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Sponsor submission of evidence	
Evaluation title:	The geko™ device for venous thromboembolism (VTE) prophylaxis
Sponsor:	Firstkind Ltd
Date sections A and B submitted:	3rd July 2013
Date section C submitted:	31st July 2013

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Abbreviations

6 keto PGF1α	6 keto prostaglandin 1α
ACT	Automated coagulation timer
AE	Adverse event
BNF	British National Formulary
CEA	Cost-effectiveness analysis
CI	Confidence interval
CQUIN	Commissioning for Quality and Innovation
DVT	Deep vein thrombosis
HRG	Healthcare Resource Group
IPC	Intermittent pneumatic compression
IQR	Interquartile range
ITT	Intention-to-treat
LDF	Laser Doppler fluxmetry
LVOT VTI	Left ventricular outflow tract velocity time integral
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMES	Neuromuscular electrostimulation
NNT	Number needed to treat
PE	Pulmonary embolism
PMS	Post market surveillance
PPG	Photoplethysmography
PSA	Probabilistic sensitivity analysis
PTS	Post-thrombotic syndrome
QIPP	Quality, Innovation, Productivity, Prevention
RCT	Randomised control trial
RR	Relative risk
SD	Standard deviation
SPG	Strain gauge plethysmography
SR	Systematic review
TAMV	Time-averaged maximum velocity

VAS	Visual analogue scale
VAT	Value added tax
VRS	Verbal response scale
VTE	Venous thromboembolism

Glossary of terms

Term	Definition
Normal clinical use setting	Three additional levels to the threshold setting
Peroneal nerve	Nerve controlling contraction of the foot, shin, and calf muscles
Threshold setting	Minimum setting to elicit a minor muscular contraction in both the calf and the foot

Instructions for sponsors

This is the template for submission of evidence to the National Institute for Health and Clinical Excellence (NICE) as part of the Medical Technologies Evaluation Programme process for developing NICE medical technologies guidance. Use of the submission template is mandatory.

The purpose of the submission is for the sponsor to collate, analyse and present all relevant evidence that supports the case for adoption of the technology into the NHS in England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Medical Technologies Evaluation Programme Methods guide' and the 'Medical Technologies Evaluation Programme Process guide' available at www.nice.org.uk/mt. After submission to, and acceptance by, NICE, the submission will be critically appraised by an External Assessment Centre appointed by NICE.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 11 of this document 'Related procedures for evidence submission'.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the case for adoption. Appendices will not normally be presented to the Medical Technologies Advisory Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the economic evidence section with 'see appendix X'.

All studies and data included in the submission must be referenced. Identify studies by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.126, rather than 'one trial126').Please use a recognised referencing style, such as Harvard or Vancouver.

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues. Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

The decision problem is summarised in Table 1 along with rationale for variation from the scope.

Table 1: Statement of the decision problem

Key parameter	Scope issued by NICE	Variation from scope	Rationale for variation
Population	People at risk of VTE and for whom current mechanical methods are impractical or contraindicated. The device is most likely to be initiated in a hospital inpatient setting	None	N/A
Intervention	geko™ neuromuscular electrostimulation device	None	N/A
Comparator(s)	Standard treatment for VTE prophylaxis include: • Mechanical methods: anti-embolism stockings, IPC, foot impulse devices, and/or • Pharmacological prophylaxis: low-molecular weight heparin, unfractionated heparin and fondaparinux For this evaluation, the comparator is: • No mechanical prophylaxis	None	N/A
Outcomes	• Venous transit time, blood flow, blood velocity • Incidence of PTS • Incidence of DVT • Incidence of PE/VTE • Patient adherence • Length of hospital stay • Device-related AEs	Additional outcomes considered: • Patient acceptance/ tolerability/comfort	Not included in final scope but is a major factor affecting patient adherence to other mechanical devices
Cost analysis	Comparator(s): • No mechanical prophylaxis Time horizon for cost analysis will be sufficiently long to reflect any differences in	None	N/A

Key parameter	Scope issued by NICE	Variation from scope	Rationale for variation
	costs and consequences between the technologies being compared Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed		
Subgroups to be considered	• Those in whom pharmacological prophylaxis is contraindicated • Those in whom pharmacological prophylaxis is indicated and prescribed	None	N/A
Special considerations, including issues related to equality	• The device may not be suitable for those with fragile skin (for example, older patients and children) and those with burns and skin conditions within the application area of the device • The device may not be suitable for those patients whose common peroneal nerve or device application site is inaccessible or where the common peroneal nerve function is impaired	None	N/A

Abbreviations: AE, adverse event; DVT, deep vein thrombosis; IPC, intermittent pneumatic compression; NICE, National Institute for Health and Care Excellence; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism.

2 Description of technology under assessment

2.1 Give the brand name, approved name and details of any different versions of the same device.

The geko™ device, powered by OnPulse™ technology.

The firefly™ device is an alternatively branded version of the geko™ device, CE Marked for the same medical purposes. It is already used widely by elite sportspeople to assist the recovery process following intense exercise. This is not considered to be a medical purpose within the meaning of the Medical Device Regulations, though it does rely on the underlying ability of the geko™ device and hence the firefly™ device to increase blood flow in the lower limbs. It has been shown to be better than graduated compression stockings in reducing perceived muscle soreness (1) but without the detrimental effect on adaptive response associated with ice baths (2).

2.2 What is the principal mechanism of action of the technology?

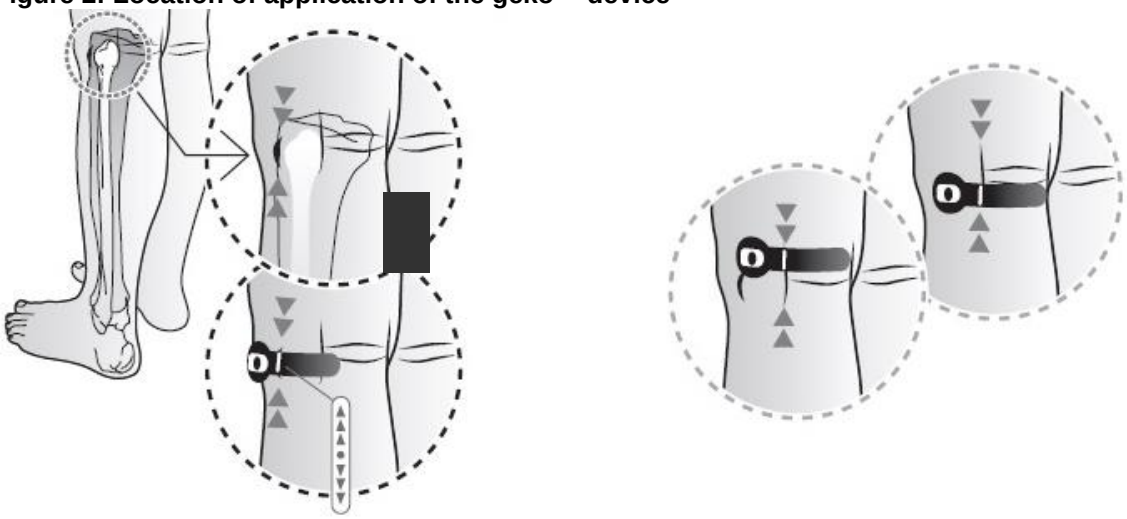
The geko™ device is a battery powered, daily disposable neuromuscular electrostimulation micro-device (Figure 1) designed and approved for use[a] to increase lower limb blood circulation, and for the prevention of venous thromboembolism (VTE). The geko™ device is applied to the fibular head (or other application site) with the tail of the device wrapped around and to the rear of the leg, below the crease of the knee (Figure 2). When activated, the device stimulates the common peroneal nerve which in turn engages the venous muscle pumps of the lower leg facilitating the emptying of veins in the lower leg, and increasing the return of blood to the heart. This imitates the process normally achieved by walking without the patient having to move or exert energy and without uncomfortable muscle movements. The device can be applied to one or both legs as prescribed by the physician and is replaced every 24hrs. An extra adhesive overlay is provided with the geko™ device to aid in adhesion when required.

[a] No data exists on the use of the geko™ device in skeletally immature individuals. Whilst none of the standards applied have indicated that there are any specific safety risks associated with teenagers, the Instructions For Use advise; ‘Only to be used by trained personnel. Keep out of the reach of children’.

Figure 1: The geko™ device

Key: A, top view; B, bottom view showing integral stimulator circuit and electrodes.

Figure 2: Location of application of the geko™ device



The primary fitting location is for the geko™ device to be positioned over the top of the fibula. Alternative fitting locations are aligned with the outer tendon, below the crease of the knee or above the crease of the knee.

Weighing only 16 g the geko™ device is self-adhesive making it easy to apply in as little as 60 seconds, discreet (around the size of a wrist-watch), and comfortable to wear. Due to its small contact area (35 cm^2), there is minimal skin contact, minimising skin irritation and sweating (Table 2). These characteristics are likely to result in improved patient compliance.

Table 2: geko™ device specifications

	Detail
Weight	16 g
Dimensions	149 mm x 42 mm x 11 mm
Area	35 cm^2
Frequency	1 Hz
Amplitude	27 mA
Pulse widths	70, 100, 140, 200, 280, 400 and 560 µs

Compared with standard compression modalities, the geko™ device has the potential to enhance the speed of patient recovery, improve patient well-being and reduce the length of hospital stay by accelerating patient self-sufficiency through the delivery of greater compliance rates associated with the use of the geko™ device technology.

3 Clinical context

3.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE.

Venous thromboembolism (VTE) is the collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is the formation of a blood clot in a deep vein and the complications arising from it can be serious and life-threatening. Clots that travel to the lungs can cause a PE, those that travel to the brain can result in a stroke and those that travel to the heart can cause a myocardial infarction.

VTE is widely considered to be largest cause of preventable deaths in healthcare. In the UK in 2004–2005, approximately 64,000 cases of VTE were under the care of a consultant within the National Health Service (NHS) (3). The incidence of VTE is known to be higher in hospitalised patients than in the general population (4). In the UK in 2005, VTE was reported as being the underlying cause of death in hospitalised patients in over 25,000 cases (4). It is estimated that the total cost (direct and indirect) to the UK of managing VTE is around £640 million (4).

The common factors associated with a greater than average risk of DVT are previous DVT or PE, age older than 40 years, cancer treatment, trauma, recent surgery, immobility, obesity and oestrogen therapy in women. In addition, surgery of the lower limb, in particular to the hip or knee, carries a specific risk of DVT ranging from 24% to 66% (5, 6).

There is significant morbidity associated with non-fatal VTE. The long-term complications of DVT can include recurrent thromboembolism and post-thrombotic syndrome (PTS) (7). The cause of PTS is thought to be damage caused by the thrombus to the venous valves, and inflammation is also thought to play a part (8). Valvular incompetence combined with persistent venous obstruction from thrombus increases the pressure in veins and capillaries. The resulting venous hypertension induces a rupture of small superficial veins, subcutaneous haemorrhage and an increase of tissue permeability. PTS is characterised by aching pain on standing and dependent oedema. The development of lipodermatosclerosis, pruritis, and exematous change are also features, as is secondary development of venous varicosities. Patients affected may suffer from ulceration of the skin, due to microtrauma, which has a high likelihood of recurrence. PTS lowers patients' quality of life after DVT, specifically with regards to physical and psychological symptoms and limitations in daily activities. PTS symptoms may not occur until a few years after the DVT. Following a symptomatic DVT, approximately 20–50% of patients develop PTS within 1–2 years, with severe symptoms including ulceration in 5–10% of cases (9). Treatment of PTS adds significantly to the cost of treating DVT. The annual healthcare cost of PTS in the United States has been estimated at $200 million, with costs over $3,800 per patient in the first year alone, and increasing with disease severity (10). A 15-year follow-up analysis in Sweden has shown that the additional long-term healthcare cost of disabling post-thrombotic complications is around 75% of the cost of primary DVT (11). PTS also causes lost work productivity: patients with severe PTS and venous ulcers lose up to two work days per year.

Maintaining peripheral blood flow in the lower limb is essential in preventing venous stasis and hence reducing the potential for DVT (12-14). Current VTE prophylaxis options for hospitalised patients include mechanical (compression stockings, intermittent pneumatic compression [IPC] and foot impulse devices) and pharmacological (anticoagulants such as heparin, fondaprinux, rivaroxaban, apixaban and dabigatran) interventions.

Pharmacological methods for the prevention of DVT reduce blood coagulability, but are intrinsically associated with significant risk of bleeding and are, therefore, contraindicated for some categories of patients (for example, stroke patients).

Mechanical methods for the prevention of DVT include graduated compression stockings and intermittent pneumatic compression (IPC) which have been proven to increase blood flow (15-17). However, individual patient compliance to compression stockings and IPC is highly variable. Most compression devices consist of plastic sleeves, which can cause sweating beneath the plastic sleeve and be uncomfortable to wear. The size, weight and external power source requirements contribute to poor compliance, which limits their efficacy. Improper use may also result in reduced efficacy (18). The reasons for noncompliance with compression stockings are typically fit and wear problems and unspecified attitudinal issues (19). Data derived from 3,144 patients with chronic venous disease demonstrated that more than 60% of patients did not use their stockings at all or abandoned them after previous trial usage (19). As noted with IPC, noncompliance with compression stockings was associated with treatment failure (19).

Mechanical methods for the prevention of DVT may be contraindicated in some patients, such as those with peripheral arterial disease or diabetic neuropathy.

Electrical stimulation of the lower limb muscles has been shown to be effective in improving blood flow and preventing stasis in patients (13, 20-22) and there is also evidence to support the clinical effectiveness of electrical stimulation in reducing the incidence of DVT (23, 24). However, the limited number of devices developed using this technology are mostly only used under general anaesthesia due to their elevated discomfort levels. Therefore, no portable, effective, minimal discomfort, easy-to-use device for blood flow enhancement and the prevention of stasis with the associated potential prevention of DVT is currently readily available to the NHS in England.

The geko™ device fills a clear, current unmet need for the prophylaxis of VTE for hospitalised patients for whom current mechanical methods of prophylaxis are impractical or contraindicated. Such patients may include stroke patients, those with morbid obesity, severe leg deformity, plaster casts, bilateral lower extremity trauma, severe or critical lower limb ischaemia, swelling of the legs (e.g. in heart failure), recent operative leg vein ligation, local leg conditions in which other mechanical devices of prophylaxis may cause damage or pain, or a known allergy to the materials used in current methods of mechanical prophylaxis.

Whilst this patient population may represent a relatively small proportion of all patients at risk of VTE, the absence of an anti-stasis treatment option for this group of patients can result in serious clinical consequences or even death.

To our knowledge there is no published data detailing the number of hospitalised patients for whom current mechanical methods of prophylaxis are impractical or contraindicated. Therefore in the absence of any data we have estimated the

approximate number of patients suitable for treatment with the geko™ device based on hospital episode statistics (HES) data and an estimate of the proportion unsuitable for mechanical prophylaxis (25). The 2011-2012 HES data showed that there were approximately 9.5 million hospital admissions for surgical procedures. It is acknowledged that for the majority of these procedures, pharmacological or current mechanical prophylaxis can be administered. We have estimated that approximately 1% of patients would be contraindicated to current methods of prophylaxis (pharmacological or mechanical) equating to approximately 95,000 patients. In a similar manner, we have estimated that approximately 5% of patients would be contraindicated to mechanical prophylaxis but be suitable for pharmacological prophylaxis equating to approximately 475,000 patients. Thus the number of patients eligible for treatment with the geko™ device is likely to lie between 95,000 and 475,000 patients per year. These patients could therefore receive pharmacological agents plus the geko™ device.

3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups and make any recommendations for their treatment. If available, these should be UK based guidelines.

Two NICE clinical guidelines exist for VTE: one guideline provides guidance on the prevention of VTE (CG92) and one on the management of VTE (CG144):

- **NICE clinical guideline 92, January 2010. 'Venous thromboembolism – reducing the risk. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital'** (3). CG92 provides information on reducing the risk of VTE (DVT and PE) in patients admitted to hospital. These guidelines assessed pharmacological prophylaxis (fondaparinux, heparin, vitamin K antagonists, aspirin, dabigatran and rivaroxaban) and mechanical prophylaxis (graduated compression stockings, foot pumps and IPC) in specific populations, dependent upon their clinical need: general medical patients, patients admitted for stroke, patients with cancer, patients with central venous catheters, patients with palliative care, patients undergoing non-orthopaedic surgery, patients undergoing orthopaedic surgery, patients with major trauma or spinal injury, patients with lower limb plaster casts, patients admitted to critical care, and women admitted to hospital whilst pregnant or up to 6 weeks post-partum. The guidelines state that the choice of mechanical prophylaxis should be based on individual patient characteristics including clinical condition, surgical procedure and patient preference. It recommends any of the following methods graduated compression stockings (thigh or knee length), foot impulse devices or IPC devices (thigh or knee length).
  The guidelines make special reference to graduated compression stockings and recommends that they should not be offered to patients who have:
    - Suspected or proven peripheral arterial disease
    - Peripheral arterial bypass grafting
    - Peripheral neuropathy
    - Cardiac failure
    - Patients with stroke

    - Leg oedema
    - Severe limb deformity
    - Local conditions in which stockings may cause damage, for example, 'tissue paper' skin, dermatitis, gangrene or recent skin graft
    - Unusual leg size or shape
- **NICE clinical guideline 144, June 2012. 'Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing'** (26). CG144 provides information on the management of adult patients with a suspected or confirmed DVT in primary, secondary or tertiary health-care settings.

The **draft version of NICE clinical guideline 46 'The prevention of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients undergoing orthopaedic surgery and other high-risk surgical procedures'** produced in 2007 (27) discussed evidence for electrical stimulation-induced contractions and based on the publications by Browse and Negus 1970 (23) and Lindstrom 1982 (24) stated that electrical stimulation was effective in promoting limb blood flow in order to reduce venous pooling/stasis and oedema.

Also available are the Scottish Intercollegiate Guidelines Network (SIGN) guidelines for Scotland and the International Consensus Statement of the International Union of Angiology:

- **SIGN guideline 122, December 2010. 'Prevention and management of venous thromboembolism'** (28). SIGN 122 provides information on the prevention of VTE in adult patient groups at risk of VTE, and the management of VTE. Mechanical prophylaxis (with compression stockings and IPC) used concomitantly with pharmacological methods is recommended in surgical patients. Compression stockings may also be used in combination with pharmacological prophylaxis in patients with evidence of superficial thrombophlebitis.
- **International consensus statement, April 2013. 'Prevention and treatment of venous thromboembolism'** (29). The international consensus statement provides information on the benefits and/or harms for the various methods for the prevention or treatment of VTE. It recommends the use of NMES in patients with multiple trauma when pharmacological and other mechanical prophylaxis cannot be used.

There are also four NICE technology appraisals providing guidance on the use of pharmacological agents; rivaroxaban (TA 261, TA170), apixaban (TA245) and dabigatran (TA157), and one interventional procedure guidance document (IPG440).

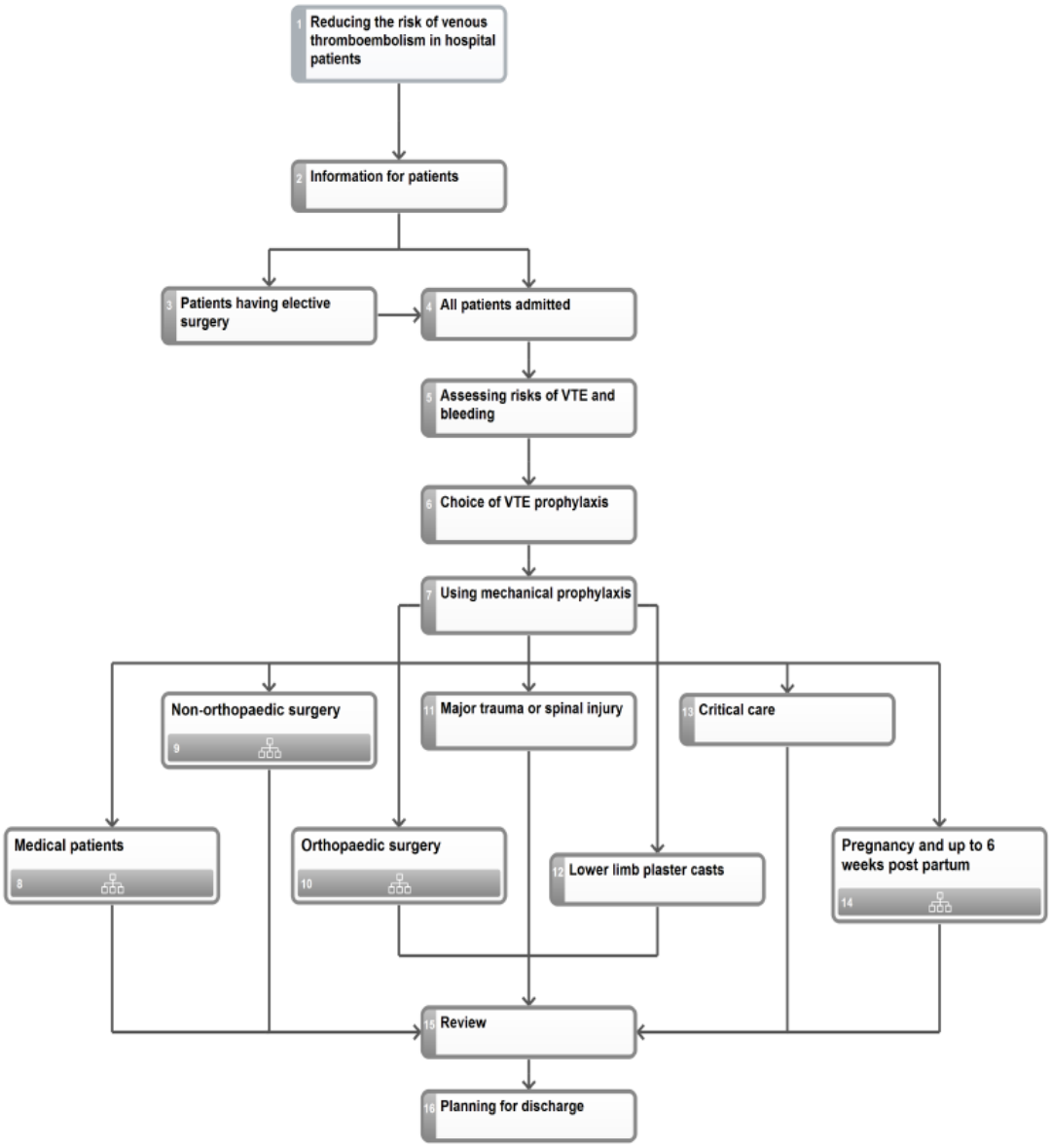
- **NICE technology appraisal 261, July 2012. 'Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism'** (30)
- **NICE technology appraisal 245, January 2012. 'Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults'** (31)
- **NICE technology appraisal 170, April 2009. 'Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults'** (32)

- **NICE technology appraisal 157, September 2008. 'Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults'** (33)
- **NICE interventional procedure 440, February 2013. 'Ultrasound-guided foam sclerotherapy for varicose veins'** (34).

3.3 Describe the clinical pathway of care that includes the proposed use of the technology.

According to NICE Guideline (CG92) and the NICE Pathway for VTE, on admission to hospital, patients should be assessed in order to identify those at increased risk of VTE (Figure 3).

Figure 3: NICE VTE pathway



Abbreviations: VTE, venous thromboembolism.

Patients should be regarded as being at increased risk of VTE if they have had or are expected to have significantly reduced mobility for 3 days or more or if they are expected to have ongoing reduced mobility relative to their normal state and have one or more risk factors.

All patients should be assessed for risk of bleeding before being offered pharmacological VTE prophylaxis. Pharmacological VTE prophylaxis should not be administered to patients with any of risk factors for bleeding, unless the risk of VTE outweighs the risk of bleeding. Pharmacological prophylaxis should be started as soon as possible after the risk assessment has been completed and continued until the patient is no longer at increased risk of VTE.

The choice of mechanical VTE prophylaxis should be based on individual patient factors including clinical condition, surgical procedure and patient preference.

Despite identifying patients at increased risk of VTE whilst in hospital according to the NICE Pathway, there is currently no VTE prophylaxis treatment option for hospitalised patients for whom current mechanical methods of prophylaxis are impractical or contraindicated.

The geko™ device fills a clear, current unmet need for this patent population and if adopted for use pre- and/or post-surgery within the NHS would provide a treatment option for the group of hospitalised patients that are currently at risk of serious clinical consequences or even death.

3.4 Please describe any issues relating to current clinical practice, including any uncertainty about best practice.

NICE guideline (CG92) does not include VTE prophylaxis for the population of interest in this submission i.e. those patients for whom current mechanical methods of prophylaxis are impractical or contraindicated. Hence it would be useful to provide the NHS with guidance for this group of patients.

3.5 Describe the new pathway of care incorporating the new technology that would exist if the technology was adopted by the NHS in England.

It is proposed that the geko™ device would provide a mechanical method of prophylaxis of VTE in patients for whom current mechanical methods are impractical or contraindicated and is likely to be administered in a hospital setting.

3.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

There is no anticipated change to services as a result of introducing the geko™ device.

3.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this

technology that are over and above usual clinical practice.

The geko™ device can be applied in as little as 60 seconds during a routine nurse check. There are no additional tests, monitoring or administration requirements over and above usual clinical practice (it is recommended that the device is checked during routine monitoring).

3.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

No additional facilities or infrastructure are required.

3.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

None.

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in section 3.9 that would no longer be needed with using this technology.

As the anticipated place in therapy for the geko™ device is for patients for whom current mechanical methods of prophylaxis are impractical or contraindicated, there would be no disinvestment as a result of the introduction of the geko™ device.

4 Regulatory information

4.1 Provide PDF copies of the following documents:

- **instructions for use**
- **CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity**
- **quality systems (ISO 13485) certificate (if required).**

Table 3: Checklist of documents submitted

Instructions for use	✓
CE mark certificate or equivalent UK regulatory approval	✓
Quality systems (ISO 13485) certificate	✓

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The geko™ device was originally CE Marked on 26th October 2010 (BSI, Notified Body 0086, certificate CE 558928) to increase blood circulation, and for the prevention of venous thrombosis. The scope of the CE Marking was extended on 20 July 2012 to include: “the prevention and treatment of oedema and promoting wound healing and the treatment of venous insufficiency and ischemia”. Subsequently the Notified Body was changed to SGS United Kingdom Ltd (Notified Body 0120, certificate GB12/87339), and the certificate appertaining to the CE Marking renewed on 15 April 2013.

4.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Details of regulatory approval for the geko™ device outside the UK are provided in Table 4.

Table 4: Regulatory approval for the geko™ device outside the UK

Area/country	Name of device	Regulatory body	Date of regulatory approval
Europe	geko™	CE Marking	26 Oct 2010
Australia	geko™	Therapeutic Goods Administration	24 Feb 2011
Canada	geko™	Health Canada	10 Jun 2011

4.4 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

The geko™ device has been launched in the UK.

4.5 If the technology has been launched in the UK provide information on the use in England.

The geko™ device has been evaluated across a number of NHS centres as part of a post-market surveillance (PMS) evaluation programme since August 2012, allowing the collection of relevant ergonomic and patient compliance data across a 24–48 hour post-operative period. Results from this have been included in Section 7.6.

5 Ongoing studies

5.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

A summary of ongoing geko™ device studies conducted within the UK is provided in Table 5.

Table 5: Summary of geko™ device ongoing studies

Location/ Study name	Study design	Comparators	Patient population	Study aim	No of Pts	Duration	Expected completion
[redacted]	Single centre, randomised, open-label, intra-patient	• geko™ device • IPC of the foot	Patients following elective THR	Lower limb circulation	[redacted]	[redacted]	Aug 2013
[redacted]	Single centre, randomised, open-label, intra-patient	• geko™ device • IPC of the calf	Patients following elective THR	Lower limb circulation	[redacted]	[redacted]	Sept 2013
[redacted]	Single centre, unblinded	• geko™ device	Vascular patients (ischemic leg, venous ulcer, arterial ulcer, stroke, graft by-pass)	Lower limb blood flow	[redacted]	[redacted]	Sept 2013
[redacted]	Single centre, open-label, intra-subject	• geko™ device	Healthy volunteers	Blood flow in deep veins of leg	[redacted]	[redacted]	Oct 2013
[redacted]	Prospective, observational	• geko™ device	Patients with chronic critical ischaemia or non-significant arterial disease	Haemodynamic efficacy and tolerability	[redacted]	[redacted]	Nov 2013
[redacted]	Multicentre, randomised, controlled	• geko™ device • TEDS	Patients following elective THR	Incidence of asymptomatic and symptomatic DVT	[redacted]	[redacted]	Dec 2013
[redacted]	Controlled, interventional	• geko™ device	Patients with venous incompetence (3 groups: superficial venous incompetence, deep venous incompetence, deep vein occlusion)	Lower limb blood flow	[redacted]	[redacted]	Feb/Mar 2014
[redacted]	Randomised, controlled	• geko™ device	Patients following infra-inguinal surgical vein revascularisation	Blood flow through graft	[redacted]	[redacted]	July 2014

Abbreviations: DVT, deep vein thrombosis; IPC, intermittent pneumatic compression; NMES, neuromuscular electrostimulation; TEDS, thromboembolism deterrent stockings; THR, total hip replacement.

5.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

No other form of assessment in the UK is currently underway or planned.

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1.1 Describe any equality issues relating to the patient population and condition for which the technology is being used.

There are no equality issues. However, the geko™ device may not be suitable for:

- those with fragile skin (for example, older patients and children) and those with burns and skin conditions within the application area of the device
- those patients whose common peroneal nerve or device application site is inaccessible or where the common peroneal nerve function is impaired.

6.1.2 Describe any equality issues relating to the assessment of the technology that may require special attention.

None.

6.1.3 How will the submission address these issues and any equality issues raised in the scope?

None.

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in Table 1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

Summary of published and unpublished clinical evidence

- Six studies assessing the effectiveness of the geko™ device in healthy volunteers were identified:
  - One published study was identified by a systematic review of the literature
  - Three accepted studies were identified by hand-searching internal company documentation
  - Three unpublished studies were identified by hand-searching internal company documentation
  - One unpublished manuscript and one published poster report on the same study
- The geko™ device is effective in reducing stasis by increasing blood flow compared with no stimulation
  - Increases in venous blood volume flow range from +14% to +326%
  - Increases in arterial blood volume flow range from +24% to +64%
  - Increases in venous peak velocity range from +41% to +221%
  - Increases in arterial peak velocity range from +1% to +24%
- The geko™ device is effective in increasing blood flow compared with intermittent pneumatic compression devices
- The geko™ device is effective in increasing blood flow either with or without plaster cast
- The geko™ device is well tolerated, with minimal/mild discomfort as measured by the discomfort visual analogue scale and verbal response score

7.1 Identification of studies

A systematic review (SR) was conducted to identify

- relevant published clinical randomised controlled trials (RCTs) and non-RCTs on the use of the geko™ device using OnPulse™ technology to increase blood circulation for the prevention of venous thromboembolism (VTE)
- published data providing an association between increased blood flow and DVT reduction for mechanical methods (neuromuscular electrostimulation [NMES] and intermittent pneumatic compression [IPC]).

7.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in section 10, appendix 1.

A systematic literature search was conducted and downloaded into a bespoke Microsoft® Access database. Searches were conducted with no restrictions on date using the following databases: The Cochrane Library, OVID MEDLINE (including MEDLINE In-process), and OVID Embase. Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for the condition (DVT) and the treatments (geko™ and terms for electrical stimulation). The full search strategy is outlined in Section 10.1.

Identified studies were independently assessed by a reviewer in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were revolved by a second reviewer. Data were extracted from eligible publications into a pre-defined table by a reviewer.

7.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Unpublished data were identified by hand-searching internal company documentation supplied by Firstkind.

7.2 Study selection

Published studies

7.2.1 Complete Table 6 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

An SR was conducted to identify clinical evidence for the geko™ device (RCTs and non-RCTs, including adverse events [AEs]). In addition, data on non-pharmacological comparator (neuromuscular electrostimulation [NMES] and intermittent pneumatic compression [IPC]) studies was sought to identify additional evidence on the association between increased blood flow and a reduction in DVT.

Inclusion and exclusion selection criteria for published studies are shown in Table 6 and 7.

Table 6: Selection criteria used to identify geko™ device published studies

Inclusion criteria	
Population	Patients or volunteers using the geko™ device using OnPulse™ technology to increase blood flow for the prevention of VTE
Interventions	geko™ OnPulse™ technology device

Outcomes	• Blood flow
	• Incidence of PE
	• Any DVT
	  ○ Asymptomatic DVT
	  ○ Symptomatic DVT
	• VTE composite
	• Major VTE
	• Hospitalisation
	• Secondary endpoints
	• PTS
	• QoL
	• Mortality and AE data
	• Resource use

Study design	RCTs, non-RCTs
Language restrictions	• English Language only. • Foreign language papers with English abstracts could be included
Search dates	No restriction
Exclusion criteria	
Population	Patients undergoing treatment of DVT
Study design	Case studies, editorials, letters, reviews
Interventions	• Anti-embolic stockings • Pharmacological interventions such LMWH

Abbreviations: AE, adverse event; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; PE, pulmonary embolism; PTS, post-thrombotic syndrome; QoL, quality of life; RCT, randomised controlled trial; VTE, venous thromboembolism.

