Thromboprophylaxis for lower limb immobilisation: An evidence synthesis

Summary of Research:

DESIGN: Systematic review, meta-analysis, decision-analytic modelling and value of information analysis.

STRATEGY FOR REVIEWING LITERATURE: Systematic reviews will be used to identify (1) randomised controlled trials (RCTs) and controlled clinical trials (CCTs) that evaluate the efficacy or effectiveness of thromboprophylaxis for lower limb immobilisation, (2) any studies of risk-stratification tools for VTE in lower limb immobilisation and (3) data sources for the decision-analytic model, such as studies that estimate the association between efficacy and effectiveness outcomes and studies that estimate the risk of bleeding-related adverse outcomes. Methodological quality will be assessed using relevant checklists for each included study type.

TARGET POPULATION: Adults with isolated lower limb injury requiring temporary immobilisation of any form.

HEALTH TECHNOLOGIES BEING ASSESSED: (1) Chemical thromboprophylaxis agents for patients with lower limb immobilisation, compared to placebo, no treatment or alternative treatment; (2) Risk prediction tools that could be used to select patients with lower limb immobilisation for thromboprophylaxis.

MEASUREMENT OF COSTS AND OUTCOMES: Meta-analysis will estimate the efficacy (symptomatic or asymptomatic venous thromboembolism (VTE)) and effectiveness (clinically significant VTE, major bleeding or mortality) of thromboprophylaxis. A systematic review and consensus elicitation of expert opinion will identify risk-prediction tools for VTE and estimate the accuracy of these methods. Further literature searches will be used to estimate key parameters for modelling. Decision-analytic modelling will simulate the management of a cohort of people with lower limb immobilisation to estimate (1) the clinical effectiveness of thromboprophylaxis, in terms of clinically significant VTE events, treatment-related adverse events and quality-adjusted life years (QALYs) accrued; (2) the cost-effectiveness of different strategies for selecting patients for thromboprophylaxis (including treating all, treating none and risk-based treatment), in terms of the incremental cost per QALY gained by each strategy compared to the next most effective alternative on the efficiency frontier; and (3) the expected value of information of further primary research.

PROJECT TIMETABLE: The project will be completed over 12 months, with the first six months focusing on systematic reviews and meta-analysis, and the second six months focussing on modelling.

EXPERTISE IN THE TEAM: The team involves a collaboration between methodological experts at the University of Sheffield who have successfully delivered similar projects in the past and international experts in prevention, diagnosis and treatment of VTE.

Background and Rationale:

What is the problem?

Venous thromboembolism (VTE) is a documented global health burden. Within the last decade, VTE has resulted in more deaths than prostate cancer, breast cancer, road traffic accidents and AIDS combined [Cohen 2007]. It is the 2nd commonest cause of vascular death after heart attack [Raskob 2014].

Temporary immobilisation of lower limb injury in a plaster cast or fitted boot is an important cause of potentially preventable VTE. Case reports, observational cohort studies and randomised controlled trials suggest that patients with lower limb immobilisation have a significant risk of VTE, morbidity and death [Chen 2006, Nilsson-Helander 2009, Healy 2010, Makhdom 2013a, Makhdom 2013b, Meek 2012, Patil S 2007]. Preventative treatment with anticoagulant drugs (thromboprophylaxis) could reduce this risk, but these drugs carry risks of adverse events, in particular an increased risk of intracranial or gastrointestinal bleeding. Thromboprophylaxis can only be justified if the benefits of reducing VTE outweigh the risks of bleeding and other side effects. Furthermore, the considerable expense of providing thromboprophylaxis to all patients with lower limb immobilisation can only be justified if it delivers meaningful improvements in health at an acceptable cost. The risk-benefit and cost-benefit ratios of thromboprophylaxis could be improved if patients were selected for treatment on the basis of risk factors for VTE, but this requires accurate and usable risk assessment methods.

What is the current evidence?

Low molecular weight heparin (LMWH) has the largest evidence base in this patient cohort and has been the subject of a recent Cochrane review, summarised below [Testroote 2014]. LMWH, a daily injectable treatment, can be painful, inconvenient and causes bruising. Direct oral anticoagulant (DOAC) medications may offer a more acceptable alternative but there are as yet no published contemporary studies using DOAC medications in this group of patients. Trials and cohort studies using aspirin are limited and have failed to demonstrate benefit in reducing the risk of VTE in people with lower limb immobilisation [Gehling 1998, Braithwaite 2015].

The Cochrane review of LMWH as an anticoagulant to prevent DVT in people with lower limb immobilisation was first published in 2008 and updated in 2014 [Testroote 2014]. The updated review included six randomised controlled trials (RCTs), published between 1993 and 2007, with a total of 1490 patients. The primary outcome was symptomatic or asymptomatic DVT, PE, or any combination of these items, as a combined symptomatic venous thromboembolism (VTE) endpoint. This is an efficacy rather than an effectiveness outcome as it includes VTE detected through asymptomatic screening that are of uncertain clinical importance. The incidence of the primary outcome ranged from 4.3% to 40% in the control group and from 0% to 37% in the prophylaxis group (overall 134/740 [18.1%] versus 75/750 [10.0%], OR 0.49, 95% confidence interval (CI) 0.34 to 0.72). Symptomatic VTE was observed in 2/658 (0.3%) patients receiving LMWH versus 16/645 (2.5%) patients in the control group (OR 0.16; 95% CI 0.05 to 0.56). PE was a rare complication in immobilisation, with only five cases being reported in the control groups and only two of these being proven by imaging. No mortality was reported in the six included studies.

