NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

The geko device for reducing the risk of venous thromboembolism

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the sponsor's submission of evidence and with the EAC report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: External Assessment Centre correspondence
- Appendix E: Sponsor's factual check of the assessment report and the External Assessment Centre's responses

1 The technology

The geko device (Firstkind Ltd) is a battery powered, disposable neuromuscular electrostimulation (NMES) micro-device that is promoted to reduce the risk of venous thromboembolism (VTE).

The geko device is applied to the fibula head (or other application site) and wrapped around the leg, below the crease of the knee. When activated, the device delivers electrical impulses that stimulate 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.

The geko device is applied by a healthcare worker to 1 or both legs as prescribed by a clinician. The device is non-invasive, small (149 mm × 42 mm × 11 mm) and lightweight (16 g), and does not restrict movement of the knee. It is available in one size and must be replaced every 24 hours. The device is self-adhesive but an extra adhesive overlay is provided if necessary. The small contact area (35 cm^2) of the device is designed to minimise skin irritation and sweating.

2 Proposed use of the technology

2.1 Disease or condition

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 of the legs 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.

In the UK in 2005, VTE was reported as being the underlying cause of death in over 25,000 hospitalised people. It is estimated that the total cost (direct

and indirect) to the UK of managing VTE is around £640 million. There is also significant morbidity associated with non-fatal VTE. The long-term complications of DVT can include recurrent thromboembolism and post-thrombotic syndrome (PTS) which is characterised by aching pain on standing and dependent oedema.

2.2 Patient group

The geko device is intended for use in hospitalised people for whom current mechanical methods of prophylaxis are impractical or contraindicated. Such patients may include those with stroke, morbid obesity, severe leg deformity, plaster casts, bilateral lower extremity trauma, severe or critical lower limb ischaemia, swelling of the legs (for example, 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.

The sponsor estimated that between 95,000 and 475,000 people per year would be eligible for treatment with the geko device. These estimates were based on 2011–2012 hospital episode statistics (HES) data which reported 9.5 million hospital admissions for surgical procedures. The EAC noted that the number of surgical admissions included 5.6 million day cases that would be considered low risk and were unlikely to be prescribed mechanical VTE prophylaxis other than anti-embolism stockings. The remaining 3.9 million would normally have their risk of VTE assessed and be provided with prophylaxis if considered to be at risk. In the absence of further data, the sponsor estimated that for 1% (95,000) of patients, all current methods of prophylaxis (pharmacological or mechanical) would be contraindicated. The sponsor also estimated that for 5% (475,000) of patients, pharmacological prophylaxis would be suitable, but not current forms of mechanical prophylaxis. The EAC noted that it is difficult to estimate how many people geko is likely to be suitable for, but believes it to be a small number.

2.3 Current management

Venous thromboembolism – reducing the risk (NICE clinical guideline 92) recommends that all people admitted to hospital should have an assessment of their risk of VTE. They should also have their risk of bleeding assessed before pharmacological prophylaxis is offered, and treatment should be determined by the balance of the risks of VTE and bleeding occurring.

Pharmacological prophylaxis should be started as soon as possible after the risk assessment has been completed and continued until the person 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. Recommended methods of mechanical VTE prophylaxis include anti-embolism stockings (thigh or knee length), foot impulse devices and intermittent pneumatic compression (IPC) devices (thigh or knee length).

NICE clinical guideline 92 makes special reference to anti-embolism 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 or other causes of sensory impairment, cardiac failure, severe leg oedema or pulmonary oedema from congestive heart failure, major limb deformity preventing correct fit, local conditions in which stockings may cause damage, for example, ‘tissue paper’ skin, dermatitis, gangrene or recent skin graft, and unusual leg size or shape.

The guideline recommends offering combined VTE prophylaxis with mechanical and pharmacological prophylaxis to people with major trauma or spinal injury, and to those having elective hip or knee replacement and hip fracture surgery. It also recommends considering offering combined VTE prophylaxis based on assessment of risks and after discussion with the person for those having other orthopaedic surgery, and to women who are pregnant or have given birth within the previous 6 weeks who are having surgery, including caesarean section.

2.4 Proposed management with new technology

It is proposed that the geko device would provide an alternative mechanical method of VTE prophylaxis in people for whom current mechanical methods are impractical or contraindicated. It is most likely to be used in hospitals.

2.5 Equality issues

The geko device may not be suitable for:

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

3 Sponsor's claimed benefits

The benefits to patients claimed by the sponsor are:

- The geko device reduces the risk of VTE via the prevention and reduction of venous stasis.
- Good patient adherence due to ease of application, which could help with a faster recovery.
- Discrete and comfortable to wear, allowing the person to retain their independence and mobility. This may help maintain patient wellbeing and ensure self-sufficiency.
- Minimal skin contact and therefore avoidance of skin irritation, skin breakdown and sweating.

The benefits to the health system claimed by the sponsor are:

- The geko device addresses an unmet need by delivering VTE prophylaxis to patient groups who cannot use standard VTE prophylaxis.
- The potential to improve speed of patient recovery and therefore reduce the length of hospital stay.

4 The evidence

4.1 Summary of evidence of clinical benefit

Overall, the sponsor identified 37 studies for full paper review, and considered 27 of these (which were either about the geko device or about blood flow and VTE prophylaxis in general with other devices) as relevant to the scope and presented the results of these in the submission. In addition, the sponsor presented an interim report from a study assessing the geko device by Khanbhai et al (2013) and some post-marketing surveillance data. Of the 27 studies presented by the sponsor, the EAC considered as relevant, and critically appraised, 15 of these (reasons for exclusion are detailed in page 22 and appendix 3.2 of the assessment report). The EAC carried out additional work (assessment report page 10) and identified a further 25 studies that were not included in the sponsor's submission, from which 5 (none of which were about the geko device) were judged to be relevant to the scope and assessed.

Seven of the 27 papers presented by the sponsor were about the geko device. Of these, 2 were published reports (Tucker et al [2010] and Warwick et al [2013]), 3 were unpublished studies (Jawad [cardiac], Jawad [coagulation] and Jawad [vs IPC]) based on a PhD thesis by Jawad (2012), and the other 2 papers reported results from the same study by Williams (a published poster [Williams published, 2013] and an unpublished manuscript [Williams unpublished, 2013]).

The EAC considered only 3 of the 7 sponsor-submitted studies fitted with the comparators and outcomes defined in the scope. Tucker et al (2010) was rejected by the EAC because the comparators were baseline measures and voluntary muscle action (dorsiflexions). It also considered that the lack of a proper control in the Warwick et al (2013) study and the use of cardiac outcomes in Jawad (cardiac) (2012) did not fit within the scope. Finally, it stated that the poster by Williams (published 2013) did not provide sufficient detail of how baseline measurements were obtained. For completeness, the methodologies of the geko studies (excluding the Williams [published 2013]

poster) presented in the sponsor submission and the interim report are described in Tables 1 and 2 below.

Table 1: Summary of study methodology from geko studies considered by the EAC to be relevant to the scope

Reference (sponsor reference)	Study aim and design	Patient population	Intervention vs Comparator	Outcomes measured	Summary of EAC commentary
Jawad (coagulation; 2012)	Investigation of use/effect of an electrical stimulation device on specific blood coagulation factors. Secondly to investigate the effectiveness and safety of the device in enhancing lower limb blood flow. Single arm, single centre, study.	Healthy volunteers (n=10)	Prototype of geko device vs no comparator	Measurements of arterial and venous blood flow were made using colour flow duplex ultrasound and laser doppler flowmetry	Used the THRIVE device (early version of geko) Subjects placed in airline seating for 4 hours. Does not mimic medical setting. Not all outcomes reported across the different interventions.
Jawad (vs IPC) 2012	Comparison of geko device against 2 IPC devices in enhancing lower limb blood perfusion. Single arm, single centre, study	Healthy volunteers (n=10)	The geko device vs 2 IPC devices	Measurements of changes in blood flow and volume, microcirculatory velocity were measured at baseline, when devices were active and at the end of each sequence.	Alternating and short application/duration of devices (30 minutes) does not mimic medical setting. No confidence intervals for estimates.
Williams et al (unpublished) (2013)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] confidence intervals [redacted]

Table 2: Summary of study methodology from geko studies considered by the EAC to be not relevant to the scope

Reference (sponsor reference)	Study aim and design	Patient population	Intervention vs Comparator	Outcomes measured	Summary of EAC commentary
Tucker et al (2010)	Evaluation of novel transdermal neuromuscular device applied to the common peroneal nerve on blood flow in the lower limb. Single arm, single centre study.	Healthy volunteers (n=30)	Prototype of geko device vs no comparator	Measurements of changes in blood flow and volume, microcirculatory flux, photoplethysmography (PPG), strain gauge plethysmography (SPG), laser doppler fluxmetry, transcutaneous oxygen tension, colour flow duplex ultrasound and pulse oximetry.	Used a prototype device: the programs did not match geko. Airline seats. Device turned on/off every 5 minutes. No confidence intervals for estimates.
Jawad (cardiac) (2012)	Investigation of effectiveness in increasing venous return of lower limb with particular reference to enhancing cardiac performance. Single arm, single centre study.	Healthy volunteers (n=9).	Prototype of geko device vs no comparator	Measurements of arterial volume flow, peak velocity, femoral vessel diameter, microcirculation, and echocardiography were taken.	Used the THRIVE device (early version of geko) Short application/duration of devices (30 minutes) Only measures arterial blood flow (not venous)
Warwick et al (2013)	To investigate the characteristics of deep venous flow, in the leg encased in a cast with use of geko, and to examine participant's tolerance of the stimulator. Single arm, single centre study.	Healthy volunteers (n=10).	The geko device vs no comparator	Measurements were taken while subject was supine, with lower leg elevation, and while standing (non-weight bearing on contralateral leg and weight-bearing with weight distributed on both legs). Patient's tolerability of device was assessed using a verbal rating score.	No time period was given for application/duration of device, or for duration of different subject positions. The measurements taken in different positions do not necessarily mimic medical patient experience.
Interim report by Khanbhai et al (2013)	[redacted]	[redacted]	[redacted]	[redacted]	This is an interim report. The EAC agreed with the sponsor's exclusion of this report from the clinical evidence.

