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Graduated compression stockings for prevention of deep vein thrombosis

in postoperative surgical patients

(HTA No. 13/72/01)

Research Protocol
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1. Title of the Project

Graduated compression stockings for prevention of deep vein thrombosis in postoperative surgical patients

2. Name of TAR team and project leads

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3. Plain English summary

Deep vein thrombosis (DVT) is a condition in which a blood clot forms in the deep veins of the lower limbs, causing a blockage. Symptoms of DVT include leg pain and/or swelling but people can develop a DVT without any obvious symptoms. If the blood clot breaks off and travels through the venous system and lodges in the lung a pulmonary embolism (PE) arises, which is potentially life threatening as it can prevent the blood reaching the lungs. DVT and PE are collectively known as venous thromboembolism (VTE).

It is estimated that up to 25,000 people in England may die each year from potentially preventable VTE that develops while they are in hospital. DVT can occur in hospitalised patients due to changes in the blood vessel wall, changes in blood flow and changes in the properties of the blood, caused by factors such as being less mobile, decreased fluid intake and excessive body fluid loss.

There is evidence that routine preventive measures (prophylaxis) reduce the risk of DVT in people who undergo surgery, reduce deaths related to DVT and reduce health service costs. Prophylaxis can be pharmacological (such as fondaparinux sodium, low molecular weight heparin or unfractionated heparin) and/or mechanical (such as use of graduated compression stockings (GCS)).

GCS exert pressure at the ankle which gradually decreases towards the knee and thigh. This is thought to increase blood flow through the veins. GCS are available as knee-length or thigh-length stockings. Whilst most of the evidence for the effectiveness of GCS is from studies using thigh-length

stockings, there is a concern that patients are less likely to wear thigh-length stockings and that they are more likely to be worn incorrectly, which can be unsafe.

A previous systematic review has looked at the evidence comparing the effectiveness of thigh-length versus knee-length GCS in hospitalised patients who have had surgery. The authors concluded that there was insufficient high quality evidence to determine whether thigh-length or knee-length stockings differ in their effectiveness in reducing the incidence of DVT. They recommended that a large multicentre randomised controlled trial (RCT) be conducted to address this issue.

The overall aim of our research is to establish the value of undertaking further research (such as the recommended RCT or other research that might be necessary) to compare thigh-length with knee-length stockings for the prevention of DVT in patients who have had surgery. Our systematic reviews of relevant evidence will be used in a decision model to estimate cost-effectiveness and the decision model will be used to undertake a value of information analysis . This will establish the expected value of undertaking additional research.

4. Decision problem

4.1 Background

Deep vein thrombosis and venous thromboembolism

Venous thrombosis is a condition in which a blood clot forms in a vein, resulting in blockage of the affected vein. It most commonly occurs in the deep veins of the lower limbs, known as deep vein thrombosis (DVT). DVT can be asymptomatic; detected by screening, or symptomatic; usually presenting as leg pain and/or swelling, as a result of occlusion of the vein. If the blood clot breaks off and travels through the venous system an embolism is created, if the clot lodges in the lung a pulmonary embolism (PE) arises. DVT and PE are collectively known as venous thromboembolism (VTE).

DVT can occur in hospitalised patients due to changes in the blood vessel wall, changes in blood flow and changes in the properties of the blood, caused by factors such as immobilisation, decreased fluid intake and excessive body fluid loss. In addition, trauma and surgery can also cause activation of the coagulation system leading to a higher risk of DVT.[2] It is estimated that between 45 and 51% of patients undergoing orthopaedic surgery develop DVT if they are not provided with adequate thromboprophylaxis, as shown in Table 1.[3]

Table 1: Incidence of DVT by specialties – risk level by patient group

Specialty	DVT % (weighted mean)
General surgery	25
Orthopaedic surgery	45-51
Urology	9-32
Gynaecological surgery	14-22
Neurosurgery (including stroke)	22-56
Multiple trauma	50
General medicine	17

Data: International Consensus Statement 1997-2002[3]

Recent data from a UK prospective cohort study (Million Women Study) reported that compared with not having surgery, women were 70 times more likely to be admitted with venous thromboembolism in the six weeks following an inpatient surgical procedure and 10 times more likely after a day-case procedure). [4] Risks remained increased 7-12 weeks post surgery and the

pattern of risk was similar for pulomonary embolism and DVT. Risk varied considerably by surgery type. It is estimated that up to 25,000 people in England may die each year from potentially preventable VTE contracted in hospital.[3]

Surgical patients and patients with trauma are at an increased risk of VTE if they meet one of the following criteria:[5]

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- one or more of the following risk factors:
    - active cancer or cancer treatment
    - age over 60 years
    - critical care admission
    - dehydration
    - known thrombophilias
    - obesity
    - personal or first-degree family history of VTE
    - use of oestrogen-containing oral contraceptives or hormone replacement therapy
    - varicose veins with phlebitis
    - or one or more significant medical comorbidities (e.g. heart disease; metabolic, endocrine or respiratory pathologies; acute infections diseases; inflammatory conditions).