Since the Cochrane review was updated a further trial of LMWH in low risk patients following lower limb surgery has reported overall event rates in control and thromboprophylaxis cohorts of 2.5% versus 1.8% for clinically important VTE (absolute risk reduction 0.8%, 95% CI -2.0 to 3.0) [Selby 2015]. This trial excluded high risk patients, included only post-operative cases and ceased recruitment following interim analysis after 265 patients were recruited against a target of 700.

The Cochrane review therefore needs updating to include recent data but other uncertainties need to be addressed. Operated patients often receive thromboprophylaxis while in hospital. A subgroup analysis of non-operated patients in the Cochrane review showed a potentially greater treatment effect, with rates of 0% to 11.8% for the primary outcome in the LMWH group and 4.3% to 17.3% for the controls (OR 0.35; 95% CI 0.19 to 0.62).

The main treatment-related adverse event is bleeding. In the Cochrane review major bleeding was reported in only two patients receiving LMWH and one receiving placebo. Meta-analysis undertaken for NICE guidance showed [NICE 2010] that LMWH thromboprophylaxis was associated with an increased risk of major bleeding across all indications (1.9% v 1.1%, odds ratio 1.82 (1.33 to 2.47)). However, this analysis included large numbers of medical and surgical inpatients who are likely to be at higher risk of bleeding than those undergoing lower limb immobilisation.

A number of risk assessment strategies have been developed to select patients for thromboprophylaxis. These include the Leiden–Thrombosis Risk Prediction for patients with cast immobilization score (LTRiP, derived from a large population-based case–control study [Nemeth 2015]), the Plymouth VTE assessment tool (derived by expert consensus [Nokes 2009]), the GEMNet guidance (produced in 2012 following a short cut systematic review of the applicable literature and expert consensus [Roberts 2013]) and the Stockport risk assessment tool (supported by the British Orthopaedic Association Standards for Trauma developed by individual expertise, http://www.boa.ac.uk/publications/stockport-vte-lower-limb-immobilisation/). There have to date been no external validation studies of these tools.

In summary, the existing evidence suggests that thromboprophylaxis can reduce the risk of DVT but it is not clear whether this translates into meaningful health benefit for patients, justifies the risk of treatment-related adverse events or is cost-effective. Risk assessment strategies could improve the ratio of benefit to risk and cost, but these have not been validated. We are not aware of any economic analysis of thromboprophylaxis for lower limb immobilisation.

What is current practice?

The limited evidence is reflected in substantial variation in both the use of thromboprophylaxis and the use of risk assessment. In many European countries thromboprophylaxis is routine [Struijk-Mulder 2010] whereas in North America recent guidelines interpret the literature as too weak to justify intervention and actively discourage thromboprophylaxis [Falck-Ytter 2012]. Current UK guidance from the National Institute for Health and Care Excellence (NICE) recommends a 'halfway house' of gestalt risk assessment and shared decision-making [NICE 2010]. This variation fosters clinical uncertainty and has led to a UK position of variable practice, using variable drug regimens throughout the NHS, with limited understanding of the safety, efficacy or cost effectiveness of local protocols.

There has been a recent move towards using the DOACs for this indication, despite the lack of applicable research or licence, based on convenience and cost implications. Personal correspondence following the last Royal College of Emergency Medicine Clinical Studies Group meeting would suggest the DOAC drugs are currently being used for this indication in at least four NHS trusts.

Risk assessment strategies in current use include the Plymouth VTE assessment tool, national guidance produced in 2012 for the Royal College of Emergency Medicine (RCEM), and several expert derived pathways supported by the British Orthopaedic Association Standards for Trauma. Uptake seems to be poor as a result of equipoise/uncertainty and many centres utilising these tools have pragmatically amended them without published supporting evidence.

What is the potential impact of thromboprophylaxis for lower limb immobilisation?
The health and economic impact of VTE thromboprophylaxis for lower limb immobilisation can be estimated using local survey data, previous research and the recent Royal College of Emergency Medicine national audit programme. A typical type 1 emergency department is likely to see, immobilise and discharge at least 360 patients per year with lower limb injury [Horner 2015]. In England currently there are 194 type 1 emergency departments (http://www.birmingham.ac.uk/Documents/college-mds/haps/projects/HCNA/001HCNAchap1.pdf). This generates a relevant annual patient population of just under 70,000 patients. The exclusion of type 2 emergency departments, minor injury units and walk-in centres likely renders this a gross underestimate of the population.

The cost of prophylactic dose LMWH is £2.82 per daily subcutaneous injection. When commenced, prophylaxis is recommended for the duration of immobilisation, usually a period of up to 6 weeks (42 days). As such, the net drug costs per patient is approximately £118.44. This figure would be higher for morbidly obese patients (who may require larger doses or twice a day injections) and excludes the additional costs of district nursing support, blood tests and monitoring, patient transport to collect prescriptions and patient time/inconvenience. These figures suggest annual NHS drug costs of £8.29million for all eligible patients to receive thromboprophylaxis. This could be reduced by using prophylaxis based on a risk assessment tool. Recent estimates suggest simple NICE guidance would have a marginal impact while use of the GEMNet stratification tool may reduce prescription and therefore costs by 50% [Horner 2015]. More onerous cumulative tools, such as the Plymouth VTE score may reduce those needing chemical prophylaxis to approximately 20% of the target population. However, these tools require the input of additional clinical time for careful risk stratification and generate additional staff costs.