A brief description of the geko studies (including the interim report and post-market surveillance data but excluding the poster by Williams 2013) is given below. Full details of the methodologies and outcomes are provided on page 42 and pages 48 to 56 (table 3.2) respectively of the assessment report.

Jawad (coagulation; 2012)

Jawad (coagulation; 2012) described measurements taken on 10 healthy volunteers using the THRIVE device (a predecessor of geko). Participants were placed in airline seating for 4 hours with the device applied for 5 minutes, every 15 minutes. All measurements were repeated in a second visit without the device to give baseline values.

A significant increase was observed in mean venous blood flow ($p \leq 0.001$) and mean venous peak velocity ($p \leq 0.001$) with the device when compared against baseline values in the same leg. The highest increase was found after 3 hours in both measures (+326% and +181% respectively) during the 4-hour session. No significant difference ($p > 0.05$) from baseline was observed in mean arterial velocity although mean arterial volume increased significantly ($p \leq 0.05$). The majority of volunteers reported mild discomfort for the electrical nerve stimulation, characterised by a mean score of 2.6 out of 5 using a verbal rating scale and 35.8 out of 100 using a visual analogue scale (higher scores on each scale indicating greater discomfort). Skin perfusion was 4.66 flux units at baseline, which escalated to 73.59 flux units after 1 hour and continued to increase reaching 75.85 flux units at 4 hours. The EAC noted that the study did not compare the results in the contralateral (unstimulated) leg during either session and stated that it was therefore difficult to ascertain the clinical significance of these values.

Jawad (vs IPC; 2012)

Jawad (vs IPC; 2012) study compared the efficacy of the geko device in enhancing lower limb blood perfusion against 2 leading IPC devices in 10 healthy volunteers. The median (inter-quartile range) values for the venous blood volume flow were 123.5 ml/min (73.4) at baseline, 163 ml/min (105.3) for geko at a normal clinical use setting, 129 ml/min (42.7) for geko at a

threshold setting (the minimum setting to elicit a minor muscular contraction in both the calf and the foot) and 118 ml/min (72.7) and 115 ml/min (60.2) for the 2 IPC devices. Therefore, the geko device statistically significantly increased venous blood volume flow (p≤ 0.001) by approximately 30% compared against the IPC devices. The geko device also increased arterial blood volume flow by approximately 30% (p≤ 0.001), arterial blood velocity by 24% (p ≤ 0.001) and total microcirculatory blood velocity by approximately 370% (p≤0.001). When using a visual analogue scale no significant differences in discomfort were found between the geko device and the IPC devices (p≥0.05).

The EAC noted that both IPC devices demonstrated an average percentage change in comparison to baseline for venous blood flow of −4%. In relation to this finding, the EAC noted the fact that the sponsor's evidence centres on the assertion that IPC devices work by increasing venous blood flow.

Williams et al (unpublished; 2013)

Williams et al (unpublished; 2013)

[redacted]

Tucker et al (2010) – excluded by the EAC from further assessment

Tucker et al (2010) conducted a preliminary study of an early prototype of the geko device. Measurements were taken on 30 healthy volunteers seated in an airline seat and provided with the stimulator on 1 leg, while the other immobile leg acted as a control. Fifteen sequential electrical stimulation programs

(varying the amplitude and frequency) were applied for 5 minutes each followed by a 10 minute recovery phase over a 4 hour period. The program sequence was reversed in a second visit 2 weeks later. Changes in measurements were compared to baseline values (at rest), and voluntary muscle action (10 dorsiflexions). The EAC rejected this study because it considered the use of baseline measures and voluntary muscle action as comparators did not fit with the scope. In all 15 stimulations, the device significantly increased both mean venous volume ($p<0.01$) and mean venous velocity ($p<0.01$) in the lower limb. Subjects rated most of the stimulation programs as minimal sensations and only the program with the highest amplitude and frequency was rated as moderate sensations.

Jawad (cardiac; 2012) – excluded by the EAC from further assessment

Jawad (cardiac; 2012) described measurements from 9 healthy volunteers using the THRIVE device. The EAC rejected this study because it considered the use of cardiac outcomes did not fit within the scope. Cardiac output results showed a statistically significant increase of 6% and 4% using pulse widths of 400 microseconds and 600 microseconds respectively ($p\leq0.05$). After electrical stimulation, femoral arterial volume flow and velocity increased by more than 50% and 24% respectively. Microvascular velocity increased by 1186% following pulse width 400 microseconds and 1552% following pulse width 600 microseconds. There was no significant change in mean vessel diameter and area.

Warwick et al (2013) – excluded by the EAC from further assessment

This study described blood flow measurements on 10 healthy volunteers in different positions with and without a leg cast. Measurements were taken with the geko device switched off and repeated with it switched on. The EAC rejected this study because it considered the use of a plaster cast as a comparator did not fit within the scope. Results showed that the geko device was effective in statistically significantly increasing venous blood flow in the lower limb both with a plaster cast (mean difference 11.5 cm/second, p=0.001 to 0.13) and without a plaster cast (mean difference 7.7 cm/second, p=0.001

to 0.75). Posture also had a statistically significant effect on peak venous blood flow when the cast was on and the geko inactive (p=0.003 to 0.69), although these differences were less pronounced than the effect of the geko device (mean difference 3.1 cm per second, range −6.5 to 10 cm/second). The geko was well tolerated, with participants generally reporting only mild discomfort using the device. The EAC noted that no time period was given for the application of the device or for the duration of different subject positions.

Khanbhai et al (2013; unpublished interim report) – excluded by the EAC from further assessment

Khanbhai et al (2013)

[redacted]

Post-market surveillance data

The sponsor's submission reported that the geko device has been evaluated across a number of NHS centres since August 2012 as part of a post-market surveillance evaluation programme, which collected relevant ergonomic and patient compliance data across a 24–48 hour post-operative period. In total, 215 responses to questionnaires assessing post-wear feedback of the geko device were received from mostly people who had had vascular or orthopaedic surgery, or non-surgical treatment. Results found that 82% of clinicians found the device easy or very easy to apply and over 80% found the device easy or very easy to start/stop and to change the settings. In over 90% of cases the geko device adhered well or very well to the leg. Eighty five per cent of patients found the device comfortable or very comfortable to wear

once applied and 92% of patients reported that their quality of sleep while wearing the geko device was normal.

Neither the sponsor nor the EAC carried out an evidence synthesis. The EAC noted similarities in the Jawad (vs IPC; 2012) and Williams (unpublished) studies which reported measurement [redacted]; however, the results of these studies could not be combined due to the different design methodologies, such as application times, ordering and settings.

4.2 Association between increased blood flow and VTE prophylaxis

The sponsor claimed that the evidence for the geko device demonstrated a clear and consistent increase in blood flow but recognised that there is no evidence relating treatment with geko to the incidence of DVT. The sponsor therefore built a case for its claim that maintaining peripheral blood flow in the lower limb is essential in preventing venous stasis and reducing the potential for DVT by presenting the evidence for more established mechanical methods such as neuromuscular electrostimulation (NMES) and intermittent pneumatic compression (IPC).

The sponsor carried out a systematic review and identified 13 studies related to NMES (7 randomised controlled trials [RCT], 6 non-RCT), and 7 related to IPC (5 RCT, 2 non-RCT). The EAC carried out a further systematic review and considered that 2 of the NMES studies identified but excluded by the sponsor were relevant, resulting in a total of 22 studies that were assessed. Details of the methodology of these studies can be found in table 3.1 (assessment report page 26). The EAC also identified a further 5 studies which used various NMES devices (see table 3.5, assessment report page 74) but concluded that they did not add any significant clinical evidence for this evaluation.

Of the 15 NMES studies assessed by the EAC, 6 studies included only healthy volunteers and 9 included medical or surgical patients. Of the 7 IPC

studies, 6 compared IPC devices or foot impulse devices (FID) with a pharmacological intervention, which the EAC did not consider relevant to the scope, and it subsequently excluded these studies.

The EAC noted that 4 of the studies (Lindstrom et al [1982], Rosenberg et al [1975], Moloney et al [1972], and Browse & Negus [1970]) used an older style of NMES device with different methodologies, which could only be used while patients were under general anaesthesia. The EAC therefore stated, in agreement with expert opinion, that the findings are potentially less applicable to later studies and devices.

A summary of key points from the NMES and IPC studies presented by the sponsor are provided in table 3.1 of the assessment report (pages 30–41), and studies presenting evidence for the effect of NMES on the incidence of DVT are described below.

