thrombosis and Haemostasis (ISTH). 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.

Our research will also produce estimates of the cost-effectiveness of using current and alternative risk assessment tools to determine thromboprophylaxis during pregnancy and in the puerperium given current evidence. This may be used to update current clinical guidelines and change clinical practice. In addition to publishing our findings in clinical journals, we will also use our links with key guideline developers such as NICE and the RCOG to ensure that our research is considered as part of their updating process for existing guidelines. We will also share our research with relevant patient groups, such as Thrombosis UK, to disseminate the research to patients and the public. This will help patients to be informed about the reason behind any changes to current practice that may come out of the research and will also provide patient groups with information to support the case for further research in this area.

In our TiLLI project (HTA15/187/06) we produced information leaflets for patients and clinicians explaining the risks and benefits of thromboprophylaxis, and we published papers that provide summaries that are accessible for clinicians who are not experts in decision-

analytic modelling in the British Journal of Haematology and the Emergency Medical Journal [52-53]. We will undertake similar dissemination activities for this project.

The funding of future research based on our research recommendations would be needed to maximise the impact of this project. A potential barrier to further research would be a lack of knowledge among clinicians, patients and researchers regarding weaknesses in the evidence-base that supports current guidelines. Our dissemination plan will address this by ensuring rapid dissemination of our findings to a wide community of clinicians, researchers and patient organisations to support development of an evidence-based case for further research.

Further research may be hindered by an unwillingness from women to participate in studies that they perceive to place themselves or their pregnancy at risk. We will aim to mitigate this risk through our qualitative work with women to ensure that future research studies included in the expected value of sample information analysis are acceptable to patients whilst providing information that will help patients make better informed decision regarding thromboprophylaxis in the future.

We anticipate that there may be some resistance from guideline developers to changing current practice based solely on the existing evidence as we expect to find that there are weaknesses in the current evidence base. The benefit of our approach is that we will be able to quantify the decision uncertainty based on current evidence and allow guideline developers to make an informed decision about whether to change current practice now or wait for further research to be completed. The methods we will use are consistent with those employed by NICE guideline development groups, which will make it easy for our research to be used to directly inform updates to the existing NICE guidelines and RCOG guidelines without substantial duplication of effort.

The longer term benefits of this project are anticipated to be that thromboprophylaxis will be better targeted to improve the balance of benefits and harms by minimising the risk of unnecessary thromboprophylaxis in lower risk women whilst ensuring that higher risk women are correctly identified and offered thromboprophylaxis. This will be achieved by identifying the evidence gaps that are associated with the greatest decision uncertainty and informing the design of future research studies to address these gaps. It is likely that this will take 5 to 10 years to achieve as it will probably involve further primary research studies being funded and then changes to current practice being achieved through updating clinical guidelines. Earlier impact may be achieved if the analysis produces insights into the relative balance of costs, benefits and harms of thromboprophylaxis based solely on current evidence that could be fed into updates of existing clinical guidelines. Specifically, NICE's 5 year update decision for NICE Guideline 89 is due in 2023 and the RCOG guideline update is currently deferred to 2021.

9.0 Project timetable

The project will take place over 15 months with cost-effectiveness modelling (including rapid reviews of evidence to inform model parameters) and expected value of perfect information analysis in months 1 to 7, qualitative work to inform potential study designs in months 8 to 10, expected value of sample information analysis in months 11 to 12 and write up and dissemination in months 13 to 15. Please see GANTT chart below.

Activity	Jan 2021	Feb 2021	March 2021	April 2021	May 2021	June 2021	July 2021	August 2021	Sept 2021	Oct 2021	Nov 2021	Dec 2021	Jan 2022	Feb 2022	Mar 2022
Systematic reviewing	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX										
Decision model design and parameterisation	XXXXX	XXXXX	XXXXX	XXXXX											
Cost effectiveness analysis and EVPI					XXXXX	XXXXX	XXXXX								
Qualitative work (workshops and surveys)								XXXXX	XXXXX	XXXXX					
EVSI											XXXXX	XXXXX			
Report writing and dissemination													XXXXX	XXXXX	XXXXX

EVPI - expected value of perfect information; EVSI - expected value of sample information

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.

We intend to identify patients and clinicians for the qualitative research through contacts in patient groups and professional clinical interest groups. We do not intend to recruit patients from NHS settings. Therefore we plan to use the University of Sheffield Research Ethics Approval procedure to obtain ethical approval for the PPI workshops and for the survey of clinicians.

12.0 Regulatory approval

Not applicable.