Table 7 Selection criteria used for published studies showing an association between increased blood flow and DVT

Inclusion criteria	
Population	• Patients at risk of VTE • Healthy volunteers
Interventions	Any intervention that demonstrates increase in blood flow such as IPC

Outcomes	• Blood flow
	• Vessel diameter
	• Incidence of PE
	• Any DVT
	  ○ Asymptomatic DVT
	  ○ Symptomatic DVT
	• VTE composite
	• Major VTE

Study design	RCTs, non-RCTs
Language restrictions	• English Language only. • Foreign language papers with English abstracts could be included
Search dates	No restriction
Exclusion criteria	
Population	Patients undergoing treatment of DVT
Study design	Case studies, editorials, letters, reviews
Interventions	• Anti-embolic stockings • Pharmacological interventions such LMWH

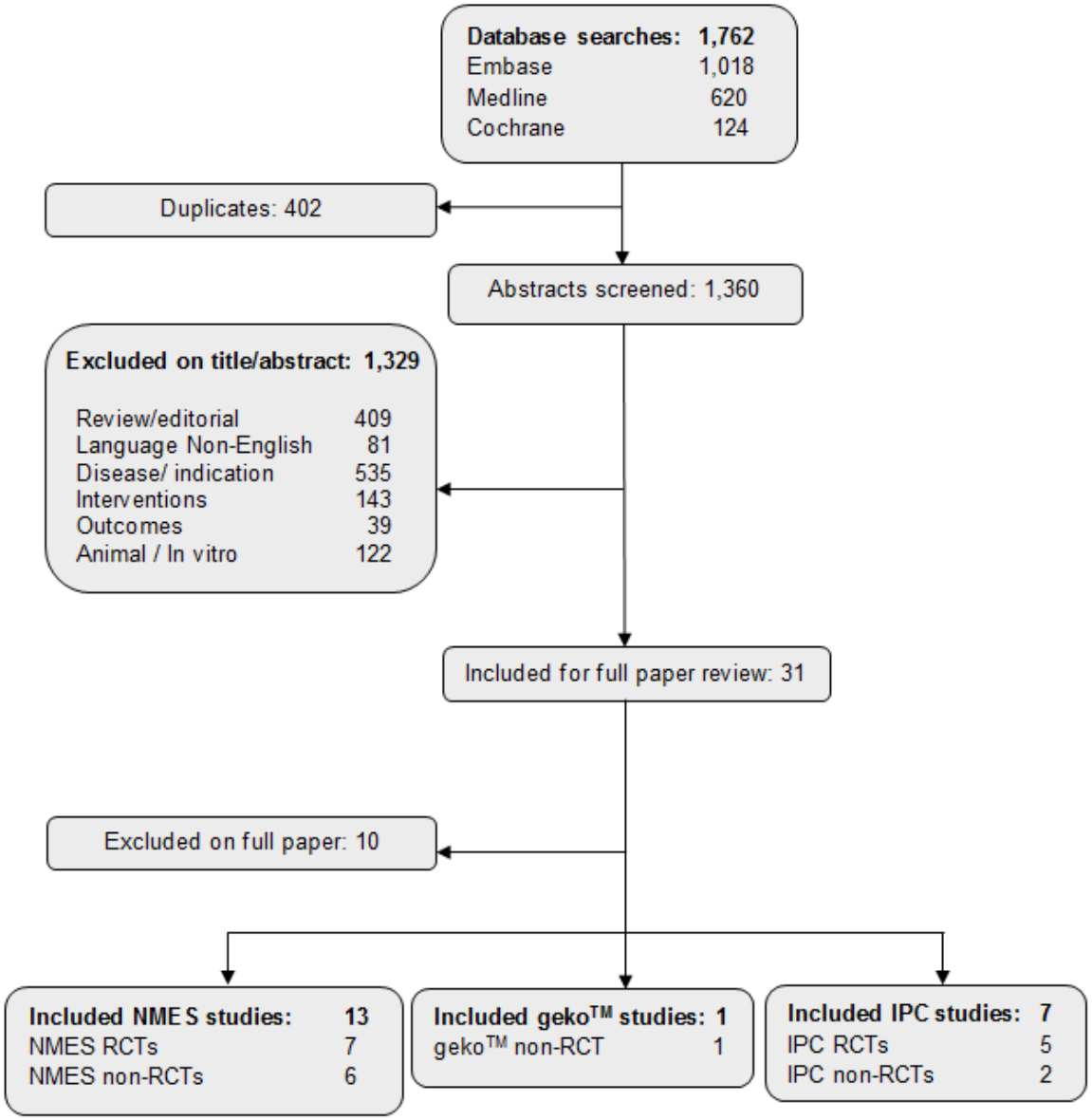
Abbreviations: DVT, deep vein thrombosis; LMWH, low molecular weight heparin; IPC, intermittent pneumatic compression; PE, pulmonary embolism; RCT, randomised controlled trial; VTE, venous thromboembolism.

7.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Following assessment and exclusion of studies based on title, abstract and full text, 21 published studies were included in the final data set (13, 20-24, 35-49). Of these, one study examined the geko^{TM} device, 13 studies examined NMES and seven reported on IPC devices. Ten studies were excluded on full text evaluation (50-59).

The systematic review schematic is shown in Figure 4.

Figure 4: Schematic for the systematic review of published studies



Abbreviations: IPC, intermittent pneumatic compression; NMES, neuromuscular electrostimulation; RCT, randomised controlled trial.

7.2.3 Complete Table 8 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Inclusion and exclusion selection criteria for unpublished studies are shown in Table 8.

Table 8: Selection criteria used for geko™ device unpublished studies

Inclusion criteria	
Population	Patients or volunteers using the geko™ device using OnPulse™ technology to increase blood flow for the prevention of VTE
Interventions	geko™ OnPulse™ technology device

Outcomes	• Blood flow
	• Incidence of PE
	• Any DVT
	  ○ Asymptomatic DVT
	  ○ Symptomatic DVT
	• VTE composite
	• Major VTE
	• Hospitalisation
	• Secondary endpoints
	• PTS
	• QoL
	• Mortality and AE data
	• Resource use

Study design	RCTs, non-RCTs
Language restrictions	• English Language only. • Foreign language papers with English abstracts could be included
Search dates	No restriction
Exclusion criteria	
Population	Patients undergoing treatment of DVT
Study design	Case studies, editorials, letters, reviews
Interventions	• Anti-embolic stockings • Pharmacological interventions such LMWH

Abbreviations: AE, adverse event; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; PE, pulmonary embolism; PTS, post-thrombotic syndrome; QoL, quality of life; RCT, randomised controlled trial; VTE, venous thromboembolism.

7.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

Three unpublished studies were identified; one of these studies, Williams unpublished 2013 (60), was based on data presented in a poster by Williams 2013 (61). No studies were excluded.

7.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in Table 6 and Table 8

The systematic review of clinical evidence identified four published and three unpublished studies of the geko™ device; please note Williams unpublished 2013 (60) is based on data presented in a poster by Williams, 2013 (61) (Table 9 and Table 10).

Table 9: List of relevant published studies

Primary study reference	Population	Intervention	Comparator
Tucker 2010 (45)	Healthy volunteers	geko™ device	None
Jawad (cardiac) 2012 (62)	Healthy volunteers	geko™ device	None
Jawad (coagulation) 2012 (62)	Healthy volunteers	geko™ device	None
Williams 2013 (61)	Healthy volunteers	geko™ device	IPC

Abbreviations: NR, not relevant.

Table 10: List of relevant unpublished studies

Primary study reference	Population	Intervention	Comparator	Publication plan
Jawad (vs IPC) 2012 (63)	Healthy volunteers	geko™ device	IPC	Submitted to Journal of Thrombosis and Haemostasis
Warwick unpublished 2013 (64)	[redacted]	[redacted]	[redacted]	[redacted]
Williams unpublished 2013 (60)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IPC, intermittent pneumatic compression.

In addition to the clinical data provided in this submission, venous transit time analysis has been conducted by an external research group led by Prof Charles McCollum. Devices for this study were donated by Firstkind. Interim data from this analysis is presented in Section 7.6 (Transit time data).

7.3.2 State the rationale behind excluding any of the published studies listed in Table 9 and Table 10.

No studies detailed in Table 9 and Table 10 were excluded.

7.4 Summary of methodology of relevant studies

7.4.1 Describe the study design and methodology for each of the published and unpublished studies using the tables below as appropriate. A separate table should be completed for each study.

No RCTs relevant to the submission were identified.

The methodology for six[b] relevant observational studies is summarised in the following tables:

- Tucker 2010 (45); Table 11
- Jawad (cardiac) 2012 (62); Table 12
- Jawad (coagulation) 2012 (62); Table 13
- Williams 2013 (61); Table 14
- Jawad unpublished (vs IPC) 2012 (63); Table 15
- Warwick unpublished 2013 (64); Table 16
- Williams unpublished 2013 (60); Table 17

Table 11: Summary of methodology for observational study, Tucker 2010

Study name (acronym)	**Tucker 2010**
Objective	To investigate the safety and efficacy of a novel neuromuscular device that augments peripheral blood flow
Location	UK
Design	Single arm, single centre, unblinded
Duration of study	2 visits of 4 hr
Population	Healthy volunteers
Sample size	30
Inclusion criteria	• Good general health/fitness • 18–65 years • BMI 18–34 Kg/m^2
Exclusion criteria	• Organ dysfunction (any clinically significant deviation from normal) • Haematological disorders, previous DVT/PE, peripheral arterial disease (ankle-brachial pressure index <0.9), varicose veins or lower limb ulceration, musculoskeletal disorders, recent surgery and recent trauma to lower limb, history of gastrointestinal, hepatic or renal, CV, endocrine, neurological, dermatological, rheumatological, metabolic (including diabetes), psychiatric, haematological (especially in relation to clotting or coagulation) or systemic disease judged to be significant • Positive pregnancy test • History of drug abuse (including alcohol) • Medication during the 30 days preceding the study and no medication during the course of the study • Smoker • Pulse rate <50 bpm • SBP>150 mmHg or <80 mmHg • DBP>90 mmHg or <60 mmHg • Donation of blood within 8 weeks of the screening period or during

[b] Note Williams unpublished 2013 and Williams 2013 report on the same study

Study name (acronym)	Tucker 2010
	investigation
Intervention(s) (n =) and comparator(s) (n =)	• All subjects were examined (n=30) • Device fitted unilaterally • Effects of electrical stimulation on lower limb blood flow investigated during a 4 hr period • A succession of 15 different stimulation programmes (Section 10.6) was applied according to a 2-dimensional matrix of amplitude and frequency. Each stimulation programme was 5 min long, followed by 5 min of response recording (stimulator off) and a 5 min recovery phase to allow vascular re-equilibration before the next sequence • During the second visit (within 2 weeks), the stimulation sequence was reversed (starting at stimulation programme 15 and proceeding to stimulation programme 1)
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	No follow-up of volunteers was conducted
Statistical tests	• ANOVA with adjusted sum of squares was conducted for each dependent parameter against stimulation settings of frequency and current • Statistical analysis for the comparison of data obtained at each stimulus and baseline or dorsiflexion was performed using Minitab software (Minitab Ltd, UK) • $p \leq 0.05$ considered to be significant • Data shown represents the mean of data obtained from 30 volunteers and the standard error of the difference
Outcomes (including scoring methods and timings of assessments)	• BP was measured before stimulation and at every hour until the end of the study period (4 hr) • Changes in BP, blood flow and volume, microcirculatory flux and physiological measures related to the heart measured using standard non-invasive techniques including PPG, SPG, laser Doppler fluxmetry, transcutaneous oxygen tension, colour flow duplex ultrasound and pulse oximetry. All parameters were measured at baseline (at rest), at voluntary muscle action (dorsiflexion), during the 5 min stimulation period and/or during the 5 min recovery phase. • Acceptance and tolerability measured by questionnaire with a VRS and VAS (described in Section 10.8)

Abbreviations: BMI, body mass index; BP, blood pressure; bpm, beats per minute; CV, cardiovascular; DBP, diastolic blood pressure; DVT, deep vein thrombosis; N/A, not applicable; PE, pulmonary embolism; SBP, systolic blood pressure; VAS, visual analogue scale; VRS, verbal response scale.

Table 12: Summary of methodology for observational study, Jawad (cardiac) 2012

Study name (acronym)	Jawad (cardiac) 2012
Objective	To investigate the effectiveness of a novel neuromuscular device in increasing venous return from the lower limb
Location	UK
Design	Single arm, single centre, unblinded
Duration of study	1 visit
Population	Healthy volunteers
Sample size	9
Inclusion criteria	• Good general health • 18–65 years • BMI 18–34 Kg/m^2
Exclusion criteria	• Organ dysfunction (any clinically significant deviation from normal) • Haematological disorders, previous DVT/PE, varicose veins or lower limb ulceration, musculoskeletal disorders, recent surgery and recent trauma to lower limb, history of gastrointestinal, hepatic or renal, CV, endocrine, neurological, dermatological, rheumatological, metabolic (including diabetes), psychiatric or systemic disease judged to be significant • Positive pregnancy test • Peripheral arterial disease (ankle-brachial pressure index <0.9) • History of drug abuse (including alcohol) • Medication during the 30 days preceding the study and no medication during the course of the study
Intervention(s) (n =) and comparator(s) (n =)	• All subjects were examined (n=9) • geko™ device fitted bilaterally • For each volunteer two different pulse width settings, 400 µs and 600 µs were used consecutively. In both settings, the frequency used was 3 Hz and the device was current modulated to provide a peak current of 20 mA • The duration of each stimulation programme was 30 minutes for each setting
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	No follow-up of volunteers was conducted
Statistical tests	• Statistical analysis performed using Minitab 16 software (Minitab Ltd, UK) • Analysis of variance using adjusted sum of squares followed by Dunnett's Test conducted for each parameter tested. A p-value of ≤ 0.05 was considered statistically significant. The data demonstrated in the results section represents the mean of data obtained from 9 volunteers. • p ≤ 0.05 considered to be significant

Study name (acronym)	Jawad (cardiac) 2012
	• Data shown represents the mean of data obtained from 9 volunteers
Outcomes (including scoring methods and timings of assessments)	• Echocardiography and colour flow duplex ultrasound measurements obtained at baseline and during the different stimulation settings • Tissue Doppler Imaging echocardiography; Two-dimensional imaging assessed ventricular and valvular movement. Motion mode measured dimensions and timing of specific cardiac events. Imaging techniques performed in 6 standard views; parasternal long axis (PLAX), parasternal short axis (PSAX), apical 4 chamber (A4C), apical 2 chamber (A2C), apical 3 chamber (A3C), arterial short axis (ASAX). • Biplane left ventricular EF to evaluate pumping action of heart, calculated using Simpson's method (ventricles of heart treated as series of discs, where ventricular length is divided into 20 equal sections) • Left ventricular filling assessed by measuring mitral inflow velocity and left ventricular diastolic volume (calculated using Simpson's method) • Cardiac output measured using LVOT VTI • Colour flow duplex ultrasound imaging performed on femoral blood vessel (15 cm proximal to patella) to measure femoral vessel diameter, peak velocity, blood volume flow, cross sectional area • LDF to measure skin microcirculatory velocity at baseline and following 10 minutes of stimulation

Abbreviations: BMI, body mass index; CV, cardiovascular; DVT, deep vein thrombosis; EF, ejection fraction; LVOT VTI, left ventricular outflow tract velocity time interval; PE, pulmonary embolism.

Table 13: Summary of methodology for observational study, Jawad (coagulation) 2012

Study name (acronym)	Jawad (coagulation) 2012
Objective	To evaluate the efficacy, safety and tolerability of a novel neuromuscular device in enhancing lower limb blood flow and its effect on blood coagulation factors
Location	UK
Design	Single arm, single centre, unblinded
Duration of study	2 visits of 4 hours
Population	Healthy volunteers
Sample size	10
Inclusion criteria	• Good general health • 18–65 years • BMI 18–34 Kg/m^2
Exclusion criteria	• Organ dysfunction (any clinically significant deviation from normal) • Haematological disorders, previous DVT/PE, varicose veins or lower limb ulceration, musculoskeletal disorders, recent surgery and recent trauma to lower limb, history of gastrointestinal, hepatic or renal, CV, endocrine, neurological, dermatological, rheumatological, metabolic (including diabetes), psychiatric or systemic disease judged to be significant

Study name (acronym)	Jawad (coagulation) 2012
	• Peripheral arterial disease (ankle-brachial pressure index <0.9) • Positive pregnancy test • History of drug abuse (including alcohol) • Medication during the 30 days preceding the study • Donation of blood within 8 weeks of the screening period or during investigation
Intervention(s) (n =) and comparator(s) (n =)	• All subjects were examined (n=10) • Device applied unilaterally and compared with unstimulated contralateral control leg • Device used at 25 mA amplitude, 3 Hz frequency and 600 µs pulse width • Stimulation applied for 5 minutes every 15 minutes followed by 10 minute recovery phase (whilst sitting in an airline seat with legs bent at the knees for 4 hours) • Volunteers were cannulated in the vein at three sites: bilaterally in the foot (dorsum or medial malleolar region) and one arm (left arm) • During second visit the same investigations were repeated without stimulation
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	No follow-up of volunteers was conducted
Statistical tests	• Statistical analysis performed using Minitab 16 software (Minitab Ltd, UK) • Analysis of variance conducted using adjusted sum of squares followed by Dunnet's Test for each parameter tested • Results obtained during stimulation study compared with those obtained during control study at each time interval with baseline values acting as reference • $p \leq 0.05$ considered to be significant • Data shown represents the mean of data obtained from 10 volunteers and are presented as mean (SD)

Study name (acronym)	Jawad (coagulation) 2012
Outcomes (including scoring methods and timings of assessments)	• LDF, Colour Flow Duplex and ultrasound (baseline, 1/2/3/4 hours) evaluated changes in lower limb blood flow, peak velocity, vessel wall diameter • Pulse oximetry measured oxygen saturation • Heart rate • Blood pressure • Blood coagulation (baseline, 1/2/3/4 hours). • Clotting time assessed by ACT System and Rotational Thromboelastometry (Rotem®). Key parameters measured at different stages of clot formation include o Clotting time: start of measurement to initiation of clotting (seconds) o Clot formation time: initiation of clotting until clot firmness of 20 mm detected (seconds) o Maximum clot firmness: firmness of clot (mm) o Maximum lysis: percentage reduction of clot firmness after MCF (breakdown of clot) • Coagulation factors assessed by ELISA; Tissue Plasminogen Activator (t-PA) Antigen, von Willebrand Factor (vWF) and 6-Keto Prostaglandin F1 alpha • Acceptance and tolerability measured by questionnaire with a VRS and VAS (described in Section 10.8)

Abbreviations: ACT, automated coagulation timer; BMI, body mass index; CV, cardiovascular; ELISA, enzyme linked immunosorbent assay; VAS, visual analogue scale; VRS, verbal response scale.

Table 14: Summary of methodology for observational study, Williams 2013

Study name (acronym)	Williams 2013
Objective	To investigate the efficacy of a novel neuromuscular device vs IPC
Location	UK
Design	Single arm, cross-over, single centre, unblinded
Duration of study	NR
Population	Healthy volunteers
Sample size	10
Inclusion criteria	NR
Exclusion criteria	NR
Intervention(s) (n =) and comparator(s) (n =)	• All subjects were examined (n = 10) • geko™ device fitted bilaterally • Effects of electrical stimulation or IPC on lower limb blood flow investigated • Stimulation at 1 Hz, 27 mA • Subjects fitted with geko™ device for 30 mins, followed by 20 mins rest, followed by IPC for 30 mins (and *vice versa*)
Baseline differences	N/A

Study name (acronym)	Williams 2013
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	No follow-up of volunteers was conducted
Statistical tests	NR
Outcomes (including scoring methods and timings of assessments)	• TAMV % change • Peak velocity % change • Flow rate % change

Abbreviations: IPC, intermittent pneumatic compression; NR, not reported; TAMV, time averaged mean velocity.

Table 15: Summary of methodology for observational study, Jawad unpublished (vs IPC) 2012

Study name (acronym)	Jawad unpublished (vs IPC) 2012
Objective	To compare the effectiveness and tolerability of the geko^{TM} device vs 2 leading IPC devices in enhancing lower limb blood perfusion
Location	UK
Design	Single arm, single centre, unblinded
Duration of study	1 visit
Population	Healthy volunteers
Sample size	10
Inclusion criteria	• Good general health/fitness • 18–65 years • BMI 18–34 Kg/m^2
Exclusion criteria	• Organ dysfunction (any clinically significant deviation from normal) • Haematological disorders, previous DVT/PE, varicose veins or lower limb ulceration, musculoskeletal disorders, recent surgery and recent trauma to lower limb, history of gastrointestinal, hepatic or renal, CV, endocrine, neurological, dermatological, rheumatological, metabolic (including diabetes), psychiatric or systemic disease judged to be significant • Peripheral arterial disease (ankle-brachial pressure index <0.9) • History of drug abuse (including alcohol) • Medication during the 30 days preceding the study and no medication during the course of the study

Study name (acronym)	Jawad unpublished (vs IPC) 2012
Intervention(s) (n =) and comparator(s) (n =)	• All subjects were examined (n=10) with all 3 devices; geko™, IPC-Huntleigh Flowtron Universal, IPC-Kendall SCD Express • Devices were fitted bilaterally • Subjects lay supine on a padded table that could be tilted manually, with their heads supported by a pillow and tilted upwards to 45°. After 30 minutes of supine rest, baseline measurements were recorded. Test devices were then fitted bilaterally to the subject's legs, in accordance to the manufacturer's instructions, in a sequential manner. The order of the device tested was made in accordance to a pre-set randomisation schedule to reduce bias. Each device was active for 30 minutes followed by a 10 minutes recovery phase, to allow vascular re-equilibration prior to applying the next device
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	No follow-up of volunteers was conducted
Statistical tests	• Statistical analysis was performed using Minitab 16 software (Minitab Ltd, UK) • Analysis of variance using adjusted sum of squares was conducted for each parameter tested • $p \leq 0.05$ considered to be significant • Data shown represents the mean of data obtained from the 10 volunteers studied
Outcomes (including scoring methods and timings of assessments)	• At the end of each programme and while the devices are still active, changes in blood flow and volume, together with microcirculatory velocity were measured using colour flow duplex ultrasound and LDF • Safety assessments included BP, transcutaneous oxygen tension and pulse oximetry • Acceptance and tolerability measured by questionnaire with a VRS and VAS (described in Section 10.8)

Abbreviations: BMI, body mass index; BP, blood pressure; IPC, intermittent pneumatic compression; LDF, laser Doppler fluxmetry; N/A, not applicable.

Table 16: Summary of methodology for observational study, Warwick unpublished 2013

Study name (acronym)	Warwick unpublished 2013
Objective	[redacted]
Location	[redacted]
Design	[redacted]

Study name (acronym)	Warwick unpublished 2013
Duration of study	[redacted]
Population	[redacted]
Sample size	[redacted]
Inclusion criteria	[redacted]
Exclusion criteria	[redacted]
Intervention(s) (n =) and comparator(s) (n =)	[redacted]
Baseline differences	[redacted]
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	[redacted]
Statistical tests	[redacted]
Outcomes (including scoring methods and timings of assessments)	[redacted]

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; N/A not applicable; VAS, visual analogue scale; VRS, verbal rating scale.

Table 17: Summary of methodology for observational study, Williams unpublished 2013

Study name (acronym)	Williams unpublished 2013 (based on Williams 2013)
Objective	
Location	
Design	
Duration of study	
Population	
Sample size	
Inclusion criteria	
Exclusion criteria	
Intervention(s) (n =) and comparator(s) (n =)	
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	
Statistical tests	
Outcomes (including scoring methods and timings of assessments)	

Abbreviations: IPC, intermittent pneumatic compression; NMES, neuromuscular electrostimulation; NR, not reported; TAMV, time averaged mean velocity.

7.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

- Data for Tucker 2010 has been taken from the published manuscript (45) and unpublished study data (65)
- Data for the Jawad (coagulation) 2012 study has been taken from a PhD thesis (62) and unpublished study data (66).
- Data for the Jawad unpublished (vs IPC) 2012 study has been taken from a manuscript in preparation (63), a PhD thesis (62) and additional unpublished study data (67)
- Data for Warwick unpublished 2013 has been taken from the accepted manuscript and unpublished study data (68)

7.4.3 Highlight any differences between patient populations and methodology in all included studies.

Baseline characteristics of volunteers were not reported in Tucker 2010, Jawad unpublished (vs IPC) 2012 or Warwick unpublished 2013. Baseline characteristics for Jawad (cardiac) 2012, Jawad (coagulation) 2012, Williams 2013 and Williams unpublished 2013 are summarised in Table 18.

Table 18: Baseline characteristics of volunteer populations in included studies

	Jawad (cardiac) 2012	Jawad (coagulation) 2012	Williams 2013	Williams unpublished 2013
Gender	• 7 males • 2 females	• 9 males • 1 females	• 4 males • 6 females	[redacted]
Age (years)				
Mean	37.33	34.6	27.1	[redacted]
SD	8.14	6.88	3.8	[redacted]
Median	33	35	NR	[redacted]
Range	30–45	26–45	NR	[redacted]
BMI (Kg/m^2)				
Mean	25.07	25.3	24.8	[redacted]
SD	3.77	2.86	NR	[redacted]
Median	24.2	24.8	NR	[redacted]
Range	20.3–31.2	20.1–30.2	NR	[redacted]

Abbreviations: NR, not reported; note: Williams unpublished 2013 and Williams 2013 report on the same study.

7.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 7.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

No subgroup analyses were undertaken in any of the studies.

7.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

All volunteers eligible to enter each study were treated and their data analysed. Five studies were single-arm studies and therefore no randomisation was performed. In the remaining study, Williams unpublished 2013, 10 eligible volunteers were randomised into two treatment arms (n=5 in each arm).

7.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

No volunteers were lost to follow-up or withdrew from any of the studies.

7.5 Critical appraisal of relevant studies

7.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in Table 19 and Table 20.

No RCTs for the geko™ device were identified and therefore none were quality assessed (Table 19).

Table 19: Critical appraisal of randomised control trials

Study name		
Study question	**Response (yes/no/not clear/NA)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	NA	NA
Was the concealment of treatment allocation adequate?	NA	NA
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	NA	NA
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	NA	NA
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	NA	NA
Is there any evidence to suggest that the authors measured more outcomes than they reported?	NA	NA
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	NA	NA

Quality assessments of observational studies are presented in Table 20.

Table 20: Critical appraisal of observational studies evaluating the geko™ device

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Tucker 2010		
Study question	yes	To investigate the safety and efficacy of a novel neuromuscular device that augments peripheral blood flow
Was the cohort recruited in an acceptable way?	yes	Volunteers recruited by advertisement to staff and students of Queen Mary University of London, Barts and The London NHS and to the general community, as approved by the Central Office for Research Ethics Committees
Was the exposure accurately measured to minimise bias?	yes	Each subject had one leg connected to stimulator and other leg immobile acting as control. 15 sequential electrical stimulations applied for 5 min each followed by 10 min recovery phase in temperature and humidity controlled environment.
Was the outcome accurately measured to minimise bias?	yes	Outcomes were measured using photoplethysmography, strain gauge plethysmography, laser Doppler fluxmetry, transcutaneous oxygen tension, pulse oximetry, superficial femoral vein blood flow and vessel diameter (ultrasound)
Have the authors identified all important confounding factors?	yes	Potential confounding factors were previous DVT/PE, peripheral arterial disease, varicose veins or lower limb ulceration, chronic disease and high systolic and diastolic blood pressures
Have the authors taken account of the confounding factors in the design and/or analysis?	yes	To minimise bias, patients with previous DVT/PE, peripheral arterial disease, varicose veins or lower limb ulceration, chronic disease and high systolic and diastolic blood pressures were excluded
Was the follow-up of patients complete?	yes	Data were acquired from all 30 volunteers
How precise (for example, in terms of confidence interval and p values) are the results?	yes	p-values and standard error reported
Jawad (cardiac) 2012		
Study question	yes	Investigate effectiveness of novel electrical stimulation device in increasing venous return from lower limb, presumed to lead to enhancement in cardiac performance in healthy individuals
Was the cohort recruited in an acceptable way?	yes	Healthy volunteers recruited by advertisement to staff and students at Barts and The London, Queen Mary University, Barts and The London NHS Trust, and to the general community as approved by the Medical Ethics Committee

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Was the exposure accurately measured to minimise bias?	yes	Custom built electrical stimulation device fitted bilaterally to peroneal nerve at frequency of 3Hz and peak current of 20mA. 2 different pulse width settings, 400µs and 600µs used consecutively. Duration of each stimulation programme was 30 minutes for each setting
Was the outcome accurately measured to minimise bias?	yes	Colour flow duplex ultrasound imaging performed to femoral blood vessel to measure diameter, peak velocity, blood volume flow and cross sectional area
Have the authors identified all important confounding factors?	yes	Potential confounding factors were organ dysfunction, haematological disorders, previous DVT/PE, varicose veins or lower limb ulceration, musculoskeletal disorders, recent surgery and recent trauma to lower limb; and history of gastrointestinal, hepatic, renal, cardiovascular, endocrine, neurological, dermatological, rheumatological, and chronic obesity (BMI >34 kg/m^2).
Have the authors taken account of the confounding factors in the design and/or analysis?	yes	Each patient acted as their own control;, patients with medical histories such as organ dysfunction, haematological disorders, previous DVT/PE, varicose veins or lower limb ulceration, musculoskeletal disorders, recent surgery and recent trauma to lower limb; and history of gastrointestinal, hepatic, renal, cardiovascular, endocrine, neurological, dermatological, rheumatological, and chronic obesity (BMI >34 kg/m^2) were excluded
Was the follow-up of patients complete?	yes	Data acquired for all volunteers
How precise (for example, in terms of confidence interval and p values) are the results?	yes	p-values, 95% confidence intervals, and standard deviation were reported
Jawad (coagulation) 2012		
Study question	yes	Evaluate effectiveness of a topical electrical nerve stimulation device in enhancing lower limb blood flow by assessing blood flow velocity and volume changes during electrical stimulation using colour flow duplex ultrasound and laser Doppler flowmetry
Was the cohort recruited in an acceptable way?	yes	Healthy volunteers recruited by advertisement to staff and students at Barts and the London, Queen Mary University, Barts and The London NHS Trust and to the general community

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Was the exposure accurately measured to minimise bias?	yes	In-house custom built electrical stimulation device applied transcutaneously to common peroneal nerve in the popliteal fossa of one leg and compared to un-stimulated contralateral control leg. Electrical stimulation device used at amplitude of 25 mA and frequency of 3 Hz with pulse width of 600 µs To minimise bias, patients with medical histories such as organ dysfunction, haematological disorders, previous DVT/PE, varicose veins or lower limb ulceration, musculoskeletal disorders, recent surgery and recent trauma to lower limb; and history of gastrointestinal, hepatic, renal, cardiovascular, endocrine, neurological, dermatological, rheumatological, and chronic obesity (BMI >34 kg/m^2) were excluded
Was the outcome accurately measured to minimise bias?	yes	Blood flow throughout different time intervals assessed by laser Doppler flowmeter
Have the authors identified all important confounding factors?	yes	Potential confounding factors were organ dysfunction, haematological disorders, previous DVT/PE, varicose veins or lower limb ulceration, musculoskeletal disorders, recent surgery and recent trauma to lower limb; and history of gastrointestinal, hepatic, renal, cardiovascular, endocrine, neurological, dermatological, rheumatological, and chronic obesity (BMI >34 kg/m^2)
Have the authors taken account of the confounding factors in the design and/or analysis?	yes	Each patient acted as their own control; to minimise bias, patients with medical histories such as organ dysfunction, haematological disorders, previous DVT/PE, varicose veins or lower limb ulceration, musculoskeletal disorders, recent surgery and recent trauma to lower limb; and history of gastrointestinal, hepatic, renal, cardiovascular, endocrine, neurological, dermatological, rheumatological, and chronic obesity (BMI >34 kg/m^2) were excluded
Was the follow-up of patients complete?	yes	Data acquired for all volunteers
How precise (for example, in terms of confidence interval and p values) are the results?	yes	p-values, 95% confidence intervals, and standard deviation were reported

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Williams 2013		
Study question	yes	Compare venous haemodynamic efficacy of a novel NMES (1Hz, 27mA) device via the common peroneal nerve with IPC (40–45mmHg, 11sec) in healthy subjects
Was the cohort recruited in an acceptable way?	yes	10 healthy subjects were recruited; ethical approval was granted for the trial
Was the exposure accurately measured to minimise bias?	yes	Baseline superficial femoral venous velocity and flow, compared with 30 mins bilateral therapy with each of two devices in interventional cross-over trial
Was the outcome accurately measured to minimise bias?	not clear	No mention of how femoral venous velocity and flow was measured
Have the authors identified all important confounding factors?	no	No mention of any confounding factors
Have the authors taken account of the confounding factors in the design and/or analysis?	yes	Each patient acted as their own control
Was the follow-up of patients complete?	yes	Data available for all volunteers
How precise (for example, in terms of confidence interval and p values) are the results?	yes	p-values reported
Jawad unpublished (vs IPC) 2012		
Study question	yes	To compare effectiveness of NMES device in enhancing lower limb blood perfusion with two leading IPC devices
Was the cohort recruited in an acceptable way?	yes	10 healthy volunteers recruited. Study approved by North London Research Ethics Committee
Was the exposure accurately measured to minimise bias?	yes	Transcutaneous electrical nerve stimulation performed using geko™ device. IPC applied bilaterally by trained staff to calf. To minimise bias, participants were instructed to have a light breakfast and avoid fatty foods and caffeine containing products. Examinations performed in temperature and humidity controlled room
Was the outcome accurately measured to minimise bias?	yes	Colour flow duplex ultrasound measurements performed by an accredited vascular ultra-sonographer. Measurements to the superficial femoral vessels were taken bilaterally

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Have the authors identified all important confounding factors?	no	No mention of any confounding factors
Have the authors taken account of the confounding factors in the design and/or analysis?	yes	Each patient acted as their own control
Was the follow-up of patients complete?	yes	Data available for all volunteers
How precise (for example, in terms of confidence interval and p values) are the results?	yes	p-values reported
Warwick unpublished 2013		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Williams unpublished 2013		
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]

7.6 Results of the relevant studies

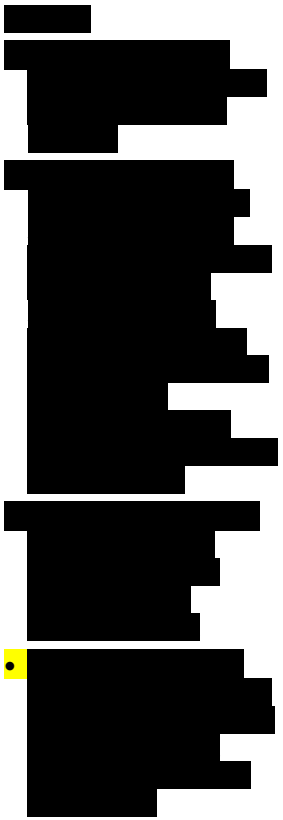
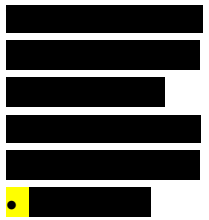
7.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in Table 21

An overview of results of outcomes pertinent to the decision problem are summarised by study in Table 21.