Lindstrom et al (1982) randomised 112 patients having abdominal surgery into 3 groups: a control group (standard care, n=50), an electrical stimulation group (n=37), and a group treated with dextran 40 (n=35). The study found that either the NMES stimulation or pharmacological intervention, when compared with the control, significantly reduced the incidence of PE (35% control vs 16% NMES vs 11% dextran 40). The incidence of DVT was numerically lower (30% control vs 14% NMES vs 20% pharmacological intervention) but did not reach statistical significance.

Rosenberg (1975) randomised 295 patients having major general surgery to receive NMES, heparin, or no specific prophylaxis. The study found a significant decrease in the incidence of major DVT using NMES when compared to no NMES (12.3% [control] vs 0% [NMES]).

Nicolaides et al (1972) randomised 116 mixed surgical patients into 2 groups: 1 receiving electrical stimulation, and 1 receiving no prophylaxis. The study reported a significant reduction in the incidence of DVT with the use of NMES (23% [control right leg], 21% [control left leg] vs 1.6% [NMES stimulated leg]).

Browse & Negus (1970) assessed DVT incidence after applying NMES to 110 patients having major surgery (with the other leg used as a control). DVT was detected in 9 stimulated legs (8.2%) and 23 unstimulated legs (20.9%) equating to a reduction of 12.7% (absolute), or 61% (relative), in the incidence (per leg) of DVT.

Moloney et al (1972) found no significant reduction in DVT incidence among a sample of surgical patients (25% [control: no NMES] vs 20% [NMES], $p>0.05$).

The EAC noted that Nicolaides et al (1983) found that the use of IPC with compression stockings was just as effective as receiving low-dose subcutaneous heparin in reducing the incidence of DVT, whereas electrical calf stimulation was not as effective (4%, 9% and 18% respectively).

Sponsor's use of evidence relating to NMES and IPC devices

In the absence of any study measuring the effect of the geko device on the incidence of DVT, the sponsor proposed that the relative risk reduction in DVT incidence after the use of NMES as reported in Browse & Negus (1970) was applicable to the geko device. Table 3 presents an overview of the sponsor's rationale for this assumption alongside EAC commentary.

Table 3: The sponsor's rationale and the EAC's comments for the assumed relative risk reduction for the geko device

Sponsor's rationale	EAC's comments
Risk for NMES based on the study by Browse & Negus (1970) is more conservative than that reported for NMES by Nicolaides (1972).	The evidence pertaining to 1 NMES device cannot be assumed to be applicable to another. For more details see section 6.1 of this overview.
The risk reduction value falls within the range (0.31–0.58) identified for IPC devices in the NICE VTE guideline. The evidence demonstrating superior increases in blood flow for the geko device compared with IPC devices suggests the reduction in relative risk for DVT obtained with the geko device would be at least equivalent to that achieved with an IPC.	IPC devices have been shown to exert additional prophylactic effects to that of increasing blood flow (Dai et al [1999]), including changes to venous volume that can reduce the shear stresses on the vessel walls and prevent damage to the endothelial linings. It is acknowledged in the literature that the exact mechanism or combination of mechanisms responsible for these devices' ability to prevent VTE is not known (Dai et al [1999] and Morris & Woodcock [2004]).
Adherence with the geko device has the potential to be greater than with IPC devices. Adherence with current mechanical methods of prophylaxis is generally considered to be low; IPC devices can have poorly fitting cuffs and lead to reduced patient mobility.	Post-market surveillance data of 215 patients found that 85.1% (n=183) of patients assessed the geko device as comfortable or very comfortable to wear once applied. Several studies assessed patients' tolerance of the geko device: 2 studies reported slightly more discomfort compared with an IPC device and 1 study reported no significant difference in patient discomfort levels. One study showed increased discomfort at the highest amplitude and frequency settings, whereas another reported that it was more tolerable when patients were wearing a plaster cast.

The EAC received conflicting expert advice on the issue of whether the treatment effect of IPC devices could be assumed for the geko device on the basis of the comparison of their effects on venous blood flow alone:

- Two experts stated that it cannot.
- One expert stated 'not absolutely – but it is strongly suggestive'. Another expert agreed with this, adding that a medical device that increases venous

blood flow may reduce the incidence of VTE, but without a controlled trial it is speculative.

- A fifth expert felt that the assumption was fair.

4.3 Advice from experts and patient organisations

Expert adviser questionnaires were completed by 10 experts at the briefing note stage. A further 3 experts, Mr Bankole Akomolafe, Ms Lynda Bonner and Professor Andrew Nicolaides, completed questionnaires during the evaluation stage. All 13 questionnaires are summarised in appendix B.

NICE's Public Involvement Programme received 1 completed questionnaire and patient organisation statement from AntiCoagulation Europe (ACE). Their comments are summarised in appendix C.

4.4 Summary of economic evidence

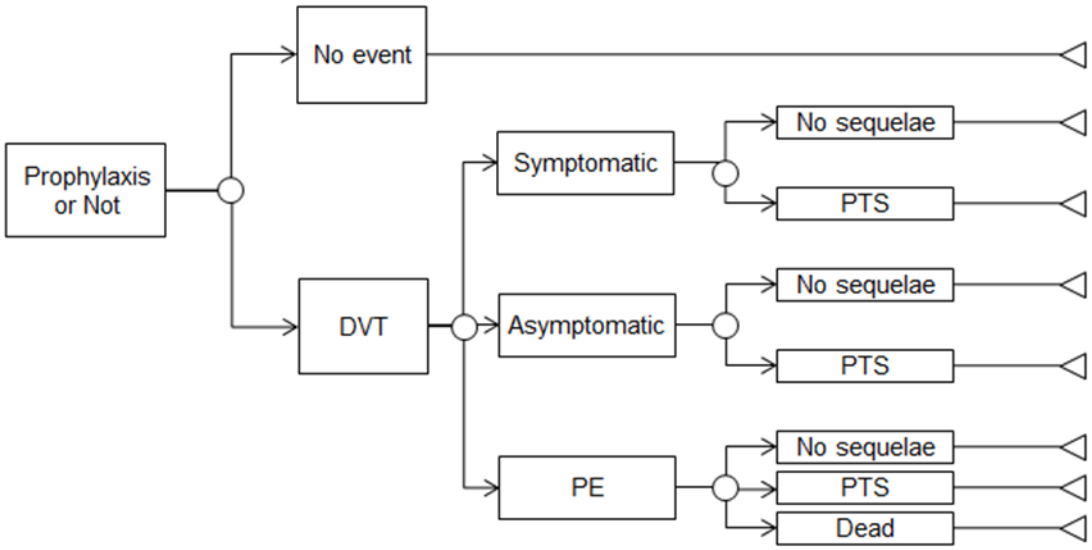
The sponsor conducted a search of the published literature and concluded that no economic evidence was available for the geko device or other NMES devices. The EAC reviewed the search strategy and agreed with the sponsor‘s conclusions.

De novo analysis

The sponsor submitted a decision tree model that estimated the cost associated with the geko device compared with no mechanical prophylaxis. The model considered patients for whom current mechanical methods of prophylaxis are impractical or contraindicated. Subgroup analysis related to the use of pharmaceutical prophylaxis (that is, combined prophylaxis), and stroke.

The decision tree structure (see figure 1) was an amended version of the model from the NICE clinical guideline on venous thromboembolism. The model assumed that patients treated with the geko device experienced a reduction in their baseline risk of DVT. Of the patients who went on to experience DVT, most would have either symptomatic or asymptomatic DVT but some progressed to PE. A proportion of patients with DVT also experienced post-thrombotic syndrome (PTS), a permanent comorbidity which could generate costs over the patient’s lifetime. Further, it was assumed that the patients who had a PE also had a risk of death.

Figure 1: Schematic of decision tree model



The time horizon for the decision tree was 1 year, in which most of the costs associated with prophylaxis, DVT and PE treatment are assumed to occur. However, the model also included the lifetime (15 years) cost of PTS. The EAC stated that it believes the model structure captures the clinical pathway of care, assumptions and health states in an appropriate manner for this evaluation.

The major difference between the model from the NICE clinical guideline and the sponsor's model is that the NICE model considered DVT and PE as separate arms, whereas the sponsor modeled PE to commonly occur as a result of DVT. The EAC commented that it believes this is a reasonable amendment to make.

Clinical parameters and variables

Most of the clinical parameters were based on the NICE clinical guideline on VTE (see table 4) below. The EAC considered that the base-case parameters and the sensitivity analysis used to investigate the uncertainty of these values was reasonable.

There is no evidence available for the reduction in relative risk of DVT associated with the use of the geko device. In the base-case analysis, the sponsor used a relative risk of 0.39, which was based on the incidence of DVT

after the use of NMES as reported in Browse & Negus (1970). The sponsor stated that this was a conservative assumption and further justified this because the value falls within the range (0.31–0.58) identified for IPC in the NICE clinical guidelines on VTE (see section 4.2 of this overview). The EAC did not agree with this assumption (see section 6 of this overview).

The sponsor used 3 clinical experts to check the validity of the model structure, inputs and assumptions (sponsor's submission page 108).