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

As with HTA15/187/06 and HTA13/21/01 we have worked with Thrombosis UK to identify a PPI representative, RC, who has relevant personal experience of VTE. 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/). RC is part of the project team. She has contributed to the drafting of this proposal and will provide PPI at project management meetings. Her role will include advising throughout the project to ensure that it captures outcomes relevant to patients and providing a link to the broader membership of Thrombosis UK. RC 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. We will also engage with the National Childbirth Trust to obtain the views of the broader population of women who may be offered thromboprophylaxis or recruited into future research studies. We will use our connections with relevant PPI groups to recruit two independent PPI members to sit on our steering committee.

Specific areas where PPI has been identified as being important are;

1. Selecting risk assessment tools for inclusion in the modelling: The use of VTE risk-assessment needs to be acceptable to women and the public. If provision of thromboprophylaxis 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 women.

Our PPI co-applicant will review the risk assessment tools identified in the literature review and, in consultation with the wider PPI groups, consider whether the tools and their use for determining thromboprophylaxis are likely to be acceptable to patients and the public. This process may highlight where a particular tool needs to be adapted for specific groups or where the language needs to be carefully considered to ensure it is acceptable to patients.

2. Ensuring that 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. Our PPI co-applicant will discuss key assumptions in the model with the project team to ensure that they reflect patient and public values. They will draw upon their own experiences and will consult with the wider PPI groups when making their judgements. They will help to determine whether certain costs and outcomes of importance 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 thromboprophylaxis is as effective as subcutaneous thromboprophylaxis.
3. Ensuring that the qualitative work with women is a) conducted in a manner which is sensitive, ethical and appropriate for participants, b) designed to capture issues important to women and c) maximises the possibility for capturing the breadth of viewpoints across groups that represent diverse cultural and socio-economic backgrounds, including across varied geographic locations across the UK.
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 co-applicant will assist in developing these outputs and will consult with the wider PPI groups to ensure comprehensibility and relevance to patients and the public. The development of decision aids and other methods for involving patients in assessing their own risk and determining their preferences regarding prophylaxis is beyond the scope of this project. However, the PPI co-applicant will consult with a broader group of patients via Thrombosis UK 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

CNP is a consultant obstetric physician and Professor of Obstetric Medicine. She was lead developer of the RCOG thromboprophylaxis guidelines. BH is a consultant haematologist and Professor of Thrombosis & Haemostasis & Medical Director of Thrombosis UK. BH was a guideline committee member for NICE Guideline 89. CNF and BH have extensive clinical expertise and research expertise in pregnancy related VTE prevention. JD is a lecturer in obstetrics and gynaecology with an interest in obstetric haematology and secondary research expertise in VTE in pregnancy. SG, SD, AP and BH were part of the core team that successfully delivered HTA15/187/06 which used decision analysis modelling to determine the cost-effectiveness of VTE thromboprophylaxis for people with lower limb immobilisation. SG, SD, BH and AP are also currently grant holders on an NIHR HTA funded project on the cost-effectiveness of VTE risk assessment tools for hospital inpatients (NIHR127454). SG, CNP and BH also undertook the DiPEP study (HTA13/21/01), which used decision analysis modelling to show that a clinical prediction rule for PE 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. FS has significant research experience in undertaking

qualitative work within the emergency care setting, including undertaking interviews and focus groups with clinicians and patients. JH has extensive experience of conducting statistical analyses to inform decision analytic models and in methodological development for multivariable prediction modelling. MC conducted the literature searches that informed the TiLLI model.

16.0 Success criteria and barriers to proposed work

The success of the decision analytic modelling will be judged by the delivery of the key model outputs, i.e. an estimate of the cost-effectiveness of using the RCOG and any alternative risk stratification tools, identification of key drivers of decision uncertainty and an estimate of the value of one of more potential future research studies. These outputs are clearly deliverable within the time, expertise and resources outlined in this proposal. Although the model inputs may be limited by the published evidence available, where these are lacking we will be able to use clinical expert elicitation to determine both the expected value of those parameters and the current uncertainty around those values. We will then be able to quantify the decision uncertainty inherent from the uncertainty around those inputs and whether further research to reduce these uncertainties is worthwhile.

The success of the qualitative work will be determined largely by whether we are able to involve the right people to provide views that represent those of patients and clinicians likely to be involved in future research or whose treatment or clinical practice is likely to be affected by future changes to the use of thromboprophylaxis informed by that research. We will mitigate these risks by ensuring that we allow sufficient time to identify participants and by making sure that we connect with relevant groups of patients and clinicians through appropriate intermediate groups.

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