The potential health impact of thromboprophylaxis is more challenging to estimate due to uncertainty around estimates of effectiveness and the baseline risk of clinically significant VTE without thromboprophylaxis. Applying estimates of VTE rates without thromboprophylaxis from the Cochrane meta-analysis (summarised above) to the number of immobilised patients suggest that without thromboprophylaxis around 12,670 (18.1%) will have VTE (asymptomatic or symptomatic) per year across the NHS and around 1750 (2.5%) will experience symptomatic VTE. While some of these patients may be diagnosed and treated acutely, many will attribute their symptoms to the limb injury and present to hospital late, or not at all. Untreated VTE has previously been shown to carry a short term mortality rate of up to 30%, principally due to pulmonary embolism (PE). Even if accurate diagnosis of VTE occurs in the acute phase, long term complications can arise. Post phlebitic leg syndrome leading to chronic pain and swelling can be seen in up to 40% of deep vein thrombosis (DVT) cases, and chronic thromboembolic pulmonary hypertension seen in between 1 to 4% PE cases, even with initial therapeutic anticoagulation [Heit 2001 and Guérin 2014]. These patients often need costly long term follow up and specialist intervention. There is also a significant psychological burden from disease and recurrent clinical symptoms are commonplace.

If estimates of effectiveness from the Cochrane meta-analysis are accurate and thromboprophylaxis were provided to 70,000 eligible patients per year 1540 cases of symptomatic VTE or 5670 cases of symptomatic or asymptomatic VTE could be prevented. The benefit of reducing VTE would need to be balanced against a potential harm of causing between 100 and 560 additional major bleeding events (depending upon whether the risk difference is 0.15% estimated from the Cochrane meta-analysis of patients with lower limb immobilisation or 0.8% estimated by NICE across all patients) and the costs of providing thromboprophylaxis outlined above.

Evidence explaining why this research is needed now:

Research recommendations in current guidance
Current international guidelines have clear recommendations for research in this area. NICE CG92 contains research recommendation 2.3 specifically addressing the need for research into the clinical and cost effectiveness of pharmacological prophylaxis for reducing the risk of VTE in patients with lower limb plaster casts [NICE 2010]. The 2012 American College of Chest Physicians (ACCP) guidance contains a grade 2C recommendation on the topic and highlights the extensive list of exclusion criteria from previous research [Falck-Ytter 2012]. In addition, Royal College of Emergency Medicine guidelines and several additional review papers published in specialist journals have called for further research to address the equipoise [Roberts 2013, Ettema 2008, Nokes 2009].

What sort of research is required?
We propose an evidence synthesis project, involving systematic review, meta-analysis, elicitation of expert consensus, decision-analytic modelling and value of information analysis. This provides a relatively quick and inexpensive way of drawing together all the existing evidence in a rational and explicit manner, exploring the trade-off between treatment harms and benefits, exploring the trade-off between sensitivity and specificity in risk assessment, estimating the cost-effectiveness of different strategies and estimating the cost-effectiveness of different options for future primary research.

We do not propose primary research to answer the research question at this stage. A large pragmatic trial could determine whether thromboprophylaxis is effective. However, there would be substantial risks associated with proceeding to a trial before undertaking pre-trial modelling. A trial would need in excess of 1000 participants to detect a plausible difference in a clinically meaningful outcome, given the low rate of symptomatic VTE observed in the control groups of previous trials. The failure of an internationally-recognised Canadian team to achieve recruitment targets in the most recent trial [Kelly 2015] highlights the potential risk of failure. Furthermore, it is not clear whether a risk-based approach might be better than thromboprophylaxis for all, and if so, what risk-based approach should be used. A cohort study to develop or validate a risk-assessment tool may be helpful but it is not clear whether participants in such a study should receive thromboprophylaxis or how a risk assessment method should weigh the relative benefits of optimising sensitivity and specificity when there is inevitably a trade-off between these parameters.

Aims and objectives:
This project aims to use existing data to estimate the effectiveness and cost-effectiveness of different strategies for providing thromboprophylaxis to people with lower limb immobilisation, determine priorities for future primary research and estimate the expected value of information provided by future primary research. Our specific objectives are:

1. To estimate the efficacy of thromboprophylaxis for preventing symptomatic or asymptomatic VTE in people with lower limb immobilisation and the effectiveness for preventing clinically important VTE.
2. To identify tools for predicting the risk of venous thromboembolism in people with lower limb immobilisation and estimate the accuracy of these tools.
3. To estimate the clinical effectiveness of strategies for providing thromboprophylaxis (including treatment for all, treatment for none and risk-based treatment), in terms of overall adverse outcomes avoided or incurred by treatment, and quality-adjusted life years (QALYs).
4. To estimate the cost-effectiveness of strategies for providing thromboprophylaxis, in terms of the incremental cost per QALY gained by each strategy compared to the next most effective strategy on the efficiency frontier.
5. To estimate the expected value of information provided by further primary research.

Research Plan:
We will use the following methods:

1. Systematic review and meta-analysis of RCTs and controlled clinical trials (CCTs) of thromboprophylaxis for people with lower limb immobilisation
2. Systematic review and expert consensus methods to identify risk-prediction tools, estimate the accuracy of these tools for predicting VTE events and estimate key parameters for modelling
3. Decision analysis modelling of clinical effectiveness and cost-effectiveness
4. Value of information analysis

Health technologies being assessed:
The health technologies are (1) chemical thromboprophylaxis agents for patients with lower limb immobilisation and (2) risk prediction tools that could be used to select patients with lower limb immobilisation for thromboprophylaxis. We will not consider mechanical thromboprophylaxis as plaster cast immobilisation precludes the application of devices to support the calf muscle pump and/or stimulate blood flow in the leg.

Chemical thromboprophylaxis in this group has been principally studied using subcutaneous low molecular weight heparin (LMWH). This is a well-established method of thromboprophylaxis and was the method used in the recent Cochrane review [Testroote 2014]. Several different agents are available and equivalent doses are used for hospital inpatients, extended spectrum groups (such as post-operative orthopaedic cases) and pregnant patients with a strong evidence base. LMWH is well tolerated in these groups and has clear acceptability for staff and patients, given the widespread utilisation across the NHS.