Table 4: Assumptions for the clinical parameters used in the model

Assumption	Justification
Underlying risk of DVT is 29.1% with no prophylaxis (sensitivity analysis used 23.8%: underlying risk of all other medical patients)	Based on the average risk of DVT for all patients having surgery as per the NICE clinical guideline on VTE. Risk of DVT for general medical patients as per the NICE clinical guideline on VTE.
The proportion of DVT progressing to a PE is assumed to be 10.5%.	The NICE clinical guideline on VTE reported the incidence of symptomatic PE at 3.1%. Assuming that PEs occur as a result of a DVT, and the underlying risk of a DVT is 29.1%, the proportion of DVTs that progress to a PE can be approximated to 10.5%.
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 the NICE clinical guideline on VTE. This is considered conservative as the fatality rate reported is as high as 44.7% for the general medical cohort.
Relative risk of a DVT after treatment with the geko device is 0.39.	The risk of DVT with NMES reported by Browse and Negus, which is within the ranges reported for IPC in the NICE clinical guideline on VTE, and more conservative than that reported for NMES by Nicolaides 1972.
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 in the NICE clinical guideline on VTE.

Costs and benefits

Technology and comparators' costs

The cost of the technology (geko) is £22 per pair exclusive of VAT. The cost per course of 6 days prophylaxis is £132.

The administration time for the geko device by a nurse was estimated to be around 1.5 minutes per day. The cost per administration of £1.02 in the sponsor's model was based on an hourly cost of £41 for a ward nurse (Curtis, 2012). However, the EAC considered that because this is a patient contact task, an hourly cost of £100 (Curtis, 2012) should be used and this would give a cost per administration of £2.50.

The comparator in the base-case analysis was no mechanical prophylaxis, and there is consequently no cost associated with it.

Resource identification, measurement and valuation

A systematic review was not conducted to identify resource data from literature; instead, estimates were based on the NICE clinical guideline on VTE. The EAC agreed this was a credible way to estimate costs and agreed that the costs described below were reasonable.

- The cost of symptomatic DVT was £1718, equal to the non-elective inpatient (long stay) NHS reference cost (QZ20Z) for DVT. The cost of managing a DVT was considered to be the same regardless of the patient's underlying condition. The sponsor recognised that this was a conservative assumption and that the cost could vary with underlying comorbidities. This uncertainty was explored through sensitivity analysis.
- The cost of PE as a result of DVT was assumed to be £2022, equal to the weighted average for non-elective inpatient (long stay) NHS reference costs for a PE without complication, PE with intermediate complications and PE with major complications (DZ09A-C). The sponsor also allowed for uncertainty in relation to the cost of PE through sensitivity analysis.
- No direct cost was estimated for asymptomatic DVT.
- Lifetime costs for PTS were included in the model. A mean life expectancy of 15 years from interim life tables for the mean age based on the NICE clinical guideline on VTE was used along with an estimate of the annual cost of PTS (discounted at 3.5%) drawn from the published literature (Caprini et al [2003]). The EAC noted that this estimate was, however, from a US study and stated that there could be differences between the approaches to clinical management of PTS in the US and the UK. In the absence of UK-based estimates, the EAC considered this estimate to be reasonable although it stated further validation with UK-based experts in the management of PTS would have been helpful. The EAC noted that uncertainty about the lifetime cost of PTS was also addressed by the sponsor through sensitivity analysis.

Sensitivity analysis

Sensitivity analysis was performed to explore the uncertainty in the cost model. One-way sensitivity analysis was performed on all model parameters using confidence interval values or ranges. Two-way scenario analysis was conducted varying the relative risk of DVT following use of the geko device and the proportion of symptomatic DVTs. In addition, probabilistic sensitivity analysis (with 10,000 iterations) was also performed using confidence intervals/ranges and the associated distributions. The EAC considered all the sensitivity analysis to be reasonable and a valid approach to test for uncertainty surrounding the parameters.

Results

Base-case analysis results

In the sponsor's model, the cost per patient estimated for the geko device was £359 and for the comparator (no prophylaxis) it was £565, resulting in a cost saving for the geko device of £206 per patient. The EAC changed the cost per administration to reflect the more appropriate hourly nurse cost. This changed the cost saving per patient from £206 to £197.

Sensitivity analysis results

Univariate sensitivity analysis showed that with changes in model parameters, the geko device was still cost saving. The sponsor also noted from the univariate analysis that the 3 factors that affected the cost analysis the most were the cost associated with PTS, relative risk of DVT associated with the geko device as a form of prophylaxis, and proportion of DVTs that are symptomatic.

Threshold analysis was also performed on all model parameters to determine the value at which the geko device would become cost neutral compared with no prophylaxis. In order for geko to be cost neutral:

- The relative risk of DVT when using the geko device needed to increase to 0.76, which is outside the range observed in for IPC in the NICE clinical guideline on VTE.
- The annual cost of PTS would need to be as low as £1242, which is more than an 80% reduction from the base assumption.
- The proportion of asymptomatic DVTs leading to PTS would need to be negative, which is implausible.
- The duration of prophylaxis with the geko device would need to be increased to 15 days.
- The baseline risk of DVT would need to be as low as 11.7% (compared with the base-case assumption of 29.1%).
- Other variables (the proportion of DVTs that are symptomatic, the proportion of symptomatic and asymptomatic DVTs and PEs that result in PTS, the proportion of DVT resulting in a PE and the cost of treating and managing symptomatic DVT) needed to be negative, which is implausible.

Sensitivity analysis was also performed based on alternative scenarios. In scenario 1, a 23.8% risk of DVT for general medical patients was used as an alternative to the base assumption of 29.1%. This resulted in savings of £143 per patient for the geko device when compared with no prophylaxis. In scenario 2, a simpler decision model with no PE health state was constructed. The geko device provided a saving of £154 per patient compared with no prophylaxis with the simple tree structure.

Two-way sensitivity analysis was performed, varying the relative risk of DVT through the use of the geko device and the proportion of symptomatic DVTs. The results showed that, for each point estimate of the relative risk of DVT when using the geko device, the proportion of symptomatic DVTs can take any positive value and the geko device will remain cost saving. Two-way sensitivity analysis was also performed varying both the duration of prophylaxis and the relative risk of DVT with the geko device. The results were the same as the threshold analysis, in which the duration of prophylaxis

with the geko device had to exceed 15 days and the relative risk of DVT had to exceed 0.76 for the geko device to not be cost saving.

Probabilistic sensitivity analysis also showed that the geko device remained cost saving in 99% of simulations performed, with a mean cost saving of −£205.40 per patient (95% CI −£202.88 to −£207.92).

The sponsor concluded that both univariate and probabilistic sensitivity analysis showed that the geko device as cost saving compared with no prophylaxis. The EAC also agreed that the sensitivity analysis covered all the uncertain variables, was well performed and that the results supported the conclusions about cost savings from the submitted model.

Subgroup analysis

The EAC stated that it considered the main base-case analysis to have covered the first subgroup in the scope: people in whom pharmacological prophylaxis is contraindicated. The sponsor performed subgroup analysis for the other subgroup in the scope: people for whom pharmacological prophylaxis is indicated and prescribed. As there was no evidence available for the effectiveness of the geko device used in combination with pharmacological prophylaxis, evidence for IPC from a Cochrane review was used. An economic model was developed using values for the relative risk of DVT with pharmacological prophylaxis alone and for pharmacological prophylaxis plus the geko device of 0.14 and 0.02, respectively.

Compared with pharmacological prophylaxis alone, the geko device in combination with pharmacological prophylaxis was cost saving for the first 2 days and cost neutral if used for 3 days. It was not estimated to be cost saving after more than 3 days of treatment, with an incremental cost of £69 after 6 days of treatment.

The sponsor also performed a subgroup analysis for stroke patients, with a baseline risk of DVT of 21.1% (29.6% of which are symptomatic and 11.5% result in PE). The results showed that the geko device would result in savings of £146 per patient compared with no prophylaxis.

The EAC's interpretation of the economic evidence

The EAC found that the general model structure was sound, and concluded that the cost model analysis showed the geko device was cost saving compared with no prophylaxis. It noted that both univariate and probabilistic sensitivity analysis supported this conclusion.

However, the EAC considered that the basic assumption around the expected impact of the geko device on the risk of DVT made the overall analysis and economic conclusions unreliable. It stated that although the model structure was robust, there is no direct evidence that the geko device can prevent DVT and it did not believe assuming the geko device is at least equivalent to IPC on the basis of blood flow results is appropriate (see section 4.1).

5 Ongoing research

The sponsor conducted a search to identify ongoing trials. From this, 8 studies were identified, all with completion dates before July 2014. Only 1 of these studies has incidence of DVT as an outcome: an RCT that is expected to finish in December 2013, comparing the geko device against IPC. See page 13 of the assessment report for the EAC's review of the relevance of the ongoing studies.

6 Issues for consideration by the Committee

6.1 Clinical evidence

Generalisability of the evidence to the use of the geko device in clinical practice

The EAC noted a number of limitations to the existing clinical evidence. All the geko studies included only healthy volunteers. The EAC considered that the population defined in the scope would include people with conditions that may impair the effectiveness of the geko device (for example, oedema, chemical or physical muscle paralysis, venous insufficiency and adipose tissue insulating the stimulation area). The EAC commented that these factors would have

been screened out by the exclusion criteria used in the submitted evidence. Therefore, the EAC considered the population used in the evidence to differ considerably from the population defined in the scope.

The EAC commented that in some of the studies, patients were positioned in economy-style airline seating, which is not representative of a typical hospital setting. The EAC further stated that this positioning has been shown to influence both blood flow and incidence of VTE.