In March 2010 the Department of Health produced a Risk Assessment for Venous Thromboembolism tool for use in hospitalised patients.[6] It is also a National Institute for Health and Care Excellence (NICE) quality standard that all patients on admission to hospital receive an assessment of individual risk of VTE and bleeding using clinical risk assessment criteria described in the national tool.[7]

Thromboprophylaxis

There is evidence that routine prophylaxis reduces morbidity, mortality and health service costs in hospitalised patients at risk of DVT and VTE.[8] Prophylaxis can be pharmacological (such as fondaparinux sodium, low molecular weight heparin or unfractionated heparin) and/or mechanical. Mechanical methods of prophylaxis include graduated compression stockings (GCS), intermittent pneumatic compression devices and pneumatic foot pumps. GCS have been shown to reduce the incidence of post-operative DVT in surgical patients to approximately 11%, whilst low dose heparin administered via subcutaneous injection reduces the rate of DVT to around 9%; used together the rate of DVT is reduced further.[9]

Graduated Compression stockings (GCS)/anti-embolism stockings

There are two different types of compression hosiery: anti-embolism stockings and graduated compression stockings (GCS). Both products offer graduated compression, and the two terms are often used interchangeably, although, anti-embolism stockings are designed for the prevention of VTE in immobile patients. For consistency with the HTA scope, we will use the more commonly used term GCS rather than ‘anti-embolism stockings’.

GCS exert graded pressure at a decreasing gradient from the ankle towards the thigh, which increases blood flow velocity and promotes venous return. In addition, preventing passive venous distension is thought to prevent sub-endothelial tears and the activation of clotting factors.[5]

The Sigel profile which equates to a graduated compression pressure profile of 18mmHg at the ankle, 14mmHg at the mid-calf, 8mmHg at the Knee (popliteal break), 10mmHg at the lower thigh and 8mmHg at the upper thigh was found to increase deep venous flow velocity by 75%.[10] The current British and European Standards for anti-embolism stockings [BS7672 (1); ENV 12719(70)] do not replicate the Sigel profile and the British Standard only requires pressure to be measured at three points rather than the five specified by Sigel.[5]

GCS are available as knee-length or thigh-length stockings. Patients report that both knee-length and thigh-length stockings are difficult to use, but knee-length stockings wrinkle less than thigh-length, and fewer patients report discomfort when using them.[11] Patient compliance is reported to be higher with knee-length stockings and thigh-length stockings are more likely to be worn incorrectly.[12, 13] Incorrectly worn stockings can be unsafe; thigh-length stockings that are fitted incorrectly or roll down can create a tourniquet effect. In addition, for some patient subgroups one length of stocking may be more appropriate than the other, for example it is widely believed that knee-length stockings are more likely to induce wound complications in patients undergoing knee replacement surgery. There are also some patients where GCS are contraindicated, such as those who have peripheral arterial disease.

4.2 Existing guidelines and systematic reviews

A rapid appraisal of the review and guideline literature was undertaken to inform the protocol and give an indication of the size of the literature. We searched key resources for published systematic reviews and guidelines on GCS, including the Cochrane Library, PROSPERO, Clinical Trials.gov, National Guidelines Clearinghouse, NIHR HTA website, TRIP, Clinical Evidence, NHS Evidence, NICE website and the NHS Clinical Knowledge Summaries database. The search identified the NICE and SIGN guidelines for the prevention of VTE,[5, 8] and two relevant Cochrane reviews,[1, 2] described below. Guidelines were also identified for several other countries, including the United States and Australia.

NICE guideline[5]

In January 2010 NICE published guideline 92 on reducing the risk of VTE (DVT and PE) in patients admitted to hospital (updating previous guideline 46).[5] The key recommendations relating to thromboprophylaxis in surgical patients are as follows:

Using mechanical VTE prophylaxis: Base the choice of mechanical VTE prophylaxis on individual patient factors including clinical condition, surgical procedure and patient preference. Choose any one of GCS (thigh or knee-length), foot impulse devices or intermittent pneumatic compression devices (thigh or knee-length).

Further recommendations are made, for example regarding correct sizing and fitting of stockings. The guideline states that patients should be encouraged to wear their stockings day and night until they no longer have significantly reduced mobility.

Pharmacological VTE prophylaxis is also recommended for surgical patients at a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Pharmacological VTE prophylaxis should also be continued until the patient no longer has significantly reduced mobility (generally 5-7 days), although for patients with hip fracture or undergoing elective hip replacement surgery, pharmacological VTE prophylaxis should be continued for 28-35 days (according to the summary of product characteristics for the individual agent being

used), and for patients undergoing knee replacement surgery, pharmacological prophylaxis should be continued for 10-14 days.

The NICE guideline states that the length of stockings is a controversial issue and there is no clear randomised evidence that one length of stocking is more effective than another. Clinical judgement, patient preference, concordance and surgical site are all important issues when deciding on stocking length.

Contraindications to GCS use are suspected or proven peripheral arterial disease; peripheral arterial bypass grafting; peripheral neuropathy or other causes of sensory impairment; any local conditions in which stockings may cause damage, such as gangrene or dermatitis; known allergy to material of manufacture; cardiac failure; severe leg oedema or pulmonary oedema from congestive heart failure; unusual leg size or shape; or major limb deformity preventing correct fit.

In February 2012 NICE published an evidence update to guideline 92.[14] New evidence was found (a Cochrane review by Sachdeva et al. 2010[1]) that supported the use of GCS in surgical patients with or without other methods of thromboprophylaxis, which is in line with current recommendations in guideline 92. The evidence update stated that the review was not able to answer the question of the efficacy of thigh-length versus knee-length GCS.

A decision-analytic model was also developed in guideline 92 to determine the most cost-effective thromboprophylaxis strategy for different hospital population subgroups (hip fracture surgery, total hip replacement, total knee replacement, general surgery and general medical admissions). VTEs and major bleeding events were modelled for the acute period (determined by the RCT follow-up, typically only 10-14 days) but Quality Adjusted Life Years (QALYs) and health service costs arising from these events were modelled over the patient's lifetime, including treatment of post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH). Results differed across the different population subgroups, although GCS either alone or combined with pharmacological prophylaxis was consistently found to be the most clinically effective and cost-effective approach for the prevention of VTE. The different results were largely driven by population differences in terms of the baseline risks of major bleeding and pulmonary embolism. The cost of GCS was assumed to be £6.36 per pair (2009 prices) but the length was not specified. In addition, no attempt was made to formally model the relative cost-effectiveness of different GCS lengths.