LMWH has some limitations. As an injection only agent, it causes a degree of pain and discomfort which is poorly tolerated by some. It also requires administration and as such patients unhappy to self-inject or elderly patients often require expensive and time consuming additional district nursing support to facilitate home medication. Lastly, there are associated complications with LMWH, principally those of bleeding and rarely Heparin induced thrombocytopenia.

Aspirin use has also been studied in this patient group, albeit with limited proof of efficacy. The attractions and benefits of aspirin include familiarity and availability, cost (10 pence daily) and clearly understood side effect profile. However, there are only two studies assessing aspirin in this context; a small pilot comparison to LMWH and a before and after interventional cohort study. Both studies fail to demonstrate any potential benefit with aspirin use and offer no clear data on clinical or cost effectiveness [Gehling 1998, Braithwaite 2015]. To our knowledge, there are no published trials of aspirin compared to placebo.

Lastly, the DOAC medications are of increasing interest to clinicians regarding this topic and offer a third option for thromboprophylaxis. There are no randomised controlled trials comparing DOACs to placebo or LMWH in this population and no observational studies assessing VTE rates in centres opting to use these agents as thromboprophylaxis for patients in temporary immobilisation. However, the DOACs present an attractive option based on applicable evidence from extrapolated orthopaedic surgical thromboprophylaxis trial in addition to their inherent acceptability and practicality [Lassen 2010a, Lassen 2010b, Raskob 2012]. DOAC prophylaxis regimens can be taken orally once or twice daily, have no additional specific contraindications from LMWH, are convenient, reliable and appear acceptable to staff and patients.

We will seek effectiveness evidence for all potential methods of providing chemical thromboprophylaxis but anticipate that the available evidence will relate to LMWH. We will use modelling to explore whether DOACs offer advantages in terms of cost-effectiveness, if equivalent effectiveness to LMWH is assumed or can be demonstrated.

Risk prediction 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. Existing risk prediction rules use either a flowchart or checklist to guide the user through the process of risk assessment and lead to a decision regarding 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. 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.

Design and theoretical/conceptual framework:
Existing knowledge suggests that thromboprophylaxis can reduce the incidence of symptomatic or asymptomatic VTE in patients with lower limb immobilisation. Research is required to determine whether this evidence of efficacy translates into clinical effectiveness and cost-effectiveness, whether further primary research is required to increase certainty, priorities for future primary research and cost-effectiveness of future research.

Our proposed research will synthesise existing evidence to increase our knowledge as follows:

1. A systematic review and meta-analysis will update the Cochrane review estimate of the efficacy of thromboprophylaxis for reducing symptomatic or asymptomatic VTE and the effectiveness of thromboprophylaxis for reducing clinically important VTE.
2. A systematic review and consensus elicitation of expert opinion will identify tools that could be used to select patients to thromboprophylaxis according to their risk of VTE and estimate the accuracy of these methods.
3. Further literature searches will be used to obtain estimates of key parameters for modelling, such as the association between efficacy outcomes (i.e. asymptomatic VTE detected by screening) and effectiveness outcomes (i.e. symptomatic VTE, post-thrombotic syndrome, VTE-related death and health utility).

4. Decision-analytic modelling will estimate the clinical effectiveness of thromboprophylaxis by simulating the management of a cohort of people with lower limb immobilisation and estimating the benefits and harms of treatment, in terms of reduced risk of VTE events, increased risk of treatment-related events and QALYs.
5. Decision-analytic modelling will estimate the cost-effectiveness of different strategies for selecting patients for thromboprophylaxis, including treating all, treating none and risk-based treatment, in terms of the incremental cost per QALY gained by each strategy compared to the next most effective strategy on the efficiency frontier.
6. Decision-analytic modelling will be used to estimate the expected value of information of further primary research and determine the optimal direction of future research (for example, whether the primary research priority should be a pragmatic randomised trial of thromboprophylaxis or a cohort study to evaluate risk-stratification methods).

Target population:
The study population will be defined as including adults >16 years of age who have isolated lower limb injury requiring temporary immobilisation in plaster cast, fitted boot or non-weight bearing with crutches. This definition will be used to select relevant studies in the literature review and define the hypothetical population in the modelling.

Exclusion Criteria:
We anticipate that the following groups will be excluded from studies identified in the literature review (although we will not specify that studies must use these exclusion criteria) and will be excluded from the hypothetical modelling population:

1. Any patient requiring hospital admission >12 hours (this group should undergo formal risk assessment and stratified thromboprophylaxis as a hospital inpatient)
2. Patients already receiving prophylactic or therapeutic dose anticoagulation
3. Patients with significant contraindications to thromboprophylaxis, to include end stage renal failure (eGFR <15ml/min), significant hepatic impairment associated with coagulopathy, active bleeding or significant risk of major bleeding (recent haemorrhagic stroke, bleeding peptic ulcer, oesophageal varices, recent spinal, brain or opthalmic surgery, significant head injury)

Setting/context:
Thromboprophylaxis for lower limb immobilisation is typically provided in the emergency department or orthopaedic outpatient ('fracture') clinics. In some other European settings these patients will have been assessed and recruited to research within a vascular specialist or haematology outpatient setting. Studies in these settings will be included for consideration within the literature review providing they meet pre-specified inclusion criteria and are applicable to the NHS.

Search strategy
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).

Systematic reviews will be used to identify (1) RCTs and CCTs that evaluate the efficacy or effectiveness of thromboprophylaxis for lower limb immobilisation, (2) any studies of risk-stratification tools for VTE in lower limb immobilisation and (3) data sources for the decision-analytic model, such as studies that estimate the association between efficacy and effectiveness outcomes and studies that estimate the risk of bleeding-related adverse outcomes.

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.