Detailed results from each study are provided in Table 22 to Table 27.

Table 21: Outcomes from published and unpublished studies – overview of results

Details	Tucker 2010	Jawad (cardiac) 2012	Jawad (coagulation) 2012	Williams 2013	Jawad unpublished (vs IPC) 2012	Warwick unpublished 2013	Williams unpublished 2013
Study overview	geko™ device optimal setting finding study	geko™ device on vascular flow and cardiac output	geko™ device on vascular flow coagulation factors	geko™ device vs IPC	geko™ device vs IPC	[redacted]	[redacted]
Size of study groups	N=30	N=9	N=10	N=10	N=10	[redacted]	[redacted]
Study duration	2 visits	1 visit	2 visits	NR	1 visit	[redacted]	[redacted]
Type of analysis	All volunteers entering the study were analysed (ITT)						
Blood volume flow (compared with baseline)	**Venous** • All stimulations showed a significant increase ($p<0.01$) • Both amplitude ($R^2=0.55$) and frequency ($R^2=0.82$) showed positive correlation	**Arterial** ($p \leq 0.05$) • geko™ 400 µs: +55% • geko™ 600 µs: +54%	**Venous CONTROL** • No significant change **Arterial CONTROL** • $p \leq 0.05$ • 1 hour: -25% • 2 hours: -10% • 3 hours: -20% • 4 hours: -11% **Venous STIMULATION** • $p \leq 0.001$ • 1 hour: +293% • 2 hours: +278% • 3 hours: +326% • 4 hours: +275% **Arterial STIMULATION** • $p \leq 0.05$ • 1 hour: +64% • 2 hours: +34%	**Venous** • Both geko™ and IPC increase venous blood volume flow compared to baseline. • The geko™ significantly increased venous flow relative to IPC ($p=0.02$)	**Venous** ($p \leq 0.001$) • geko™ NCU: +33% • geko™ TS: +14% • IPC-HF: -4% • IPC-Kendall: -4% **Arterial** ($p \leq 0.001$) • geko™ NCU: +30% • geko™ TS: -7% • IPC-HF: -9% • IPC-Kendall: -16%	NR	[redacted]

Details	Tucker 2010	Jawad (cardiac) 2012	Jawad (coagulation) 2012	Williams 2013	Jawad unpublished (vs IPC) 2012	Warwick unpublished 2013	Williams unpublished 2013
			• 3 hours: +47% • 4 hours: +43%				
Blood velocity (compared with baseline)	**Venous** • All stimulations showed a significant increase ($p<0.01$) • Both current ($R^2=0.74$) and frequency ($R^2=0.72$) showed positive correlation	**Arterial** ($p \leq 0.05$) • geko™ 400 µs: +24% • geko™ 600 µs: +24%	**Venous CONTROL** • No significant change **Arterial CONTROL** • No significant change **Venous STIMULATION** • $p \leq 0.001$ • 1 hour: +125% • 2 hours: +150% • 3 hours: +181% • 4 hours: +140% **Arterial STIMULATION** • No significant change	**Peak velocity** • Both geko™ and IPC increase peak velocity compared to baseline. • The increase from baseline was numerically higher with the geko™ device relative to IPC. The increase was not statistically significant ($p=0.06$) **Venous TAMV** • Both geko™ and IPC increase TAMV compared to baseline. • The increase from baseline was numerically higher with the geko™ device relative to IPC. The increase was not statistically significant ($p=0.71$)	**Venous** ($p \leq 0.001$) • geko™ NCU: +174% • geko™ TS: +73% • IPC-HF: +166% • IPC-Kendall: +143% **Arterial** ($p \leq 0.001$) • geko™ NCU: +24% • geko™ TS: +2% • IPC-HF: -4% • IPC-Kendall: -1%		

Details	Tucker 2010	Jawad (cardiac) 2012	Jawad (coagulation) 2012	Williams 2013	Jawad unpublished (vs IPC) 2012	Warwick unpublished 2013	Williams unpublished 2013
Discomfort assessment	**VRS** • Majority of stimulation programmes: minimal sensation • Positive correlation with both frequency and current		**VRS** ($p \leq 0.05$) • No significant change **VAS** • No significant change	NR	**VRS** ($p \leq 0.05$) • geko™ NCU: mild discomfort • other devices: minimal sensation **VAS** • No significant change		

Abbreviations: CI, confidence interval; HF, Huntleigh Flowtron; IPC, intermittent pneumatic compression; NCU, normal clinical setting; TS, threshold setting; VAS, visual analogue scale; VRS, verbal rating score.

Table 22: Results from Tucker 2010

Tucker 2010				
All 30 volunteers were analysed for all outcomes (ITT analysis)				
Outcome	**Results (see also supplementary Figure 5 to Figure 8 under table)**		**Statistical analysis**	**Interpretation**
Venous blood volume flow	Amplitude/frequency	% change from baseline±SED	p<0.01	• All stimulations showed a significant increase in venous blood flow compared with baseline • Both amplitude and frequency showed a positive correlation with venous blood flow
	1 mA/1 Hz	170.4±14.86		
	1 mA/3 Hz	211.4±14.86		
	1 mA/5 Hz	264.0±14.86	Amplitude; R^2=0.55 Frequency; R^2=0.82	
	5 mA/1 Hz	193.7±14.86		
	5 mA/3 Hz	237.8±14.86		
	5 mA/5 Hz	312.8±14.86		
	10 mA/1 Hz	197.1±14.86		
	10 mA/3 Hz	249.0±14.86		
	10 mA/5 Hz	356.1±14.86		
	20 mA/1 Hz	210.2±14.86		
	20 mA/3 Hz	259.4±14.86		
	20 mA/5 Hz	313.5±14.86		
	40 mA/1 Hz	225.3±14.86		
	40 mA/3 Hz	230.3±14.86		
	40 mA/5 Hz	381.4±14.86		

Tucker 2010				
All 30 volunteers were analysed for all outcomes (ITT analysis)				
Outcome	**Results (see also supplementary Figure 5 to Figure 8 under table)**		**Statistical analysis**	**Interpretation**
Venous peak velocity	Amplitude/frequency 1 mA/1 Hz 1 mA/3 Hz 1 mA/5 Hz 5 mA/1 Hz 5 mA/3 Hz 5 mA/5 Hz 10 mA/1 Hz 10 mA/3 Hz 10 mA/5 Hz 20 mA/1 Hz 20 mA/3 Hz 20 mA/5 Hz 40 mA/1 Hz 40 mA/3 Hz 40 mA/5 Hz	%change from baseline±SED 151.42±12.44 195.68±12.44 242.95±12.44 176.78±12.44 226.98±12.44 291.44±12.44 185.57±12.44 232.53±12.44 318.57v±12.44 198.57±12.44 251.17±12.44 304.30±12.44 202.41±12.44 281.31±12.44 359.06±12.44	p<0.01 Amplitude; R^2=0.74 Frequency; R^2=0.72	• All stimulations showed a significant increase in venous blood flow compared with baseline • Both amplitude and frequency showed a strong positive correlation with venous blood flow

Tucker 2010					
All 30 volunteers were analysed for all outcomes (ITT analysis)					
Outcome	**Results (see also supplementary Figure 5 to Figure 8 under table)**			**Statistical analysis**	**Interpretation**
Discomfort	Amplitude/frequency	VRS mean±SED	VAS mean±SED	NR	• For VRS, the majority of stimulation programmes were rated by volunteers as minimal sensation • VRS showed a correlation with both amplitude and frequency • Using VRS and VAS, only the stimulation programme using highest amplitude and highest frequency (40 mA/5 Hz) reached a moderate discomfort level
	1 mA/1 Hz	1.67±0.084	17±1.69		
	1 mA/3 Hz	1.85±0.084	22±1.69		
	1 mA/5 Hz	2.28±0.084	30±1.69		
	5 mA/1 Hz	1.9±0.084	22±1.69		
	5 mA/3 Hz	2.12±0.084	27±1.69		
	5 mA/5 Hz	2.7±0.084	37±1.69		
	10 mA/1 Hz	2.02±0.084	26±1.69		
	10 mA/3 Hz	2.3±0.084	31±1.69		
	10 mA/5 Hz	2.3±0.084	42±1.69		
	20 mA/1 Hz	2.18±0.084	29±1.69		
	20 mA/3 Hz	2.37±0.084	34±1.69		
	20 mA/5 Hz	3.05±0.084	47±1.69		
	40 mA/1 Hz	2.52±0.084	36±1.69		
	40 mA/3 Hz	3.03±0.084	46±1.69		
	40 mA/5 Hz	3.83±0.084	52±1.69		

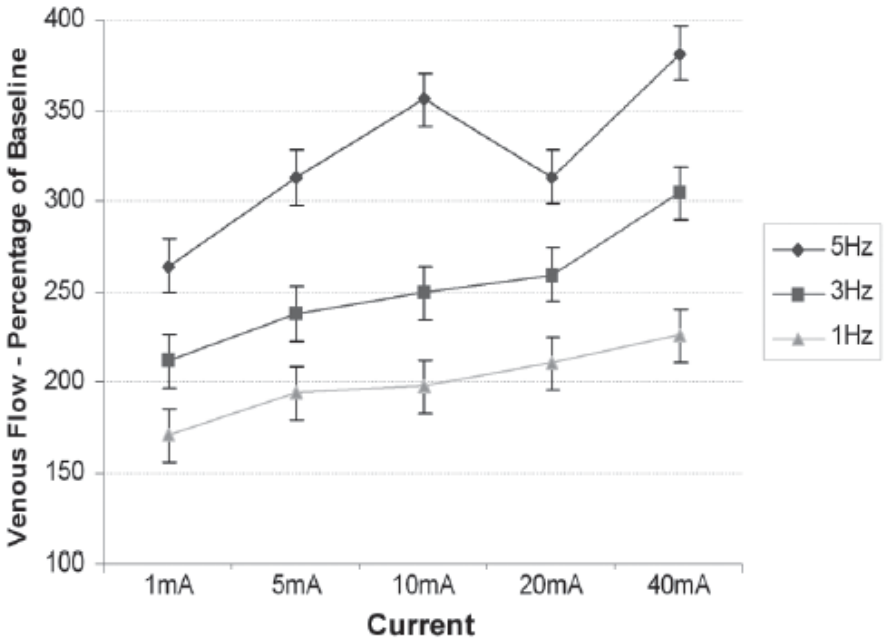
Tucker 2010				
All 30 volunteers were analysed for all outcomes (ITT analysis)				
Outcome	**Results (see also supplementary Figure 5 to Figure 8 under table)**		**Statistical analysis**	**Interpretation**
Skin microcirculatory assessments	Amplitude/frequency 1 mA/1 Hz 1 mA/3 Hz 1 mA/5 Hz 5 mA/1 Hz 5 mA/3 Hz 5 mA/5 Hz 10 mA/1 Hz 10 mA/3 Hz 10 mA/5 Hz 20 mA/1 Hz 20 mA/3 Hz 20 mA/5 Hz 40 mA/1 Hz 40 mA/3 Hz 40 mA/5 Hz	% change from baseline±SED 398.0.4±108.6 784.2±108.6 1488.4±108.6 506.2±108.6 927.3±108.6 2141.4±108.6 517.3±108.6 1107.3±108.6 2438.1±108.6 534.1±108.6 1254.2±108.6 2495.5±108.6 546.8±108.6 978.1±108.6 2074.1±108.6	$p<0.01$ $R^2=0.86$ $p=0.04$	• Amplitude and frequency had significant effects on microcirculatory flux • Both showed strong positive correlation with frequency on skin microcirculatory assessments • Significant increase in skin temperature for stimulated vs unstimulated leg
Mean vessel diameter	No significant change			

Tucker 2010				
All 30 volunteers were analysed for all outcomes (ITT analysis)				
Outcome	**Results (see also supplementary Figure 5 to Figure 8 under table)**		**Statistical analysis**	**Interpretation**
Venous emptying	Amplitude/frequency	% of full flexion ±SED	p=0.0004 R^2=0.56	• All values were at least 50% of full dorsiflexion • Higher amplitudes produced significant venous emptying
	1 mA/1 Hz	51.22±4.474		
	1 mA/3 Hz	51.18±4.474		
	1 mA/5 Hz	57.32±4.474		
	5 mA/1 Hz	56.95±4.474		
	5 mA/3 Hz	65.94±4.474		
	5 mA/5 Hz	66.13±4.474		
	10 mA/1 Hz	59.31±4.474		
	10 mA/3 Hz	68.01±4.474		
	10 mA/5 Hz	66.23±4.474		
	20 mA/1 Hz	59.71±4.474		
	20 mA/3 Hz	72.76±4.474		
	20 mA/5 Hz	66.04±4.474		
	40 mA/1 Hz	69.86±4.474		
	40 mA/3 Hz	77.09±4.474		
	40 mA/5 Hz	92.53±4.474		

Tucker 2010				
All 30 volunteers were analysed for all outcomes (ITT analysis)				
Outcome	**Results (see also supplementary Figure 5 to Figure 8 under table)**		**Statistical analysis**	**Interpretation**
Calf circumference change	Amplitude/frequency	% of full flexion±SED	p<0.001	• Values were between 55% and 70% of full dorsiflexion • Frequency had significant positive effect on muscular contraction
	1 mA/1 Hz	57.70±8.26		
	1 mA/3 Hz	65.68±8.26	R^2=0.84	
	1 mA/5 Hz	63.92±8.26		
	5 mA/1 Hz	58.51±8.26		
	5 mA/3 Hz	59.56±8.26		
	5 mA/5 Hz	70.09±8.26		
	10 mA/1 Hz	59.45±8.26		
	10 mA/3 Hz	56.90±8.26		
	10 mA/5 Hz	59.46±8.26		
	20 mA/1 Hz	56.11±8.26		
	20 mA/3 Hz	66.06±8.26		
	20 mA/5 Hz	64.50±8.26		
	40 mA/1 Hz	62.79±8.26		
	40 mA/3 Hz	58.94±8.26		
	40 mA/5 Hz	70.43±8.26		
Conclusions Neuromuscular stimulation with the geko™ device significantly enhances both venous blood volume and venous velocity in the lower limb, compared with baseline (measurements were increased up to 25-fold in the stimulated leg compared with baseline and the unstimulated leg). Skin temperature was increased using all stimulation programmes in the stimulated leg compared with the unstimulated leg. Because metabolism is not altered during the stimulation programmes, this increase in skin temperature is an indicator of increased blood flow, even in the superficial layers of the skin. Ultrasound measurements confirmed an increase in venous volume and venous velocity in the stimulated leg at all stimulations compared with baseline. Measurements showed that all stimulations produced values between 55% and 70% of dorsiflexion, indicating that increases in microcirculatory flux are possible without substantive distortion of the calf.				

Abbreviations: ITT, intention-to-treat; PPG, photoplethysmography; SED, standard error of the difference; SPG, strain gauge plethysmography; VAS, visual analogue scale; VRS, verbal response score.

Figure 5: Tucker 2010, venous volume blood flow and peak velocity



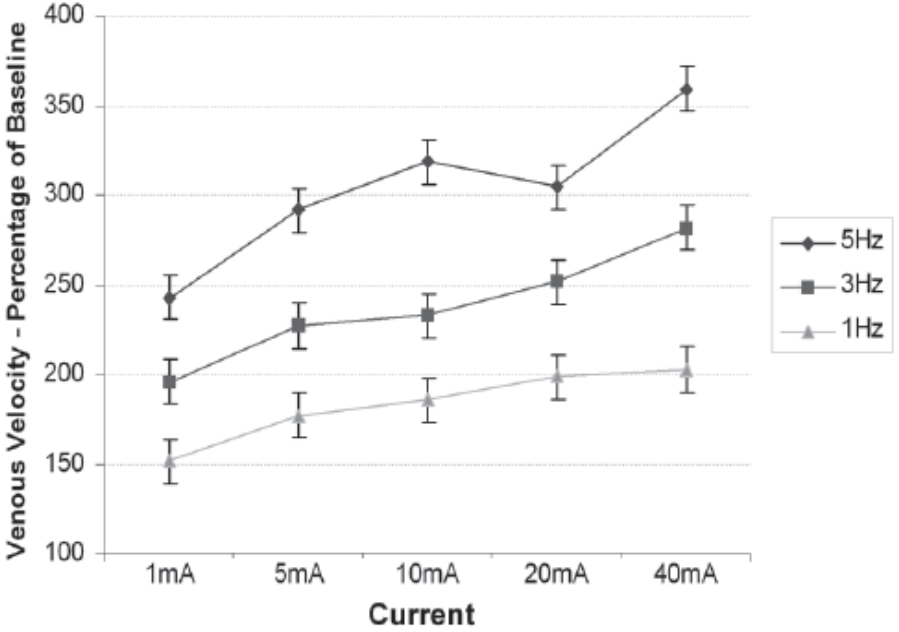
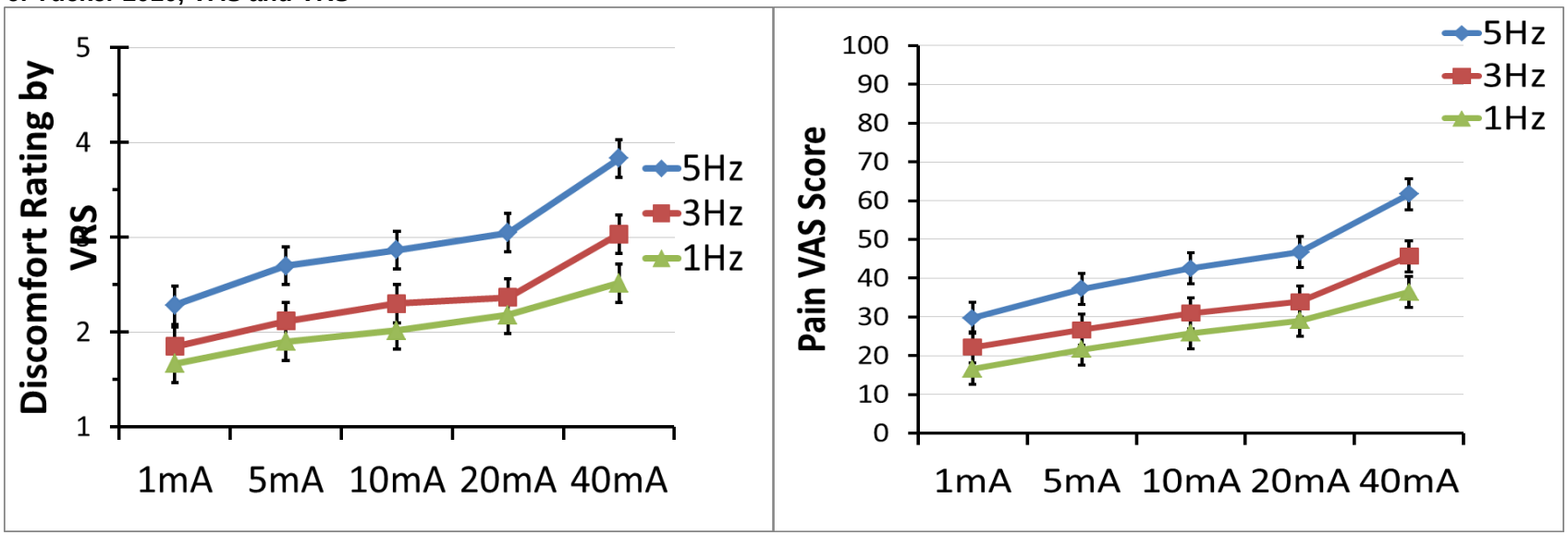
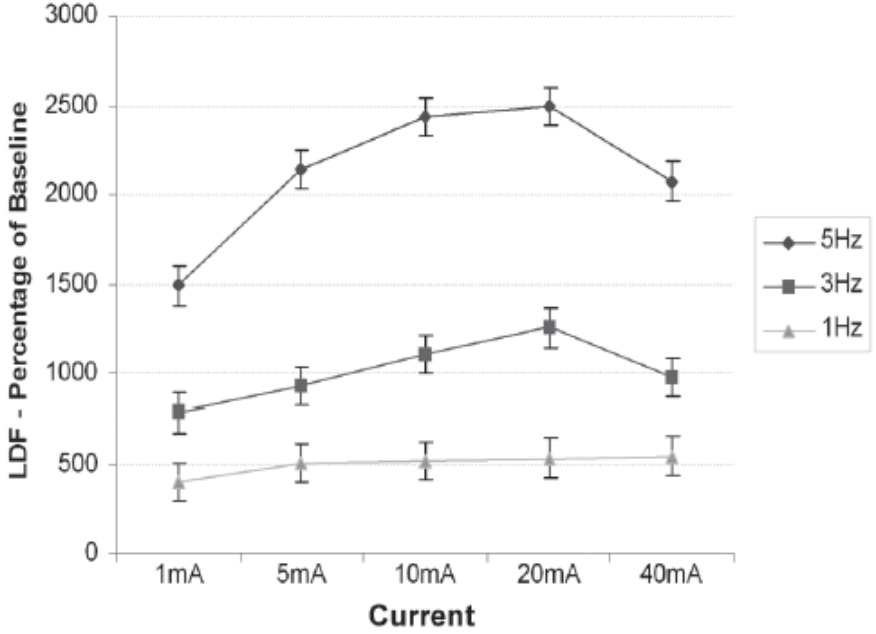


Figure 6: Tucker 2010, VAS and VRS



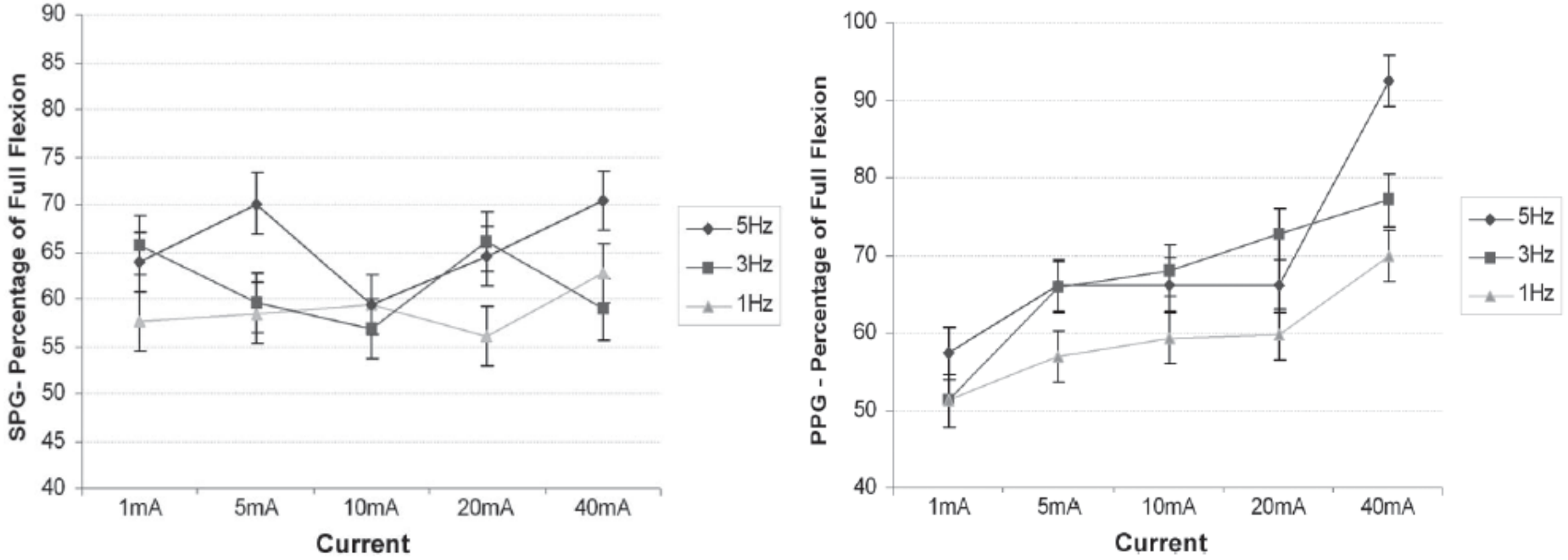
Abbreviations: VAS, visual analogue scale; VRS, verbal response score.

Figure 7: Tucker 2010, skin microcirculatory assessments



Abbreviations: LDF, Laser Doppler fluxmetry.

Figure 8: Tucker 2010, calf circumference change (SPG) and venous emptying (PPG)



Abbreviations: PPG, photoplethysmography; SPG, strain gauge plethysmography.

Table 23: Results from Jawad (cardiac) 2012

Jawad (cardiac) 2012				
All 9 volunteers were analysed for all outcomes (ITT analysis)				
Outcome	**Results**		**Statistical analysis**	**Interpretation**
Arterial blood volume flow	Baseline 400 µs 600 µs	mL/min, mean±SD 174.1±39.2 258.8±65.6 273.1±97.1	p ≤ 0.05	• Significant difference between 400 µs and 600 µs pulse widths • Highest mean value obtained using pulse width 600 µs • Average percentage change vs baseline approximately similar for both pulse widths (55% for 400 µs and by 54 % for 600 µs)
Arterial peak velocity	Baseline 400 µs 600 µs	cm/sec, mean±SD 81.19±13.62 101.60±22.43 100.90±26.37	p ≤ 0.05	• Significant difference between 400 µs and 600 µs pulse widths • Use of electrical nerve stimulation at both pulse widths resulted in equal increases of 24%
Skin microcirculatory assessments	Baseline 400 µs 600 µs	Flux units, mean±SD 7.71 ±3.39 107.5±68.1 117.9 ±67.8	p ≤ 0.05	• Significant difference after electrical nerve stimulation compared with baseline • Average percentage change vs baseline, higher with 600 µs pulse width (1,552%) than pulse width 400 µs (1,186%)
Mean vessel diameter and area	No significant difference			

Jawad (cardiac) 2012				
All 9 volunteers were analysed for all outcomes (ITT analysis)				
Outcome	**Results**		**Statistical analysis**	**Interpretation**
Cardiac output	Baseline 400 µs 600 µs	LVOT VTI cm, mean±SD 59.89±3.72 60.33±4.44 62.56 ±4.80	$p \leq 0.05$	• Significant increase in LVOT VTI by 6% following pulse width 400 µs and 4% following pulse width 600 µs • Other cardiac parameters remained stable prior to and following electrical nerve stimulation
Conclusions Neuromuscular stimulation with the geko™ device was effective in increasing cardiac output and vascular flow. Of all of the cardiac parameters assessed, the only significant difference seen was in cardiac output. In comparison with baseline, 6% and 4% augmentation in cardiac output was seen using pulse width 400 µs and 600 µs, respectively. The reasons for this are unclear as heart rate was not monitored. Analysis of diastolic function parameters suggests that electrical stimulation does not alter the filling pattern of the left ventricle. A statistically significant augmentation was observed in vascular flow parameters both at the arterial and microvascular level. Arterial volume flow increased by more than 50% following electrical stimulation and arterial peak velocity increased by 24%. Microvascular velocity increased by 1,186% following pulse width 400µs and 1,552% following pulse width 600µs. These increases may be due to the increased vessel flow provided by the venous valve system when active. This provides direct auxiliary assistance to the heart by reducing the pressure difference between inflow and outflow to the ventricle. Alternatively, a substantial up-regulation of the use of smaller vessels in the skin and possibly other organs may provide a large increase in the total available cross-sectional area and therefore a drop in vascular resistance.				

Abbreviations: ITT, intention-to-treat; LVOT VTI, left ventricular outflow tract velocity time integral; SD, standard deviation.