SIGN guideline[8]

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline 122 on the prevention and management of VTE in December 2010 (updating previous guidelines 62 and 36).[8] The key recommendations relating to thromboprophylaxis in surgical patients are as follows:

General surgery: patients undergoing abdominal surgery who are at risk due to the procedure or personal risk factors should receive thromboprophylaxis with mechanical methods unless contraindicated and either subcutaneous low molecular weight heparin, unfractionated heparin or fondaparinux.

Orthopaedic surgery: patients undergoing total hip replacement or total knee replacement surgery should receive pharmacological prophylaxis (with low molecular weight heparin, fondaparinux, rivaroxaban or dabigatran) combined with mechanical prophylaxis unless contraindicated. Extended prophylaxis should be given.

The SIGN guideline states that studies comparing above-knee with below-knee stockings have been too small to determine whether or not they are equally effective, although a meta-analysis

suggested no major difference in efficacy in surgical patients.[15] The guideline recommends that above-knee or below-knee GCS may be used for prophylaxis of DVT in surgical patients provided that there are no contraindications and that attention is paid to correct fitting and application. Contraindications are massive leg oedema; pulmonary oedema (e.g. heart failure); severe peripheral arterial disease; severe peripheral neuropathy; major leg deformity; and dermatitis.

Cochrane review: knee-length versus thigh-length GCS[2]

A Cochrane review undertaken by Sajid et al., published in 2012, included three small RCTs that compared the effectiveness of thigh-length versus knee-length GCS in hospitalised postoperative surgical patients. There was no statistically significant difference in clinical effectiveness between the two stocking lengths in terms of reducing the incidence of DVT; however there was significant heterogeneity amongst the trials, as well as considerable methodological limitations. The authors concluded that there was insufficient high quality evidence to determine whether thigh-length or knee-length stockings differ in their effectiveness in terms of reducing the incidence of DVT in hospitalised patients. They recommended that a large multicentre RCT be conducted to address this issue.

Cochrane review: elastic compression stockings for prevention of DVT[1]

A Cochrane review undertaken by Sachdeva et al., published in 2010, included eighteen RCTs that compared the effectiveness of GCS, with or without another method of DVT prophylaxis, versus no stockings, in hospitalised patients. Eight RCTs compared GCS alone with no stockings; there was a statistically significant lower incidence of DVT in the stocking group, compared with no stockings. Ten RCTs compared GCS alongside another prophylactic method versus the other method alone; there was a statistically significant lower incidence of DVT in the stocking plus other prophylactic method group, compared with the other method alone group. The authors concluded that GCS are effective at diminishing the risk of DVT in hospitalised patients. However, where stated, all of the included RCTs used thigh-length stockings. The authors of this review also recommended an RCT comparing thigh-length with knee-length GCS.

4.3 Research aims and objectives

The aim of the research is to establish the expected value of undertaking additional research comparing the relative effectiveness of thigh-length versus knee-length GCS, in addition to standard pharmacological prevention, for prevention of DVT in surgical patients. There are two key objectives:

- To undertake an evidence sythesis by systematic review to estimate clinical effectiveness and inform key clinical parameters for a decision model
- To develop a decision model to estimate cost-effectiveness and to undertake a value of information analysis

5. Methods for systematic review of clinical evidence

There are four key clinical areas that are expected to inform the decision model:

(i) the relative effectiveness of thigh-length versus knee-length stockings for prevention of DVT in surgical patients;
(ii) baseline risk of DVT;
(iii) the clinical consequences of DVT; and
(iv) patient adherence.

Systematic reviews of the evidence will be undertaken to inform these parameters. In the first instance, for each question, existing systematic reviews will be sought. The primary literature will then be searched to update the existing systematic reviews where they are considered out of date. The expected scope of each of the reviews is outlined below. The systematic reviews will be conducted and reported following the general principles recommended in CRD's guidance[16] and the PRISMA statement.[17] The research protocol will be registered on the international prospective register of systematic reviews (PROSPERO).

(i) Effectiveness of thigh-length versus knee-length stockings

A systematic review will be undertaken to evaluate the relative effectiveness of thigh-length versus knee-length GCS, in addition to standard pharmacological prevention, for surgical patients at risk of DVT. Due to the anticipated paucity of research evidence directly comparing thigh-length stockings with knee-length stockings,[2] in addition to seeking studies directly comparing the two types of stockings, data will also be sought comparing thigh-length stockings with a control treatment, and studies comparing knee-length stockings with a control treatment. It is anticipated that the indirect evidence will be used in a network meta-analysis to strengthen statistical comparisons rather than basing comparisons solely on the direct evidence. The systematic review will be based on relevant existing systematic reviews and additional studies identified.

Search strategy

A systematic search of the relevant guideline and systematic review databases will be undertaken. The following databases will be searched: Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), PROSPERO, Health Technology Assessment database (HTA), National Guidelines Clearinghouse, TRIP, Clinical Evidence, NHS Evidence and NHS Clinical Knowledge Summaries. Based on our preliminary scoping searches the most up to date relevant reviews are a Cochrane review of knee-length versus thigh-length GCS for prevention of DVT in postoperative surgical patients[2] and a Cochrane review of GCS for prevention of deep vein thrombosis.[1] These reviews searched the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Peripheral Vascular Diseases Group Specialised Register, which is constructed from weekly electronic searches of MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health (CINAHL), The Allied and Complementary Medicine Database (AMED), and through handsearching relevant journals.