Review strategy

For the main systematic review of the efficacy and effectiveness of thromboprophylaxis we will update the searches of an existing Cochrane review [Testroote 2014] and select studies that fulfil the following criteria:

1. Design : RCTs and CCTs
2. Population: Patients receiving lower limb immobilisation
3. Intervention: Chemical thromboprophylaxis
4. Control: Placebo, no treatment or alternative treatment
5. Outcome: Symptomatic or asymptomatic DVT, PE, major bleeding or mortality

For the systematic review of VTE risk-prediction tools in lower limb immobilisation we will search the electronic databases and other sources from inception to present and select any studies that fulfil the following criteria:

1. Design: Any
2. Population: Patients receiving lower limb immobilisation
3. Intervention: Any risk-prediction method for VTE
4. Outcome: Symptomatic or asymptomatic DVT, PE or mortality

Literature searches for key parameters in the model will be developed as the project progresses, in response to the needs of the model.

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. The decisions will be coded and recorded on a reference management database by the Project Manager.

Data extraction

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. Moreover, as the main systematic review of the efficacy and effectiveness of thromboprophylaxis updates an existing review [Testroote 2014] all relevant data will be extracted from the review in the first instance, but will be cross checked for accuracy with the original papers. If necessary, additional data will be extracted from the original papers.

The following standardised data will be extracted from each eligible study: date, setting, population characteristics (age, sex, reason for immobilisation), intervention (thromboprophylaxis used, duration of treatment), comparison (placebo, no treatment, alternative treatment), primary outcome measure and results of key outcomes (symptomatic and asymptomatic DVT, PE, mortality,

major and non-major bleeding, post-thrombotic syndrome, heparin induced thrombocytopenia). If appropriate, the authors of the primary studies will be contacted for missing data.

Outcome definitions

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 or peroneal veins of the leg.

Asymptomatic DVT: a DVT found on routine surveillance screening of the leg, in the absence of symptoms such as leg pain, swelling or discolouration.

Symptomatic DVT: a DVT found in a patient with symptoms of leg pain, swelling or discolouration.

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].

Non-major bleeding: as defined by International Society of Thrombosis and Haemostasis [Schulman 2005].

Quality assessment

The quality of all relevant studies will be assessed using the Cochrane Risk of Bias (ROB) tool for randomised controlled trials [Higgins 2011] and the Cochrane Risk of Bias in Non-randomized Studies of - Interventions (ROBINS-I) assessment tool for controlled clinical trials [Sterne 2016]. The quality of any studies of risk-prediction methods will be assessed using an adapted version of the framework described by Altman et al [Altman 2001] that we have used in a previous evidence synthesis projects [Goodacre 2013, Ward 2013].

Data synthesis:

Meta-analysis will be used to estimate the summary effect of thromboprophylaxis upon the key outcomes listed above. We will specifically estimate efficacy, in terms of the effect on asymptomatic and symptomatic VTE, and effectiveness, in terms of the effect on clinically significant VTE, major bleeding and mortality.

All analyses will be performed using a Bayesian framework. Binary outcome measures will be analysed using a Binomial likelihood function with a logit link function; this models the observed data exactly and avoids assuming asymptotic normality for the sample treatment effect in each study. A random effects model will be used to model the population specific treatment effects in each study. The models will be completed by giving the uncertain parameters non-informative (or reference) prior distributions. However, when there are few studies in a particular meta-analysis, reference prior distributions for variance parameters are not uninformative; in such situations, weakly informative prior distributions will be used to represent reasonably plausible prior information but without having to assume that the between-study standard deviation is zero.

Results will be presented as (median) odds ratio from the random effects mean posterior distribution (and 95% credible interval), and the (median) between-study standard deviation from its posterior distribution (and 95% credible interval). In addition, to account for heterogeneity the predictive distribution of the effect in a randomly chosen new study will also be presented. Where possible, heterogeneity of treatment effects between studies will be explored using meta-regression. If appropriate data are available we will explore the following potential treatment effect modifiers: (1) Population characteristics (proportion male, baseline risk of VTE); (2) Type of injury (fractures, Achilles tendon rupture, other soft tissue injury); (3) Treatment of injury (surgical v

conservative, above v below knee immobilisation); (4) Thromboprophylactic agent used; (5) Duration of thromboprophylaxis.

Where there are multiple treatments being compared across multiple studies but with common treatments that link the studies, a network-meta-analysis will be performed. In this case, consideration will be given to assessing inconsistency between direct and indirect estimates of treatment effect where arms form feedback loops in the network of evidence.

We have not planned *a priori* to undertake data synthesis on any data sought in the literature searches for the purposes of populating the decision analysis model (such as estimates of the sensitivity and specificity of risk-assessment methods or studies estimating the risk of clinically meaningful outcomes associated with asymptomatically detected DVT). We will review any available studies and select the study that expert opinion judges to best fulfil the requirement of a valid and precise estimate that in most applicable to our defined study population. If there is uncertainty in this judgment then sensitivity analysis will be undertaken using estimates from alternative data sources.

Expert consensus methods

We will use expert consensus methods to identify and refine potential risk-prediction tools for VTE in people with lower limb immobilisation. We have used a similar approach to develop clinical decision rules for evaluation in a current HTA-funded project (DiPEP, HTA 13/21/01). We will assemble a group of experts in haematology, emergency medicine and orthopaedics. A modified Delphi survey will be used to identify existing risk-prediction tools and select risk factors that the experts consider likely to be sufficiently accurate, measurable and frequent, and thus most useful for risk prediction. The Delphi technique will consist of a series of consecutive structured surveys of experts' opinions, interspersed with moderated feedback to participants, aiming to reach a concordant group response. An internet based Delphi process will subsequently be conducted using an established commercial online survey platform (SmartSurvey) and pre-piloted questionnaires. Any risk-prediction tools or risk factors that have consensus support will then be considered at a round-table expert consensus meeting. The experts will select existing risk-prediction tools or construct risk-prediction tools from the selected risk factors. The aim will be to identify up to five different risk-prediction tools that reflect a range of alternatives in terms of the trade-off between sensitivity and specificity for predicting VTE. If existing data are inadequate to estimate sensitivity and specificity for each rule the expert group will be asked to produce a consensus estimate of sensitivity and specificity for each rule with associated estimates of the uncertainty around these parameters.