Table 24: Results from Jawad (coagulation) 2012

Jawad (coagulation) 2012							
All 10 volunteers were analysed for all outcomes (ITT analysis)							
Outcome	**Results**					**Statistical analysis**	**Interpretation**
Blood volume flow		Arterial volume flow mL/min		Venous volume flow mL/min		Control study Arterial; $p \leq 0.05$ Venous; $p>0.05$ Stimulation study Arterial; $p \leq 0.05$ Venous; $p \leq 0.001$	• In comparison with arterial blood flow results obtained in the control study, mean arterial blood flow increased following stimulation, $p \leq 0.05$ • In the stimulation study, mean arterial and venous volume flow increased substantially from baseline and was sustained
	Control study						
		Mean±SD	% change from baseline	Mean±SD	% change from baseline		
	Baseline	125±47.4	N/A	62.23±33.4	N/A		
	1 hour	93.4±35.2	-25.3	54.7±38.7	-12.1		
	2 hours	112.9±40.4	-9.7	61.5±37.7	-1.1		
	3 hours	100.0±45.5	-20.0	59.0±44.3	-5.1		
	4 hours	111.20±29.30	-11.0	77.0±74.4	+23.7		
	Stimulation study						
		Mean±SD	% change from baseline	Mean±SD	% change from baseline		
	Baseline	176.6±65.6	N/A	59.4±41	N/A		
	1 hour	288.7±127.2	+63.5	233.76±114.5	+293.4		
	2 hours	237.3±81.7	+34.4	224.6±76.3	+278.1		
	3 hours	259.4±71.9	+46.9	253±86.8	+325.9		
	4 hours	253±100.1	+43.3	223±76.9	+275.4		
Peak velocity		Arterial velocity cm/sec		Venous velocity cm/sec		Control study Arterial; $p>0.05$ Venous; $p>0.05$	• In the control study, no significant difference from baseline was observed in venous
	Control study						

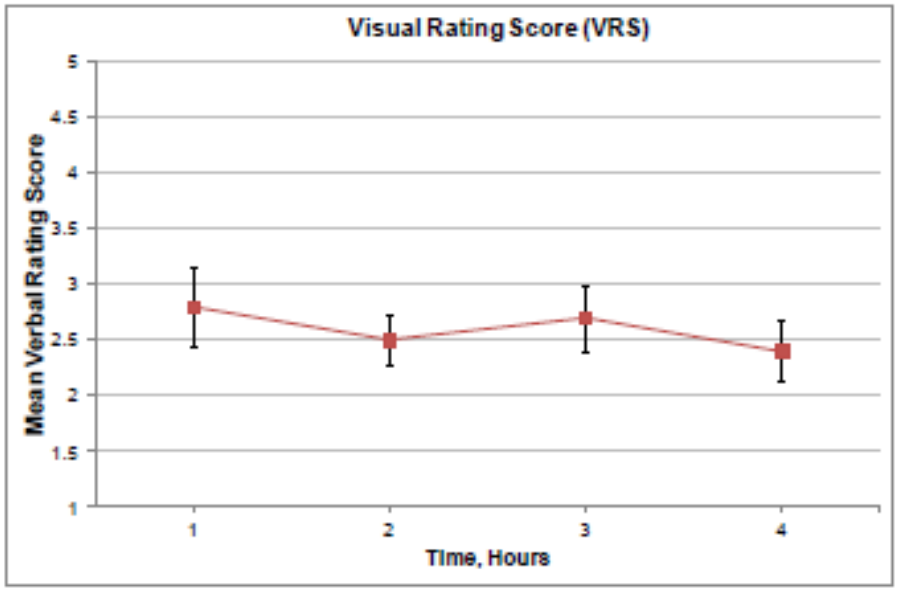
<table>
<tr><th colspan="10">Jawad (coagulation) 2012</th></tr>
<tr><td colspan="10">All 10 volunteers were analysed for all outcomes (ITT analysis)</td></tr>
<tr><th>Outcome</th><th colspan="7">Results</th><th>Statistical analysis</th><th>Interpretation</th></tr>
<tr><td rowspan="12"></td><td></td><td colspan="2">Mean±SD</td><td colspan="2">% change from baseline</td><td>Mean±SD</td><td>% change from baseline</td><td rowspan="12">Stimulation study
Arterial; p>0.05
Venous; p ≤ 0.001</td><td rowspan="12">femoral velocity or arterial femoral velocity
• In the stimulation study, no significant difference from baseline was observed in arterial femoral velocity
• However, in the stimulation study, a significant difference from baseline was reported in the venous femoral velocity</td></tr>
<tr><td>Baseline</td><td colspan="2">58.01±9.48</td><td colspan="2">N/A</td><td>11.28±2.62</td><td>N/A</td></tr>
<tr><td>1 hour</td><td colspan="2">55.27±12.69</td><td colspan="2">-4.7</td><td>10.35±4.34</td><td>-8.2</td></tr>
<tr><td>2 hours</td><td colspan="2">55.66±9.19</td><td colspan="2">-4.1</td><td>10.72±2.76</td><td>-5.0</td></tr>
<tr><td>3 hours</td><td colspan="2">54.54±8.22</td><td colspan="2">-6.0</td><td>11.21±4.33</td><td>-0.6</td></tr>
<tr><td>4 hours</td><td colspan="2">57.21±7.41</td><td colspan="2">-1.4</td><td>10.26±2.30</td><td>-9.0</td></tr>
<tr><td colspan="7">Stimulation study</td></tr>
<tr><td></td><td colspan="2">Mean±SD</td><td colspan="2">% change from baseline</td><td>Mean±SD</td><td>% change from baseline</td></tr>
<tr><td>Baseline</td><td colspan="2">69.92±21.32</td><td colspan="2">N/A</td><td>10.70±4.32</td><td>N/A</td></tr>
<tr><td>1 hour</td><td colspan="2">70.47±28.50</td><td colspan="2">+0.8</td><td>24.09±8.30</td><td>+125.1</td></tr>
<tr><td>2 hours</td><td colspan="2">76.04±16.47</td><td colspan="2">+8.8</td><td>26.82±6.57</td><td>+150.1</td></tr>
<tr><td>3 hours</td><td colspan="2">83.69±13.03</td><td colspan="2">+19.7</td><td>30.07±13.32</td><td>+181.0</td></tr>
<tr><td>4 hours</td><td colspan="2">82.23±15.56</td><td colspan="2">+17.6</td><td>25.67±5.54</td><td>+139.9</td></tr>
<tr><td rowspan="5">Discomfort</td><td></td><td colspan="3">VRS</td><td colspan="3">VAS</td><td rowspan="5">p>0.05</td><td rowspan="5">• No significant difference following stimulation at each time point
• Using VRS, the majority of volunteers reported mild discomfort for the electrical nerve stimulation, characterised by a</td></tr>
<tr><td></td><td>25%</td><td>Median</td><td>75%</td><td>25%</td><td>Median</td><td>75%</td></tr>
<tr><td>1 Hour</td><td>2</td><td>3</td><td>3</td><td>19.25</td><td>37.5</td><td>58.5</td></tr>
<tr><td>2 Hours</td><td>2</td><td>3</td><td>3</td><td>18</td><td>29.5</td><td>50</td></tr>
<tr><td>3 Hours</td><td>2</td><td>3</td><td>3</td><td>20.25</td><td>27.5</td><td>48.75</td></tr>
</table>

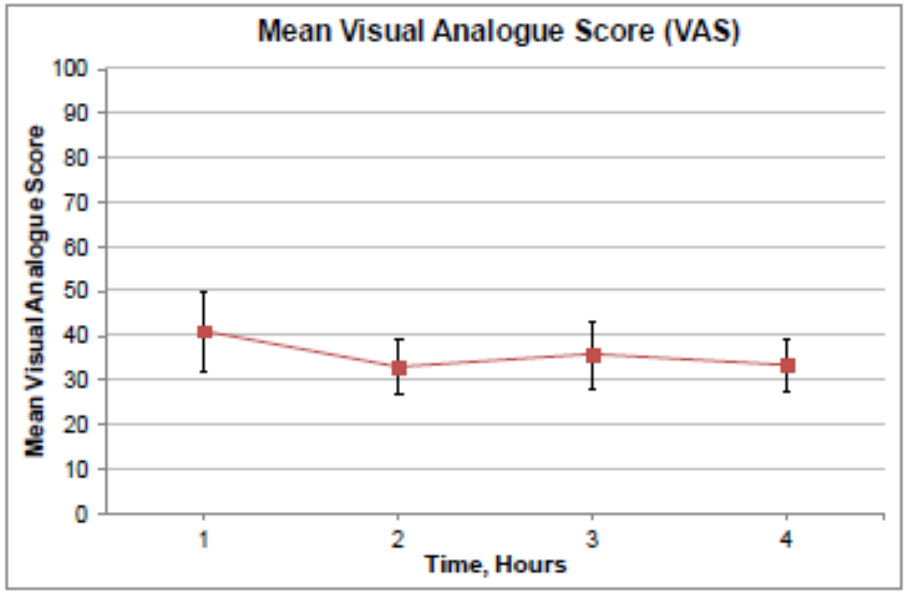
Jawad (coagulation) 2012									
All 10 volunteers were analysed for all outcomes (ITT analysis)									
Outcome	**Results**							**Statistical analysis**	**Interpretation**
	4 Hours	2	2	3	24	28	38.75		mean score of 2.6 out of 5 at all timepoints • Using VAS, stimulation was rated at minimal sensation, characterised by a mean score of 35.8 out of 100 at all timepoints
Skin microcirculatory assessments		LDF flux units		LDF flux units				Control study Arterial; p>0.05 Venous; p>0.05 Stimulation study Arterial; p>0.05 Venous; p ≤ 0.001	• In the control study, no significant difference was observed in either leg • In the stimulation study, a significant difference was observed between the stimulated and passive legs • In the stimulation study, mean values in the passive leg remained stable throughout
	Control study								
		Right leg Mean±SD		Left leg Mean±SD					
	Baseline	4.43 (5.83)		8.58 (2.45)					
	1 hour	3.78 (5.52)		6.73 (2.13)					
	2 hours	3.79 (5.76)		6.74 (2.01)					
	3 hours	3.75 (6.40)		7.48 (3.01)					
	4 hours	4.27 (6.62)		9.84 (6.45)					
	Stimulation study								
		Passive leg Mean±SD		Stimulated leg Mean±SD					
	Baseline	7.35 (6.14)		4.66 (5.09)					
	1 hour	9.36 (6.52)		73.6 (62.4)					
	2 hours	7.74 (4.40)		70.4 (62.3)					
	3 hours	8.77 (6.42)		73.9 (56.5)					
	4 hours	7.79 (5.99)		75.8 (54.1)					

Jawad (coagulation) 2012			
All 10 volunteers were analysed for all outcomes (ITT analysis)			
Outcome	**Results**	**Statistical analysis**	**Interpretation**
Mean vessel diameter	No significant change		
Clotting time assessments and coagulation factors	• Levels of tissue plasminogen activator antigen significantly reduced throughout stimulation and control studies, but greater reduction observed in stimulation study than control study • No significant changes in von Willebrand factor seen throughout stimulation and control studies • Assessment of prostacyclin by measuring its stable marker 6 keto PGF1α, showed a non-significant change at all sites following stimulation. However, analysis of 6 keto PGF1α during the control study showed conflicting results between sites • Statistically significant drop in blood clotting times observed throughout the study period although all blood clotting times reported were within the normal range • Whilst no significant changes in endogenous thrombin potential levels or peak height were observed, significant increases in lag time and time to peak were demonstrated		
Conclusions Neuromuscular stimulation with the geko™ device resulted in significant increases in velocity and blood volume flow. The greatest peak venous velocity measurement obtained was 30 cm/sec, reached at 3 hours. Significant increases in venous blood volume flow were demonstrated. Following a baseline volume flow of 109.49 mL/min the greatest venous volume was reported at 3 hours (253.6 mL /min), equating to an average percentage increase from baseline ranging from 403% to 581%. A significant increase in arterial volume flow was also reported. The highest increase in arterial volume flow in the stimulation study was reported at 3 hours (259.4 mL/min), contrasting with a decrease from 124.99 mL/min at baseline to 111.2 mL/min at 4 hours in the control study. This suggests a possible systemic effect of the stimulation device. Skin perfusion was 4.66 flux units at baseline, which escalated to 73.59 flux units following 1 hour and continued to increase reaching 75.85 flux units at 4 hours.			

Abbreviations: ITT, intention-to-treat; LDF, laser Doppler fluxmetry; SD, standard deviation; VAS, visual analogue scale; VRS, verbal response score.

Figure 9: Jawad (coagulation) 2012, VRS and VAS





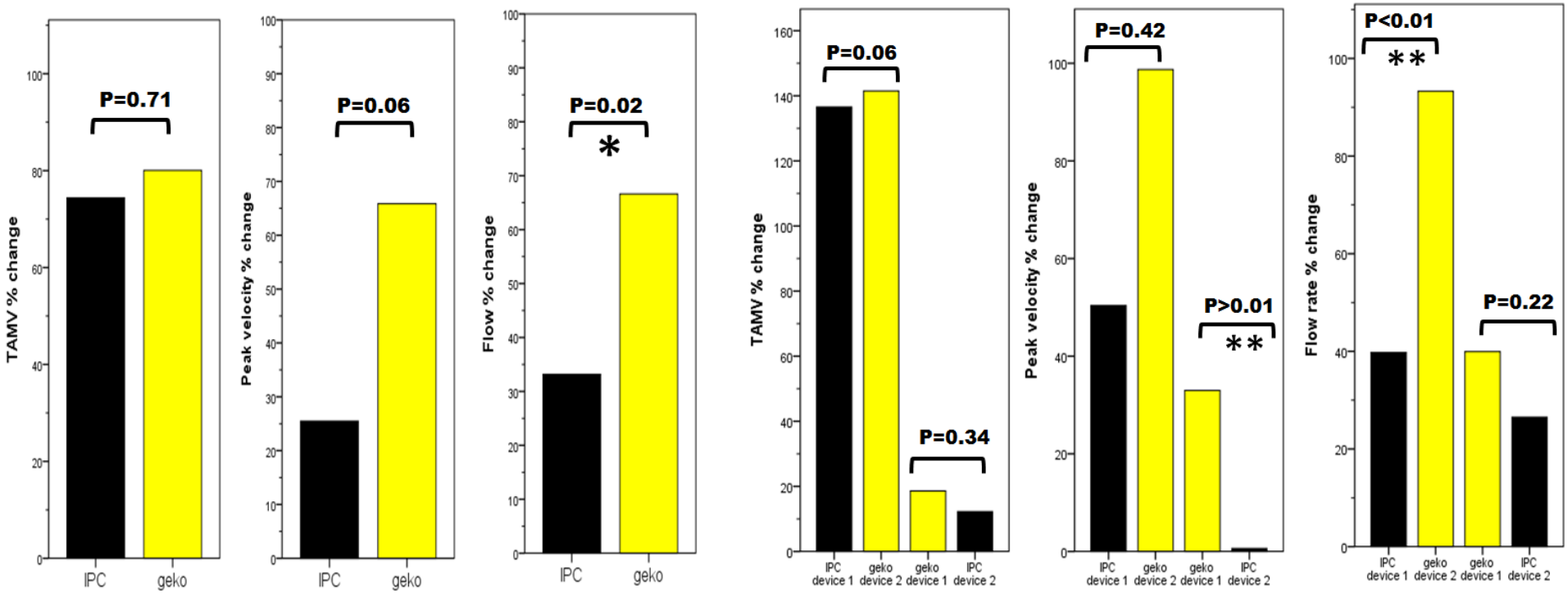
Results from Williams 2013

All 10 volunteers in the Williams 2013 study were analysed for all outcomes (ITT analysis). The geko™ device was found to be:

- significantly better than IPC at increasing venous blood flow (p=0.02) (Figure 10)
- equivalent to IPC at increasing venous peak velocity (p=0.06) although the difference neared significance (Figure 10)
- equivalent to IPC when analysing TAMV (p=0.71) (Figure 10)

Blood volume flow, peak velocity, and TAMV with use of the geko™ device before or after IPC were also evaluated (Figure 10). The use of IPC before the geko™ device augments its haemodynamic effect, but when used after the geko™ device, IPC negates its haemodynamic effect.

Figure 10: Results of Williams 2013



Conclusions

Neuromuscular stimulation with the geko™ device was effective in increasing TAMV, peak velocity and blood flow rate and it was equivalent and/or better at improving the haemodynamic flow in the leg of healthy volunteers. The use of IPC before the geko™ device augments its haemodynamic effect but its use after the geko™ device negates its haemodynamic effect.

Table 25: Results from Jawad unpublished (vs IPC) 2012

Jawad unpublished (vs IPC) 2012							
All 10 volunteers were analysed for all outcomes (ITT analysis)							
Outcome	**Results**					**Statistical analysis**	**Interpretation**
Blood volume flow		Venous volume flow mL/min		Arterial volume flow mL/min		$p \leq 0.001$	• Significant difference in both venous and arterial blood volume flow between the devices • Highest median venous and arterial blood flow volumes were achieved following use of the geko™ device at the normal clinical use setting • Highest average percentage change in both arterial and venous volume flow achieved following use of geko™ device at normal clinical use setting
		Median (IQR)	Average % change	Median (IQR)	Average % change		
	Baseline – no device	123.5 (73.4)	N/A	197.5 (135.8)	N/A		
	geko™ NCU	163 (105.3)	+33%	244.5 (125)	+30%		
	geko™ TS	129 (42.7)	+14%	170 (107.5)	-7%		
	IPC-Huntleigh	118 (72.7)	-4%	181.5 (70.5)	-9%		
	IPC-Kendall	115 (60.2)	-4%	158 (73)	-16%		
Peak velocity		Venous velocity cm/sec		Arterial velocity cm/sec		$p \leq 0.001$	• Significant difference between the devices • Substantial increase in venous velocity of 174% following the use of geko™ device at normal clinical use setting, equivalent to IPC devices • Median venous velocity values reported following use of geko™ device at normal clinical use setting equivalent to that of the IPC devices during the inflation phase • Highest increase in arterial velocity reported following use of geko™ device at normal clinical use setting
		Median (IQR)	% change	Median (IQR)	% change		
	Baseline – no device	13.8 (5.4)	N/A	83.15 (24.23)	N/A		
	geko™ NCU	38.3 (10.35)	174%	98.25 (27.70)	+24%		
	geko™ TS	22 (12.75)	73%	84.75 (22.10)	+2%		
	IPC-Huntleigh – inf.	37 (14.25)	166%	81.9 (20.40)	-4%		
	IPC-Huntleigh – def.	14.7 (8.35)		79.7 (17.15)			
	IPC-Kendall – inf.	33.7 (14.63)	143%	80.3 (17.85)	-1%		
	IPC-Kendall– def.	12.6 (5.2)		85 (15.2)			

<table>
<tr><th colspan="8">Jawad unpublished (vs IPC) 2012</th></tr>
<tr><td colspan="8">All 10 volunteers were analysed for all outcomes (ITT analysis)</td></tr>
<tr><th>Outcome</th><th colspan="5">Results</th><th>Statistical analysis</th><th>Interpretation</th></tr>
<tr><td rowspan="6">Discomfort by VRS and VAS</td><td rowspan="2"></td><td colspan="3">VRS</td><td colspan="3">VAS</td><td rowspan="6">VAS; p>0.05

VRS; p ≤ 0.05</td><td rowspan="6">• Using VAS, no significant between devices
• Using VRS, the discomfort level following use of the geko™ device at the normal clinical use setting was only rated as mild discomfort (the other devices studied were rated at minimal sensation)</td></tr>
<tr><td>25%</td><td>Median</td><td>75%</td><td>25%</td><td>Median</td><td>75%</td></tr>
<tr><td>geko™ NCU</td><td>3</td><td>3.5</td><td>4</td><td>36.50</td><td>46.5</td><td>58.00</td></tr>
<tr><td>geko™ TS</td><td>2</td><td>2.5</td><td>3</td><td>18.25</td><td>37</td><td>60.00</td></tr>
<tr><td>IPC-Huntleigh</td><td>1</td><td>2</td><td>2.75</td><td>13.75</td><td>27</td><td>43.75</td></tr>
<tr><td>IPC-Kendall</td><td>1.25</td><td>2</td><td>3</td><td>14.00</td><td>31</td><td>45.75</td></tr>
<tr><td>Skin microcirculatory assessments by LDF</td><td colspan="3">Baseline – no device
geko™ NCU
geko™ TS
IPC-Huntleigh
IPC-Kendall</td><td colspan="3">Median (IQR)
9.45 (7.61)
35.46 (24.26)
27.13 (24.92)
6.67 (7.89)
6.71 (12.58)</td><td>p ≤ 0.001</td><td>• Significant difference between devices
• Use of geko™ device showed significant increase in microcirculatory blood velocity by over 300% and 345% compared with a ~50% increase following the use of IPC</td></tr>
<tr><td>Mean vessel diameter</td><td colspan="7">No significant difference</td></tr>
<tr><td colspan="8">Conclusions
Neuromuscular stimulation with the geko™ device significantly improved lower limb blood flow when compared with the two IPC devices studied. A significant increase (~30%) in the femoral venous and arterial blood flow volume was observed following use of the geko™ device, especially at higher pulse widths. Arterial peak velocities were higher when using the geko™ device (especially at higher pulse widths) than when using IPC devices. (Note: a fall in arterial velocity was observed following the use of IPC devices, which may be of concern especially in patients with peripheral arterial disease). The data also showed that the geko™ device is as efficient as the IPC devices during the inflation period in increasing peak venous velocity. Although use of the geko™ device at lower pulse widths demonstrated lower increases (73%) than higher pulse widths (174%), it is still considered more effective than the IPC devices (9–11%) during the deflation period. Microcirculatory blood velocity in the skin increased substantially by ~370% following the use of the geko™ device compared with 44–59% following use of IPC devices.</td></tr>
</table>

Abbreviations: def., deflation; inf., inflation; IPC, intermittent pneumatic compression; IQR, interquartile range; ITT, intention-to-treat; NCU, normal clinical use; TS, threshold setting; VAS, visual analogue scale; VRS, verbal response score.

Figure 11: Jawad unpublished (vs IPC) 2012, VRS and VAS

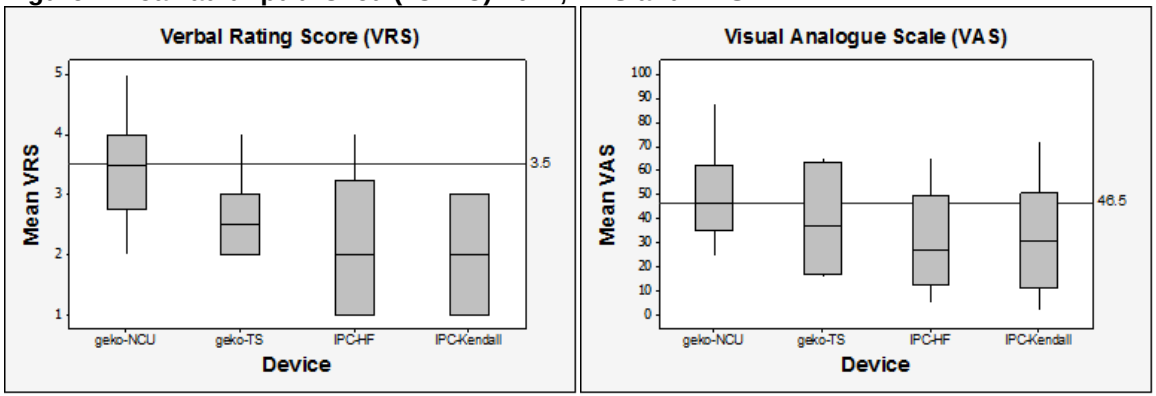


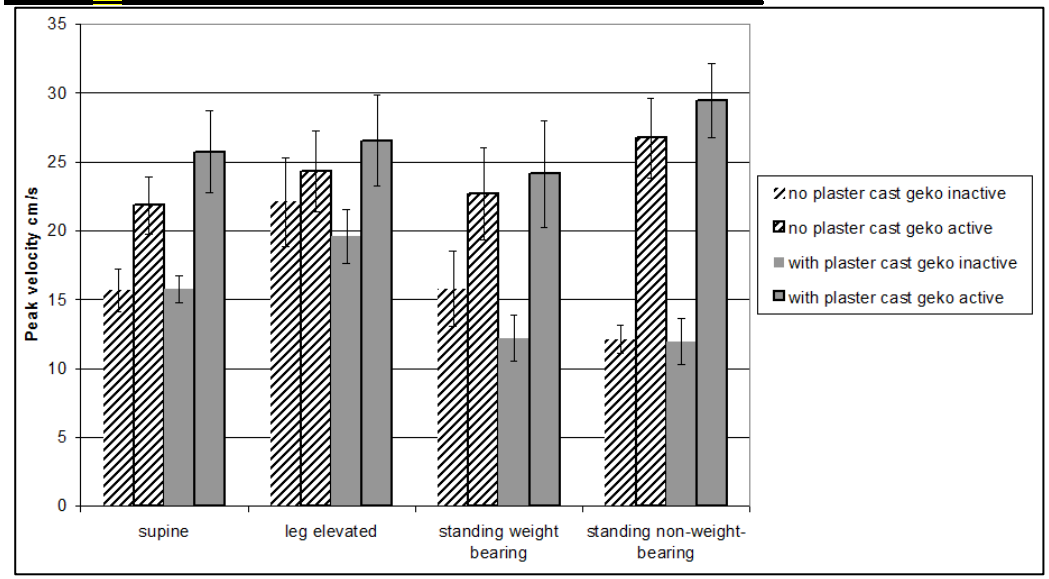
Table 26: Results from Warwick unpublished 2013

Warwick unpublished 2013						
[redacted]						
Outcome	[redacted]				[redacted]	[redacted]
Venous peak velocity (cm/sec)	[redacted]					
Discomfort by VRS	[redacted]				NR	

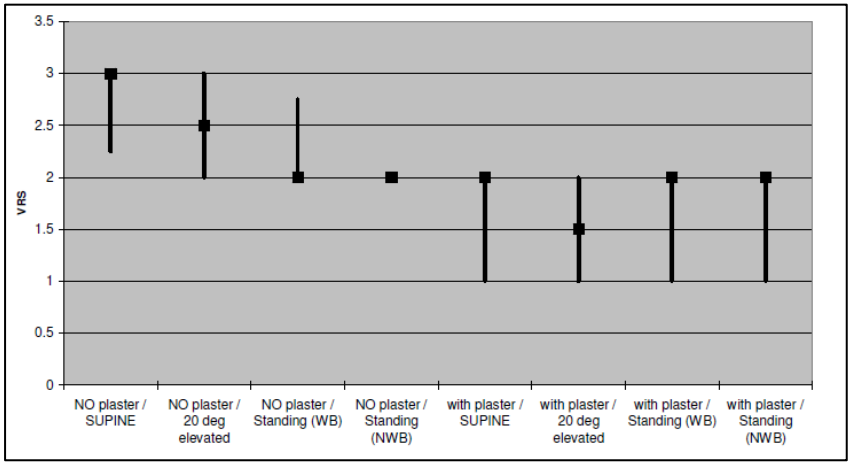
Warwick unpublished 2013						
[redacted]						
Outcome	[redacted]				[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]	[redacted]		
Discomfort by VAS		[redacted]			[redacted]	[redacted]
	[redacted]	[redacted]				
	[redacted]	[redacted]				
	[redacted]	[redacted]				
	[redacted]	[redacted]				
	[redacted]	[redacted]				
	[redacted]	[redacted]				
	[redacted]	[redacted]				
	[redacted]	[redacted]				
Mean vessel area	[redacted]					
[redacted]						

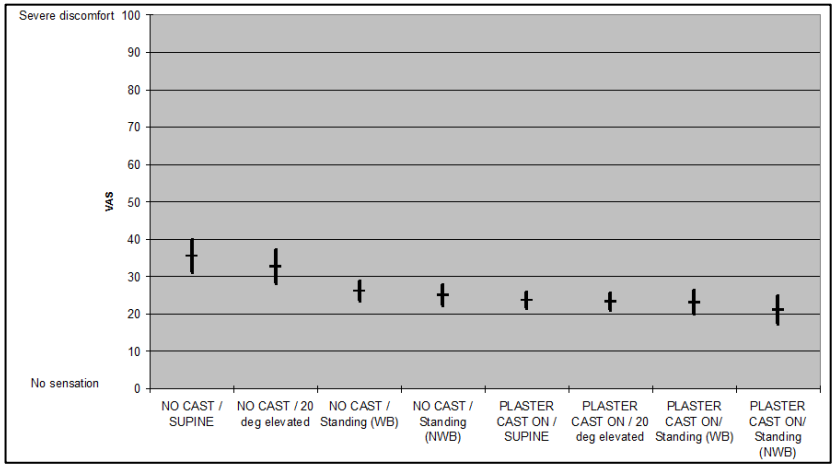
Abbreviations: CI, confidence interval; ITT, intention-to-treat; VAS, visual analogue scale; VRS, verbal response score.

12


35
30
25
20
15
10
5
0
Peak velocity cm/s
supine
leg elevated
standing weight bearing
standing non-weight-bearing
no plaster cast geko inactive
no plaster cast geko active
with plaster cast geko inactive
with plaster cast geko active

13


3.5
3
2.5
2
1.5
1
0.5
0
VRS
NO plaster / SUPINE
NO plaster / 20 deg elevated
NO plaster / Standing (WB)
NO plaster / Standing (NWB)
with plaster / SUPINE
with plaster / 20 deg elevated
with plaster / Standing (WB)
with plaster / Standing (NWB)


Severe discomfort
No sensation
100
90
80
70
60
50
40
30
20
10
0
VAS
NO CAST / SUPINE
NO CAST / 20 deg elevated
NO CAST / Standing (WB)
NO CAST / Standing (NWB)
PLASTER CAST ON / SUPINE
PLASTER CAST ON / 20 deg elevated
PLASTER CAST ON/ Standing (WB)
PLASTER CAST ON/ Standing (NWB)

[redacted] 27 [redacted]

Williams unpublished 2013			
[redacted]			
Outcome	[redacted]	[redacted]	[redacted]
Blood volume flow	[redacted]	[redacted]	• [redacted]
Peak velocity	[redacted]	[redacted]	• [redacted]
TAMV	[redacted]	[redacted]	• [redacted]

Williams unpublished 2013			
[redacted]			
Outcome	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Tolerability compared with inflated sphygmomano-meter cuff	[redacted]	[redacted]	• [redacted]
Blood volume flow	[redacted]	[redacted]	• [redacted]
Peak velocity	[redacted]	[redacted]	geko™ first; p=0.069

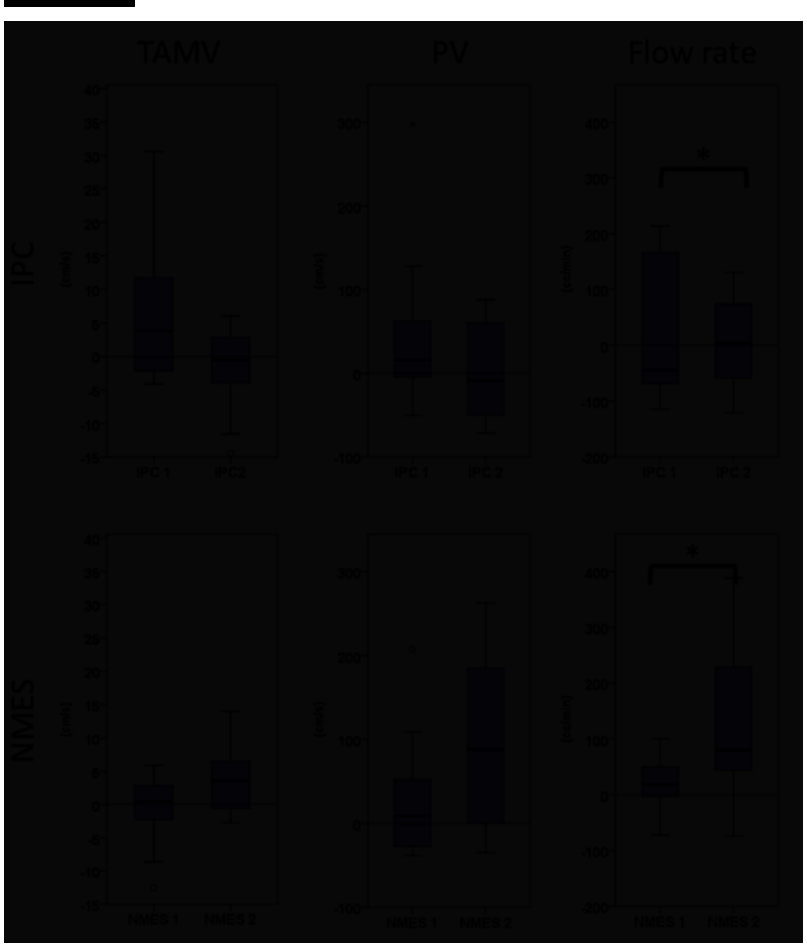
Williams unpublished 2013			
[redacted]			
Outcome	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	
TAMV	[redacted]	[redacted]	
	[redacted]	[redacted]	
	[redacted]	[redacted]	
	[redacted]	[redacted]	
[redacted]			

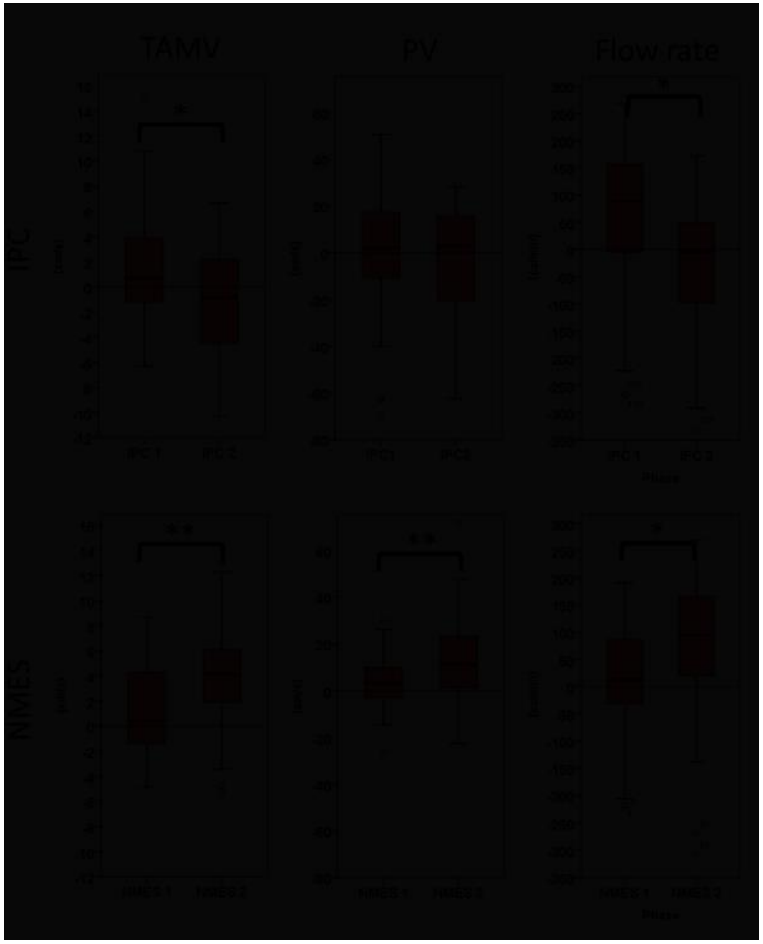
†Tolerability was assessed on a score of 1 (painless) to 10 (as painful as a sphygmomanometer cuff inflated to 100 mmHg).
Abbreviations: IPC, intermittent pneumatic compression; ITT, intention-to-treat; TAMV, time averaged maximum velocity.