In order to bring the searches for these two reviews up to date, systematic searches of electronic sources for RCTs published since January 2010 (the date of the search in the earlier Cochrane review[1]) will be undertaken. The following databases will be searched: MEDLINE, MEDLINE In-Process, EMBASE, CINAHL, AMED and CENTRAL. In addition, information on studies in progress, unpublished research or research reported in the grey literature will be sought by searching relevant databases including ClinicalTrials.gov and Current Controlled Trials.

A draft search strategy for trials of effectiveness developed for Ovid MEDLINE can be found in Appendix A. This strategy will be further developed and converted to run appropriately on other databases. The strategy combines terms for GCS, terms for thrombosis and terms for RCTs. No language limits will be applied to the search strategies.

In addition, clinical advisors will be consulted for additional potentially relevant studies, and reference lists of newly identified included studies and relevant reviews and guidelines will also be manually searched.

Study selection
Titles and abstracts of studies identified by the searches will be independently assessed for inclusion by two reviewers using the criteria outlined below. Disagreements will be resolved through discussion and, where necessary, by consultation with a third reviewer. For studies of potential relevance, full papers will be assessed independently by two reviewers with disagreements resolved by the same procedure.

Inclusion and exclusion criteria
Participants
Studies of surgical patients at risk of DVT will be included; day surgery patients will be included as well as inpatients. Studies will be included regardless of the participants' level of risk for DVT, and the issue of level of risk addressed in the analysis.

Interventions
Studies assessing thigh-length GCS (with or without standard pharmacological prevention) or knee-length GCS (with or without standard pharmacological prevention) will be included.

Comparators
Studies comparing thigh-length with knee-length GCS will be included. In addition, studies comparing thigh-length or knee-length GCS (with or without standard pharmacological prevention) with no GCS (with the same standard pharmacological prevention as in the GCS group), will also be included, as long as the length of stocking used is clear and if different lengths were used, they were analysed separately.

Setting
Hospital and community.

Outcomes
Incidence and type of DVT (i.e. symptomatic or asymptomatic). DVT data will be included only if diagnosed using radioiodine (125I) fibrinogen uptake, venography, Doppler ultrasound or magnetic resonance imaging (MRI) (as used in the rview for the NICE Guideline). Complications and consequences associated with DVT (such as the incidence of PE, incidence of post-thrombotic syndrome (and its associated complications) and mortality) and adverse effects related to the use of GCS will be assessed. Patient compliance and preference and cost implications will also be assessed.

Study design
Systematic reviews and RCTs will be included in the assessment of the relative effectiveness of thigh-length versus knee-length GCS.

Data extraction and quality assessment
Data relating to study design, population characteristics, intervention characteristics (e.g. type of stocking, duration of use, co-interventions including pharmacological prophylaxis), details of outcome measures used and results will be extracted by one reviewer using a piloted and standardised data extraction form. Dichotomous outcomes will be extracted as relative risks and continuous outcomes as mean differences (with 95% confidence intervals).

RCTs will be assessed for risk of bias using the Cochrane Risk of Bias Tool.[18]

Extracted data will be checked for accuracy by a second reviewer. Disagreements will be resolved through consensus and, if necessary, a third reviewer will be consulted. Authors of studies will be

contacted for clarification and missing data as necessary. Data from studies with multiple publications will be extracted and reported as a single study.

Methods of analysis and synthesis

In the first instance, study characteristics and quality assessment will be presented in a series of structured tables. Where there are sufficient clinically homogeneous data, a network meta-analysis will be undertaken using approaches outlined by the NICE Decision Support Unit.[19] Direct comparisons will also be made to allow exploration of consistency.[20]

If sufficient data are available the effect of duration of stocking use and baseline risk of DVT on outcome will be explored. Ideally an analysis of risk would be based on risk criteria stated in the NICE guideline and national risk assessment tool (e.g. age, obesity, concomitant conditions, anaesthetic and surgical time, expected significant reduction in mobility).[5] However, outside an individual patient data (IPD) analysis, such an approach is not feasible. Possible alternative approaches will be explored but the most likely approach with the trial level data is that risk will be explored by type of surgery, an approach that has been used previously to inform the NICE guideline (in the review to underpin the NICE Guideline effectiveness data were synthesised separately by type of surgical procedure). Risk will be explored in the network meta-analysis if the trials are available to populate a network and, if not, by using the direct evidence. Heterogeneity will be described (based on population, intervention (such as brand of stocking and duration of use), setting, specified pharmacological prophylaxis, measurement of outcome and study characteristics (such as year of study) and, data permitting, will be investigated using subgroup analysis or covariate analysis as appropriate.

(ii) Baseline risk of DVT

The risk of DVT in surgical patients is likely to vary based on patient-specific and procedure-specific risk factors. The review of RCTs of effectiveness of thigh-length and knee-length GCS will provide some data on baseline risk of DVT from the no prophylaxis arms of the trials. To supplement these data and ensure that the best available data are used for the model, searches for existing systematic reviews of risk of DVT in surgical populations will be undertaken, as well as searching national and international guidelines, for example the American College of Chest Physicians guidelines for prevention of thrombosis which searched for large population-based observational studies to estimate expected baseline risk of VTE in the absence of prophylaxis. Our searches will aim to identify studies exploring the risk in different patient population groups, for example different age groups. Reference checking and contact with experts will also be used.