The EAC stated that, from its understanding of the geko device, in order to function as VTE prophylaxis, the device would need to be in place for a minimum of 24 hours without interruptions. However, it noted that in the submitted evidence, the longest period of time for which the device was continuously active was 30 minutes. Although the post-market surveillance data were collected across a 24–48 hour postoperative period, no details were provided about the duration of use of the geko device and therefore the EAC was unable to consider the data in this context.

Suitability of venous blood flow as a surrogate for measuring VTE prophylaxis

The sponsor's case for the clinical effectiveness of the geko device, in the absence of directly-observed VTE outcomes in patients, is that an increase in blood flow is a credible surrogate for reduction in risk of VTE. Taking into account a review by Ciani et al (2013) that demonstrated, when compared with equivalent trials, surrogates give over-optimistic results, the EAC has concluded that this is a flawed assumption.

The EAC's opinion was based on the belief that venous thrombosis has 3 major risk factors, known as Virchow's Triad. It stated that although it agreed that venous stasis is a risk factor, it does not believe the literature shows it is essential for venous thrombosis (Morris & Woodcock [2004]). The EAC also noted results from a study by Proctor et al. [2001]), which highlighted the difficulties in assuming that an increase in venous blood flow leads to a

reduction in the risk of VTE (see the assessment report page 90 for further details).

The EAC asked expert advisers whether the mild dorsal flexion and increased venous blood flow created by the geko device could be expected to translate throughout the lower limb and prevent VTE. Two experts considered that if it increased venous flow sufficiently then there would be a rationale to expect that it might prevent VTE; however, a prospective RCT with DVT as an endpoint would be needed to demonstrate this conclusively. The other 3 respondents had experience of using the device and referred to ultrasound clips demonstrating blood movement and an ongoing study. The EAC examined the same video footage and agreed that the effects shown were promising. It believes that if the completed study were to show this level of clearance was achievable, this would demonstrate a possible mechanism by which the geko device may be expected to reduce the risk of thrombosis.

Relevance of the evidence for other NMES or IPC devices that have demonstrated efficacy in reducing the incidence of DVT

The EAC concluded that the evidence on one NMES device cannot be assumed to be applicable to another. It noted that other NMES and muscle electrostimulation (MEST) devices use transcutaneous stimulation, usually applied in the vicinity of the muscles to be stimulated rather than the more indirect application of the geko device at a point higher on the neural pathway. The EAC suggested, taking into account expert advice, that this introduces an additional uncertainty, as the type of muscle contractions caused by the geko device would need to be shown to be effective in reducing the incidence of DVT.

The EAC also noted that some types of NMES/MEST devices have been found to be ineffective in preventing VTE in the past, referencing Moloney et al (1972). The EAC commented, with agreement from expert advice, that the device used in this study (along with the devices used in Lindstrom et al [1982], Browse & Negus [1970] and Rosenberg et al [1975]) use different

methodologies, so the findings are potentially less applicable to later studies and devices.

The sponsor justified its assumption for the treatment effect of the geko device by stating that the risk reduction falls within the range identified for IPC in the NICE clinical guideline on VTE. It assumed that the reduction in relative risk of DVT obtained with the geko device would be at least equivalent to that achieved with IPC. The EAC was not convinced that this assumption was sound. Further details of the sponsor's proposition and the EAC's considerations are described in section 4.1 of this overview.

6.2 Economic evidence

Assumption that the geko device would be at least equivalent to IPC at reducing the risk of VTE

In the economic model, the sponsor assumed that the reduction in relative risk of DVT obtained with the geko device would be at least equivalent to that achieved with IPC. The EAC stated that it was not convinced that it is sound to infer that the efficacy of the geko device is at least equivalent to that of IPC. The EAC's rationale is described in table 3 of this overview.

7 Authors

Chris Chesters, Technical Analyst
Bernice Dillon, Technical Adviser

NICE Medical Technologies Evaluation Programme

October 2013

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- Clinch J, Healey A, Keevil S et al. (2013) The geko™ electro-stimulation device for venous thromboembolism prophylaxis

B Submissions from the following sponsors:

- Firstkind Limited

C Related NICE guidance

- Ultrasound-guided foam sclerotherapy for varicose veins NICE interventional procedure guidance 314 (2013)
- Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults. NICE technology appraisal guidance 245 (2012)
- Rivaroxaban for the treatment of deep vein thrombosis and prevention NICE technology appraisal guidance 261 (2012)
- Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing: NICE clinical guideline 144 (2012)
- Venous thromboembolism: reducing the risk: Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital NICE clinical guideline 92 (2010)
- Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults. NICE technology appraisal guidance 170 (2009)
- Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults NICE technology appraisal guidance 157 (2008)
- Venous thromboembolism NICE pathway (accessed 3rd October 2013)

D References

Browse NL, Negus D (1970) Prevention of postoperative leg vein thrombosis by electrical muscle stimulation. An evaluation with 125I-labelled fibrinogen. British Medical Journal 3 615–618

Caprini JA, Botteman MF, Stephens JM et al. (2003) Economic burden of long-term complications of deep vein thrombosis after total hip replacement surgery in the United States. Value in health. The Journal of the International Society for Pharmacoeconomics and Outcomes Research 6 (59-74

Dai G, Gertler JP, Kamm RD (1999. The effects of external compression on venous blood flow and tissue deformation in the lower leg. Journal of Biomechanical Engineering 121 557-564

Ciani O, Buyse M, Garside R et al. (2013) Comparison of treatment effect sizes associated with surrogate and final patient relevant outcomes in randomized controlled trials: meta-epidemiological study. British Medical Journal. doi: 10.1136/bmj.f457

Jawad H (2012) PhD thesis. The effect of a novel stimulation method for improving lower limb blood flow in healthy volunteers. Available at: https://qmro.qmul.ac.uk/xmlui/handle/123456789/3120. Last accessed 22nd May 2013

Lindstrom B, Holmdahl C, Jonsson O et al. (1982) Prediction and prophylaxis of postoperative thromboembolism--a comparison between peroperative calf muscle stimulation with groups of impulses and dextran 40 British Journal of Surgery 69 633-637

Moloney GE, Morrell TM, Fell RH (1972). The effect of electrical stimulation of the legs on postoperative thrombosis. British Journal of Surgery 59 65–68

Morris RJ, Woodcock JP (2004). Evidenced-based compression: prevention of stasis and deep vein thrombosis. Annals of Surgery 239 62–71.

Nicolaides AN, Kakkar V, Field ES et al. (1972) Venous stasis and deep-vein thrombosis. British Journal of Surgery 59 713–717

Proctor MC, Greenfield LJ, Wakefield TW et al. (2001) A clinical comparison of pneumatic compression devices: The basis for selection. Journal of Vascular Surgery 34 459–464.

Roberts VC, Sabri S, Pietroni MC et al. (1970) Postoperative leg vein thrombosis. British Medical Journal 4 556

Rosenberg IL, Evans M, Pollock A (1975). Prophylaxis of postoperative leg vein thrombosis by low dose subcutaneous heparin or preoperative calf

muscle stimulation: a controlled clinical trial. British Medical Journal 22 (649–651

Tucker A, Maass A, Bain D et al. (2010) Augmentation of venous, arterial and microvascular blood supply in the leg by isometric neuromuscular stimulation via the peroneal nerve. International Journal of Angiology 19 E31–E37.

Warwick D, Shaik A, Gadola S et al. 2013) Neuromuscular electrostimulation via the common peroneal nerve promotes lower limb blood flow in a below knee cast: a potential for thromboprophylaxis. Bone and Joint Research179–185

Williams KJ, Moore HM, Ellis M et al. (Manuscript in progress). Haemodynamic changes with the use of neuromuscular electrical stimulation compared to intermittent pneumatic compression. Not yet published.

Williams KJ, Moore HM, Ellis M et al. (2013). Intermittent pneumatic compression and neuromuscular electrical stimulation of the leg: venous haemodynamic effects 14th annual meeting of the European Venous Forum in collaboration with the Balkan Venous Forum and the Serbian College of Phlebology

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Mr Sameh Dimitri
Consultant General and Vascular, The Vascular Society

Professor Charles McCollum
Consultant Vascular Surgeon, The Vascular Society

Mr John Mosley
Consultant General and Vascular Surgeon, The Vascular Society

Mr John Scurr
Consultant General and Vascular Surgeon, The Vascular Society

Professor Gerard Stansby
Professor of Vascular Surgery, The Vascular Society

Mr David Warwick
Reader in Orthopaedic Surgery, British Orthopaedic Association

Twelve experts commented on the technology as follows:

- Eight have had direct involvement with the technology, two have managed patients on whom it is used in another part of their care pathway. Three would like to use the technology but it is not available to them.
- Six experts have been involved in research on this technology. One was involved in the initial validation of the effect of electrical stimulation of the calf muscles. One is currently conducting a study on how the geko device influences calf volume and transit time in healthy volunteers and patients with venous disease. One has looked at the effect of the device on post-operative vasuclar surgery patients. One has looked at the effect on those

wearing plaster casts. The last three are currently awaiting publication in peer reviewed journals.