[redacted] 14

Abbreviations: IPC, intermittent pneumatic compression; PV, peak velocity; TAMV, time averaged maximum velocity.

15


TAMV
PV
Flow rate
IPC
NMES
IPC1
IPC2
NMES1
NMES2


TAMV
PV
Flow rate
IPC
NMES

Post-market surveillance data

In addition to the study data detailed, post-market surveillance (PMS) has been conducted (69). In total, 215 responses to questionnaires assessing post-wear feedback on the ergonomics and comfort of the geko™ device have been received. The patients assessed in the PMS were mainly post-operative vascular, post-operative orthopaedic, non-surgery vascular.

Results from this surveillance show that:

- 81.9% of clinicians found the geko™ device easy or very easy to apply
- 47.0% of clinicians took less than one minute to fit the geko™ device and 34.4% took 1–5 minutes
- In 83.3% of cases the geko™ device was described as easy or very easy to start/stop
- In 84.2% of cases it was easy or very easy to change the settings on the geko™ device
- 85.1% of patients found the geko™ device comfortable or very comfortable to wear once applied
- In 90.7% of cases the geko™ device adhered well or very well to the leg
- 91.8% of patients reported that their quality of sleep while wearing the geko™ device was normal; 5.7% reported worse sleep and 2.5% reported better sleep.

This feedback demonstrates that the geko™ device is considered easy to use (for both application and manipulation) and comfortable to wear.

[redacted]

7.6.2 Justify the inclusion of outcomes in Table 21 from any analyses other than intention-to-treat.

No analyses other than intention-to-treat (ITT) were conducted.

7.7 Adverse events

In section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

7.7.1 Using the previous instructions in sections 7.1 to 7.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

Studies on adverse events were searched for in the SR described previously in Sections 7.1 to 7.5. No studies primarily designed for safety were identified.

7.7.2 Provide details of all important adverse events reported for each study.

Adverse events were not an outcome in any of the studies.

7.7.3 Describe all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude).

None.

7.7.4 Provide a brief overview of the safety of the technology in relation to the scope.

In the studies providing the evidence for this submission, parameters used to assess the overall safety of the geko™ device, such as tissue oxygen levels, oxygen saturation, heart rate and blood pressure showed no significant changes with the use of the geko™ device.

The only known adverse event is skin irritation or inflammation, which has previously been reported for other NMES devices using hydrogel electrodes. Firstkind is aware of 13 events of possible skin irritation, giving a possible frequency of 0.1%. It is acknowledged that the incidence of skin irritation maybe underreported.

7.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

7.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

N/A.

7.8.2 *If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.*

Evidence synthesis was not considered appropriate due to the high degree of heterogeneity between study methodologies:

- A range of settings (frequency, amplitude) were utilised when using the geko™ device.
- Only two outcomes were analysed across the majority of the studies (arterial/venous blood flow and arterial/venous peak velocity).
- The way in which the outcomes were reported differ between studies
- The comparator arms differ between studies
- Due to the nature of the intervention, all studies were unblinded.

The overall results and critical appraisal are provided in Section 7.6 and Section 7.5.

7.9 Interpretation of clinical evidence

7.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology.

Clinical benefit

The clinical data presented in Section 7.6 demonstrated the benefits of treatment with the geko™ device.

- **Increased vascular blood volume flow and blood velocity**
  - Tucker *et al,* 2010 showed that the geko™ device significantly enhanced (up to 25-fold) both venous volume and venous velocity in the lower limb, compared with baseline. Observed venous blood flow increases in the superficial femoral vein (up to 100%) are higher than those observed in previous studies of foot or calf muscle electrical stimulation (up to 25%) (71).
  - Jawad unpublished (vs IPC) 2012 showed a significant increase (~30%) in the femoral venous and arterial blood flow volume following use of the geko™ device.
  - Jawad unpublished (cardiac) 2012 showed that arterial volume flow increased by more than 50% following electrical stimulation and arterial peak velocity increased by 24%.
  - Jawad unpublished (coagulation) 2012 showed that the greatest peak venous velocity and blood volume flow measurements were reached at 3 hours. [redacted]
- **Increased skin capillary blood flow**
  - Tucker et al, 2010 showed increased skin temperature in the stimulated leg compared with the unstimulated leg. Because metabolism is not altered during stimulation, this increase in skin temperature is an indicator of increased blood flow, even in the superficial layers of the skin.

- Jawad unpublished (cardiac) 2012 showed that microvascular velocity increased by over 1,000%. This increase may result from increased vessel flow provided by the venous valve system when active, providing direct auxiliary assistance to the heart by reducing the pressure difference between inflow and outflow to the ventricle. Alternatively, a substantial up-regulation of the use of smaller vessels in the skin and possibly other organs may provide a large increase in the total available cross-sectional area and therefore a drop in vascular resistance.

- **The geko™ device is effective with or without a plaster cast**

[redacted]

- **The geko™ device is more effective than IPC**
  - Jawad unpublished (vs IPC) 2012 showed that the geko™ device significantly improved arterial and venous blood velocity when compared with IPC devices. The geko™ device demonstrated higher increases (73–174%) than the better IPC device (11%). Microcirculatory blood velocity in the skin increased substantially by ~370% following use of the geko™ device compared with 44–59% following use of IPC devices.

[redacted]

Increased blood flow results in a reduction in DVT

The studies of the geko™ device demonstrated a clear and consistent increase in blood flow, but did not directly measure incidence of DVT. Therefore the SR was also designed to identify published studies assessing blood flow and/or DVT.

- **Immobility leads to venous stasis and increased risk of DVT**
  - It has long been recognised that immobility results in venous stasis, increasing the risk of DVT. Simple leg exercise regimens have been proven to reduce venous stasis by increasing blood volume flow and decreasing the popliteal vein cross-sectional area (14).
  - A recent study by Broderick 2009 demonstrated that within a 4 hour period of bed rest popliteal venous blood flow and heart rate decreased by 45% and 10%, respectively. Electrical stimulation applied to the calf muscles was found to normalise popliteal venous blood flow and heart rate (12).
- **IPC devices reduce the incidence of DVT**
  - The NICE VTE guidelines assessed the efficacy of IPC and found that it was an effective method of prophylaxis. IPC reduced the risk of DVT between 42% (RR 0.31; patients with hip fracture) and 69% (RR 0.58; patients with total knee replacement) (3).
  - A review conducted by the Cochrane group (72) has also shown that IPC devices reduce the incidence of DVT; combined prophylaxis using a

pharmacological agent and IPC reduced incidence of DVT by 84% when compared with pharmacological agents alone.
    - The SR identified seven studies of IPC devices (see Section 10.6) which analysed the effects of IPC on incidence of DVT in populations of patients undergoing surgery. Five of these publications were for RCTs (37, 43, 44, 47, 48) and two for non-RCTs (40, 41). These individual studies show that IPC devices can reduce the incidence of DVT in populations of patients.
- **Compression stockings reduce the incidence of DVT**
    - A review by the Cochrane group (73) has shown that compression stockings reduce the incidence of DVT by 65% when compared with no compression stockings, and by 75% when stockings are combined with pharmacological agents vs pharmacological agents alone.
- **NMES increases blood flow and reduces the incidence of DVT**
    - The SR identified studies analysing the effect of NMES on either blood flow or DVT (see Section 10.3). Eight studies showed that NMES increases blood flow in both patient (13, 21, 49) and healthy volunteer populations (20, 22, 35, 38, 39) and a further three studies showed that NMES reduced the incidence of DVT in patient populations (23, 24, 42).
        - Browse and Negus 1970 (23) electrically stimulated one leg of 110 patients undergoing major surgery, the other leg acting as a control. Types of surgery included abdominal surgery, bilateral herniorrhaphy, haemorrhoidectomy, head and neck surgery and simply mastectomy. Deep vein thrombosis was detected using the ^{125}I-labelled fibrinogen test in 9 stimulated legs (8.2%) and 23 unstimulated legs (20.9%). This equates to a reduction of 12.7% (absolute), or 61% (relative), in the incidence (per leg) of DVT.
        - Rosenberg 1975 (42) evaluated the impact of heparin calcium, intermittent electrical calf muscle stimulation and no specific prophylaxis on the incidence of DVT measured via the ^{125}I-labelled fibrinogen test. All patients were over 40 years of age, undergoing a major general surgical operation for which they were expected to be in hospital for at least one week. The results from 273 operations were analysed and 118 legs in 84 patients showed positive results indicative of DVT. Neither method of prophylaxis was found to reduce the incidence of DVT below control levels in patients undergoing bladder, prostate, and miscellaneous surgery. In patients who had a laparotomy (n=194), the heparin calcium group had a significantly lower incidence of both minor and major venous thrombosis (7.3% and 0% compared with 23.6% and 20.2% in the control group). Electrical stimulation did not affect the rate of minor thrombosis but the incidence of major thrombosis was significantly lower at 4.0%. In patients with malignant disease heparin calcium proved effective as a prophylaxis but electrical stimulation was ineffective. When a laparotomy was performed for benign disease heparin calcium significantly reduced the incidence of both major and minor venous thrombosis whereas electrical stimulation prevented major thrombosis alone.
        - Lindstrom 1982 (24) assessed the efficacy of three methods of VTE prophylaxis in patients scheduled for major abdominal surgery. All patients were above 40 years of age or had malignant disease. Patients were randomised to one of three groups: control group (standard practice in the

ward), stimulation group (optimised bilateral calf muscle stimulation during the entire operation) and Dextran group (500ml dextran 40 given preoperatively and during the first and third postoperative day). Both types of prophylaxis significantly reduced the incidence of PE, while the incidence of DVT was numerically lower but did not reach statistical significance. The incidence of DVT in patients with malignant disease was significantly lower in the stimulation group compared to the control group.

- The SR also identified two NMES publications which analysed both blood flow and incidence of DVT (46, 74) (see Section 10.3).
  - Nicolaides 1972 (74) analysed blood flow and incidence of DVT in 116 patients (56 controls treated with routine physiotherapy only and 60 patients with one stimulated and one unstimulated leg). Blood flow in the femoral vein was detected using the Doppler blood flow and DVTs were detected using the ^{125}I-labelled fibrinogen test. In the control group, 18 out of 56 patients (32%) had DVT (in seven of those patients, the DVTs were bilateral). In the stimulated group, 9 out of 60 patients (15%) had DVT (one patient was bilateral); a 63% relative reduction in DVT. When the legs in each group were analysed separately, one DVT (1.7%) was observed in the stimulated legs compared with an average of 12.5 (22.3%) in the legs in the control group, resulting in a 92% relative reduction in DVT.
  - Velmahos 2005 (46) analysed blood flow and incidence of DVT in 47 trauma patients (26 patients receiving NMES and 21 control patients) contraindicated for heparinisation. When analysed at 7–15 days, 7 patients (27%) in the stimulated group and 6 patients (28.5%) in the control group had developed DVT, p=0.91. However, the results were confounded by patients being treated with heparin once no longer contraindicated (generally 3–5 days after admission).

- **The geko™ device is expected to result in a reduction in DVT that is at least equivalent to IPC**
  - The clinical evidence presented in Section 7.6 demonstrated that stimulation with the geko™ device results in significant increases in blood flow compared with IPC. The expected reduction in DVT is therefore at least equivalent to that seen with IPC.

Tolerance

Discomfort assessment by VAS and VRS showed that the geko™ device is well tolerated, with the majority of volunteers rating the sensation as minimal or mild. Interestingly, VAS scores were significantly lower (more comfortable) when wearing a plaster cast than when not.

In addition, PMS data show that 85.1% of patients consider the geko™ device comfortable or very comfortable to wear once applied (69).

Clinical harms

Generally the geko™ device was found to be safe when testing healthy volunteers. Duplex ultrasound measurements showed no significant change in mean vessel diameter throughout the stimulation, a strong indicator of the safety of the device as there were no significant physiological changes of measures related to the heart.

Pulse oximetry measurements showed no statistically significant changes in mean oxygen saturation or heart rate. No clinically significant changes in blood pressure were observed.

Summary

The clinical evidence demonstrates that the geko™ device is an effective and safe option for improving circulatory dynamics in the arterial, venous and microcirculatory vasculature of the lower limb. It is a generally well accepted, tolerated and easy-to-use device for the prophylaxis of VTE.

It is proposed that the geko™ device would provide a mechanical method for the prophylaxis of VTE in patients for whom there is currently no treatment option i.e. for patients where current mechanical methods are either impractical or contraindicated. The geko™ device fills a clear, current unmet need for this patent population and if adopted for use within the NHS would provide a treatment option for the group of hospitalised patients that are currently at risk of serious clinical consequences or even death.

7.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

All six[c] geko™ device studies demonstrate an increase in blood volume flow and peak velocity, regardless of postural position (supine, sitting, leg elevated, standing and weight bearing, standing but non-weight bearing) and whether the subject was wearing a plaster cast or not.

Not dissimilar to other medical devices studies, the study populations are relatively small in number. While the studies were conducted on healthy volunteers, there is no reason to suspect that benefits would not translate to hospitalised patients as it is the increase in blood flow that results in a reduction of venous stasis.

7.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and system-benefits described in the scope.

7.9.3.1 Patient benefits

Reduced risk of VTE via the prevention and reduction of venous stasis

The clinical data presented in Section 7.6 has shown that the geko™ device consistently increases blood flow, and in the two studies with IPC as a comparator, the geko™ device produced a statistically significant increase in vascular blood flow and velocity over IPC. Published evidence identified through the systematic review has proven that using an NMES device increases blood flow leading to a decrease in the incidence of DVT. Therefore the enhanced blood flow observed during treatment with the geko™ device is expected to equate to a reduction in the incidence of VTE.

[c] Note Williams unpublished 2013 and Williams 2013 report on the same study

Good patient compliance due to ease of application which could help with a faster recovery

The geko™ device is easy to apply, taking as little as 60 seconds. PMS data (69) show that 81.9% of clinicians found the geko™ device easy or very easy to apply; the geko™ device was easy or very easy to start/stop in 83.3% of cases and the settings were easy or very easy to change in 84.2% of cases. Non-compliance is expected to be minimal due to the comfort of the geko™ device.

Discrete and comfortable to wear, allowing the person to retain their independence and mobility, which may help maintain patient well-being and ensure self-sufficiency

The geko™ device is small, weighing 16 g and measuring 149 x 42 x 11 mm and is therefore discrete to wear. Because of its size, a patients' ability to be mobile is not restricted by the size or location of application of the geko™ device. Results from the studies show that the geko™ device is well tolerated, with most subjects reporting mild or minimal discomfort. Of note, subjects reported that VAS scores were significantly lower (more comfortable) when wearing a plaster cast than when not.

In addition PMS data (69) show that 85.1% of patients found the geko™ device comfortable or very comfortable to wear once applied. The PMS data also showed that 91.8% of patients reported that their quality of sleep was normal; 5.7% reported worse sleep and 2.5% reported better sleep.

Minimal skin contact and therefore avoidance of skin irritation, skin breakdown and sweating

The surface area of the geko™ device is 35 cm^2, considerably smaller than current methods of mechanical VTE prophylaxis. As a result, skin irritation, skin breakdown and sweating is minimal when using the geko™ device. Thirteen events of possible skin irritation have been reported to Firstkind, giving a possible frequency of 0.1%. It is acknowledged that the incidence of skin irritation maybe underreported.

7.9.3.2 Healthcare system benefits

Addressing unmet need by delivering VTE prophylaxis to patient groups who cannot currently use the standard VTE prophylaxis

The geko™ device addresses the unmet need in those patients groups not able to utilise currently available mechanical methods of VTE prophylaxis due to its novel design and mechanism of action. Such circumstances may include treatment of patients with the following:

- stroke
- morbid obesity, severe leg deformity, below knee plaster casts
- bilateral lower extremity trauma
- severe or critical lower limb ischaemia
- swelling of the legs (e.g. in heart failure)
- recent operative leg vein ligation
- local leg conditions in which other mechanical methods of prophylaxis may cause damage or pain (e.g. gangrene, infected wounds, local ulcers, cellulitis, recent skin graft or fragile 'tissue paper' skin)

- a known allergy to the materials used in current methods of mechanical prophylaxis.

The size and location of application of the geko™ device means that it may be used in many of these patients groups.

Potential to improve speed of patient recovery and therefore reduce in-hospital length of stay

A challenge to the NHS is to improve the speed of patient recovery, thereby reducing in-hospital length of stay, as has been done successfully following hip and knee joint replacement surgery (75). The best-in-class enhanced recovery pathways promote early mobilisation after surgery. Barriers to early mobilisation include decreased strength post-operatively (76) and joint swelling (77). Electrical stimulation has been shown to have beneficial effect in fracture healing (78), wound healing (79) and oedema reduction (80), and is therefore likely to improve the speed of patient recovery.

NHS targets

In an attempt to reduce avoidable deaths, disability and chronic ill health from VTE, recently published Commissioning for Quality and Innovation (CQUIN) guidance stipulates that at least 95% of adult inpatients should have a VTE risk assessment on admission to hospital (81). Despite this assessment, there is currently no treatment option for the group of patients for whom current mechanical methods of prophylaxis are impractical or contraindicated, if they are identified and the geko™ device would address this unmet need, thus helping to support centres to meet the NHS Quality, Innovation, Productivity, Prevention (QIPP) agenda.

7.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

While the studies were conducted on healthy volunteers, there is no reason to suspect that benefits would not translate to hospitalised patients as it is the increase in blood flow that results in a reduction of venous stasis.

7.9.5 Based on external validity factors identified in 7.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

There are a number of patients for whom there is currently no treatment option i.e. for patients where current mechanical methods are impractical or contraindicated. The geko™ device fills a clear, current unmet need for this patent population and if adopted for use within the NHS would provide a treatment option for the group of hospitalised patients that are currently at risk of serious clinical consequences or even death.

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt.

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt.

Summary of economic evidence

- No studies on the cost-effectiveness of neuromuscular electrostimulation (NMES) devices, including the geko™ device were identified by the systematic review
- A *de novo* cost analysis, using a decision tree structure, was conducted to analyse the cost impact of the geko™ device for the prevention of venous thromboembolism (VTE)
- In the base case analysis when both pharmacological agents and mechanical devices are contraindicated or impractical, based on a cost of £22 per pair and a duration of prophylaxis of 6 days, use of the geko™ device resulted in savings of £206 per patient compared with no prophylaxis
    - Univariate sensitivity analysis showed that the top three drivers are the cost of post-thrombotic syndrome, the relative risk reduction in deep vein thrombosis (DVT) associated with the geko™ device, and the proportion of deep vein thromboses that are symptomatic
    - Probabilistic sensitivity analysis showed that the geko™ device remained cost saving in 99% of simulations performed. The mean cost saving was £205.40 per patient (95% confidence interval: -£202.88 to -£207.92)
    - In a hypothetical cohort of 100 patients at risk of venous thromboembolism, use of the geko™ device would result in a reduction of 18 DVTs (4 symptomatic and 14 asymptomatic) and two pulmonary embolisms (PE)
    - The number of patients needed to treat to prevent one DVT would be 5.65 and to prevent one PE would be 53.7
- Two subgroup analyses were conducted
    - In patients using combined prophylaxis (the geko™ device with pharmacological agents) versus pharmacological agents alone, the combined prophylaxis resulted in an incremental cost of £69 over 6 days
        - The geko™ device in combination with pharmacological agents is cost

saving if applied for 1–3 days compared with pharmacological agents alone

- In stroke patients, the geko™ device results in savings of £146 per patient

8 Existing economic evaluations

8.1 Identification of studies

8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

A literature search was conducted (using a modified search strategy for each database) and downloaded into a bespoke Access database. Searches were conducted using the following databases: NHS EED database in the Cochrane Library, OVID MEDLINE (including MEDLINE In-process), Econlit and OVID Embase. Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for the condition (VTE) and the treatments (the geko™ device and terms for electrical stimulation) and an economic search filter. Electronic searches were supplemented by hand searching the following sources: manufacturer databases and the Cost-Effectiveness Analysis (CEA) Registry. Full search strategies are outlined in Section 10.3.

Identified studies were independently assessed by a reviewer in order to ascertain they met the pre-defined inclusion exclusion criteria and any discrepancies were revolved by a second reviewer. Data were extracted from eligible publications into a pre-defined table by a reviewer.

In total, 27 publications were identified through the electronic searches, and their titles and abstracts reviewed. All 27 publications were excluded prior to assessment of full paper. No studies were found on the cost-effectiveness of neuromuscular electrostimulation (NMES) devices.

8.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Selection criteria used for the economic systematic review is provided in Table 28.

Table 28: Selection criteria used for health economic studies

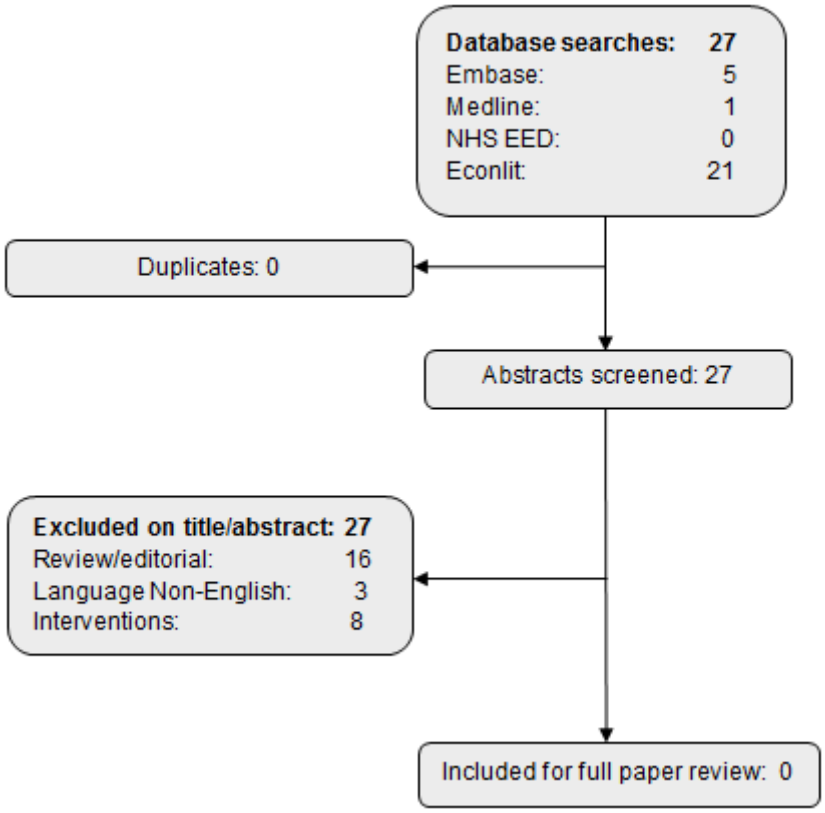
Inclusion criteria	
Population	Patients using the geko™ OnPulse™ technology device for the prevention of VTE
Interventions	• geko™ OnPulse™ technology device • NMES
Outcomes	• QoL • Mortality • Resource use
Study design	Cost/economic evaluations
Language restrictions	• English Language only • Foreign language papers with English abstracts could be included
Search dates	• Medline: 1946 to 30th July 2013 • Embase: 1974 to 29th July 2013 • NHS EED (The Cochrane Library): 1968 to 29th July 2013 • Econlit: 1969 to 30th July 2013
Exclusion criteria	
Population	Patients undergoing treatment for VTE
Interventions	• Compression stockings • IPC • Pharmacological interventions such LMWH

Abbreviations: IPC, intermittent pneumatic compression; LMWH, low molecular weight heparin; NMES, neuromuscular electrostimulation; QoL, quality of life; VTE, venous thromboembolism.

8.1.3 *Report the numbers of published studies included and excluded at each stage in an appropriate format.*

The schematic describing the flow of studies in the economic systematic review is presented in Figure 16.

Figure 16: Schematic for the systematic review of cost-effectiveness evidence



8.2 *Description of identified studies*

8.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in Table 29

N/A. No studies were identified, therefore Table 29 was not completed.

Table 29: Summary list of all evaluations involving costs

Study, Year	Location of study	Summary of model	Intervention/ comparator	Patient population	Costs	Patient outcomes	Results
Author, year (ref)							
Study 2							
Etc.							

Abbreviations: ICER, incremental cost-effectiveness ratio, QALY(s), quality-adjusted life year(s).

8.2.2 Provide a complete quality assessment for each cost-effectiveness study identified. A suggested format is shown in Table 30.

N/A. No studies were identified, therefore Table 30 was not completed.

Table 30: Quality assessment of health economic studies

[Study name]		
Study design		
Study question	**Response (yes/no/not clear/NA)**	**Comments**
1. Was the research question stated?		
2. Was the economic importance of the research question stated?		
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?		
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?		
5. Were the alternatives being compared clearly described?		
6. Was the form of economic evaluation stated?		
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?		
8. Was/were the source(s) of effectiveness estimates used stated?		
9. Were details of the design and results of the effectiveness study given (if based on a single study)?		
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?		
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?		
12. Were the methods used to value health states and other benefits stated?		
13. Were the details of the subjects from whom valuations were obtained given?		
14. Were productivity changes (if included) reported separately?		

[Study name]		
Study design		
Study question	**Response (yes/no/not clear/NA)**	**Comments**
15. Was the relevance of productivity changes to the study question discussed?		
16. Were quantities of resources reported separately from their unit cost?		
17. Were the methods for the estimation of quantities and unit costs described?		
18. Were currency and price data recorded?		
19. Were details of price adjustments for inflation or currency conversion given?		
20. Were details of any model used given?		
21. Was there a justification for the choice of model used and the key parameters on which it was based?		
22. Was the time horizon of cost and benefits stated?		
23. Was the discount rate stated?		
24. Was the choice of rate justified?		
25. Was an explanation given if cost or benefits were not discounted?		
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?		
27. Was the approach to sensitivity analysis described?		
28. Was the choice of variables for sensitivity analysis justified?		
29. Were the ranges over which the parameters were varied stated?		
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)		
31. Was an incremental analysis reported?		
32. Were major outcomes presented in a disaggregated as well as aggregated form?		
33. Was the answer to the study question given?		
34. Did conclusions follow from the data reported?		
35. Were conclusions accompanied by the appropriate caveats?		
36. Were generalisability issues addressed?		

9 De novo cost analysis

The geko™ device is a neuromuscular electrostimulation (NMES) device for the prophylaxis of venous thromboembolism (VTE)[d]. The clinical evidence submitted in Section 7 demonstrates that the geko™ device increases blood flow. Previous studies of NMES and intermittent pneumatic compression (IPC), which both act via increased blood flow, have demonstrated a reduction in DVT. Use of the geko™ device, which has shown a significantly enhanced blood flow relative to IPC is therefore expected to result in a reduction in DVT that is at least equivalent to that demonstrated with IPC.

9.1 Description of de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

No published cost-effectiveness studies of NMES devices were identified by the systematic review of economic evidence, and therefore it was necessary to conduct a *de novo* cost analysis.

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

The base case analysis considers patients for whom current mechanical methods of prophylaxis are impractical or contraindicated. This definition has the potential to encompass a small but very diverse range of patients with varying underlying comorbidities including stroke patients, those with morbid obesity, severe leg deformity, plaster casts, bilateral lower extremity trauma, severe or critical lower limb ischaemia, swelling of the legs (e.g. in heart failure), recent operative leg vein ligation, local leg conditions in which other mechanical devices of prophylaxis may cause damage or pain, or a known allergy to the materials used in current methods of mechanical prophylaxis.

Given the diverse range of patients, we have assessed the impact of the geko™ device in a mixed patient population unsuitable for mechanical prophylaxis. This group of patients is based on the NICE VTE guidelines (3).

This analysis will demonstrate how the underlying risk of VTE affects the overall cost impact of introducing the geko™ device.

[d] A short video of how the geko™ device works can be accessed at http://gekodevices.com/en-uk/technology/what-it-does-and-how-it-works/

Technology and comparator

9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

In the base case analysis it is assumed that the patients considered are those for whom current mechanical methods of prophylaxis are impractical or contraindicated. In line with the NICE scope, the comparator is therefore assumed to be no prophylaxis.

Model structure

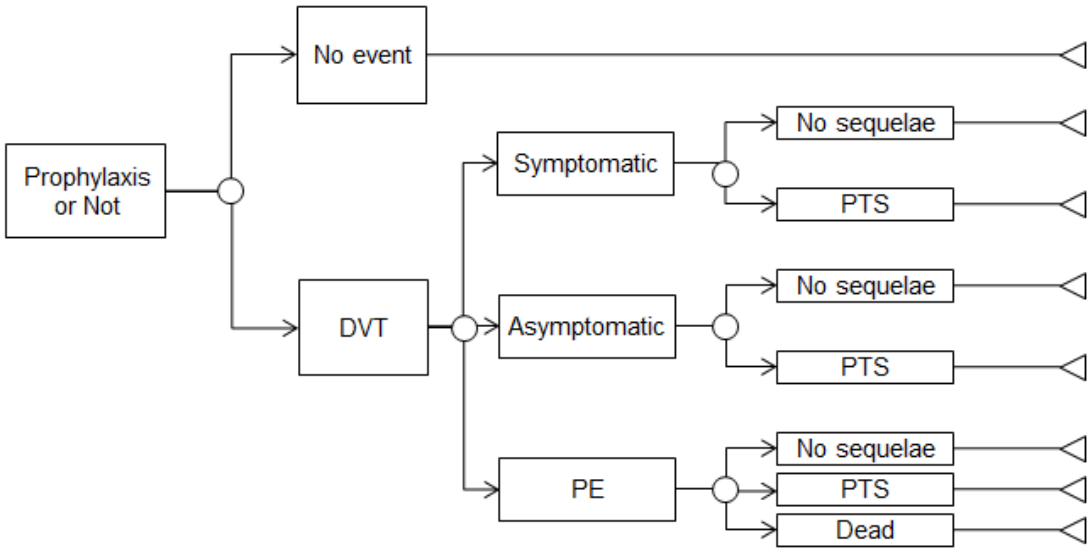
9.1.4 *Provide a diagram of the model structure you have chosen.*

The model consists of a decision tree structure (Figure 17) which is repeated for the different prophylaxis strategies considered. This model is an amended version of the decision tree structure used in the NICE VTE guidelines (3).

In the model, patients have an underlying risk of DVT which is subsequently reduced in patients receiving prophylaxis (using treatment-specific relative risks) in line with clinical practice. The model then assumes that a proportion of the DVT will progress to a PE (82) while the remaining DVTs will be split between asymptomatic and symptomatic DVT. Subsequently a proportion of each group of patients will experience post-thrombotic syndrome (PTS), a permanent comorbidity resulting from a VTE. In addition, patients who experience a PE will also have a risk of death.

The decision tree covers a non-defined short time period with the costs associated with prophylaxis, DVT and PE treatment assumed to happen within a year at most. However, with the inclusion of PTS, the model considers the associated costs for the lifetime of the patient.

Figure 17: Model structure



Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; PTS, post-thrombotic syndrome.

9.1.5 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

The primary aim of prophylaxis is to prevent DVT and subsequent sequelae; as such, the decision tree structure reflects the impact of prophylaxis. The approach employed reflects the pathway of care reported in the NICE VTE guidelines (3) and in Section 3.3.