The most appropriate source of synthesised evidence for the model will be identified (based on scope and quality of the review). If the synthesised evidence is considered potentially out of date, searches of the primary literature will be undertaken, to update. Standard processes will be used to reduce error and bias in the review process, as in the review of effectiveness, described above.

(iii) The clinical consequences of DVT (mortality and morbidity)

In the event that the review of RCTs of effectiveness of thigh-length and knee-length GCS does not provide sufficient data on the short term (e.g. pulmonary embolism) and longer term (e.g. post thrombotic syndrome) consequences of DVT, we will supplement this by searching for the best available evidence using as systematic an approach as possible within the time constraints of the review. In the first instance a similar approach to (ii) will be undertaken; searches for existing systematic reviews, as well as national and international guidelines will be performed. Reference checking and contact with experts will also be used.

The most appropriate source of synthesised evidence for the model will be identified (based on scope and quality of the review). If the evidence is considered potentially out of date, searches of the primary literature will be undertaken, to update.

(iv) Patient adherence and preference

The review of RCTs of effectiveness of thigh-length and knee-length GCS may provide some data on patient adherence and preference. To supplement these data, and ensure that the best available data are used for the model, systematic reviews will be sought and relevant guidelines checked for relevant observational studies of patient adherence and preference, comparing thigh-length with knee-length GCS amongst surgical patients. These will be supplemented by searches for more recent literature as well as contact with experts.

6. Methods of systematic review of cost-effectiveness evidence and development of decision model

(i) Identifying and systematically reviewing published cost-effectiveness studies

Systematic searches will be undertaken to identify existing published studies reporting the cost-effectiveness of graduated compression stockings for the prevention of deep vein thrombosis in postoperative surgical patients. For the purposes of identifying relevant cost-effectiveness studies we will apply the same (population and intervention) inclusion criteria applied in the clinical review and we will only include studies which consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses).

The previous NICE Clinical Guideline included a review of published cost-effectiveness studies using a comprehensive search strategy designed to find any applied study estimating the cost or cost-effectiveness of any prophylaxis intervention. The searches undertaken for this guideline were undertaken up to December 2008. We intend to use the existing search results and studies identified from the guideline and also update the search results from December 2008 onwards. The following databases will be searched as part of this update: MEDLINE, EMBASE, CENTRAL and EconLit. In addition, searches of NHS EED and HEED will be carried out, along with a search of the Economics Working Papers archive (IDEAS).

The quality of the cost-effectiveness studies will be assessed according to a checklist updated from that developed by Drummond et al. (2005)[21] and Philips et al. (2004).[22, 2322, 23] This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by NICE. This information will be tabulated and summarised within the text of the report. In particular, information will be extracted on the comparators, study population, main analytic approaches (e.g. patient-level analysis/decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality-of life, direct costs (medical and non-medical) and productivity costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic/probabilistic sensitivity analysis).

The review will examine in detail the full economic evaluations that meet the inclusion criteria, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing economic evaluations. This review will also be used to identify the central issues associated with adapting existing decision models to address the specific research question posed and to assist in the development of a new decision model drawing on the issues identified in the clinical and cost-effectiveness review.

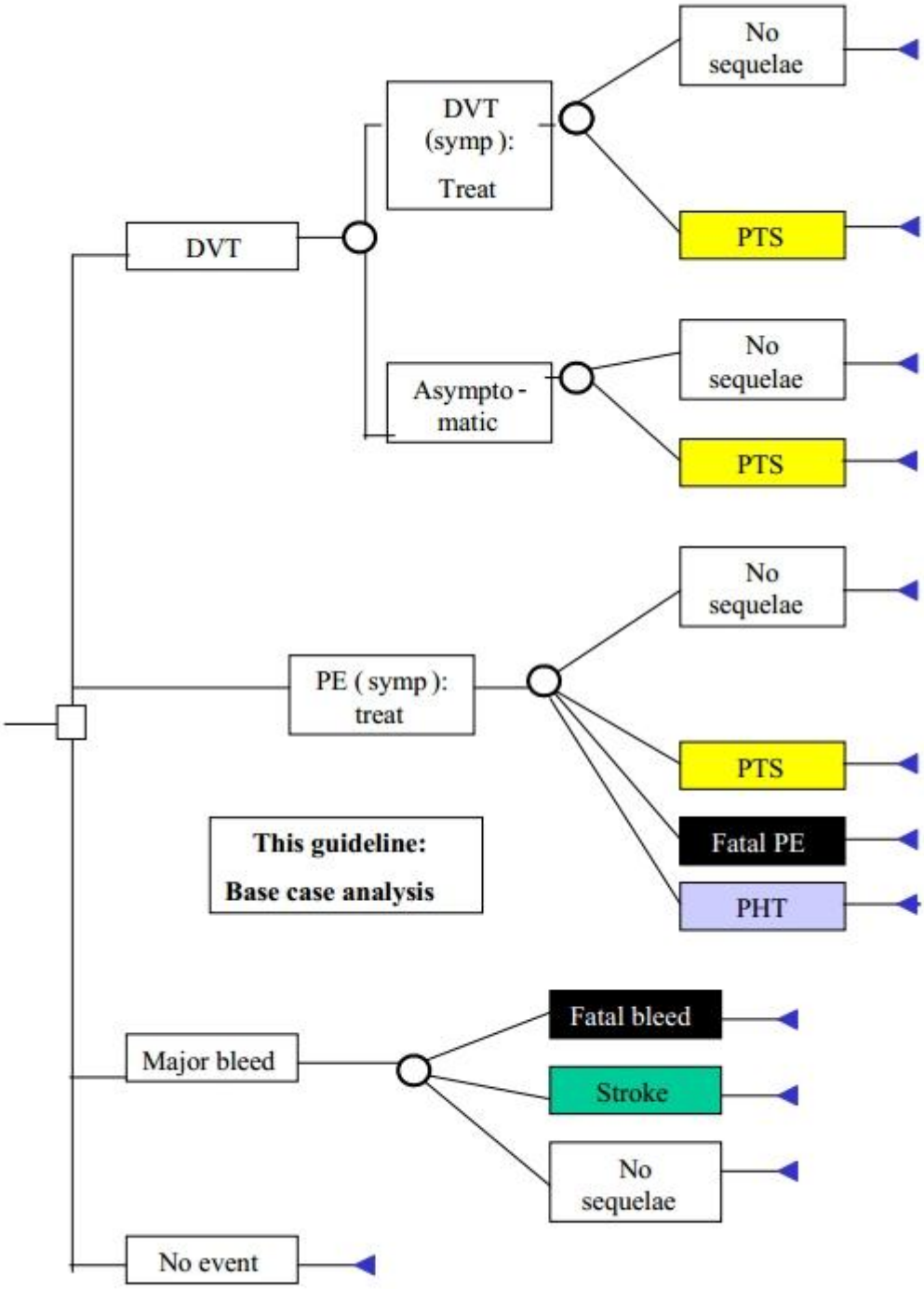
(ii) Development of a new decision-analytic model