The elicitation will follow a formal, transparent and documented process according to the Sheffield Elicitation Framework (SHELF) protocol (http://www.tonyohagan.co.uk/shelf/). We will assemble a panel of 4-8 clinical experts in haematology, orthopaedics and emergency medicine. They will be presented with summaries of existing data estimating the risk of developing DVT following lower limb immobilisation, any available data estimating the effect of clinical predictors upon this risk (for example, Wahlsten 2015), and estimates of the prognostic value of clinical risk predictors for DVT in the general population or other at-risk populations, such as post-operative patients or medical inpatients. They will then be presented with case scenarios representing the key risk strata for the selected risk prediction methods and be asked to estimate the risk of developing DVT without thromboprophylaxis.

When multiple parameters are involved such that expert beliefs' about the true value of one parameter affect expert beliefs' about the true value of another parameter (i.e. the parameters are correlated), the problem will be structured so that one parameter is defined as a function of another parameter. We will also explore innovative ways of discouraging over-optimistic in expert

assessment of prognostic performance by, for example, anchoring or linking estimates so that positive predictive value cannot be increased using a particular threshold without sacrificing negative predictive value.

Decision analysis modelling:
We will build a decision-analytic model to simulate the management of a hypothetical cohort of patients undergoing lower limb immobilisation. The study population will be defined as outlined in the Target Population section above. The characteristics of the population (age, sex, reason for immobilisation, duration and method of immobilisation, 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 thromboprophylaxis, including treatment for all, treatment for none and treatment based on VTE risk prediction. The process for identifying potential risk-based strategies will be as follows:

1. Literature searches, a survey of current NHS practice and contact with external experts will identify strategies that have been empirically tested or are currently used in practice.
2. Expert consensus methods will be used to select up to five strategies reflecting a range of trade-offs between sensitivity and specificity for predicting subsequent VTE.

Each patient in the cohort will be attributed characteristics by sampling from the estimated distribution of the characteristic. Each strategy will be applied to each patient in the cohort to determine whether they receive thromboprophylaxis or not, according to their characteristics and the treatment criteria for the strategy under consideration. Patients who are given thromboprophylaxis are then at risk of treatment-related adverse events with a probability determined by our meta-analysis. A sensitivity analysis will be undertaken in which the risks of thromboprophylaxis are alternatively estimated from existing meta-analysis of the risks of thromboprophylaxis in the general inpatient population [NICE 2010].

Simulated patients will also be placed into one of the following four categories by sampling from a distribution estimated from the risk of developing clinically significant VTE with and without thromboprophylaxis, derived from the meta-analysis:

1. Thromboprophylaxis is given and VTE occurs
2. Thromboprophylaxis is given and VTE does not occur
3. Thromboprophylaxis is not given and VTE occurs
4. Thromboprophylaxis is not given and VTE does not occur

This then determines whether each patient develops clinically significant VTE or not. Primary analysis will estimate rates of symptomatic DVT, PE and mortality for each group using the meta-analysis. A sensitivity analysis will use estimates of asymptomatic VTE from the meta-analysis combined with other data sources (studies estimating the association between asymptomatic and clinically important VTE) to estimate the risk of clinically significant VTE.

The sensitivity and specificity of each method for predicting development of DVT will be estimated by expert consensus (along with an estimate of the uncertainty around these parameters), with reference to data from the literature review where available. In doing this we will force the experts to assume a trade-off between sensitivity and specificity that reflects a typical Receiver-Operator Characteristic curve for clinical risk prediction methods. This will ensure that the comparison of strategies genuinely examines the trade-off between sensitivity and specificity, and is not undermined by unrealistic estimates of optimal risk prediction.

Each patient in the cohort will accrue costs and outcomes determined by whether they receive thromboprophylaxis or not, whether they developed clinically significant VTE, and whether they suffer any treatment-related adverse events. We will update estimates from our previous model of diagnostic strategies for DVT [Goodacre 2006] to estimate costs of care and quality-adjusted life expectancy related to VTE and treatment-related adverse events.

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].

The methodology most appropriate for this project will be decided in the context of the data found within the literature review and the advice from our team of clinical and subject experts. The health economics lead (SD) has published cost-effectiveness analyses using Markov [Bansback 2007] and decision tree methodologies [Davis 2012] and a Decision Support Unit technical guide on the use of patient-level simulation.

Parameter estimates for the model will be obtained from a combination of sources, including the published literature. 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.

To calculate the QALY loss associated with clinical outcomes (symptomatic DVT, PE, post-thrombotic syndrome, thromboprophylaxis-related adverse events) we will search for literature- based estimates of the impact of these outcomes on health-related quality of life (HRQoL). Where they exist, generic preference based estimates of utility from instruments such as the EuroQol-5 Dimension (EQ-5D) will be used as per NICE guidance on the methods of technology appraisal [NICE 2013].

Differences in resource use between the different thromboprophylaxis strategies, including medications, clinical time to implement risk stratification, management of DVT-related adverse events and management of thromboprophylaxis-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].