9.1.6 Provide a list of all assumptions in the cost model and a justification for each assumption.

Table 31: Model assumptions

Assumption	Justification
Decision tree structure	Model is an amended version of the decision tree structure used in the NICE VTE guidelines (3) because: • PE most commonly results from a DVT; model structure has therefore been amended to reflect the clinical path of a patient • Primary clinical outcome considered is DVT because direct data is available for NMES reducing DVT but not PE • Typically DVT and PE are reported independently and so it is not possible to determine the proportion of symptomatic and asymptomatic DVT that will lead to a PE. In our analysis, because the risk of a PE and risk of symptomatic DVT are parameter inputs, any increase in the proportions of patients within these health states will decrease the proportion of patients within the asymptomatic DVT health state (as the overall number of patients remains constant)
In any comparison, each method of prophylaxis considered is given for the same duration Note: Duration of prophylaxis is tested in sensitivity analysis (Table 51)	Risk of VTE is not related to the prophylaxis provided, but the underlying medical condition of the patient
Underlying risk of DVT is 29.1% with no prophylaxis Note: Underlying risk of all other medical patients (23.8%) was tested in sensitivity analysis (Table 49)	Based on the average risk of DVT for all surgical-related patients as per the NICE VTE clinical guidelines (3) Risk of DVT for general medical patients as per NICE VTE clinical guidelines (3)
The proportion of DVT progressing to a PE is assumed to be 10.5%.	NICE VTE clinical guidelines (3) report the incidence of symptomatic PE at 3.1%. Assuming that PEs occur as a result of a DVT, and the underling risk of a DVT is 29.1%, the proportion of DVTs that must progress to a PE can be approximated to 10.5%

Assumption	Justification
There is a 6% chance of death resulting from a PE. No other mortality is considered	PE fatality rate based on general surgery patients from NICE VTE clinical guidelines (3) This is considered conservative as the fatality rate reported is as high as 44.7% for the general medical cohort
RR of a DVT for the geko™ device is 0.39	Risk for NMES reported by Browse and Negus (23) This RR is within the ranges reported for IPC in the NICE VTE clinical guidelines (0.31 for TKR up to 0.58 for hip fracture surgery) (3) and more conservative than that reported for NMES by Nicolaides, 1972 (74)
Cost of a symptomatic DVT is equal to the non-elective inpatient (Long Stay) NHS reference cost for a DVT (HRG data: QZ20Z)	The source of costs is based on guidance in the NICE technology appraisals methods guide (83) and MTEP methods guide (84)
No direct cost associated with asymptomatic DVT†	By definition the patient does not know they have the DVT and therefore they will not present for treatment
Cost of a PE is equal to the weighted average non-elective inpatient (Long stay) NHS reference costs for a PE without complication, with intermediate CC and with major complications (HRG data: DZ09A-C)	The source of costs is based on guidance in the NICE technology appraisals methods guide (83) and MTEP methods guide (84)
PTS occurs in • 25% of patients with symptomatic DVT • 15% of patients with asymptomatic DVT • 25% of patients with a PE	Based on assumptions made within the NICE VTE clinical guidelines (3)
Cost associated with PTS last for the life time of the patient Note: Costs associated with PTS are tested in sensitivity analysis (Table 48)	In those patients in whom it occurs it is assumed that PTS is a life-long condition Costs based on figures reported by Caprini, 2003 (85) Costs are discounted at a rate of 3.5%
Model considers a hypothetical cohort of patients with a mean life expectancy of 15 years	Mean age and proportion male/female based on NICE VTE guidelines (3) Life expectancy calculated from interim life tables, ONS (86) Calculations are provided in Section 10.9
All other costs are assumed to occur within the first year and as such are not discounted	Standard model assumption
Cost of managing a DVT is equivalent irrespective of the patients underlying condition	This is a conservative assumption It could be hypothesised that DVT in patients with significant underlying comorbidities may be more costly to treat
Major bleeds are not considered	Base case analysis does not include pharmacological prophylaxis and therefore risk of bleeds is not relevant

Abbreviations: DVT, deep vein thrombosis; HRG, Healthcare Resource Group; IPC, intermittent pneumatic compression; NHS, National Health Service; NMES, neuromuscular electrostimulation; PE, pulmonary embolism; PTS, post-thrombotic syndrome; RR, relative risk; TKR, total knee replacement surgery; VTE, venous thromboembolism.
†The costs associated with PTS following an asymptomatic DVT are considered separately.

9.1.7 Define what the model's health states are intended to capture.

The model captures the following four health states:

- DVT - the development of a blood clot in a major deep vein in the leg, thigh, pelvis, or abdomen, which may result in impaired venous blood flow and consequent leg swelling and pain
- PE - a blockage in one or more arteries in the lung. In most cases, PE is caused by blood clots that travel to the lungs from another part of the body, most often as a result of DVT
- PTS - a constellation of signs and symptoms that frequently follows a vascular thrombosis, ranging from pain, skin pigmentation, and swelling in the lower extremities to the formation of recurring venous leg ulcers.
- Death - a proportion of patients experiencing a PE will die (no other mortality is considered in this analysis).

9.1.8 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Key additional features of the model are presented in Table 32.

Table 32: Key features of the model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Life time – assumed to be 15 years in the base case	Damage caused by VTE leading to PTS is permanent and therefore lasts for the duration of the patient's life. A generic, at risk, population was considered, with an assumed 15-year life expectancy	NICE VTE guidelines (3) ONS (86)
Discount of 3.5% for costs	Cost of PTS is the only parameter considered beyond 1 year – this is adjusted to reflect discounting at 3.5%	Follows NICE reference case	MTEP methods guide (84)
Perspective (NHS/PSS)	NHS	Follows NICE reference case	MTEP methods guide (84)
Cycle length	Not relevant to model structure		

Abbreviations: NHS, National Health Service; PSS, Personal Social Services; PTS, post-thrombotic syndrome; VTE, venous thromboembolism.

9.2 Clinical parameters and variables

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

There are currently no clinical trials demonstrating the relative risk (RR) reduction of VTE associated with the use of the geko™ device as a prophylaxis. Two studies measuring the incidence of DVT following use of NMES demonstrated a RR reduction in the incidence of DVT of 61% (Browse and Negus (23)) and 92% (Nicolaides 1972 (74)).

Maintaining peripheral blood flow in the lower limb is essential in preventing venous stasis and hence reducing the potential for DVT. IPC is a technology routinely used within the UK NHS for the prophylaxis of VTE, the underlying mechanism of which is the increase in lower limb blood flow. The clinical evidence presented in Section 7.6 demonstrated that stimulation with the geko™ device results in significantly greater increases in blood flow compared with IPC and so it could be hypothesised that the RR reduction in DVT obtained with the geko™ device would be at least equivalent to that achieved with IPC. The NICE VTE guidelines assessed the efficacy of IPC and found that it was an effective method of prophylaxis with a RR reduction between 42% (RR 0.58) in patients with hip fracture surgery and 69% (RR 0.31) in patients with total knee replacement (3). It can be argued that the risk reduction between the geko™ device and IPC would be at least comparable because in addition to the improved blood flow observed following use of the geko™ device, compliance with current mechanical methods of prophylaxis is generally considered to be low. This can be attributed to poorly fitting cuffs and reduced mobility, since patients must be connected to a pump. Because of the small size, ease of application and the ability to wear the geko™ device during normal activities it can be hypothesised that compliance with the geko™ device has the potential to be greater than observed with IPC, and therefore associated efficacy may be higher with the geko™ device than other mechanical methods. The RR reduction demonstrated by Browse and Negus falls within the range identified for IPC in the NICE VTE guidelines. It is therefore conservatively assumed that the geko™ device would achieve the same RR reduction as that reported by Browse and Negus. The relative risk reduction for VTE is varied in sensitivity analysis.

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Post-thrombotic syndrome (PTS) is a permanent comorbidity resulting from a VTE, continuing for the life time of the patient. As such, the associated costs are extrapolated for the average lifetime of the patient, assumed to be 15 years, and discounted at a rate of 3.5% in line with the MTEP methods guide and NICE reference case (83, 84). The model uses a simple, single input for the cost of PTS and therefore this lifetime cost is estimated separately from the main model.

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what

sources of evidence were used, and what other evidence is there to support it?

There are no clinical trials demonstrating a direct RR reduction associated with use of the geko™ device as a prophylaxis for VTE. Section 7 summarises the increased blood volume flow, increased blood velocity and decreased venous transit time that is observed following use of the geko™ device, and its statistically significantly greater improvements in these outcomes over IPC systems. These surrogate endpoints from the studies of the geko™ device are expected to translate into a RR reduction of DVT at least equivalent to those published for NMES and IPC.

9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

No adverse events were considered in this analysis. When considering other forms of prophylaxis, this assumption could be deemed to be conservative.

The only known adverse event with the geko™ device is skin irritation or inflammation, which has previously been reported for other NMES devices using hydrogel electrodes. Firstkind is aware of 13 events of possible skin irritation, giving a possible frequency of 0.1%. It is acknowledged that the incidence of skin irritation maybe underreported. These events are not considered to result in discontinuation of prophylaxis or to require additional resources and are therefore excluded from the model.

Current modalities of VTE prophylaxis are associated with adverse events:

- Use of anti-coagulants is associated with a risk of bleeding, often resulting in patients being contraindicated for their use.
- Many existing forms of mechanical prophylaxis are associated with skin breaks, ulcers, blisters or skin necrosis.

Given that these prophylaxis options are not considered in the base case we have excluded any adverse events from this analysis.

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

General information regarding the collection of expert opinion is provided in Table 33. Experts' names and titles, and the questions/discussion points used to structure the interview is provided in a data-on-file document (87).

Table 33: Summary of collection of expert opinion

	Detail
Criteria for selecting experts	Known experts with a publication record in the field were approached
Number of experts approached	3
Number of experts who participated	3
Background evidence provided	Experts were verbally informed of the geko™ device technology and model structure, inputs and assumptions.

	Detail
Method used to collect and collate opinions	Interview notes were assessed for consensus and differences in opinion
Medium used to collect opinions	Direct interview or telephone interview
Questions asked	Details of the questions used to structure the interview are provided in a data on file document (87) Questions covered validity of model structure, inputs and assumptions
Use of iteration	None

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission. A suggested format is provided in Table 34

A list of all variables used in the economic analysis is provided in Table 34.

Table 34: Summary of variables applied in the cost model

Variable	Mean value	Range or 95% CI (distribution)	Source
Baseline risk of DVT	29.1%	Lower 95% CI: 28.1% Upper 95% CI: 30.1%	NICE VTE guidelines (3)
Proportion of DVTs that are symptomatic	20%	5% to 30%	Mean value is an assumption, range is based on: THR=16.7%‡ (88) TKR=4.5%‡ (88) General surgery and general medical=6.2% (3) Stroke=29.6%§ (89)
Proportion of symptomatic DVT resulting in PTS	25%	Lower 95% CI: 2.13% Upper 95% CI: 28.7%	NICE VTE guidelines (3)
Proportion of asymptomatic DVT resulting in PTS	15%	Lower 95% CI: 11.9% Upper 95% CI: 18.1%	NICE VTE guidelines (3)
Proportion of symptomatic PE resulting in PTS	25%	Lower 95% CI: 2.13% Upper 95% CI: 28.7%	NICE VTE guidelines (3)
Proportion of DVT leading to a PE	10.5%	Lower -25%: 7.9% Upper +25%: 13.1%	Estimated from NICE VTE guidelines (3)
PE fatality	6.0%	Lower 95% CI: 2.6% Upper 95% CI: 9.4%	NICE VTE guidelines (3)
RR of DVT with the use of the geko™ device	0.39	0.31–0.58	Browse and Negus (23) and NICE VTE guidelines (3)
Cost of the geko™ device per pair	£22 (Excluding VAT)	N/A	FirstKind, data on file (90)

Variable	Mean value	Range or 95% CI (distribution)	Source
Cost of pharmacological prophylaxis	£2.95 (Weighted average price of pharmacological prophylaxis)	Lower range: £2.10 (Rivaroxaban 10 mg daily) Upper range: £6.28 (Fondaparinux 2.5 mg daily)	BNF 65, 2013. Health and Social Care Information Centre, prescription cost analysis for England 2012
Staff nurse cost per hour	£41	£31–51	Curtis, 2012 (91)
Administration time (mins) for the geko™ device	1.5	1–3 (Gamma)	FirstKind, data on file (90)
Administration time (mins) for pharmacological prophylaxis	2.5	2–3 (Gamma)	NICE VTE guidelines (3)
Duration of prophylaxis (days)	6	5–7 (Gamma)	NICE scope
Cost of DVT	£1,718	Lower 95% CI: £1,642 Upper 95% CI: £1,793 (Gamma)	NHS reference costs, 2011–12 (92) NHS trusts and NHS foundation trusts – Non-Elective Inpatient (Long Stay) HRG data QZ20Z
Cost of PE	£2,022	Lower 95% CI: £1,940 Upper 95% CI: £2,103 (Gamma)	NHS reference costs, 2011–12 (92) NHS trusts and NHS foundation trusts – Non-Elective Inpatient (Long Stay) HRG data Weighted average of DZ09A-C
Cost of PTS	£7,682	Lower range: £3,716 Upper range: £18,024† (Gamma)	Caprini 2003 (85) Costs converted from US$ to UK£ using purchasing power parities (93) and inflated to 2012 costs using inflation indices from Curtis, 2012 (91)

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; N/A, not applicable; NICE, National Institute of Health and Care Excellence; PE, pulmonary embolism; PTS, post-thrombotic syndrome; RR, relative risk; SC, subcutaneous; VTE, venous thromboembolism .

†This range is based on 100% mild to moderate PTS for the lower value and 100% severe PTS for the upper value; ‡Patients in this trial received pharmacological prophylaxis; §discussed further in Section 9.6.3.

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

In the base case, a unit cost of £1,718 was assumed for the management of a patient with DVT, this was based on the cost of a non-elective inpatient (Long stay) for Healthcare Resource Groups (HRG) QZ20Z (Deep Vein Thrombosis) in NHS Reference Costs 2011–12 (92).

Similarly, a unit cost of £2,022 was estimated for managing a patient with PE. This was based on the weighted average cost of non-elective inpatient (Long stay) for HRG DZ09A-C (Pulmonary Embolus with A: Major complications, B: intermediate complications, C: without complications) from NHS Reference Costs 2011–12 (92).

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

N/A.

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

A systematic review was not conducted to identify relevant resource data from the published literature. Resource use was identified via existing NICE clinical guidelines for venous thromboembolism (3).

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model.

Details around selection of clinical experts and assessment of their opinion has previously been provided in Section 9.2.5.

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

The cost of the geko™ device is £22 per pair exclusive of VAT.

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

The list price of the geko™ device is used in the base case analysis. An incremental cost of administration is also included. It is assumed that the device will take a staff nurse approximately 1.5 minutes on average to apply[e].

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. A suggested format is provided in Table 35 and Table 36 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.

The unit costs of the geko™ device are given in Table 35.

Table 35: Costs per treatment/patient associated with the technology in the cost model

Component of prophylaxis	Cost per unit	Cost per course†	Source
geko™ device	£22 per pair (excluding VAT)	£132	FirstKind, data on file (90)

†Assuming 6 days of prophylaxis.

Drug prices were taken from the current British National Formulary (BNF 65) for the recommended thrombo-prophylactic dose (Table 36). An average unit price was estimated based on the BNF prices and quantity dispensed from the Health and Social Care Information Centre, prescription cost analysis for England 2012. The same data was then used to generate an average cost of pharmacological prophylaxis for the sub-population analysis.

It should be noted that the costs associated with pharmacological prophylaxis are only considered in a subgroup analysis and will not impact the base case analysis directly. In the subgroup analysis, the cost of pharmacological prophylaxis is equal in both arms and so will therefore be cancelled out. We have simply included if for completeness.

[e] The geko™ device can be applied in as little as 60 seconds. It is anticipated that the geko™ device would be administered during a routine nurse check. Administration takes slightly longer for the first application, but is quicker on subsequent applications.

Table 36: Cost per treatment/patient associated with pharmacological prophylaxis

Drug	Dose	Injections/ dose per day	Drug cost per day†	Source
LMWH‡	Average of: Dalteparin 5,000 units SC daily Enoxaparin 4,000 units SC daily Tinzaparin 4,000 units SC daily	1	£2.86	BNF 65, March–September 2013 (94)
UFH	5,000 units every 12 hours	2	£4.56	
Fondaparinux sodium	2.5 mg SC daily	1	£4.70	
Dabigatran	220 mg daily	1	£2.29	
Rivaroxaban	10 mg daily	1	£1.32	
Average pharmacological prophylaxis cost per day			**£2.95**	

Abbreviations: BNF, British National Formulary; LMWH, low molecular weight heparin; SC, subcutaneous; UFH, unfractionated heparin.
†Cost per day is weighted based on quantity dispensed from the Health and Social Care Information Centre, prescription cost analysis for England 2012; ‡Doses quoted are those for general medicine, not specific surgeries.

The daily cost of nurse time for each method of prophylaxis is also included (Table 37) using the same assumptions as detailed in CG92.

Table 37: Prophylaxis – Testing and nurse time

Prophylaxis	Nurse time per administration	Cost per administration†	Cost per course of prophylaxis‡
geko™ device	1.5 minutes per day	£1.02	£6.15
Pharmacological prophylaxis	2.5 minutes per injection	£1.71	£10.25

†Staff nurse cost of £41 per hour taken from Unit Costs of Health and Social Care 2012; ‡Assuming 6 days of prophylaxis.

In general, the duration of prophylaxis can vary substantially from patient to patient depending on the underlying rational for prophylaxis but is generally continued until the risk of VTE recedes with recovery and mobilisation. It is typically assumed that prophylaxis will be provided for 5–7 days, but may be significantly less in many surgical pathways such as total hip replacement (1–2 days). In this analysis it is assumed that all methods of prophylaxis will be administered for the same duration; in the base case this is for 6 days. Duration of prophylaxis is varied in sensitivity analysis.

Health state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented in Table 38. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

A list of the health states and associated costs in the economic model is provided in Table 38.

Table 38: List of health states and associated costs in the economic model

Health state	Cost (95% CI or Range)	Source
Symptomatic DVT	£1,718 (Lower 95% CI: £1,642 Upper 95% CI: £1,793)	NHS reference costs, 2011–12 (92) NHS trusts and NHS foundation trusts Non-Elective Inpatient (Long Stay) HRG data QZ20Z
Asymptomatic DVT	£0	Assumption. By definition the patient does not know they have the DVT and therefore they will not present for treatment
PE	£2,022 (Lower 95% CI: £1,940 Upper 95% CI: £2,103)	NHS reference costs, 2011–12 (92) NHS trusts and NHS foundation trusts – Non-Elective Inpatient (Long Stay) HRG data Weighted average of DZ09A-C
PTS	£7,682 (Lower range: £3,716 Upper range: £18,024)†	Caprini, 2003 (85) Costs were converted from US$ to UK£ using purchasing power parities (93) and inflated to 2012 costs using inflation indices from Curtis, 2012 (91) Annual cost is then assumed to last for 15 years and discounted at 3.5% p.a.

Abbreviations: DVT, deep vein thrombosis; HRG, Healthcare Resource Group; NHS, National Health Service; p.a., per annum; PE, pulmonary embolism; PTS, post-thrombotic syndrome.
†This range is based on 100% mild to moderate PTS for the lower value and 100% severe PTS for the upper value.

In the base case, NHS reference costs have been used for symptomatic DVT and PE. It is assumed that there are no costs associated with asymptomatic DVT. The long term cost of PTS has been estimated from Caprini, 2003 (85), a US-based study which considers the long-term complications of a DVT following total hip replacement surgery. Costs were converted from US$ to UK£ using purchasing power parities (93) and inflated to 2012 costs using inflation indices from Curtis, 2012 (91). The study differentiates between mild-to-moderate and severe PTS, but as the model considers PTS as a single state, the rates reported by Caprini have been used to weight the converted costs into an annual figure.

The model assumes that this is an annual cost incurred for the remaining time-horizon (15 years in the base case). These annual costs are discounted at a rate of 3.5% in line with NICE best practice resulting in an average total cost for PTS of £7,682. This is comparable with the cost of PTS used in the NICE VTE guidelines which was reported as £7,551 (3).

Adverse-event costs

9.3.9 Complete Table 39 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

N/A. Adverse events reported with the use of the geko™ device are rare and unlikely to require treatment (skin irritations with a frequency of 0.1%). Therefore no adverse events are included in the model.

Table 39: List of adverse events and summary of costs included in the cost model

Health states	Items	Value	Reference
Adverse event 1	Technology		
	Staff		
	Hospital costs		
	Etc		
	Total		
Adverse event 2 etc			

Abbreviations:

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

None.

9.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The geko™ device has the potential to improve speed of patient recovery and therefore reduce in-hospital length of stay as its design and size mean that it is not a barrier to mobilisation, unlike other currently available mechanical forms of VTE prophylaxis.

9.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

Uncertainty around structural assumptions has been investigated in one-way sensitivity analysis (Table 40), multi-way sensitivity analysis (Table 41) and probabilistic sensitivity analysis (PSA) (Table 42).

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what

was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

One-way sensitivity analysis was performed on all model parameters using the confidence intervals/ranges defined in Section 9.2.6. Two-way scenario analysis was conducted varying the RR of DVT following use of the geko™ device and the proportion of symptomatic DVTs. In addition, probabilistic sensitivity analysis (PSA) was also undertaken using the same confidence intervals/ranges and the associated distributions as detailed in Section 9.2.6.

9.4.3 Complete the following tables as appropriate to summarise the variables used in the sensitivity analysis.

A summary of variables used in one-way scenario-based deterministic sensitivity analysis is provided in Table 40.

Table 40: Variables used in one-way scenario-based deterministic sensitivity analysis

Variable	Base case value	Range of values	Source
Baseline risk of DVT	29.1%	28.1–30.1%	See Table 34
Relative risk of DVT with the geko™ device	0.39	0.31–0.58	
Proportion of DVTs that are symptomatic	20%	5–30%	
Proportion of DVTs leading to a PE	10.5%	7.9%–13.1%	
Proportion of symptomatic DVT resulting in PTS	25%	21.3–28.7%	
Proportion of asymptomatic DVT resulting in PTS	15%	11.9–18.1%	
Proportion of PE resulting in PTS	25%	21.3%–28.7%	
PE fatality	6.0%	2.6%–9.4%	
Staff nurse cost per hour	£41	£31–51	
Administration time with the geko™ device	1.5 mins	1–3 mins	
Duration of prophylaxis	6 days	5–7 days	
Cost of DVT	£1,718	£1,642–1,793	
Cost of PE	£2,022	£1,940–£2,103	
Cost of PTS	£7,682	£3,716–18,024†	

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; PTS, post-thrombotic syndrome.
†This range is based on 100% mild to moderate PTS for the lower value and 100% severe PTS for the upper value.

A summary of variables used in multi-way scenario-based sensitivity analysis is provided in Table 41.

Table 41: Variables used in multi-way scenario-based sensitivity analysis

Variable	RR of DVT	Proportion of symptomatic DVT	Duration of prophylaxis (days)
Base case	0.39	20%	6
Scenario analysis 1	0.08, 0.31, 0.45, 0.58	0–100%	
Scenario analysis 2	0.1–1.0 (in 0.1 increments)		1–10

Abbreviations: DVT, deep vein thrombosis; RR, relative risk.

During probabilistic sensitivity analysis (PSA), 10,000 iterations were performed and a summary of variables used is provided in Table 42.

Table 42: Variables used in probabilistic sensitivity analysis

Variable	Base case value	Range	Distribution
Baseline risk of DVT	29.1%	28.1–30.1%	Beta
Relative risk of DVT with the geko™ device	0.39	0.31–0.58	Lognormal
Proportion of DVTs that are symptomatic	20%	5–30%	Beta
Proportion of DVTs leading to a PE	10.5%	7.9%–13.1%	Beta
Proportion of symptomatic DVT resulting in PTS	25%	21.3%–28.7%	Beta
Proportion of asymptomatic DVT resulting in PTS	15%	11.9–18.1%	Beta
Proportion of PE resulting in PTS	25%	21.3–28.7%	Beta
PE fatality	6.0%	2.6%–9.4%	Beta
Staff nurse cost per hour	£41	£31–51†	Gamma
Administration time with the geko™ device	1.5 mins	1–3 mins	Gamma
Duration of prophylaxis	6 days	5–7 days	Gamma
Cost of DVT	£1,718	£1,642–1,793	Gamma
Cost of PE	£2,022	£1,940–£2,103	Gamma
Cost of PTS	£7,682	£3,716–18,024‡	Gamma

Abbreviations: DVT, deep vein thrombosis; PTS, post-thrombotic syndrome.
†Estimated as ±25% of the base value; ‡Range is based on 100% mild to moderate PTS for the lower value and 100% severe PTS for the upper value.

9.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

The cost of the geko™ device was excluded as it was considered constant at £22 per pair excluding VAT.

9.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base case analysis

9.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in Table 43.

Base case results are presented in Table 43.

Table 43: Base case results

Comparator	Total cost per patient
geko™ device	£359
No prophylaxis	£565
Difference	**-£206**

9.5.2 Report the total difference in costs between the technology and comparator(s).

Use of the geko™ device would result in savings of £206 per patient compared with no prophylaxis.

9.5.3 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in Table 44.

A summary of costs by category of cost per patient is provided in Table 44.

Table 44: Summary of costs by category of cost per patient

Item	Cost intervention (geko™ device)	Cost comparator (No prophylaxis)	Increment	Absolute increment	% absolute increment
Technology cost	£132.00	£0.00	£132.00	£132.00	96%
Administration cost	£6.15	£0.00	£6.15	£6.15	4%
Total	**£138.15**	**£0.00**	**£138.15**	**£138.15**	**100%**

9.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in Table 45.

A summary of costs by health state per patient is provided in Table 45.

Table 45: Summary of costs by health state per patient

Health state	Cost intervention (geko™ device)	Cost comparator (No prophylaxis)	Increment	Absolute increment	% absolute increment
DVT	£39.11	£99.94	-£60.83	£60.83	18%
PE	£24.19	£61.82	-£37.63	£37.63	11%
PTS	£157.85	£403.40	-£245.55	£245.55	71%
Total	**£221.15**	**£565.16**	**-£344.01**	**£344.01**	**100%**

Abbreviations: DVT, deep vein thrombosis; PTS, post-thrombotic syndrome.

9.5.5 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in Table 46.

N/A.

Table 46: Summary of costs by adverse events per patient

Adverse event	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Adverse event 1					
Adverse event 2					
Total					

Abbreviations:

Sensitivity analysis results

9.5.6 Present results of deterministic one-way sensitivity analysis of the variables described in Table 40.

Univariate sensitivity analysis

Univariate sensitivity analysis shows that in the base case the top three drivers are:

- cost of PTS
- relative risk of DVT associated with the geko™ device as a prophylaxis
- proportion of DVTs that are symptomatic.

Based on the ranges defined previously, all parameter changes result in the geko™ device being cost saving when compared with no prophylaxis.

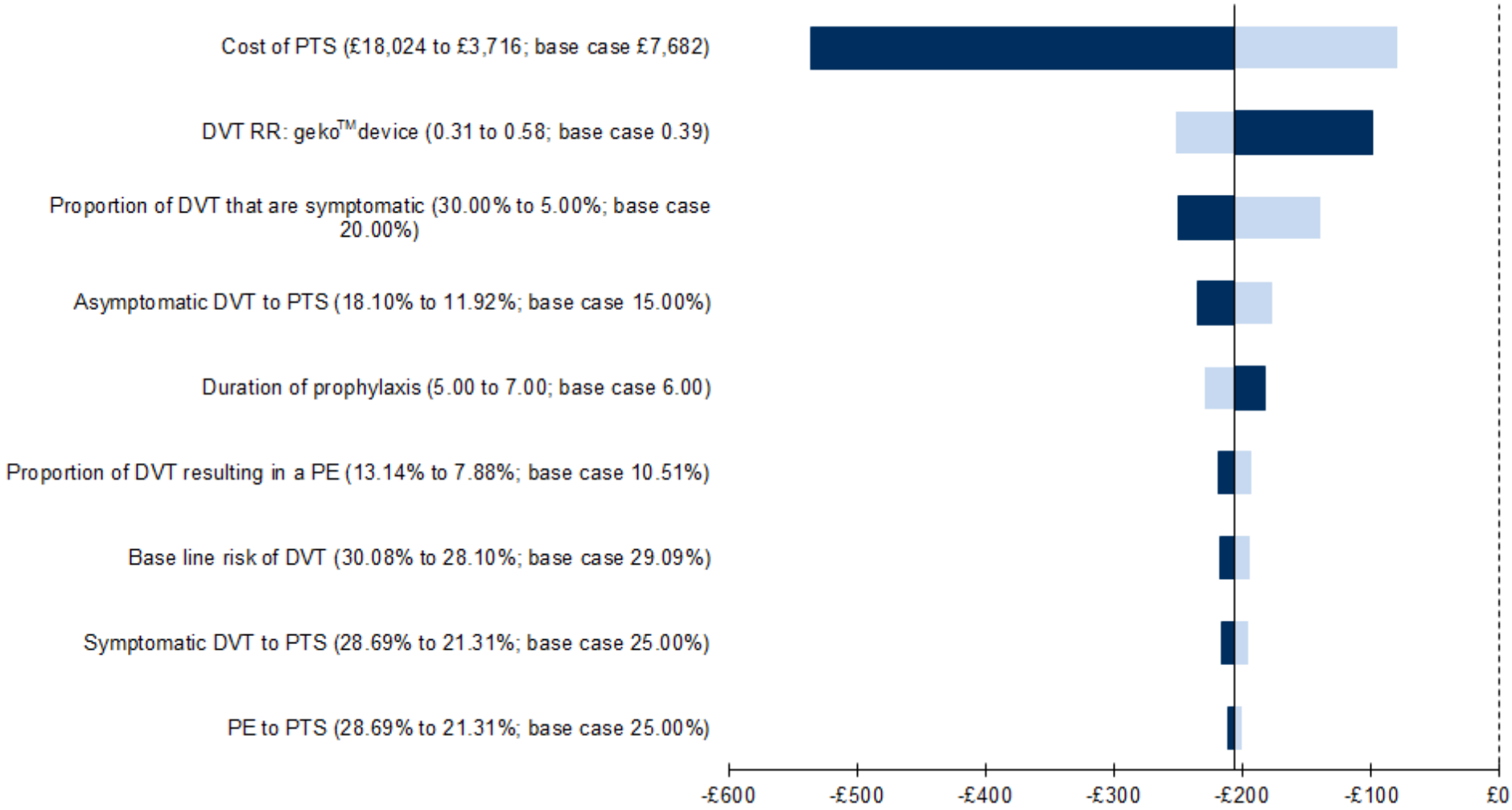
Table 47 shows the results of the univariate analysis and these results are also presented graphically in Figure 18.

Table 47: Results of univariate analysis

Variable	CE with low value	CE with high value
Cost of PTS (£18,024 to £3,716; base case £7,682)	-£79.09	-£536.41
DVT RR: geko™ device (0.31 to 0.58; base case 0.39)	-£251.81	-£99.22
Proportion of DVT that are symptomatic (30.00% to 5.00%; base case 20.00%)	-£139.83	-£249.88
Asymptomatic DVT to PTS (18.10% to 11.92%; base case 15.00%)	-£176.74	-£235.17
Duration of prophylaxis (5.00 to 7.00; base case 6.00)	-£228.89	-£182.84
Proportion of DVT resulting in a PE (13.14% to 7.88%; base case 10.51%)	-£192.88	-£218.84
Base line risk of DVT (30.08% to 28.10%; base case 29.09%)	-£194.16	-£217.57
Symptomatic DVT to PTS (28.69% to 21.31%; base case 25.00%)	-£195.81	-£215.91
PE to PTS (28.69% to 21.31%; base case 25.00%)	-£200.58	-£211.14
Cost of Symptomatic DVT (£1,793 to £1,642; base case £1,718)	-£203.19	-£208.53

Abbreviations: CE, cost-effectiveness; DVT, deep vein thrombosis; PTS, post-thrombotic syndrome; RR, relative risk.
Note: only the top ten drivers are shown.

Figure 18: Results of univariate analysis



Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; PTS, post-thrombotic syndrome; RR, relative risk.

Threshold analysis has been performed on all model parameters to determine at which value they would result in the use of the geko™ device being cost neutral compared to no prophylaxis. In this analysis all other parameters are kept at their original value.

Table 48: Results of threshold analysis

Variable	Base case (CI: Lower - Upper)	Cost neutral
Cost of PTS	£7,682 (£3,716 to £18,024)	£1,242
DVT RR: geko™ device	0.39 (0.31 to 0.58)	0.76
Proportion of DVT that are symptomatic	20.00% (5.00% to 30.00%)	-26.77%
Asymptomatic DVT to PTS	15.00% (11.92% to 18.10%)	-6.78%
Duration of prophylaxis	6.00 (5.00 to 7.00)	14.94
Proportion of DVT resulting in a PE	10.51% (7.88% to 13.14%)	-31.16%
Base line risk of DVT	29.09% (28.10% to 30.08%)	11.68%
Symptomatic DVT to PTS	25.00% (21.31% to 28.69%)	-50.67%
PE to PTS	25.00% (21.31% to 28.69%)	-118.97%
Cost of Symptomatic DVT	£1,718 (£1,642 to £1,793)	-£4,095

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; PTS, post-thrombotic syndrome; RR, relative risk.
†Outside plausible range.

In this analysis when parameters are considered individually, in order for the geko™ device to be cost neutral:

- the cost of PTS would need to be as low as £1,242 close to the lower confidence interval
- the relative risk when using the geko™ device would need to be 0.76, outside the range observed in the NICE VTE guidelines for IPC
- the proportion of asymptomatic DVTs leading to PTS would need to be negative - implausible
- the duration of prophylaxis with the geko™ device would need to increase to 15 days
- the baseline risk of DVT would need to be as low as 11.7%.

The proportion of DVTs that are symptomatic, the proportion of symptomatic, asymptomatic DVTs and PEs that result in PTS, the proportion of DVT resulting in a PE

and the cost of treating/managing symptomatic DVT need to be negative in order to result in the geko™ device being cost-neutral which in all cases, would be impossible.