A new decision-analytic model will be developed to estimate the cost-effectiveness of knee-length versus thigh-length graduated compression stockings for prevention of deep vein thrombosis in postoperative surgical patients. The model will be developed in accordance with the NICE reference case. The perspective will be that of the National Health Service (NHS) and Personal Social Services. Productivity costs are not included within this perspective but may be included as a secondary analysis. Both cost and Quality-Adjusted Life Years (QALYs) will be discounted at 3.5%.
The specific objectives of the cost-effectiveness analysis are:

- To structure an appropriate decision model to characterise patients' care and subsequent prognosis and the impacts of alternative therapies, in a way that is clinically acceptable.
- To populate this model using the most appropriate data identified systematically from a series of inter-related reviews using published literature and routine data sources.
- To relate intermediate outcomes to final health outcomes, expressed in terms of QALYs. This is necessary in order to provide decision makers with an indication of the health gain achieved by each intervention, relative to its additional cost, in units which permit comparison with other uses of health service resources.
- To quantify the cost and QALY impact of any adverse effects related to the use of knee or thigh-length stockings.
- To estimate the mean cost-effectiveness of knee-length versus thigh-length stockings (in addition to standard pharmacological prevention) based on an assessment of long-term NHS and Personal Social Service costs and quality-adjusted survival.
- To characterise the uncertainty in the data used to populate the model and to present the uncertainty in these results to decision makers. A probabilistic model will be developed which requires that each input in the model is entered as an uncertain, rather than a fixed, parameter. Using Monte Carlo simulation, this parameter uncertainty is translated into uncertainty in the overall results. This ultimately helps decision makers understand the probability that, in choosing to fund an intervention, they are making the wrong decision – that is, decision uncertainty. This is presented using cost-effectiveness acceptability curves which show the probability that each intervention is cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY.
- Consistent with available evidence, variability in cost-effectiveness will be investigated by clinical subgroups. For each subgroup, separate incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves will be presented, and an optimal strategy will be identified using the threshold cost per QALY estimates.
- To undertake additional sensitivity/scenario analyses to address the impact of key assumptions in the model. We anticipate that one specific scenario will explore issues around the potential impact of compliance

The model structure and design will be informed by existing cost-effectiveness studies, discussions with our clinical advisors and the nature of the existing clinical effectiveness evidence. Previous models for the prevention and management of VTE have used decision-tree and Markov model approaches. The cost-effectiveness analysis used to inform NICE Clinical Guideline 92 was based on a decision tree (see Figure 1).

Figure 1: Decision tree (NICE Clinical Guideline 92)



Within this model structure, VTEs and major bleeding events were modelled for the acute period (which was determined by the RCT follow-up, typically only 10-14 days). However, the longer term QALYs and health service costs arising from these events were modelled over the patient's lifetime, including treatment of post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (PHT). While this approach seems reasonable for modelling one-off interventions which are focused on the acute period, depending upon the clinical effectiveness evidence identified, it may be necessary to extend or adapt this structure to capture longer-term risks of VTEs, particularly if evidence is identified which provides a basis for estimating the clinical effectiveness of

different treatment durations related to the prevention of the initial VTE and any subsequent recurrent VTEs. In this eventuality it will be necessary to adapt the decision-tree structure either using discrete intervals (i.e. to reflect the risk of VTE over discrete periods of time) or to employ a Markov-structure to reflect the continuing risk of VTE over time and the potential for VTE recurrence. Figure 2 shows a decision-tree structure using discrete intervals used to inform the risk of recurrent VTE as part of the economic analysis. Figure 3 also shows how the recurring risk of VTE over time was modelled using a Markov-structure to inform the cost-effectiveness estimates of alternative treatment durations. The figures provided are illustrative and do not necessarily reflect the final structure (or cycle length) that will be used.