- Four experts thought that the geko was a significant modification of an existing technology and seven thought it was thoroughly novel. One expert states that the miniaturisation and tolerability is novel but the concept is not new. One states that the simplicity is the novel aspect and the lack of interference with post-operative mobility and recovery.
- All 12 experts state that the most appropriate use is DVT prophylaxis. Two state that it could be used for difficult to heal leg ulcers. One expert believes it should be used to treat post-operative oedema and chronic ischaemia.
- Three experts state that a comparator is pharmacological prophylaxis. Eight experts state that a comparator is compression stockings. Five experts state that the nearest comparator is mechanical foot pumps. One expert stated no thromboprophylaxis.
- One expert stated the Veinoplus as a competing product. The other experts are not aware of any competing products. One stated that various commercially available transcutaneous muscle stimulations can be found.
- Six experts state that this device can be used on a portable basis so the patient can remain ambulatory. One expert believes there are minimal risks when using this device. Two experts have stated that it is beneficial when other methods are contraindicated such as anticoagulants and compression stockings and mechanical compressors. Five state that it is beneficial to patients because it is simple to use.
- Six believe that the additional benefits are likely to be realised in practice. Two state that pricing may be an issue. Two are unsure.
- Three experts state that the additional benefits for the healthcare system are that it is simple to use, small in size and allows the patient to be portable. One expert thinks it may be easier to use on some patients. One expert believes it could reduce DVTs. Two experts' believe this is a more practical solution and could displace current methods. Two experts believe it could be particularly useful for certain patient groups that current devices are unable to treat.

- Ten experts believe that minimal or no training would be required to use this device. One expert stated training would be required, and another stated staff would need to be trained to observe for any side-effects of the device as well as how to use it.
- Five experts believe that the cost of geko could be much cheaper than the current methods. Two were unable to comment. One expert stated that the cost of the device needs to be carefully calculated against its potential claim that reducing stasis will positively impact on clinical outcomes.
- Nine experts believe it would be useful for NICE to produce guidance on this device. One expert believes that it is too early to introduce this technology for any clinical applications and another states we would need to be sure that patients who are unconscious or who have leg odema or limited leg sensitivity are not developing side-effects from using the device.

Appendix C: Comments from patient organisations

Advice and information was sought from patient and carer organisations. The following patient and carer organisations responded:

AntiCoagulation Europe

- The patient group believes this could be useful for people with restricted mobility and contributing factors who can be at a higher risk of a blood clot. They state that if it is used whilst in hospital or post discharge to reduce potential risk, this would provide reassurance in preventing a DVT. The ability to increase mobility and return to normal day to day activities may avoid the need for continuing pharmacological interventions.
- An advantage may be that the device could be applied within a primary care setting which would be more convenient and timely for the patient and reduce costs for hospitals.
- The subgroups that could benefit are high risk individuals with reduced mobility in community settings such as care homes. It may give added protection and benefit in increasing circulation and may reduce pharmacological treatment.
- Hospital inpatients with medical conditions, reduced mobility and those recovering from surgery may benefit as the device is easy to apply, doesn't restrict movement as does the IPC method and doesn't require the personal fitting of the compression stocking which may cause discomfort and irritation.
- Individuals who wish to prevent risk of DVT through long distance travel such as flying/driving.
- Social stigma: Yes, if individuals who are advised to wear compression stockings find them challenging to put on and uncomfortable to wear for long periods of time. The stockings are very noticeable and this may cause embarrassment to some individuals resulting in lack of compliance.

- Disadvantages include skin allergies/reaction and physical interference - if patient unstable or unsteady on feet and prone to falls/ slips.

- With daily application required - in a primary care setting, attendance to a clinic, surgery or community visit may be demanding.
- Equality issues: This device may be advantageous for the older population and should consider how this device can assist in preventing DVT for the groups assessed to be at higher risk due to immobiilty or physical disability.
- Usefulness of NICE guidance: Without NICE guidelines for geko, healthcare professionals may not consider this innovative technology as a benefit for people and this will limit access by patients.
- Obstacles include the [lack of] awareness of the development and availability of device and the education or training for healthcare professional and the uncertainty as to the commissioning of new technologies - burden of cost, responsibility.

AntiCoagulation Europe also provided a statement about the geko device during the evaluation stage which discussed some of the benefits of the geko device and noted some of the issues with other mechanical VTE prophylaxis methods.

Appendix D: External Assessment Centre correspondence

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the assessment report Overview, and is made available at public consultation.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
2 & 3	**Sponsor – FirstKind**	**Appendix 1**	**Questions clarifying clinical submission - Teleconference**
2 & 3	**Sponsor – FirstKind**	**Appendix 2**	**Questions clarifying clinical submission – in writing**
2 & 3	**Sponsor – FirstKind**	**Appendix 3**	**Demonstration of geko**
2, 3 & 6	**Expert Advisers - Multiple**	**Appendix 4**	**Questions clarifying clinical submission**
2, 3, 5 & 6	**Expert Adviser – Prof Gerry Stansby, Professor of Vascular Surgery**	**Appendix 5**	**Questions clarifying clinical submission**
3	**Expert Advisers - Multiple**	**Appendix 6**	**Question regarding the duration of application of the geko device/side-**

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
			effects
All	**Expert Advisers – Multiple**	**Appendix 7**	**Multiple questions post receipt of NICE comments regarding draft report**
3	**Expert Advisers- Multiple**	**Appendix 8**	**Question regarding the effect of mobility on the risk of DVT**

Appendix 1

Questions Posed to Sponsor in Introductory Tele-Conference (between KITEC, NICE & Sponsor) Held on the 11th of July 2013

Please find KITEC's questions in black and Sponsor's replies in red

1. What is the mode of action of Geko?
   Geko is a neuromuscular stimulator. It is positioned on the common peroneal nerve. When turned on, it stimulates all muscle pumps in the leg and causes the leg to 'twitch' once per second. This causes an increase in blood flow & blood velocity.

2. The clinical submission mentions both blood flow & blood velocity as contributing to DVT incidence. Which is the more important measurement?
   Both are important and relate directly to DVT incidence. An increase in either of these measurements will be advantageous to the prevention of DVTs.

3. The clinical submission states that the spanner search on MBase was for 1980 – 2010. Is there a reason that MBase was not searched up to the present day?
   That was an error, all databases were searched up until May '13. We will double check what search parameters were entered and get back to you.

4. Page 22 of the submission refers to an on-going study being conducted in Bournemouth/Poole states the use of TEDS as a comparator. TEDS is a brand name of a particular anti-embolism stocking that is commonly used as a generic name. Can you confirm that it is the TEDS brand that is being used? Are the stockings being used thigh or knee length? What is the sample size for this study?
   The stockings used in this study are 'Saphena Medical' below knee stockings. The sample size is estimated to be 20 patients.

5. Is the sample data in Jawad (vs IPC) 2012 the same as that used in Jawad (cardiac) 2012 and Jawad (coagulation) 2012?
   Yes, they are both chapters from her PhD thesis.

6. Page 15 of the submission states that '2011-2012' HES data showed that there were approximately 9.5 million hospital admissions for surgical procedures'. Could we clarify that this figure pertains only to surgical (and not medical) admissions?
   Yes, this pertains only to surgical patients.

7. Page 15 of the submission states that '1% of patients would be contraindicated to current methods of prophylaxis' and later that '5% of patients would be contraindicated to mechanical prophylaxis' alone. Could you clarify where these figures come from?
   These figures are estimates.

8. What is the published GEKO study identified through the SR?
   Tucker et al 2010 (ref # 45)

9. Page 14 of the submission states that 'Data derived from 3,144 patients with chronic venous disease demonstrated that more than 60% of patients did not use their stockings.' Could you please clarify if chronic venous disease stockings are different to anti-embolism stockings?
   There is no difference chronic venous disease stockings & anti-embolism stockings. All stockings are graded according to how high the interface is. It is recommended that grades 2-4 are used for both DVT prophylaxis and Peripheral Vascular Disease. The stockings used in the quoted paper had a pressure of 25 mm of Hg and, therefore, would be suitable for either applications.

Appendix 2

Questions Posed to Sponsor via Email on the 19th of July 2013

Please find KITEC's questions in black and Sponsor's replies in red

1. The systematic review date span:

The search dates are unrestricted, but the date spans stated on page 100 are restrictive.

- Could the sponsor please confirm the start dates for Medline and Embase and the end date for Embase?

The searches were conducted via OVID as follows:

- Medline: 1950 to 18th May 2013

Embase: 1980 to 18th May 2013.

2. The systematic review exclusions:

The exclusions listed in Table 6 on page 27 state "Non mechanical prophylaxis devices [sic] such as compression stockings". Compression stockings are a mechanical prophylactic device. The only non-mechanical prophylaxis available is pharmacological, which is already covered by the second exclusion statement. This is further complicated by the inclusion of some compression stocking evidence on page 90.

- Can the sponsor please confirm the excluded interventions, and do they overrule the inclusions? For example, if a study compared a pharmacological method with a mechanical method, would it be excluded?

The primary purpose of the systematic review was to identify studies of the geko™ device, as per the MTEP methods guide (1). The secondary purpose was to determine the link between an increase in blood flow and reduction in DVT as there is no direct evidence for the reduction of DVT following use of the geko™ device. Both purposes were addressed under a single search strategy.
In line with the main comparator defined in the NICE scope (i.e., no treatment), pharmacological agents and compression stockings were excluded interventions in the systematic review. NMES and IPC devices were included in the systematic review to provide evidence to show that increased blood flow results in a reduction in DVT.
In Table 6, the exclusion criteria should state:
Anti-embolic stockings
Pharmacological interventions such as LMWH.
Compression stockings are a static form of mechanical compression and as their mechanism of action is different from NMES and IPC, they were excluded from the SR. Pharmacological agents are non-mechanical and were also excluded.
The text around compression stockings on page 90 of the submission is provided as part of the overall body of evidence for VTE prophylaxis showing a link between increased blood flow and a reduction in the risk of DVT. This specific text relates to a Cochrane systematic review of evidence (Sachdeva 2010 (2)), rather than a primary publication of clinical study data.
Exclusion criteria overrule inclusion criteria and therefore, any study that compared a pharmacological agent with a mechanical method was excluded.