Scenario analysis

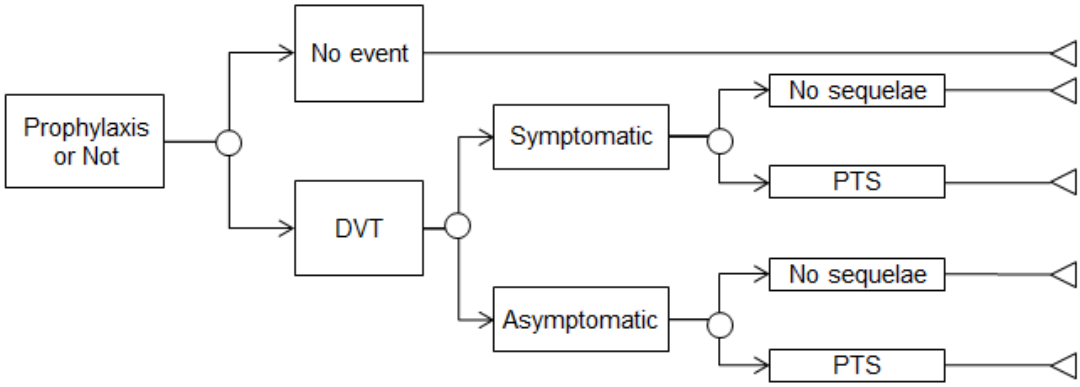
Scenario 1: In a separate scenario analysis considering general medical patients (using the 23.8% risk of DVT reported in the NICE VTE guidelines but using all other base case assumptions), use of the geko™ device results in savings of £143 per patient (Table 49).

Table 49: Scenario 1 results, using 23.8% risk of DVT for medical admissions

Comparator	Total cost per patient
geko™ device	£319
No prophylaxis	£462
Difference	**-£143**

Scenario 2: An additional scenario analysis using a simpler decision tree structure, with no health state for PE, was conducted (Figure 19). Uncertainties around the incidence of PE exist and therefore removing PE from the model provides a conservative assessment of the cost impact of the geko™ device.

Figure 19: Scenario 2, alternative model structure



Abbreviations: DVT, deep vein thrombosis; PTS, post-thrombotic syndrome.

Despite the removal of PE as a separate health state in the model, the geko™ device remains cost saving, result in savings of £154 per patient compared with no prophylaxis.

Table 50: Scenario 2 results, using a model structure without a PE health state

Comparator	Total cost per patient
geko™ device	£326
No prophylaxis	£480
Difference	**-£154**

9.5.7 Present results of deterministic multi-way scenario sensitivity analysis described in Table 41.

The proportion of DVTs that are symptomatic is one of the key drivers and as stated previously is also one of the biggest unknowns. The threshold analysis in Section 9.5.6

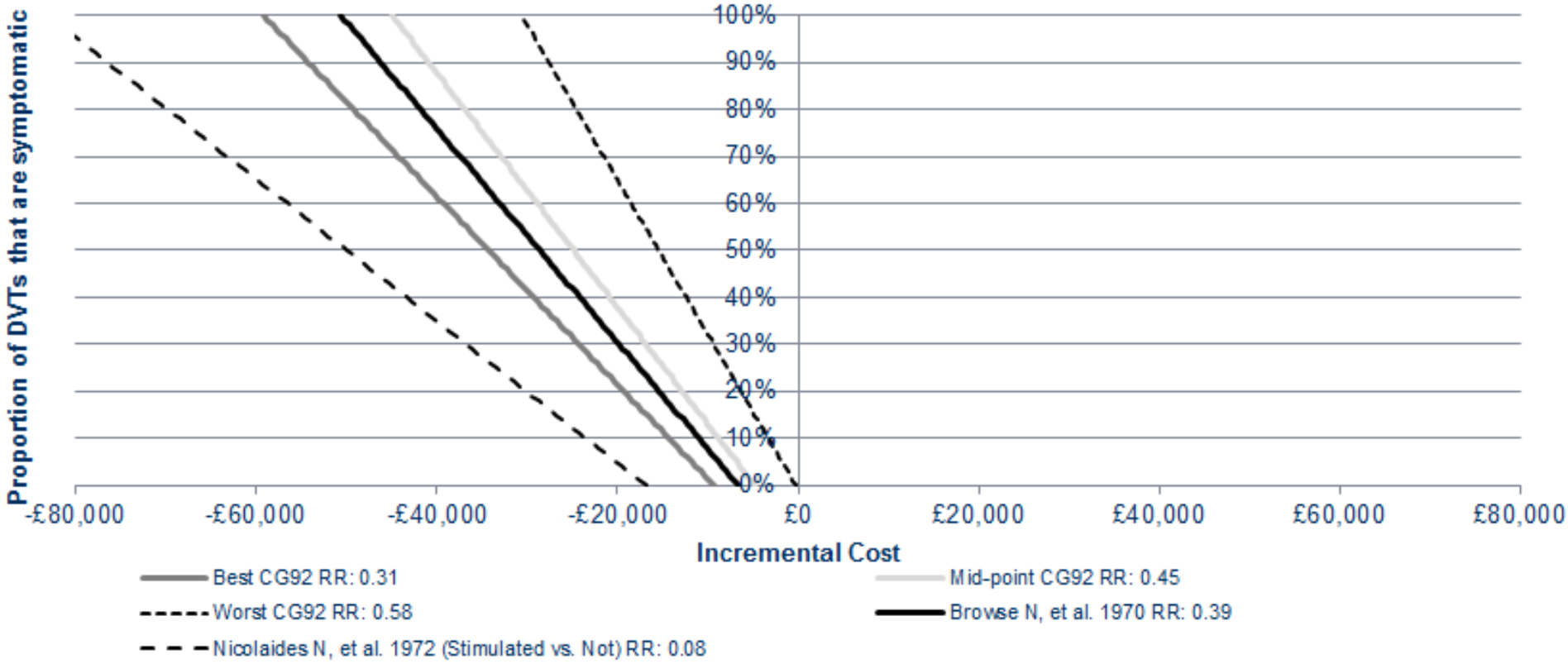
shows that under the current baseline assumptions, use of the geko™ device would be cost neutral when the proportion of DVT that are symptomatic is less than zero. This means that any values within the plausible range would result in the geko™ device being a cost saving option compared with no prophylaxis.

Scenario 1: RR of DVT with the geko™ device vs proportion of symptomatic DVTs

Another key driver is the relative risk of DVT associated with the geko™ device, a parameter obtained from published evidence from NMES studies. A two-way sensitivity analysis was performed varying the relative risk of DVT with prophylaxis using the ranges discussed in Section 9.2.1 and varying the proportion of DVTs that are symptomatic (Figure 20).

Each line represents a point estimate for the relative risk of DVT when using the geko™ device. For each point estimate, the proportion of DVT that are symptomatic can take any positive value and the geko™ device will remain cost saving.

Figure 20: Results of two-way sensitivity analysis varying the RR of DVT with the geko™ device and the proportion of symptomatic DVTs



Abbreviations: DVT, deep vein thrombosis; RR, relative risk.

Scenario 2: RR of DVT with the geko™ device vs duration of prophylaxis

Duration of prophylaxis is intrinsically linked to the cost associated with the geko™ device and will therefore be a key driver of overall costs. A two-way sensitivity analysis was performed varying both the duration of prophylaxis and the relative risk of DVT with the geko™ device and the results are presented in Table 51. The threshold analysis previously presented in Table 48 had already demonstrated that with the baseline RR of DVT, duration of prophylaxis with the geko™ device had to exceed 15 days to result in an incremental cost (the duration of prophylaxis used in the base case is 6 days). Conversely with the baseline duration of prophylaxis, the RR of DVT had to exceed 0.76 to result in an incremental cost (the RR of DVT used in the base case is 0.39).

Table 51: Results of two-way sensitivity analysis varying the RR of DVT with the geko™ device and the duration of prophylaxis

Duration of prophylaxis (days)	RR of DVT with the geko™ device								
	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1
1	-£33	-£90	-£147	-£203	-£260	-£316	-£373	-£429	-£486
2	-£10	-£67	-£123	-£180	-£237	-£293	-£350	-£406	-£463
3	£13	-£44	-£100	-£157	-£214	-£270	-£327	-£383	-£440
4	£36	-£21	-£77	-£134	-£190	-£247	-£304	-£360	-£417
5	£59	£2	-£54	-£111	-£167	-£224	-£280	-£337	-£394
6	£82	£25	-£31	-£88	-£144	-£201	-£257	-£314	-£370
7	£105	£48	-£8	-£65	-£121	-£178	-£234	-£291	-£347
8	£128	£71	£15	-£42	-£98	-£155	-£211	-£268	-£324
9	£151	£94	£38	-£19	-£75	-£132	-£188	-£245	-£301
10	£174	£117	£61	£4	-£52	-£109	-£165	-£222	-£278

Abbreviations: DVT, deep vein thrombosis; RR, relative risk.

9.5.8 Present results of the probabilistic sensitivity analysis described in Table 42.

The results of the PSA were very robust, with the geko™ device remaining cost saving in 99% of simulations performed. The mean cost saving was -£205.40 per patient (95% CI: -£202.88 to -£207.92).

9.5.9 What were the main findings of each of the sensitivity analyses?

Both univariate and probabilistic sensitivity analysis show that the geko™ device remains a cost minimising prophylaxis option when compared with no prophylaxis. Within univariate analysis only the lowest cost assumptions for PTS resulted in a nominal incremental cost while the PSA showed the results to be extremely stable with 99% of simulations resulting in cost savings.

9.5.10 What are the key drivers of the cost results?

In the base case, the top three drivers are:

- cost of PTS

- DVT RR reduction associated with the geko™ device
- proportion of DVTs that are symptomatic.

Miscellaneous results

9.5.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

DVTs avoided

In a hypothetical cohort of 100 patients there would be:

- 29 DVTs (6 symptomatic and 23 asymptomatic) 3 PE with no prophylaxis
- 11 DVT (2 symptomatic / 9 asymptomatic) and 1 PE with use of the geko™ device.

This results in a reduction of 18 DVTs (4 symptomatic / 14 asymptomatic) and 2 PE following use of the geko™ device.

Number needed to treat

The number needed to treat (NNT):

- to prevent one DVT would be 5.65
  - to prevent a symptomatic DVT would be 28.24
  - to prevent an asymptomatic DVT would be 7.06
- to prevent one PE would be 53.7
- to avoid one PE-related death would be 895.

Since use of the geko™ device is cost saving compared with no prophylaxis it can be considered a dominant treatment option (i.e. cost saving and additional clinical benefit).

9.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

9.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in Table 1 and sections 3.2 and 7.4.4.

Subgroup 1: Combined prophylaxis

Combined modalities of prophylaxis are more effective than single modalities in VTE (72, 73). The base case analysis considers patients are for whom current mechanical methods of prophylaxis are impractical or contraindicated. There is a sub-group of patients within this population in whom pharmacological prophylaxis is indicated and prescribed but who may also benefit from the incremental inclusion of mechanical prophylaxis but current methods are impractical or contraindicated. Because of the advantages of the geko™ device (such as its size, location of fitting and ease of use) over existing mechanical methods, the geko™ device could be considered for use in combination with pharmacological prophylaxis, for example in patients with peripheral arterial disease undergoing total hip replacement surgery.

Subgroup 2: Stroke patients

VTE is a significant risk in patients who have had a stroke. Of patients in hospital following a stroke, VTE has been detected in 20–42% (95-97). As a result, NICE recommends the initiation of prophylaxis in stroke patients, however due to the risk of bleeding, IPC is the preferred method of prophylaxis (3). Mechanical prophylaxis may be used for a short period of time until the risk of bleeding is quantified (i.e. until the type of stroke, such as haemorrhagic or ischaemic, is determined). Some patients may be contraindicated for IPC compression (those with dermatitis, leg ulcers, severe oedema, severe peripheral vascular disease and congestive heart failure), or no IPC pumps are available at that time.

9.6.2 Define the characteristics of patients in the subgroup(s).

Subgroup 1: Combined prophylaxis

Patients at high risk of developing VTE, including patients undergoing surgery. These patients are unsuitable for IPC, but suitable for pharmacological prophylaxis.

Sub group 2: Stroke patients

Patients admitted to hospital within 3 days of acute stroke (patients were immobile, i.e. could not mobilise to the toilet without the help of another person).

9.6.3 Describe how the subgroups were included in the cost analysis.

Subgroup 1: Combined prophylaxis

There is currently no data available showing that the introduction of the geko™ device in combination with pharmacological prophylaxis would result in an incremental reduction in VTE. However, a recent Cochrane review demonstrated a significant reduction in DVT for combined IPC of the leg with pharmacological prophylaxis versus pharmacological prophylaxis alone in high-risk patients. In this review, the incidence of DVT for pharmacological prophylaxis alone is estimated at 4.21% while the combined modalities significantly reduced the incidence to 0.65%. Using the prior assumption that the geko™ device would be comparable in efficacy to IPC we have performed an analysis using these data points.

The economic model was built to use an underlying risk of DVT as a starting point. Therefore, relative risks were back-calculated for pharmacological and pharmacological plus the geko™ device prophylaxis to reflect the point estimates above (Table 52).

Table 52: Relative risks of DVT for pharmacological prophylaxis alone vs pharmacological with the geko™ device

Prophylaxis	DVT relative risk
Pharmacological alone	0.14
Combination: geko™ device + pharmacological	0.02

Abbreviations: DVT, deep vein thrombosis.

The cost of pharmacological prophylaxis is presented in Section 9.1.6 however, it should be noted that because this cost is applied to both treatment arms it will essentially be cancelled out in subsequent calculations and is therefore irrelevant but included for completeness.

Sub group 2: Stroke patients

Data around the risk of DVT in a population of stroke patients has been taken from the recent CLOTS 3 study publication (89). In this randomised controlled trial of 2,876 patients, 21.1% of patients in the control arm (no IPC) experienced a DVT, of which 29.6% were symptomatic (6.3% of the cohort) and 11.5% result in a PE (2.4% of the cohort).

9.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

Subgroup 1: Combined prophylaxis

If all other baseline parameters are constant, use of the geko™ device in combination with pharmacological therapies alone would result in an incremental cost of £69 per patient for the modelled 6 days of treatment (Table 53).

Table 53: Subgroup 1 results: Combined prophylaxis

Prophylaxis	Total per patient cost
Pharmacological alone	£110
Combination: geko™ + Pharmacological	£179
Difference	**£69**

A combined prophylaxis approach could be beneficial for a shorter period of time in some patients (e.g. patients who may be immobile for restricted periods of time such as those with total hip replacement surgery). The geko™ device is cost saving for the first 2 days of combined prophylaxis and cost neutral if used for 3 days. This short use of combined prophylaxis may well be typical for many care pathway scenarios and the geko™ device may therefore represent a viable economic solution when compression is contraindicated, such as in patients with total hip replacement surgery.

Table 54: Subgroup 1 results: Combined prophylaxis with varied duration of prophylaxis

Duration of prophylaxis (days)	Incremental cost per patient
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]

Sub group 2: Stroke patients

In stroke patients, when using a baseline risk of DVT of 21.1% (29.6% of which are symptomatic and 11.5% result in a PE) and keeping all other parameters the same as the base case, the geko™ device would result in savings of £146 per patient compared with no prophylaxis (Table 55).

Table 55: Subgroup 2 results: Stroke patients

Prophylaxis	Total per patient cost
geko™ device	£321
No prophylaxis	£467
Difference	**-£146**

In the CLOTS 3 study, the mean duration of IPC prophylaxis was 12.5 days. When the duration of prophylaxis is varied in this patient subgroup, use of the geko™ device remains cost saving for up to 12 days (Table 56).

Table 56: Subgroup 2 results: Stroke patients with varied duration of prophylaxis

Duration of prophylaxis	Incremental cost per patient
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]
11	[redacted]
12	[redacted]
13	[redacted]

Use of IPC in the CLOTS 3 study reduced the incidence of DVTs to 16.2%, resulting in a risk reduction of 0.76 compared with no IPC prophylaxis. However, there are a number of limitations with the CLOTS 3 study:

- Patients experienced a delay between onset of stroke and randomisation. In 57% of cases, the delay was more than 1 day
- Many patients (24%) received warfarin or heparin at recruitment or had thrombolysis since admission, therefore masking the incremental benefit of IPC
- Only 31% of patients achieved perfect adherence[f] to IPC. Because of the design and comfort of the geko™ device, post-market surveillance results (discussed in Section 7.6.1) indicate that non-compliance with the geko™ device will be minimal
- In addition, the exclusion criteria include contraindications to IPC such as dermatitis, leg ulcers, severe oedema, severe peripheral vascular disease and congestive cardiac failure, thus excluding some patients that may be suitable for the geko™ device.

The RR reduction quoted in the CLOTS 3 study was therefore not considered to be applicable to the geko™ device within routine clinical practice. However for completeness, analyses using the CLOTS 3 risk reduction were conducted and the results can be found in Section 10.10.

[f] Perfect adherence (100% adherence) is defined as wearing IPC from randomisation until the patient regained mobility, was discharged from a participating hospital, died or until 39 days or until a delayed second screening compression duplex ultrasound.

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

N/A.

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The data inputs were cross-checked and the model calculations were verified by a second health economist. The details of this are presented in Section 10.11.

9.8 *Interpretation of economic evidence*

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

No cost analysis studies for NMES were identified by the systematic review and therefore no comparisons can be drawn. Pharmacological and mechanical prophylaxis is routinely used within the NHS and has been proven to be a cost-effective method for the prevention of VTE compared with no prophylaxis (3).

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

The cost analysis is relevant to patients at high risk of VTE who require prophylaxis but for whom current mechanical methods of prophylaxis are impractical or contraindicated.

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The economic model is based on the current NICE guidelines for the prevention of VTE, which were drawn up following an extensive systematic review, meta-analysis and consultation. However, uncertainties exist around the baseline risk of VTE within the eligible population (due to difficulties in defining these patients). Best estimates based on VTE guidelines were used and these were noted to be comparable to those observed in the CLOTS study.

Whilst there is a lack of direct evidence for reduction of DVT following use of the geko™ device, direct clinical evidence has demonstrated that the geko™ device is better than IPC at increasing blood flow and increased blood flow has been shown to reduce the incidence in DVT in studies of IPC, NMES and compression stockings. Previous studies of NMES have shown a reduction in DVT and the model uses a risk reduction from an NMES study (23) which falls within the range defined for IPC. Sensitivity analysis using the risk reduction observed with use of IPC presented in the NICE VTE guidelines shows that even at the lowest reported value, the geko™ device remains cost saving. Threshold analysis shows that the risk reduction could drop to 0.76 before leading to an incremental cost. Given the favourable tolerability profile and the ease of use of the

geko™ device, post-marketing surveillance results indicate that non-compliance with the geko™ device will be minimal. It is acknowledged that adherence is an issue with IPC devices (18) and therefore it is expected that the cost savings obtained with the geko™ device may be even greater than modelled.

In addition to being cost saving, use of the geko™ device will also reduce the number of DVT, PE and associated PTS (and potentially deaths) and can therefore be considered a dominant treatment strategy. The geko™ device is also seen to be cost saving in scenarios even when PE is excluded.

In conclusion, the economic model is based on a robust model structure and despite limitations regarding certain input assumptions, extensive sensitivity analyses demonstrate that the geko™ device is cost saving in the majority of scenarios. The geko™ device offers a treatment choice for patients with a clear unmet need who cannot currently receive any method of VTE prophylaxis.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

A comparison to other methods of prophylaxis could be conducted, but this analysis would need to consider adverse events (such as bleeds, pressure sores and skin breaks). Inclusion of either/both these parameters is likely to demonstrate that the geko™ device is even more cost saving.

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10 Appendices

10.1 Appendix 1 Search strategy for clinical evidence (section 7.1.1)

The following information should be provided:

10.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **The Cochrane Library**

The following databases were searched during the systematic review of clinical evidence:

- Medline and Medline In-Process
- Embase
- The Cochrane Library

10.1.2 The date on which the search was conducted

The searches were conducted on 18th May 2013. There was no date limitation placed on the searches.

10.1.3 The date span of the search

- Ovid MEDLINE(R) and Ovid MEDLINE (R) In-Process 1950 to present.
- Embase (Ovid), 1980 to 2010 Week 36.
- The Cochrane Library, to present.

10.1.4 The complete search strategy used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

All the following searches were combined and inclusion/exclusion criteria applied.

Clinical searches

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present; Searched on May 18th 2013

1	exp thromboembolism/	40767
2	*Embolism/	6651
3	exp thrombophlebitis/	20698
4	((venous or vein) adj (thrombosis or thrombus or thromboembolism)).mp.	45120
5	(dvt or vte).mp.	9462
6	exp deep vein thrombosis/	42336

7	or/1-6	100197
8	electrostimulation/	0
9	Electric Stimulation Therapy/	16020
10	Electric Stimulation/	103299
11	(Electrical muscle stimulation or EMS).mp.	7598
12	(electric$ adj5 stimulat$).tw.	51474
13	electromyostimulation.mp.	100
14	electr$ therapy.tw.	6328
15	geko.mp.	12
16	(pulse adj2 tech$).mp.	1501
17	nmes.mp.	457
18	neuromuscular electrical stimulation.mp.	452
19	exp Intermittent Pneumatic Compression Devices/	347
20	IPC.mp.	2048
21	virchow.mp.	1295
22	foot impulse.mp.	5
23	calf muscle pump.mp.	117
24	((soleal or foot) adj2 pump).mp	68
25	or/8-18	152491
26	or/19-24	3798
27	25 or 26	156254
28	7 and 27	620

Embase 1980 to 2010 Week 36; Searched on May 18th 2013

1	exp thromboembolism/	318280
2	exp vein thrombosis/	84125
3	exp thrombophlebitis/	17196
4	((venous or vein) adj (thrombosis or thrombus or thromboembolism)).mp.	91130
5	exp deep vein thrombosis/	33262
6	(dvt or vte).mp.	15165
7	or/1-6	324779
8	neuromuscular electrical stimulation/	531
9	(Electrical muscle stimulation or EMS).mp.	9657
10	electrostimulation therapy/	11003
11	Electrical muscle stimulation.mp.	226
12	(neuromuscular electrical stimulation or NMES).mp.	1098
13	electric stimulation/	71942
14	electrostimulation/	71942
15	(neuromuscular adj5 stimulat$).tw.	1550

16	(peroneal adj5 stimulat$).tw.	711
17	(electric$ adj5 stimulat$).tw.	61781
18	electromyostimulation.mp.	124
19	geko.mp.	11
20	(pulse adj2 tech$).mp	1697
21	electrotherapy.tw.	1365
22	nmes.mp	615
23	or/8-22	124557
24	intermittent pneumatic compression device.mp.	564
25	IPC.mp.	2796
26	virchow.mp.	1663
27	foot impulse.mp	8
28	calf muscle pump.mp.	165
29	((soleal or foot) adj2 pump).mp	101
30	or/24-29	5188
31	23 or 30	129691
32	31 and 7	1274
33	limit 32 to English	1018

The Cochrane Library, to present; Searched on May 18th 2013

1	exp thromboembolism/	1200
2	*Embolism/	8
3	exp thrombophlebitis/	1069
4	((venous or vein) adj (thrombosis or thrombus or thromboembolism)).mp.	4770
5	(dvt or vte).mp.	1578
6	exp Venous Thrombosis/	1953
7	or/1-6	6013
8	(neuromuscular adj5 stimulat$).tw.	344
9	(Electrical muscle stimulation or EMS).mp	357
10	electric stimulation therapy/	1203
11	Electrical muscle stimulation.mp.	54
12	(neuromuscular electrical stimulation or NMES).	171
13	electric stimulation/	1324
14	electrostimulation.tw.	267
15	(peroneal adj5 stimulat$).tw.	42
16	(electric$ adj5 stimulat$).tw.	3304
17	electromyostimulation.mp.	35
18	electrotherapy.tw.	218
19	intermittent pneumatic compression device.mp	14

20	IPC.mp.	153
21	virchow.mp.	22
22	foot impulse.mp	3
23	calf muscle pump.mp	20
24	((soleal or foot) adj2 pump).mp	41
25	or/8-24	5573
26	25 and 7	124

10.1.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Additional studies were identified by hand searching the following resources:

A search of the website www.clinicaltrials.gov was conducted to identify any ongoing trials. The website was searched using the terms “geko”, “DVT and electrical stimulation”.

One RCT that commenced in April 2013 was identified (NCT01835990). This International study is yet to recruit patients but will compare the geko™ device with IPC for the incidence of DVT in trauma patients.

10.1.6 The inclusion and exclusion criteria.

Selection criteria used to identify geko™ and NMES published studies

Inclusion criteria	
Population	Patients or volunteers using the geko™ OnPulse™ technology device for the prevention of DVT
Interventions	geko™ OnPulse™ technology device

Outcomes	• Blood flow
	• Incidence of PE
	• Any DVT
	  ○ Asymptomatic DVT
	  ○ Symptomatic DVT
	• VTE composite
	• Major VTE
	• Hospitalisation
	• Secondary endpoints
	• PTS
	• QoL
	• Mortality and AE data
	• Resource use

Study design	RCTs, non-RCTs
Language restrictions	• English Language only. • Foreign language papers with English abstracts could be included
Search dates	No restriction
Exclusion criteria	
Population	Patients undergoing treatment of DVT
Study design	Case studies, editorials, letters, reviews
Interventions	• Anti-embolic stockings • Pharmacological interventions such LMWH

Abbreviations: AE, adverse event; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; PE, pulmonary embolism; PTS, post-thrombotic syndrome; QoL, quality of life; RCT, randomised controlled trial; VTE, venous thromboembolism.

Selection criteria used for published studies showing an association between increased blood flow and DVT

Inclusion criteria	
Population	• Patients at risk of DVT • Healthy volunteers
Interventions	Any intervention that demonstrates increase in blood flow such as IPC

Outcomes	• Blood flow
	• Vessel diameter
	• Incidence of PE
	• Any DVT
	  ○ Asymptomatic DVT
	  ○ Symptomatic DVT
	• VTE composite
	• Major VTE

Study design	RCTs, non-RCTs
Language restrictions	• English Language only. • Foreign language papers with English abstracts could be included
Search dates	No restriction
Exclusion criteria	
Population	Patients undergoing treatment of DVT
Study design	Case studies, editorials, letters, reviews
Interventions	• Anti-embolic stockings • Pharmacological interventions such LMWH

Abbreviations: DVT, deep vein thrombosis; LMWH, low molecular weight heparin; IPC, intermittent pneumatic compression; PE, pulmonary embolism; RCT, randomised controlled trial; VTE, venous thromboembolism.

10.1.7 The data abstraction strategy.

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Relevant information was extracted into a pre-defined Microsoft Word table by a reviewer. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion.

10.1.8 Excluded second pass studies.

	Study	Reason for exclusion
1	Dejode, L. R., M. Khurshid, et al. (1973). "The influence of electrical stimulation of the leg during surgical operations on the subsequent development of deep-vein thrombosis." British Journal of Surgery 60(1): 31-32.	Study design
2	Hardwick, M. E., P. A. Pulido, et al. (2011). "A mobile compression device compared with low-molecular-weight heparin for prevention of venous thromboembolism in total hip arthroplasty." Orthopaedic Nursing 30(5): 312-316.	Pharmacological intervention
3	Khouli, H., J. Shapiro, et al. (2006). "Efficacy of deep venous thrombosis prophylaxis in the medical intensive care unit." Journal of Intensive Care Medicine 21(6): 352-358.	Study design
4	Moloney, G. E., M. T. Morrell, et al. (1972). "The effect of electrical stimulation of the legs on postoperative thrombosis." British Journal of Surgery 59(1): 65-68.	Study design- letter
5	Morita, H., C. Abe, et al. (2006). "Neuromuscular electrical stimulation and an Ottoman-type seat effectively improve popliteal venous flow in a sitting position." Journal of Physiological Sciences 56 (2): 183-186.	Outcomes – patient position
6	Norgren, L., S. Toksvig-Larsen, et al. (1998). "Prevention of deep vein thrombosis in knee arthroplasty. Preliminary results from a randomized controlled study of low molecular weight heparin vs foot pump compression." International Angiology 17(2): 93-96	Pharmacological intervention
7	Pollock, A. V. (1977). "Calf-muscle stimulation as a prophylactic method against deep vein thrombosis." Triangle 16(1): 41-45.	Study design- review
8	Pollock, A. V. (1978). "Electrical stimulation of the calf." Scottish Medical Journal 23(4): 332-333.	Study design- review
9	Powley, J. M. and F. S. Doran (1973). "Galvanic stimulation to prevent deep-vein thrombosis." Lancet 1(7800): 406-407.	Study design- review
10	Turpie, A. G. G., K. A. Bauer, et al. (2007). "Fondaparinux combined with intermittent pneumatic compression vs. intermittent pneumatic compression alone for prevention of venous thromboembolism after abdominal surgery: a randomized, double-blind comparison." Journal of Thrombosis & Haemostasis 5(9): 1854-1861.	Pharmacological intervention

10.2 Appendix 2: Search strategy for adverse events (section 7.7.1)

The clinical search strategy as detailed in Appendix 1 was also used to capture adverse event data.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **The Cochrane Library**

N/A

10.2.2 The date on which the search was conducted

N/A

10.2.3 The date span of the search

N/A

10.2.4 The complete search strategy used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

N/A

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

N/A

10.2.6 The inclusion and exclusion criteria.

N/A

10.2.7 The data abstraction strategy.

N/A

10.3 Appendix 3: Search strategy for economic evidence (section 8.1.1)

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **EconLIT**
- **NHS Economic Evaluation Database (NHS EED)**

10.3.2 The date on which the search was conducted.

The searches were conducted on 29th or 30th July 2013.

10.3.3 The date span of the search.

- Ovid MEDLINE(R) 1946 to present.
- Embase (Ovid), 1974 to present.
- NHS EED (The Cochrane Library), 1968 to present.
- Econlit (Ovid) 1969 to present.

10.3.4 The complete search strategies used, including all the search term textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

All the following searches were combined and inclusion/exclusion criteria applied.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present, searched 30th July 2013

1	exp thromboembolism/	42630
2	*Embolism/	6826
3	exp thrombophlebitis/	20873
4	((venous or vein) adj (thrombosis or thrombus or thromboembolism)).mp.	48029
5	(dvt or vte).mp.	10322
6	exp deep vein thrombosis/	44002
7	or/1-6	104771
8	(neuromuscular adj5 stimulat$).tw.	1368
9	(Electrical muscle stimulation or EMS).mp.	8059
10	electric stimulation therapy/	16642
11	Electrical muscle stimulation.mp.	178
12	(neuromuscular electrical stimulation or NMES).mp.	710
13	electric stimulation/	108162
14	electrostimulation.tw.	2632
15	(peroneal adj5 stimulat$).tw.	614
16	(electric$ adj5 stimulat$).tw.	54303
17	(electromyostimulation or geko).mp.	119

18	electrotherapy.tw.	934
19	or/8-18	153993
20	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	516
21	exp Cost-Benefit Analysis/	60362
22	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	61670
23	(cost utility analys* or (cost-utility adj1 analys*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1550
24	(cost consequence analys* or (cost-conseq* adj1 analys*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	124
25	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	7103
26	or/20-25	63910
27	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	10806
28	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	49570
29	exp decision theory/ or exp decision trees/	9678
30	decision tree.mp.	3365
31	models, economic/	6127
32	(markov or deterministic).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	24011
33	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	138813
34	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	370
35	(incremental-cost or incremental cost).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	5879
36	(ICER or QALY or DALY or WTP or TTO).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	7182

37	27 and (or/28-36)	3791
38	26 or 37	65003
39	7 and 19	229
40	38 and 39	1

Embase 1974 to present; Searched on 29th July 2013

1	exp thromboembolism/	328221
2	exp vein thrombosis/	86759
3	exp thrombophlebitis/	17333
4	((venous or vein) adj (thrombosis or thrombus or thromboembolism)).mp.	94752
5	exp deep vein thrombosis/	34463
6	(dvt or vte).mp.	16027
7	or/1-6	335029
8	neuromuscular electrical stimulation/	588
9	(Electrical muscle stimulation or EMS).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	10159
10	electrostimulation therapy/	11368
11	Electrical muscle stimulation.mp.	238
12	(neuromuscular electrical stimulation or NMES).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1207
13	electric stimulation/	73211
14	electrostimulation/	73211
15	(neuromuscular adj5 stimulat$).tw.	1633
16	(peroneal adj5 stimulat$).tw.	725
17	(electric$ adj5 stimulat$).tw.	63215
18	electromyostimulation.mp.	132
19	or/8-18	125194
20	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2550
21	exp "cost benefit analysis"/	65476
22	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	67156
23	(cost utility analys* or (cost-utility adj1 analys*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	5538
24	"cost utility analysis"/ or economic evaluation/	12241
25	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	92105
26	"cost effectiveness analysis"/	89561

27	or/20-26	157849
28	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	19823
29	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	48273
30	exp decision theory/ or "decision tree"/	7023
31	decision tree.mp.	8089
32	economic model.mp.	1710
33	(markov or deterministic).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	22540
34	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	190552
35	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	555
36	(incremental-cost or incremental cost).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	7766
37	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	10447
38	or/29-37	272243
39	28 and 38	5695
40	27 or 39	158580
41	7 and 19 and 40	5

NHS EED, 1968 to present; Searched on 29th July 2013

1	exp thromboembolism/	45
2	*Embolism/	0
3	exp thrombophlebitis/	25
4	((venous or vein) adj (thrombosis or thrombus or thromboembolism)).mp.	251
5	(dvt or vte).mp.	133
6	exp Venous Thrombosis/	124
7	or/1-6	277
8	(neuromuscular adj5 stimulat$).tw.	1
9	(Electrical muscle stimulation or EMS).mp.	13
10	electric stimulation therapy/	28

11	Electrical muscle stimulation.mp.	0
12	(neuromuscular electrical stimulation or NMES).mp.	2
13	electric stimulation/	6
14	electrostimulation.tw.	0
15	(peroneal adj5 stimulat$).tw.	0
16	(electric$ adj5 stimulat$).tw.	50
17	electromyostimulation.mp.	0
18	electrotherapy.tw.	3
19	geko.mp. [mp=title, text, subject heading word]	0
20	or/8-19	67
21	7 and 20	0

Econlit 1969 to present; Searched on 30th July 2013

1	thromboembolism.mp.	4
2	embolism.mp.	6
3	thrombophlebitis.mp. [mp=heading words, abstract, title, country as subject]	0
4	((venous or vein) adj (thrombosis or thrombus or thromboembolism)).mp.	11
5	(dvt or vte).mp.	10
6	deep vein thrombosis.mp. [mp=heading words, abstract, title, country as subject]	8
7	or/1-6	21

10.3.5 Details of any additional searches, (for example, searches of company databases [include a description of each database]).