The baseline economic analysis will assume that LMWH is used for thromboprophylaxis. A secondary analysis will be undertaken in which DOACs are used instead to determine whether the cost-effectiveness of thromboprophylaxis strategies depends on the agent used. Costs of prescribing and administering DOACs will replace the costs of prescribing and administering LMWH. Initial analysis will assume that the relative effectiveness and risks of adverse outcomes with DOACs and LMWH can be extrapolated from comparisons in other settings. Sensitivity analysis will test whether conclusions are robust to variation in these assumptions.

Analyses will be undertaken to identify the key parameters determining the cost-effectiveness of the different thromboprophylaxis treatment 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.

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 (for example, whether the primary research priority should be a pragmatic randomised trial of thromboprophylaxis or a cohort study to evaluate risk-stratification methods). 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 et 2015].

Dissemination and projected outputs:
The main outputs of this project will be estimates of clinical effectiveness and cost-effectiveness of thromboprophylaxis for lower limb immobilisation and an estimate of the expected value of information provided by further research. We anticipate that the research will determine future NICE guidance with respect to the use of thromboprophylaxis in lower limb immobilisation and will determine the direction of future primary research.

We will target the projected outputs of this project at patients, professionals, guideline developers and research funders. We have well-developed links with the patient and public representative organisations, the clinical community, professional bodies, NICE and research commissioners.

Patients:
We will produce a plain language information leaflet for patients explaining and if possible quantifying the risks and benefits of thromboprophylaxis for lower limb immobilisation.

Professionals:
We will produce a summary of our findings for clinicians that compares the estimated risks of VTE and bleeding related complications for people with lower limb immobilisation, with and without thromboprophylaxis, and stratified according to risk factors or risk-assessment tools.

Guideline developers:
We will produce estimates of the cost-effectiveness of different thromboprophylaxis strategies and identify the most cost-effective strategy for the NHS.

Research funders:
We will produce an estimate of the expected value of information of future primary research, identify the key priority for further research and estimate what future research would be cost-effective.

We will ensure that our research addresses the needs of the NICE CG92 Guideline Development Group (GDG) and that our findings are made available to the GDG in a timely manner. We will also disseminate our findings in the following ways:
1. We will send a scientific summary of our findings along with access to the full report to organisations responsible for producing guidelines and professional or academic bodies with an interest in this area, including the Royal College of Emergency Medicine, the British Orthopaedic Association and the American Thoracic Society.

2. We will disseminate plain language summaries of our findings to patient and public representative organisations.
3. We will disseminate the plain language information leaflet for patients along with the summary of our findings to organisations responsible for producing guidelines and organisations responsible for providing care for people with lower limb immobilisation.
4. Scientific papers produced in this project will be submitted to high profile journals that provide open access and are widely read by those responsible for treating patients with lower limb immobilisation.
5. Findings will be submitted for presentation at relevant conferences. We will also develop supporting material to assist dissemination at professional meetings.
6. We will publicise key scientific outputs by issuing press releases to established media contacts, making research team members available for interview, and using our website, blog, facebook page and twitter feed.

Plan of investigation and timetable:
The project will commence on 1st November 2016 and complete by 31st October 2017. There will be three phases, although development of the model (including literature searches and expert consensus methods) will commence in phase 1:

1. November 2016 to April 2017: Systematic reviews and meta-analysis
2. May to July 2017: Decision analysis modelling
3. August to October 2017: Writing up and dissemination

We will provide one progress report by 30th April 2017 that will report progress with the systematic reviews and meta-analysis, and describe initial model structure.

Project management
The University of Sheffield will be the sponsor and the project will be undertaken in the School of Health and Related Research (ScHARR). Daniel Horner will be seconded to ScHARR for one day per week to lead the project. Steve Goodacre will take ultimate responsibility for delivering the project. Abdullah Pandor will be responsible for day to day management of the project, with support from a Clerical Assistant.

A project management group consisting of all the investigators will meet every six weeks either by teleconference or in person. The core project team of SG, DH and AP will meet more frequently, along with clinical and methodological experts at key times.

A stakeholder group of clinical experts with an interest in VTE will be formed and will be consulted for expert advice at key times in the project.

The core project team will make telephone or email contact with the patient and public representatives at the beginning and end of the project and at key times in between, such as when patient/public input is required in the modelling or prior to meetings or dissemination activities arranged by Thrombosis UK and the Sheffield Emergency Care Forum.

Approval by ethics committees
Not required – entirely secondary research.

Patient and Public Involvement
Patient and public representation will be provided by representatives from Thrombosis UK and the Sheffield Emergency Care Forum.

Beverley Hunt is co-founder and Medical Director of Thrombosis UK, which campaigns to raise awareness of thrombosis (http://www.thrombosis-charity.org.uk). She has asked Thrombosis UK to identify an appropriate individual to act as a representative and facilitate patient involvement in the project.

The Sheffield Emergency Care Forum is a public and patient representative group involved in emergency care research (http://secf.org.uk) that has provided public involvement to many emergency care evaluations undertaken by researchers in Sheffield [Hirst 2016]. The proposal has been reviewed by four members of the Forum who agreed that this was an important question and that evidence synthesis was an appropriate first step in finding an answer. Shan Bennett, has agreed to act as a representative for the group and to facilitate patient involvement. She has previously undertaken this role in a similar HTA-funded project, the DiPEP study (Diagnosis of Pulmonary Embolism in Pregnancy).

Patient and public representatives will meet regularly with members of the project team to discuss progress and ensure that the research is acceptable and relevant to patients and the public. We will use our regular PPI meetings to explain the key elements of the decision-analysis model and engage PPI representatives in examining model assumptions, uncertainties and outputs. We will specifically ask patient and public representatives to:

1. Consider how they value the different outcomes in the analysis.
2. Review plain language descriptions of the strategies investigated in the decision-analytic model (along with their modelled outcomes), comment on the acceptability of strategies to patients and review all plain language outputs from the project.
3. Provide guidance on the direction of future research.
4. Help to develop outputs, such as information leaflets, specifically aimed at explaining the risks and benefits of thromboprophylaxis to patients.
5. Help to disseminate the findings of our study to patients and the public through public meetings, social media and mainstream media contacts.