3. The link between the selection criteria and the inclusion and exclusion criteria:
Table 6 (page 27), Table 7 (page 28), and appendix 9.1.6 (starting on page 104):
The inclusion criteria in Table 6 and appendix 9.1.6 includes geko only, but in appendix 9.1.6 the heading states it is being used to identify geko and NMES published studies.

- Can the sponsor please explain this discrepancy?
- Figure 4 (page 29), the schematic for the systematic review, shows 13 NMES studies, 1 Geko study and 7 IPC studies being identified. Can the sponsor please explain how NMES and IPC studies were found if these terms were not included in the inclusion criteria?

Tables 6 and 7 list different criteria, so the selection outcome cannot be the same.

- Can the sponsor please explain why a schematic (like figure 4) was not included that relates to table 7?

The wording for the included population changes from VTE in tables 6 and 7 to DVT in the tables in appendix 9.1.6.

- Can the sponsor please explain this discrepancy?

As discussed in the answer to question 2, a single systematic review was conducted in order to identify:

1) geko™ device studies (Table 6)
2) mechanical prophylaxis studies providing evidence that an increase in blood flow leads to a reduction in the risk of DVT (Table 7).

Whilst separate tables of inclusion and exclusion criteria are provided, the search was conducted as a single entity and therefore only one flow diagram is provided (Figure 4). The results of the systematic review were subdivided at the final stage in order to address the two bullets above.

NMES and IPC studies were identified through specific terms included in the search strategy (Appendix 9.1.4 and below) :

- NMES terms: electrostimulation/,Electric Stimulation Therapy/,Electric Stimulation/,(Electrical muscle stimulation or EMS), (electric$ adj5 stimulat$), electromyostimulation, electr$ therap, (pulse adj2 tech$), nmes, neuromuscular electrical stimulation
- IPC terms: Intermittent Pneumatic Compression Devices/, IPC, foot impulse, calf muscle pump, ((soleal or foot) adj2 pump).

The use of the term DVT in Appendix 9.1.6 should read VTE.

4. The EAC note that few of the identified studies listed as ‘GEKO’ studies included the name of the device.

- Can the sponsor please explain how such studies were identified in the SR?

This is true. Few of the identified studies listed as ‘geko™ device’ studies included the name of the device, thus ‘geko’ and ‘NMES’ were used as search terms within the systematic review. Publications relating to the geko™ device were identified via the sponsor’s database.

5. Can the sponsor please elaborate on the exclusion criteria of the ten published studies (ref 50, 51, 52, 53, 54, 55, 56, 57, 58, 59)?

Answer

Ref in submission	Reference	Reason for exclusion
50	Dejode L R, Khurshid M, Walther W W. The influence of electrical stimulation of the leg during surgical operations on the subsequent development of deep-vein thrombosis	Study design - review, no clinical data
51	Pollock A V. Calf-muscle stimulation as a prophylactic method against deep vein thrombosis, Triangle, 1977, 16 (1) 41-5.	Study design - review, no clinical data
52	Pollock A V. Electrical stimulation of the calf. Scottish Medical Journal, 1978, 23 (4) 332-3.	Study design - review, no clinical data
53	Powley J M, Doran F S. Galvanic stimulation to prevent deep-vein thrombosis, Lancet, 1973, 1 (7800) 406-7.	Study design - review, no clinical data
54	Turpie A G G, Bauer K A, Caprini J A, Comp P C, Gent M, Muntz J E, Apollo I. 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	Pharmacological intervention. IPC/ fondaparinux vs IPC. As IPC is in both groups cannot determine efficacy of IPC

	Thrombosis & Haemostasis	
55	Hardwick M E, Pulido P A, Colwell C W, A mobile compression device compared with low-molecular-weight heparin for prevention of venous thromboembolism in total hip arthroplasty , Orthopaedic Nursing, 2011, 30 (5) 312-6.	Pharmacological intervention
56	Khouli H, Shapiro J, Pham V P, Arfaei A, Esan O, Jean R, Homel P. Efficacy of deep venous thrombosis prophylaxis in the medical intensive care unit, Journal of Intensive Care Medicine, 2006, 21 (6) 352-8.	Pharmacological intervention, some patients received heparin but results not stratified by pharma / device
57	Moloney G E, Morrell M T, Fell R H. The effect of electrical stimulation of the legs on postoperative thrombosis, British Journal of Surgery, 1972, 59 (1) 65-8.	Study design - letter
58	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
59	Norgren L, Toksvig-Larsen S, Magyar G, Lindstrand A, Albrechtsson U. 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, 1998, 17 (2) 93-6.	Pharmacological intervention

6. Can the sponsor please explain why a search of unpublished NMES and IPC studies was not conducted?

Unpublished studies of competitor technologies are not in the public domain, and therefore it would not be possible for the sponsor to identify them. Searches for studies were conducted in the databases recommended in the MTEP methods guide (1): Medline, Medline (R) In-Process, Embase and The Cochrane Library. Unpublished studies of the geko™ device were identified by hand-searching and included within the submission.

References

1. National Institute for Health and Clinical Excellence. Medical Technologies Evaluation Programme: Methods guide. Available at: http://www.nice.org.uk/media/3A6/09/MedicalTechnologiesEvaluationProgrammeMethodsGuideMarch2012.pdf. (Last accessed 16 Jul 2013). April 2011.
2. Sachdeva A, Dalton M, Amaragiri SV, Lees T. Elastic compression stockings for prevention of deep vein thrombosis. Cochrane database of systematic reviews. 2010(7):CD001484.

Appendix 3

Minutes from the Sponsor's Demonstration of geko at KITEC on the 19th of July 2013

Present:

KITEC: Elizabeth Morris, James Clinch, Ana Pascoal, Murali Radhakrishnan Kartha, Tiago Rua

FirstKind: Tony Humphries, Dawn Smiles

Minutes:

FirstKind visited KITEC to perform a product demonstration.

Tony started by describing how the device works:

- Activates common peroneal nerve (which is around the fibula head). The patent for the device covers this method of application.
- Two electrodes – 27 Amps, with 7 possible pulse widths between 70ms and 560ms. Repeats every second, no matter which pulse width is chosen.
- Battery lasts approximately 60 hours. The software switches it off at 30 hours – repeatability, couldn't reliably guarantee it would be 60 hours otherwise.
- Hydrogel used for conductivity.
- They have found levels 3 and 4 were suitable for ~80% of people (anecdotal)

- Skin prep – exfoliate to remove moisturisers, clean using alcohol wipes
- Device mimics approximately 70% of walking
- They don’t expect muscle fatigue
- 90% of patients said it didn’t affect sleep
- Athletes use far lower setting than medical.
- Fatty tissue and fluid may be an issue

Demonstration using ultrasound:

- Used Tony Humphries leg.
- Placed geko and measured blood flow before and after switching it on
- Rest blood volume – 18.49ml/min
- geko blood volume – 122.89ml/min
- Shown doppler images of vein and artery

Further questions:

- Shown ultrasound video of valve – from a new study by Prof Nicolaides (one of the NICE expert advisers)
- Also videos of femoral, popliteal, gastrocnemius and soleus veins
- Allergies – don’t have to use the overlay if patient is allergic to plasters
- On-going studies mentioned – Bournemouth (asymptomatic DVT study), Southampton (IPC vs geko), Basingstoke (foot squeeze vs geko), Chester (patient population)
- Name – from young son of CEO, who said it looked like one.
- Videos of blood flow in veins are available on youtube.

Appendix 4

Questions Posed to Expert Advisers via Email on the 22nd of July 2013

Please find KITEC's questions in black and Expert Advisers' replies in red

The device creates a mild dorsal flexion every second increasing peak blood velocity in the superficial femoral vein, as measured using doppler ultrasound. My interest is in how well this increase in flow would translate throughout the lower limb, in particular to the areas thought to be at higher risk, such as the valve cusps and soleal sinuses etc.

I would be very interested in either your direct experiences of the device, or any other input you feel relevant.

Reply 1: Prof Andrew Nicolaides (Received 22nd of July 2013)

Three randomised controlled studies in the 1970s have demonstrated that electrical calf muscle stimulation reduces postoperative DVT. All devices used in these studies didincrease the velocity in the femoral vein. By extrapolation, the geko device should do the same, but its efficacy needs to be tested in prospective RCT with DVT as the endpoint.

Reply 2: Prof Gerard Stansby (Received 22nd of July 2013)

I don't have any data on this – and I am not sure how you could measure flow at more distal sites other than by Duplex of the Popliteal vein by example or perhaps by plethysmography to get an overview?

A key question is whether increased flow occurs in both the sitting and lying positions.

Reply 3: Dr John Mosley (Received 23rd of July 2013)

The Geko device stimulates the peroneal nerve and hence the peroneal muscle as such it causes slight abduction rather than dorsi flexion. In our experience in patients with DVT it increased PSV but does not increase mean blood flow in the popliteal vein and in has no effect on the soleal veins.