Additional studies were identified by hand searching the following resources:

- Firstkind website
- Cost-Effectiveness Analysis (CEA) Registry.

10.3.6 The inclusion and exclusion criteria.

Inclusion criteria	
Population	Patients using the geko™ OnPulse™ technology device for the prevention of VTE
Interventions	• geko™ OnPulse™ technology device • NMES
Outcomes	• QoL • Mortality • Resource use
Study design	Cost/economic evaluations
Language restrictions	• English Language only • Foreign language papers with English abstracts could be included
Search dates	• Medline: 1946 to 30th July 2013 • Embase: 1974 to 29th July 2013 • NHS EED (The Cochrane Library): 1968 to 29th July 2013 • Econlit: 1969 to 30th July 2013
Exclusion criteria	
Population	Patients undergoing treatment for VTE
Interventions	• Compression stockings • IPC • Pharmacological interventions such LMWH

Abbreviations: IPC, intermittent pneumatic compression; LMWH, low molecular weight heparin; NMES, neuromuscular electrostimulation; QoL, quality of life; VTE, venous thromboembolism.

10.3.7 The data abstraction strategy.

No studies meeting the economic systematic review inclusion criteria were identified.

10.4 Appendix 4: Resource identification, measurement and valuation (section 9.3.2)

A systematic review was not conducted to identify relevant resource data from the published literature. Resource use was identified via existing NICE clinical guidelines for venous thromboembolism (3).

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***NHS EED***
- ***EconLIT***

N/A.

10.4.2 The date on which the search was conducted.

N/A.

10.4.3 The date span of the search.

N/A.

10.4.4 The complete search strategies used, including all the search terms textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

N/A.

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

N/A.

10.4.6 The inclusion and exclusion criteria.

N/A.

10.4.7 The data abstraction strategy.

N/A.

10.5 *Appendix 5. NMES studies identified by the SR*

10.5.1 *NMES studies identified by the SR*

Primary study reference	Population	Intervention	Comparator	Study demonstrated increase in blood flow	Study reported incidence of DVT
Broderick 2013 (21)	Patients undergoing THA	NMES (DUO-STIM) operated limb	NMES (DUO-STIM) unoperated limb	✓	✗
Broderick 2011 (49)	Patients undergoing THA or TKA	NMES (DUO-STIM)		✓	✗
Browse and Negus 1970 (23)	Patients undergoing major surgery	NMES (Type V MkIII or battery-operated Medelec TS2) stimulated leg	non-stimulated leg	✗	✓
Corley 2012 (35)	Healthy volunteers	NMES (DUO-STIM)	Control (no NMES)	✓	✗
Czyrny 2010 (38)	Healthy volunteers	NMES (Focus Neuromuscular Stimulation System)	IPC	✓	✗
Faghri 1997 (13)	Patients undergoing THA or TKA	NMES (eight-channel laboratory constructed electrical stimulator)	IPC	✓	✗
Griffin 2010(22)	Healthy volunteers	VEINOPLUS stimulator – NMES device that contracts calf muscles		✓	✗

Primary study reference	Population	Intervention	Comparator	Study demonstrated increase in blood flow	Study reported incidence of DVT
Izumi 2010 (39)	Healthy volunteers	TpTENS	Other methods (electrical muscle stimulation, IPC, active ankle motion and calf squeeze)	✓	✗
Kaplan 2002 (20)	Healthy volunteers	NMES (Focus Neuromuscular Stimulation System)	Non-stimulated lower extremity	✓	✗
Lindstrom 1982 (24)	Patients undergoing major abdominal surgery	ES	Control or Dextran	✗	✓
Nicolaides 1972 (74)	Patients undergoing a variety of operations	ES (selective treatment unit)	Control group (traditional hospital physiotherapy)	✓	✓
Rosenberg 1975 (42)	Patients undergoing major general surgery	ES (Thrombo-phylactor)	Heparin or control (no specific prophylaxis)	✗	✓
Velmahos 2005 (46)	Trauma patients with injury severity score higher than 9	MES	Control (standard care)	✓	✓

Abbreviations: ES, electrical stimulation; MES, muscular electrostimulation; NMES, neuromuscular electrostimulation; THA, total hip arthroplasty; TKA, total knee arthroplasty; TpTENS; Thrombo-prophylactic transcutaneous electrical nerve stimulation.

10.5.2 *Critical appraisal of NMES studies identified by the SR*

10.5.2.1 Observational studies

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Broderick 2013		
Study question	yes	Two study questions. 1. To establish if patients in post-operative period have a similar tolerance for NMES as in previous studies 2. To determine if applying NMES in post-operative patients increases venous outflow from the lower limb over resting conditions
Was the cohort recruited in an acceptable way?	yes	Patients who had undergone THA at a hospital in Limerick, Ireland
Was the exposure accurately measured to minimise bias?	yes	NMES applied to the calf muscles of each leg using skin surface electrodes; NMES voltage applied to the operated limb and the un-operated limb was not significantly different
Was the outcome accurately measured to minimise bias?	yes	Outcomes measured using Duplex Doppler ultrasound and VAS to assess pain
Have the authors identified all important confounding factors?	No	Confounding factors were not discussed although authors considered practical limitations and stated that the protocol adopted needed further refinement for the immediate post-operative period
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Contralateral limb was used as a control. Patients with diabetes and peripheral vascular disease were excluded.
Was the follow-up of patients complete?	yes	-
How precise (for example, in terms of confidence interval and p values) are the results?	yes	p values and standard deviations reported
Broderick 2011		

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Study question	yes	To assess patient tolerance of NMES in the presence of metallic implants and to measure venous outflow from the legs associated with a tolerable NMES intensity
Was the cohort recruited in an acceptable way?	yes	Patients who had undergone orthopaedic surgery in Galway University hospitals, Ireland were recruited at least 3 weeks post-surgery
Was the exposure accurately measured to minimise bias?	yes	Stimulation intensity in volts corresponding to sensory threshold, motor threshold, pain threshold and pain tolerance was measured in the operated limb versus control limb.
Was the outcome accurately measured to minimise bias?	yes	Outcomes were measured using Duplex Doppler ultrasound and VAS to assess pain
Have the authors identified all important confounding factors?	yes	Sensitivity at the wound site or the use of pain management in the early post-operative period may confound results relating to NMES discomfort/origin of pain; contralateral limb acted as a control
Have the authors taken account of the confounding factors in the design and/or analysis?	yes	Authors recruited patients after they had come off post-operative pain management and at least 3 weeks after surgery
Was the follow-up of patients complete?	no	Two patients out of 20 could not have blood flow measurements taken as it was too difficult for them to keep their leg in the desired position long enough for the operator to take the measurement
How precise (for example, in terms of confidence interval and p values) are the results?	yes	Error bars and p values reported
Browse and Negus, 1972		
Study question	yes	To evaluate the effectiveness of calf muscle stimulation in preventing postoperative deep vein thrombosis
Was the cohort recruited in an acceptable way?	yes	Study was restricted to volunteers of both sexes over the age of 40 who were undergoing surgical operations of moderate or major severity

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Was the exposure accurately measured to minimise bias?	yes	The calf muscles were stimulated to contract briefly and intermittently every two seconds; good muscle contractions were obtained with a potential difference of 15 volts in the lightly anaesthetised patient, rising to 45 volts in the presence of neuromuscular blocking agents; stimuli was applied immediately after the induction of anaesthesia and continued until the end of the operation
Was the outcome accurately measured to minimise bias?	yes	The I-fibrinogen uptake test was used to diagnose venous thrombosis
Have the authors identified all important confounding factors?	yes	A fresh wound or haematoma makes the I-fibrinogen uptake test unreliable; exposed iliac veins or vena cava can be damaged and add an uncontrolled local cause for venous thrombosis
Have the authors taken account of the confounding factors in the design and/or analysis?	yes	Contralateral limb was used as a control; leg to be stimulated was chosen by random selection; patients having operations on the legs and those having aorta-iliac arterial surgery or any operation in which the iliac veins or vena cava were exposed and likely to be damaged were also excluded.
Was the follow-up of patients complete?	yes	-
How precise (for example, in terms of confidence interval and p values) are the results?	yes	p-values reported
Griffin 2010		
Study question	yes	The study was designed to determine: 1. dependence of venous blood velocity and ejected volume on the rates of stimulated calf contractions 2. clinical factors affecting efficacy in healthy individuals
Was the cohort recruited in an acceptable way?	yes	Normal volunteers recruited from two general hospital notice boards and a General Practitioner's waiting room

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Was the exposure accurately measured to minimise bias?	yes	Intensity of stimulus gradually increased until highest intensity comfortably tolerated by each participant was established. To further minimise bias, patients with superficial or DVT, previous varicose vein surgery, congestive heart failure, patients with pacemaker, lower limb arterial disease or active clinically suspected infection were excluded
Was the outcome accurately measured to minimise bias?	yes	Popliteal vein imaged in a longitudinal section using ultrasonic scanner and broad bandwidth linear array transducer
Have the authors identified all important confounding factors?	yes	Patients with superficial or DVT, previous varicose vein surgery, congestive heart failure, patients with pacemaker, lower limb arterial disease or active clinically suspected infection were excluded
Have the authors taken account of the confounding factors in the design and/or analysis?	yes	Using subgroups of gender, popliteal cross-sectional area and age were compared and logistic regression analysis was performed with peak systolic velocity and volume ejected per minute as dependent variables with value above or below the median and clinical parameters as covariates
Was the follow-up of patients complete?	yes	-
How precise (for example, in terms of confidence interval and p values) are the results?	yes	p-values reported
Izumi 2010		
Study question	yes	To investigate the effects of thrombo-prophylactic transcutaneous electrical nerve stimulation (TpTENS) of the peroneal nerve on venous blood flow in the limbs of volunteers compared with other mechanical methods of thromboprophylaxis
Was the cohort recruited in an acceptable way?	yes	10 healthy volunteers recruited. Ethics committee approval and informed written consent obtained prior to study
Was the exposure accurately measured to minimise bias?	no	Data were not shown regarding stimulation parameters or length of time stimuli applied
Was the outcome accurately measured to minimise bias?	yes	Pulsed Doppler mode was used to record the blood flow continuously during the application of each method of flow stimulation. Three measurements were taken for each type of stimulation and an average calculated

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Have the authors identified all important confounding factors?	no	Limited details regarding confounding factors; patients were healthy volunteers
Have the authors taken account of the confounding factors in the design and/or analysis?	no	No adjustment for confounding factors described an authors noted that as results obtained from healthy volunteers may not be applicable to older patients
Was the follow-up of patients complete?	yes	All patients
How precise (for example, in terms of confidence interval and p values) are the results?	yes	p-values reported
Kaplan 2002		
Study question	yes	To determine if mild electrical stimulation of the plantar foot muscles, or the calf muscles, significantly increases venous blood flow velocity in the femoral and popliteal veins of subjects seated for four hours
Was the cohort recruited in an acceptable way?	yes	49 healthy subjects were recruited. Institutional Review Board approval and informed consent was obtained
Was the exposure accurately measured to minimise bias?	yes	Electrical stimulation was delivered by The FocusTm Neuromuscular Stimulation System. Stimulation was increased to an intensity sufficient to create a slight visible muscle twitch. The non-stimulated lower extremity served as the simultaneous control. Time of measurement and stimulation (yes/no) were recorded
Was the outcome accurately measured to minimise bias?	yes	Popliteal and femoral venous blood flow velocities measured bilaterally using Doppler ultrasound. Person evaluating Doppler ultrasound was blinded as to the limb stimulated
Have the authors identified all important confounding factors?	no	Confounding factors were not described
Have the authors taken account of the confounding factors in the design and/or analysis?	no	Study design did not appear to take into account confounding factors although all subjects were healthy volunteers
Was the follow-up of patients complete?	yes	-

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
How precise (for example, in terms of confidence interval and p values) are the results?	yes	p-values reported
Nicolaides 1972		
Study question	yes	To determine the most effective electrical stimulus in preventing stasis in the soleal veins and to use it in a clinical trial to evaluate its effectiveness in preventing DVT
Was the cohort recruited in an acceptable way?	yes	Patients undergoing a variety of operations were recruited, no further details relating to recruitment were provided
Was the exposure accurately measured to minimise bias?	yes	Intensity/duration of stimuli was recorded and a continuous reading of mean blood velocity was obtained via a pen recorder.
Was the outcome accurately measured to minimise bias?	yes	A Doppler blood flow detector was used and all patients were screened by I-labelled fibrinogen test. Legs were scanned before and immediately after operation
Have the authors identified all important confounding factors?	yes	Authors recorded age, presence of obesity, history of DVT/PE, presence of varicose veins, and malignancy. Authors also mention that results may be affected by factors such as older age and presence of additional risk factors
Have the authors taken account of the confounding factors in the design and/or analysis?	yes	Patients were comparable with regard to the distribution of factors which affect the incidence of venous thromboembolism
Was the follow-up of patients complete?	yes	All patients
How precise (for example, in terms of confidence interval and p values) are the results?	yes	p values reported

Abbreviations: DVT, deep vein thrombosis; IPC, intermittent pneumatic compression; NMES, neuromuscular electrostimulation; THA, total hip arthroplasty; VAS, visual analogue scale.

10.5.2.2 RCTs

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Corley 2012		
Was randomisation carried out appropriately?	not clear	Subjects were randomly assigned to control and stimulation groups; method of randomisation was not described
Was the concealment of treatment allocation adequate?	NA	Due to the nature of the intervention, blinding was not possible
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	yes	No significant differences noted between groups
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	NA	Due to the nature of the intervention, blinding was not possible
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	no	-
Is there any evidence to suggest that the authors measured more outcomes than they reported?	no	-
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	no	-
Czyrny 2010		
Was randomisation carried out appropriately?	yes	Randomisation by computer-generated protocol as to which leg would be treated and the order in which the type of therapy was to be given
Was the concealment of treatment allocation adequate?	NA	Due to the nature of the intervention, blinding was not possible
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	yes	Study sample equally distributed in the two sequences in terms of age, gender and BMI

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	NA	Due to the nature of the intervention, blinding was not possible, although the independent reader who read Doppler tracings was blinded
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	no	-
Is there any evidence to suggest that the authors measured more outcomes than they reported?	no	-
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	no	-
Faghri 1997		
Was randomisation carried out appropriately?	not clear	Patients were randomised to a control group or an experimental group; method of randomisation was not described
Was the concealment of treatment allocation adequate?	NA	Due to the nature of the intervention, blinding was not possible
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	not clear	Comparability between groups was not described
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	NA	Due to the nature of the intervention, blinding was not possible
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	no	-
Is there any evidence to suggest that the authors measured more outcomes than they reported?	no	-
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	no	-

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Lindstrom 1982		
Was randomisation carried out appropriately?	yes	Patients were randomly assigned to treatment groups according to a previously prepared list in order they were accepted for the study
Was the concealment of treatment allocation adequate?	NA	Due to the nature of the intervention, blinding was not possible
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	yes	Groups were comparable in age, number of patients with malignant disease and time of operation
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	NA	Due to the nature of the intervention, blinding was not possible; only physicians who examined the scans and chest X-ray films for diagnosis of PE were described as blinded
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	no	-
Is there any evidence to suggest that the authors measured more outcomes than they reported?	no	-
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	no	-
Rosenberg 1975		
Was randomisation carried out appropriately?	no	Randomisation into three groups was by month of birth
Was the concealment of treatment allocation adequate?	NA	Due to the nature of the intervention, blinding was not possible
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	not clear	Comparability between groups was not described
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	NA	Due to the nature of the intervention, blinding was not possible

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	not clear	14 patients were withdrawn because of failure to observe the protocol, four because they died within four days, and four because heparin prophylaxis was stopped after reactionary haemorrhage; no details were provided regarding which groups these patients were assigned to
Is there any evidence to suggest that the authors measured more outcomes than they reported?	no	-
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	no	-
Velmahos 2005		
Was randomisation carried out appropriately?	yes	Randomisation by a computer generated system
Was the concealment of treatment allocation adequate?	NA	Due to the nature of the intervention, blinding was not possible
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	no	NMES patients had more neurologic injuries, control patients were older and had more major operations, all other baseline characteristics were balanced between the two groups
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	NA	Due to the nature of the intervention, blinding was not possible
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	yes	Four patients from the NMES group and nine from the control arm were excluded from analysis because of lack of outcome evaluation
Is there any evidence to suggest that the authors measured more outcomes than they reported?	no	-
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	no	-

Abbreviations: BMI, body mass index; IPC, intermittent pneumatic compression; ITT, intent-to-treat; NMES, neuromuscular electrostimulation; PE, pulmonary embolism.

10.6 *Appendix 6. IPC studies identified by the SR*

Primary study reference	Population	Intervention	Comparator	Study demonstrated increase in blood flow	Study reported incidence of DVT
RCTs					
Nicolaides 1983 (37)	Major abdominal surgery	IPC and compression stockings	ES or low dose heparin	✘	✓
Pitto 2004 (47)	Patients undergoing THR	IPC (foot pump – AV impulse system)	LMWH	✘	✓
Santori 1994 (43)	Patients undergoing THR	IPC (foot pump – AV impulse system)	Heparin	✘	✓
Sobieraj-Teague 2012 (44)	High-risk neurosurgical patients	Venowave calf compression device	Control	✘	✓
Warwick 2002 (48)	Patients undergoing TKR	IPC (foot pump – AV impulse system)	Enoxaparin 40mg	✘	✓
Non-RCTs					
Kurtoglu 2005 (40)	Multi-trauma patients undergoing major abdominal surgery for whom anticoagulation was contraindicated	IPC (calf pump - Flowtron Excel Prophylatic D.V.T. system Model AC 550)	None	✘	✓
Pitto 2008 (41)	Patients undergoing THR or TKR	IPC (foot pump – AV impulse system) and stockings	Non stocking group	✘	✓

10.6.1 *Critical appraisal of IPC studies identified by the SR*

10.6.1.1 Observational studies

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Kurtoglu 2005 (40)		
Study question	yes	Study aim was to evaluate the safety and efficacy of IPC in prevention of DVT and PE in high-risk patients in an intensive care unit for whom anticoagulation is contraindicated due to high risk of bleeding.
Was the cohort recruited in an acceptable way?	yes	Patients were recruited between October 2001 and June 2002 from the intensive care unit at the Trauma and Surgical Emergency Service of Istanbul Medical Faculty.
Was the exposure accurately measured to minimise bias?	yes	Mean duration of IPC was noted.
Was the outcome accurately measured to minimise bias?	yes	For the investigation of DVT and PE, venous duplex ultrasonography of lower extremities and spiral thorax CT scanning were performed, respectively.
Have the authors identified all important confounding factors?	yes	The onset of DVT and PE, age and gender of the patients and diagnoses were also assessed.
Have the authors taken account of the confounding factors in the design and/or analysis?	yes	As above.
Was the follow-up of patients complete?	yes	Patients were followed for the nine month study period.
How precise (for example, in terms of confidence interval and p values) are the results?	no	No confidence intervals or p-values were reported but evidence of DVT was not found via venous duplex scans and only one patient (2.6%) had symptomatic PE detected by spinal thorax CT.
Pitto 2008 (41)		
Study question	yes	The hypothesis was that in the postoperative management of patients undergoing total hip and knee replacement, foot pumps without the additional use of graduated compression stockings did not affect the efficacy of DVT prophylaxis, did not increase the risk of side-effects and did improve patient compliance.

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	yes	All patients admitted at one single institution from January 2003 to December 2005 with degenerative osteoarthritis of the hip or knee for total hip or total knee replacement management were considered for inclusion.
Was the exposure accurately measured to minimise bias?	yes	Daily mean use was measured using an internal compliance metre within the foot pump.
Was the outcome accurately measured to minimise bias?	yes	The primary outcome measure was the incidence of DVT, monitored with regular clinical examinations during the hospital stay and at the 6-week follow-up.
Have the authors identified all important confounding factors?	yes	The use of foot pumps with or without stockings was not randomised, additional chemical prophylaxis was not used in approximately one half of the patients of the intervention group managed without stockings.
Have the authors taken account of the confounding factors in the design and/or analysis?	yes	Authors noted that two groups of patients were reasonably homogeneous, and demographic differences were not statistically significant and limitations of the study (such as those described above) were considered in the discussion.
Was the follow-up of patients complete?	yes	Follow-up was for 6-weeks and details of discontinuations and deaths were captured.
How precise (for example, in terms of confidence interval and p values) are the results?	yes	Study was adequately powered to detect a 20% difference in the effectiveness and safety of the two interventions for the prophylaxis of DVT; The continuous demographic data of the two groups of patients were analysed using a two-tailed, unpaired t-test. For rank-scaled data, median values were given with the interquartile range. Relative frequencies of unpaired samples were compared using Fisher's exact test. Unpaired groups of continuous data without the assumption of a normal distribution were compared by means of the Mann-Whitney U-test. Two-sided p values of $p \leq 0.05$ were considered to be significant.

10.6.1.2 RCTs

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Nicolaides 1983 (37)		
Was randomisation carried out appropriately?	yes	After stratification according to risk of DVT, patients were randomised to one of three groups to ensure there was an equal distribution of high- and low-risk patients in each group; randomisation was carried out via the drawing and opening of sealed envelopes.
Was the concealment of treatment allocation adequate?	NA	Due to the nature of the treatments evaluated, concealment was not possible.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	yes	Similar proportions of low- to high-risk patients were included in each group.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	NA	Due to the nature of the treatments evaluated, concealment was not possible.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	no	-
Is there any evidence to suggest that the authors measured more outcomes than they reported?	no	-
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	no	-

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Pitto 2004 (47)		
Was randomisation carried out appropriately?	yes	Randomisation was performed using sealed envelopes containing a slip indicating the allocation, which had been derived from a computer-generated sequence.
Was the concealment of treatment allocation adequate?	NA	Due to the nature of the treatments evaluated, concealment was not possible.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	yes	There were no statistically significant differences between the two groups for any of these factors.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	nA	Due to the nature of the treatments evaluated, concealment was not possible.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	no	-
Is there any evidence to suggest that the authors measured more outcomes than they reported?	no	-
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	no	-
Santori 1994 (43)		
Was randomisation carried out appropriately?	yes	Randomisation was by a casual numbers tables, using sequentially numbered, sealed envelopes.
Was the concealment of treatment allocation adequate?	NA	Due to the nature of the treatments evaluated, concealment was not possible.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	yes	The two groups were well matched for age, sex, indication for total hip replacement, duration of operation, total blood loss and amount of blood transfused.

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	NA	Due to the nature of the treatments evaluated, concealment was not possible.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	no	-
Is there any evidence to suggest that the authors measured more outcomes than they reported?	no	-
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	no	-
Sobieraj-Teague 2012 (44)		
Was randomisation carried out appropriately?	yes	Patients were randomised by use of a computer generated randomisation sequence concealed in sequentially numbered, opaque, sealed envelopes prepared by a statistician not otherwise involved in the study. Surgical patients were randomised in the postoperative recovery room. Non-surgical patients were randomised immediately prior to study entry.
Was the concealment of treatment allocation adequate?	NA	Due to the nature of the treatments evaluated, concealment was not possible.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	yes	The groups were well balanced with respect to demographic characteristics and the distribution of neurosurgical diagnoses and procedures. The use of graduated compression stockings was similar in the two groups, but more patients randomised to the control group received postoperative prophylaxis with an anticoagulant or aspirin (34.7% vs. 25.3%).

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	NA	Due to the nature of the treatments evaluated, concealment was not possible.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	no	-
Is there any evidence to suggest that the authors measured more outcomes than they reported?	no	-
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	no	-
Warwick 2002 (48)		
Was randomisation carried out appropriately?	yes	Randomisation was performed using sealed envelopes containing a the allocation, which had been derived from a computer-generated sequence.
Was the concealment of treatment allocation adequate?	NA	Due to the nature of the treatments evaluated, concealment was not possible.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	yes	Baseline demographics were similar between groups.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	NA	Due to the nature of the treatments evaluated, concealment was not possible.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	no	-
Is there any evidence to suggest that the authors measured more outcomes than they reported?	no	-

Study question	Response (yes/no/not clear/NA)	How is the question addressed in the study?
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	yes	Secondary outcomes were, whenever possible, presented on an intention-to-treat basis irrespective of whether the patient had proceeded to venography

10.7 *Appendix 7. Stimulation programme sequence from Tucker 2010*

Table 57: Stimulation programme sequence, Tucker 2010

Programme number	Amplitude, mA	Frequency, Hz
1	1	1
2	1	3
3	1	5
4	5	1
5	5	3
6	5	5
7	10	1
8	10	3
9	10	5
10	20	1
11	20	3
12	20	5
13	40	1
14	40	3
15	40	5

Note: Programme current settings were defined on the bench (not in contact with a human body). Peak voltage was measured (using an oscilloscope) between terminals across a fixed 2000 ohm resistor. The equivalent current was then calculated by Ohm's law (voltage = current × resistance). In vivo, variations in skin resistance, tissue resistance and quality of contact will give varying values of both current and voltage (because the device has a substantial internal resistance); therefore, the values given serve only to identify the setting and do not necessarily represent the actual value of current delivered to the subject

10.8 *Appendix 8. Description of VRS and VAS*

Verbal rating scale (VRS)

Table 58: Description of VRS

Score	Description
1	No sensation
2	Minimal discomfort
3	Mild discomfort
4	Moderate discomfort
5	Severe discomfort

Visual analogue scale (VAS)

The VAS is a 10 cm scale with 0 cm indicating no sensation and 10 cm indicating severe discomfort.

10.9 *Appendix 9. Calculation of life expectancy for model time horizon*

Table 59: Life expectancy calculations for model time horizon

	Hip fracture	THR	TKR	General surgery	General medical
Mean age (years)†	82	70	70	60	74
% male†	23	38	42	50	47
LE male (years)	7.14	14.43	14.43	22.17	11.72
LE female (years)	8.43	16.73	16.73	25.07	13.70
Ave LE (years)	8.13	15.86	15.76	23.62	12.77

Abbreviations: LE, life expectancy; THR, total hip replacement; TKR, total knee replacement.
†Mean age and % male as presented in Table 4.3 of NICE VTE guidelines (3).

The overall average was therefore 15.23 years, hence the use of a 15 year time horizon.

10.10 *Appendix 10. Economic evaluation using RR reduction from CLOTS 3 study*

Table 60: Subgroup 2 results: Stroke patients using a varied duration of prophylaxis and DVT RR of 0.76

Duration of prophylaxis	Incremental cost per patient
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]
11	[redacted]
12	[redacted]
13	[redacted]

10.11 *Appendix 11. Validation of economic model*

Data input page	Set data for checks	Expected result	Checked
Patient characteristics	Baseline risk of any DVT, PE, Proportion of DVT resulting in a PE and PE fatality set to 50% (PE and PE fatality included). Set the proportion of DVTs that are symptomatic, symptomatic DVT => PTS, Asymptomatic DVT => PTS and PE => PTS set to 50%, 50%, 30% and 20% respectively.	Risk of symptomatic DVT = 25% as expected	✓
Prophylaxis data	For each of the prophylaxis options (apart from combo geko + pharmacological option) the unit cost per day is set to £10.00, the nurse time (mins) to 10.00, the duration of prophylaxis to 1. The staff nurse cost per is set to £60.00. (Leave None as zero cost and resources)	• Cost of prophylaxis = (£10 + [(£60/10)*10]) * 1 = £20 as expected • The combo cost (geko + pharmacological) = (£20 + [(£60/10)*20]) + (£20 + [(£60/10)*20]) = £40 as expected	✓
Prophylaxis data	Set the RR of geko™ device to 0.5	• Expect 50% reduction in risk of DVT –View Engine/Results	✓
Event Costs	Set cost of symptomatic, asymptomatic, PTS and PE to £1,000, £2,000, £3,000 and £4,000 respectively	• View results	✓
Engine	Check: No prophylaxis decision tree	**No prophylaxis: % and pts** • % with DVT = 50% as expected => 50 pts • % symptomatic = 50% as expected => 25 pts (50% of 50pts) • % asymptomatic = 0% as expected => 0 pts (0% of 50pts) • % with PE = 50% as expected => 25 pts (50% of 50pts) • % symp DVT with PTS = 50% as expected => 12.5 pts (50% of 25 pts) • % PE with PTS = 20% as expected => 5 pts (20% of 25 pts) • % PE that are fatal = 50% as expected = 12.5 pts (50% of 25pts) **No prophylaxis: Costs**	✓

Data input page	Set data for checks	Expected result	Checked
		• Symptomatic: 25 pts * £1,000 **=> £25,000 as expected** • Symptomatic DVT with PTS: 12.5 pts * £3,000 => **£37,500 as expected** • Asymptomatic: 0pts * £2,000 => **£0 as expected** • Asymptomatic DVT with PTS: 0 pts * £3,000 **=> £0 as expected** • PE: 25pts * £4,000 => **£100,000 as expected** • PE with PTS: 5 pts * £3,000 => **£15,000 as expected**	
Engine	Check: geko™ decision tree	**Expect results to be half of no prophylaxis (plus additional cost of geko™)** ***geko™: % and pts*** • % with DVT = 25% as expected [(Baseline risk (50%) * RR (50%)]=> **25 pts** • % symptomatic = 50% as expected => **12.5 pts** (50% of 25 pts) • % asymptomatic = 0% as expected **=> 0 pts** (0% of 25 pts) • % with PE = 50% as expected => **12.5 pts** (50% of 25 pts) • % symp DVT with PTS = 50% as expected **=> 6.25 pts** (50% of 12.5 pts) • % PE with PTS = 20% as expected => **2.5 pts** (20% of 12.5 pts) • % PE that are fatal = 50% as expected **= 6.25 pts** (50% of 12.5 pts) **Patient numbers half as expected** ***geko™: Costs*** • Cost of geko™: £20 * 100 pts **=> £2,000 as expected** • Symptomatic: 12.5 pts * £1,000 **=> £12,500 as expected** • Symptomatic DVT with PTS: 6.25 pts * £3,000 **=> £18,750 as expected** • Asymptomatic: 0pts * £2,000 **=> £0 as expected** • Asymptomatic DVT with PTS: 0 pts * £3,000 **=> £0 as expected** • PE: 12.5pts * £4,000 => **£50,000 as expected** • PE with PTS: 2.5 pts * £3,000 **=> £7,500 as expected** **Costs half as expected**	✓
Engine	General	• Inputs pull through correctly and engines work correctly	✓
Results	Check: Costs	• Cost of prophylaxis (geko™): Prophylaxis = 100 * £20 = **£2,000 as expected** • Cost of DVT (geko™): Symptomatic: 12.5 pts * £1,000 **=> £12,500 as expected** • Cost of PE: 12.5pts * £4,000 => **£50,000 as expected** • Cost of PTS: Symptomatic DVT with PTS: 6.25 pts * £3,000 => £18,750	✓

Data input page	Set data for checks	Expected result	Checked
		PLUS PE with PTS: 2.5 pts * £3,000 => £7,500 => **£26,250 as expected** • Total costs: £2,000+£12,500+£50,000+£26,250 => **£90,750 (correct)** • Cost of no prophylaxis = 100 * £0 = **£0 as expected** • Cost of DVT (geko™): Symptomatic: 25 pts * £1,000 **=> £25,**000 as expected • Cost of PE: 25 pts * £4,000 => **£100,000 as expected** • Cost of PTS: Symptomatic DVT with PTS: 12.5 pts * £3,000 => £37,500 PLUS PE with PTS: 5 pts * £3,000 => £15,000 => **£52,500 as expected** • Total costs: £0+£25,000+£100,000+£52,500 => **£177,500 (correct)** • Difference in costs: £90,750 - £177,500 **=> -£86,750 (correct)** • Per patient £86,750/100 => **-£868**	
Results	General	• Number of patients with DVT, PE and PTS and associated costs pulling through correctly from engine worksheet	✓

11 Related procedures for evidence submission

11.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.
- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

11.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and highlight information that is submitted under 'commercial in confidence' in blue and information submitted under 'academic in confidence' in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

11.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there

are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).