Figure 2: Risk of recurrent VTE (NICE Clinical Guideline 144)

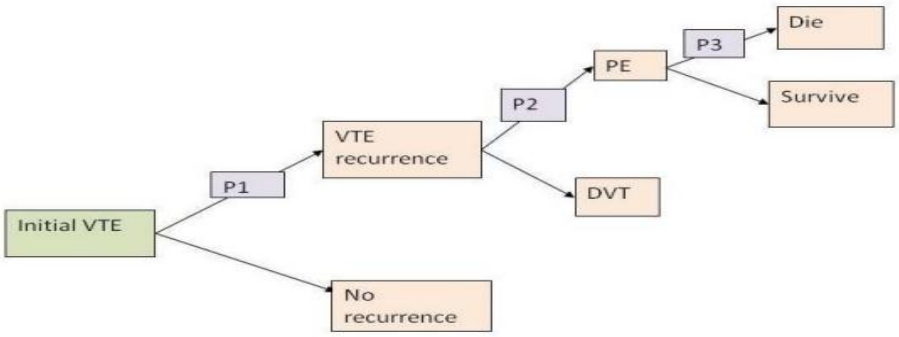
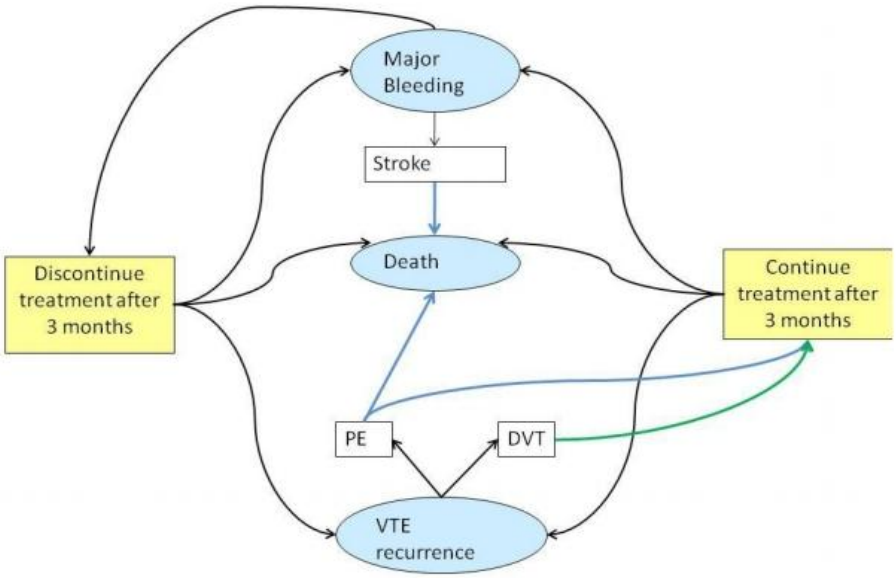


Figure 3: Markov model (NICE Clinical Guideline 144)



When the model structure is finalised and the final health states have been determined, we will also undertake a separate search of health-related quality of life data to help inform the QALY estimates. This review will only consider studies which have reported utility estimates for the health states included. This search will be restricted to a review of existing registries of cost-utility studies (e.g. the

Cost-Effectiveness Analysis Registry published online by Center for Evaluation of Value and Risk in Health at the Tuft's Medical Center at https://research.tufts-nemc.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx) and relevant references cited within these studies. Should suitable evidence not be identified for particular health states, then additional focused searches will be undertaken to identify alternative utility estimates from the published literature.

7. Value of information analysis and future research priorities

To evaluate future research priorities and to establish whether investment in a large scale randomised trial (or alternative design) is likely to be cost-effective, we will use formal methods based on value of information approaches. These approaches will assess the need for major investment in future research and also prioritise the potential research questions including relevant parameters to inform a full trial.[24]

The expected value of perfect information (EVPI) will be estimated for the overall decision problem and for key parameters.[25] EVPI represents the expected costs of decision uncertainty since perfect information would eliminate the possibility of making the wrong decision. Hence, EVPI for the overall decision problem represents the value of eliminating all uncertainty and EVPI for key parameters (termed partial EVPI) represents the value of eliminating uncertainties in particular subsets of parameters. Separate analyses will be undertaken to reflect the variability considered in the decision model itself. Per patient EVPI estimates will be scaled up to reflect the relevant UK population size and will adopt an appropriate time-horizon.

EVPI also represents the maximum amount that a decision-maker should be willing to pay for additional evidence to inform this decision in the future. EVPI provides an upper bound on the value of additional research. This valuation provides an initial hurdle, acting as a necessary requirement for determining the potential efficiency of further primary research. Applying this decision rule, additional research should only be considered if the EVPI exceeds the expected cost of the research. In addition to providing a global estimate of the total cost of uncertainty related to all inputs in the model, EVPI can also be estimated for individual parameters (and groups of parameters) contained in the model. The objective of this analysis (termed partial EVPI) is to identify the model parameters where it would be most worthwhile obtaining more precise estimates.

At the end of this phase, the results will be presented to our clinical advisors and discussed with the York Clinical Trials Unit to obtain their feedback and to identify key issues related to the potential design, feasibility and costs of a subsequent trial. Results will be presented for the total population and for specific subgroups. The results of partial EVPI will be presented for individual parameters and also for groups of parameters according to specific research designs (e.g. those parameters which would be most appropriately informed from future RCTs versus those which might be more efficiently obtained from observational designs).

8. The Project Team

8.1 The TAR Centre

The Centre for Reviews and Dissemination (CRD) is part of the National Institute for Health Research (NIHR) and is a department of the University of York. CRD undertakes high quality systematic reviews of research about the effects of interventions used in health and social care (www.york.ac.uk/inst/crd).