Expertise

This project will involve collaboration between clinical experts in VTE and a methodological team that have successfully delivered a number of HTA-funded evidence synthesis projects. Steve Goodacre and Daniel Horner will be co Chief Investigators, combining the former's experience of delivering evidence synthesis with the latter's enthusiasm and expertise in VTE. It will provide Dr Horner with the opportunity to develop Chief Investigator experience under expert guidance, thus increasing research capacity in the clinical community.

Daniel Horner is an emergency physician with a clinical and academic interest in venous thromboembolic disease. He is co-chair of the VTE committee at Salford Royal NHS Foundation Trust, regional network co-lead for Injuries and Emergencies research across the comprehensive research network in the North West and a full member of the Research and Publications committee for the Royal College of Emergency Medicine. Dr Horner was co-author for the national guideline from the Royal College of Emergency Medicine on thromboprophylaxis for ambulatory patients with temporary lower limb immobilisation published in 2012. He has an extensive publication trail related to venous thromboembolism from his MD thesis and an active interest in acute VTE research with national and international collaborators.

Steve Goodacre is a leading expert in emergency care research and has been Chief Investigator for several major national evaluations. One of his main research interests is using decision analysis modelling and cost-effectiveness analysis to guide policy and practice in emergency care. He has

previously led four successfully completed HTA-funded evidence synthesis projects evaluating diagnostic tests for deep vein thrombosis, management of minor head injury, management of suspected acute coronary syndrome and pre-hospital non-invasive ventilation for acute respiratory failure.

Beverley Hunt is an international expert in thrombosis and acquired bleeding disorders, and has a large clinical practice. She sits on the national VTE board in England and advises the Welsh Government. She runs a research group with over 280 peer-reviewed publications to her name and won the BMJ Research paper of the year 2011 with the CRASH-2 team. She is a Co-Founder and Medical Director of the thrombosis charity, 'Lifeblood: the thrombosis charity', now Thrombosis UK which was Health Charity of the Year 2010. She also is part of a global team organising the "World Thrombosis Day". Her Thrombosis committee have produced a free award-winning, downloadable iphone app containing a multitude of thrombosis guidelines in elegant algorithms: http://itunes.apple.com/gb/app/thrombosis-guidelines/id448736238?mt=8

Jonathan Keenan is an experienced Orthopaedic and Trauma Surgeon working in a Major Trauma Centre. He is a member of the Trust Thrombosis Committee and is VTE lead for Trauma and Orthopaedics. He has a longstanding interest in VTE, particularly in patients treated with lower limb immobilisation. He has published on this topic and has co-developed a risk assessment score for these patients. His other publications are in trauma care and joint replacement surgery.

Kerstin de Wit is a staff physician who works in both thrombosis medicine and emergency medicine in Hamilton, Canada. She is an assistant professor with McMaster University and is the Division of Emergency Medicine research director. She has an MD from University of Manchester and a Masters of Epidemiology from University of Ottawa. Dr de Wit's main clinical expertise is as a venous thrombosis specialist. A large part of her work clinical workload is in prevention and treatment venous thrombosis associated with orthopaedic surgery. She adds to our team as an expert in quality of life measurement in venous thrombosis. She has a proven track record in clinical research in diagnosis of venous thrombosis and bleeding.

Matt Stevenson has a wide experience of different mathematical modelling techniques and has worked extensively for NICE and the NCCHTA. He is technical director of ScHARR-TAG (one of ten academic units contracted to work for NICE and the HTA) and a member of NICE appraisal committee C. In 2007 he was an invited expert to a NICE workshop to help formulate further the NICE reference case for evaluating the cost-effectiveness of diagnostic techniques, and is a member of the working party currently updating NICE's method guide.

Sarah Davis is a health economist who has over 10 years of experience of modelling to inform NICE guidance including Technology Appraisals and Clinical Guidelines. She has particular expertise in modelling the cost-effectiveness of using risk prediction tools to identify and treat people at risk of fragility fracture. She is currently a member of the NICE Highly Specialised Technologies Evaluation Committee.

John Stevens is a Reader in Decision Science, Director of the Centre for Bayesian Statistics in Health Economics (CHEBS) and a member of the ScHARR-TAG Management Team. He is an expert in the application of Bayesian statistics to economic analysis, and has worked on a variety of projects for NICE and the NCCHTA. He is a past member of NICE Appraisal Committee C. He also has extensive experience of pharmaceutical drug development.

Abdullah Pandor is Deputy Director of ScHARR-TAG and an experienced systematic reviewer who was project manager for successful HTA-funded evidence synthesis projects evaluating the cost-

effectiveness of investigation and hospital admission for minor (GCS 13-15) head injury (HTA 07/37/08) and pre-hospital non-invasive ventilation for acute respiratory failure (HTA 11/36/09).

Tim Nokes is a Consultant Haematologist at Derriford Hospital in Plymouth. He has been working in Plymouth for nearly 16 years and has a subspeciality interest in Haemostasis and Thrombosis. He is the Trust lead for VTE prevention and their Trust has been a National Exemplar Centre for VTE prevention, since 2010 (re-inspected in 2015). He works very closely with Jonathan Keenan (Orthopaedic Consultant) and together, they have introduced strict thromboprophylaxis guidelines for orthopaedic patients, demonstrating a significant fall in VTE rates. They have also produced a plaster cast risk assessment document which has been used regularly within the Trust for 8 years (and adopted by a number of Trusts around the UK). It has been through two updates and demonstrated reductions in cast associated VTE rates.

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