The Centre for Health Economics (CHE) was established at the University of York in 1983, and was one of the world's first research institutes dedicated to the study of the economics of health and health care. CHE conducts and disseminates high quality and scientifically rigorous research on the costs and benefits of health care technologies and public health interventions.

8.2 Expertise in the TAR team and author contributions

Dave Fox, Information Officer, CRD, has seven years experience in the design, conduct and reporting of literature searches and has supported numerous systematic reviews and health technology assessments. Dave has contributed to the protocol and will undertake the literature searches for the systematic review and the associated bibliographic management.

Professor Stephen Palmer, CHE, has worked in economic evaluation for over 20 years and currently leads the programme of work at CHE for NICE. His principal areas of expertise relate to the methodology and application of decision-analytic modelling and Bayesian approaches to Health Technology Assessment. Stephen has contributed to the protocol and will provide input at all stages of the project.

Fiona Paton, Research Fellow, CRD, many years experience in systematic reviews and systematic review methodology. She has worked on health technology assessments for NICE, the HTA programme, the Department of Health and other agencies. Fiona will be involved in all aspects of the review process.

Eleftherios Sideris, Career Development Intern, CHE, has a background in business administration and is a recently qualified health economist (MSc in Health Economics, University of York). He will provide input at all stages of the project.

Dr Eldon Spackman, Research Fellow, CHE, has worked in economic evaluation for nine years. He has undertaken decision-analytic modelling for NICE, the HTA programme, the Department of Health and other agencies. Eldon has contributed to the protocol and will provide input at all stages of the project.

Ros Wade, Research Fellow, CRD, has over ten years experience in systematic reviews and systematic review methodology. She has worked on health technology assessments for NICE, the HTA programme, the Department of Health and other agencies. Ros has contributed to the protocol and will be involved in all aspects of the review process.

Dr Nerys Woolacott, Senior Research Fellow, CRD, is TAR project manager at CRD and has twelve years of experience in health technology assessment, systematic reviews and review methodology. Nerys has produced and managed a large number of technology assessments and systematic reviews for HTA, NICE, Department of Health and others. Nerys will be responsible for managing the review and will provide input at all stages of the project.

8.3 Advisory group

Clinical advice for the review will be provided by Professor Gerard Stansby, Professor of Vascular Surgery, the Newcastle upon Tyne Hospitals NHS Foundation Trust, Mr Peter Millner, Consultant Orthopaedic and Spinal Surgeon at Leeds General Infirmary, Dr David Keeling, Consultant Haematologist, Oxford University Hospitals, and Ms Hayley Flavell, Anticoagulant and Thrombosis

Consultant Nurse at the Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust. A ward based nurse experienced in dealing with compression stockings will also be recruited to this advisory group. They will provide advice on clinical aspects during the project and comment on the draft report.

In addition Professor David Torgerson, Director of the York Trials Unit, will provide expert advice in relation to the proposed value of information analysis, including issues related to trial feasibility, design and costs and he will also comment on the draft report.

In order to capture the patient's perspective in this work, we have one patient volunteer, Mrs Kaye Norman, who has experience of GCS post-cardiac surgery. On her suggestion we have contacted a local cardiology rehabilitation clinic (York Hospital), which is considering our request that attending post-surgery patients would be willing to comment on our interpretation of the evidence, the first phase of the economic modelling, and discuss the gaps in the evidence and the proposed research from a patient's perspective. We will report on how successful this process is.

9. Project timetable and milestones

The project will take place over a 6 month period following approval of the protocol by HTA. Assuming that approval is obtained by Monday 14th January, the key milestones are as follows:

6 month timetable from 14 January 2014 to 14 July 2014

Task	1	2	3	4	5	6
Systematic review						
Protocol development	■					
Literature searches	■	■				
Screening and study selection	■	■	■			
Data extraction, quality assessment, checking		■	■	■		
Synthesis			■	■		
Value of information analysis						
Literature searches	■					
Screening and study selection	■					
Data extraction, quality assessment, checking		■				
Model development		■	■	■		
Model results				■	■	
Value of information analysis – EVPI					■	■
Value of information analysis - EVSI					■	■
Report						
Report writing					■	■

A progress report will be submitted on 14 May 2014.

The end date of 14 July 2014 is the planned submission date for the draft HTA report. We anticipate that the process of peer review, editing proofs, and dissemination will extend three months beyond this date.

10. Competing interests of authors

None of the authors have any competing interests to declare.

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Appendix A

The following draft strategy was designed to identify RCTs of all forms of graduated compression stockings or bandages to prevent all forms of thrombosis in all patients. The strategy will be adapted to run on other databases.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Date of search: 11th September 2013

terms for thrombosis
1 exp "embolism and thrombosis"/ (174565)
2 (thrombos$ or thrombus$ or thrombotic or thrombolic$ or thromboembol$ or thromboprophyla$ or embol$).ti,ab. (235689)
3 (DVT$ or PE or PTS).ti,ab. (36139)
4 1 or 2 or 3 (322207)
terms for compression stockings
5 Stockings, Compression/ or Compression Bandages/ (1151)
6 (stocking$ or hose or hosiery or tights or sock$ or TEDS).ti,ab. (10609)
7 (compression adj3 bandage$).ti,ab. (505)
8 5 or 6 or 7 (11685)
9 4 and 8 (1470)
terms for RCTs
10 randomized controlled trial.pt. (384981)
11 controlled clinical trial.pt. (89120)
12 randomized.ab. (300435)
13 placebo.ab. (161777)
14 drug therapy.fs. (1748887)
15 randomly.ab. (212635)
16 trial.ab. (316395)
17 groups.ab. (1352813)
18 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (3383334)
19 9 and 18 (550)