It does not seem to work if the limb is oedematous and it tends to fall of and is difficult to keep attached to the leg.

Reply 4: Dr Sameh Dimitri (Received 24th of July 2013)

I have experience with the device and am able to expand upon the blood flow query within the deep veins. I have seen ultrasound clips demonstrating blood movement using colour-flow doppler, within the gastrocnemius and tibial veins. I believe a study is currently underway with Professor Nicolaides investigating the ability of the Geko to achieve second-by-second clearance of these thrombi-forming veins.

Prior to applying for ethical approval to undertake this study, I have personally seen colour-doppler video images which were recorded to demonstrate the feasibility of viewing these veins. These images would be available with consent; they showed second-by-second, anti-stasis clearance of the individual deep veins - with only the soleal vein being impossible to see.

Proven clearance of these veins will be unique, as neither IPC nor stockings have demonstrated this (due to the impracticality of scanning with these garments). This study will possibly emphasise the benefit of the device in patients who are contraindicated for other anti-stasis modalities.

Reply 5: Prof David Warwick (Received 28th of July 2013)

We have a study accepted for publication in the Bone and Joint Research Journal which shows (sample 10 volunteers):
Geko™ was effective in significantly increasing venous blood flow in the lower limb both with a plaster cast (mean difference 11.5cm/sec^{-1}, p=0.001-0.13) and without a plaster cast (mean difference 7.7cm/sec^{-1}, p=0.001-0.75). Posture also had a significant effect on peak venous blood flow when the cast was on and the geko inactive (p=0.003-0.69), although these differences were less

pronounced than the effect of the geko (mean difference = 3.1cm/sec^{-1}, range -6.5 to 10cm/sec^{-1}). The geko™ was well tolerated, with participants generally reporting only mild discomfort using the device

In other words, we do have evidence that the GEKO increases deep venous flow; we do not have data for the smaller soleal veins. The device offers a mechanical option for those in a plaster cast for whom other modalities would not be practical.

These data are not yet in the public domain until published (which should be soon) but I provide them in confidence.

Reply 6: Prof Charles McCollum (Received 30th of July 2013)

I attach a report that we sent to SkyMedical (the manufacturers of the GEKO) which may have been part of their submission to NICE. I have little clinical experience of GEKO and on theoretical grounds had expected that the increase in venous flow in the leg would probably be a consequence of increased arterial flow by stimulating muscle activity rather than by stimulating calf muscle pump function. The attached study was designed to determine whether GEKO influenced arterial blood flow and whether it had an effect on calf muscle pump function. We were surprised to find that GEKO does appear to have had an effect on calf pump function in addition to increasing overall blood flow. It is increasing to see the progressively increasing effect of GEKO at each setting: being particularly effective in sitting and lying patients but requiring the highest setting for patients whilst standing. We are drafting a manuscript with a view to publication.

Appendix 5

Questions Posed to Prof Gerard Stansby via Email on 23rd of July 2013

Please find KITEC questions in black and Expert Adviser's replies in red

There has been duplex in the popliteal vein, photoplethysmography at the dorsal foot vein and strain gauge plethysmography at the mid-calf. These too would suggest an increase in blood flow.
Although I feel the comparator in that situation (the patient performing 10 dorsiflexions) may not be described fully enough.

It's really a question of whether any of this would be ever be sufficient to show a mechanism by which this device could work?
And there is still a lack of clinical trial evidence of course.

Reply (Received 23rd of July 2013)

I think it is reasonable to consider that a device that increased venous flow and prevented venous stasis would reduce VTE – and if the increases in flow were similar or better than those with intermittent compression devices it would be reassuring - but obviously a clinical trial would be required to prove it conclusively

As well as flow I think venous volume is important – in distended veins you are more likely to get stasis behind valves etc.

Appendix 6

Questions Posed to Expert Advisers via Email on 9th of August 2013

Please find KITEC's questions in black and Expert Advisers' replies in red

Our understanding is that, in order to function as VTE prophylaxis, the geko device would need to be in situ for a minimum of 24 hours, without interruptions. All clinical evidence we have found, however, involves the device being used for limited periods of time (between 5 minutes and 4 hours). Therefore, we would be interested to know if you are aware of any on-going or planned studies in which the device will remain in situ for an extended period of time (at least 8 hours)?

On a similar note, would you suspect there would be any adverse effects from prolonged use of the geko device, such as muscle fatigue or cramps?

Reply 1: Prof David Warwick (Received 10th of August 2013)

This is a very pertinent question. I am not aware of any evidence and it is something that should be considered.

Reply 2: Prof Charles McCollum (Received 12th of August 2013)

You are entirely correct: I don't know of anybody who has done studies on the GEKO device over 24 hours or longer. The study we did, using three different settings on GEKO, clearly shows augmented flow and calf muscle pump function in the highest GEKO setting which would not be tolerable by a patient for more than 2-3 hours, but which would be fine during anaesthesia. What we have not yet done is to measure these physiological measures at the optimal level (where the patient is aware that the GEKO is causing stimulation in their leg but where there is no discomfort). We would also want to repeat these studies after 24 hours use,

firstly to assess whether the subject found the GEKO comfortable over 24 hours and to see whether there is any change in venous function over the 24 hour period. Perhaps you could encourage the manufacturers (Sky Medical) to undertake this type of research and to test efficacy over 48-96 hours.

Reply 3: Dr Sameh Dimitri (Received 14th of August 2013)

In specific response to longer-term use of the device: a post-marketing surveillance programme was participated in at the Countess of Chester Hospital; it looked at patient tolerability, duration of wear, detachment of device, etc. The overall results were encouraging. The Countess of Chester Hospital was one of many hospitals across the UK that took part in this post-marketing feedback. The total number of patient questionnaires recorded countrywide were 215 (post-op vascular, post-op orthopaedic and non-surgery vascular patients). Please find some of the salient aspects below:

Results from this surveillance show that:

- 15% of patients wore the device for >20 hours in one day
- 47.0% of clinicians took less than one minute to fit the device and 34.4% took 1–5 minutes
- 85.1% of patients found the device comfortable or very comfortable to wear once applied
- In 90.7% of cases the device adhered well or very well to the leg
- 91.8% of patients reported that their quality of sleep while wearing the device was normal; 5.7% reported worse sleep and 2.5% reported better sleep.

This information is not confidential and could be provided directly from the company, if you wanted to see it. Furthermore, I believe there is a study underway where device application will be for a duration of 24 hours. Bournemouth Orthopaedics are currently running a clinical trial looking at the device on patients for a 24 hour period.

In addition, I have attached a paper from New Zealand that documents a treatment duration of 8.4 ± 3.4 hours in rugby players and an arterial ulcer case study from Australia documenting 24 hours per day use for a 3 week period.

Finally, to answer your query regarding adverse events from prolonged stimulation (e.g. fatigue or muscle cramps); there has been no evidence of this. The Geko device is licensed for 28 days use – it has been used on patients from 24 hours to 48 hours

consecutively – and also in wound healing patients up to 8 hours per day, for a duration of 4 weeks (I believe Mr Deen Jameel from Wigan was responsible for some work in this area).

Reply 4: Prof Charles McCollum (Received 19th of August 2013)

I have already suggested to SkyMedical that they should do venous volume and transit time studies (which we can do) on the GEKO at the optimal setting immediately after fitting the device, perhaps at 6 hours (later the same day) and then at 24 hours to assess both comfort and acceptability to the patient at the optimal setting and efficacy in terms in of venous transit times and leg vein volumes over time. I am waiting to hear whether they plan to commission this: I think it would be important research.

Appendix 7

Questions Posed to Expert Advisers via Email on 21st of August 2013

Please find KITEC's questions in black and Expert Advisers' replies in red

1. There are various different types of neuromuscular and muscular electrical stimulation devices described in the literature. They use various types of electrodes, which can be placed in a variety of locations on the lower limb. The type of electrical stimulation applied varies in current, frequency and pulse duration. Would it be fair to assume that prophylactic effects from one device would be similar to another?

2. Would a medical device's demonstration of increasing venous blood flow be enough for you to consider it to have a prophylactic effect on VTE?

3. Can the same efficacy be assumed for geko™ and IPC devices based on a comparison of their effects on venous blood flow alone?

4. The sponsor has used the relative risk of NMES device (Browse and Negus 1970) for geko™ in their cost model, due to lack of evidence. Is this reasonable?

Reply 1: Prof Gerard Stansby (Received 21st of August 2013)

1) Only if the device(s) produces a meaningful calf contraction each time and in all (or nearly all) patients – it is the calf contraction that is producing the beneficial effect – so if this occurs the devices would potentially have the same effect. However I suspect that not all devices will trigger the same contraction – and this may relate to positioning and thresholds

2) It would be an important finding but for most other prophylactic methods we require a trial showing clinical effectiveness in reducing VTE.

3) Not absolutely – see above – but strongly suggestive – but the demonstration needs to have been in the context in which it is used clinically in a range of patients – not just short term in normal controls.

4) Do you mean relative risk for VTE? I haven't managed to get hold of the original paper but I think the rate in the NMES group was still quite high – so my instinct is that this might not be OK to use. What other assumptions and estimates were in the model and was there a sensitivity analysis?

Reply 2: Prof Andrew Nicolaides (Received 21st of August 2013)

The answer is No for all 4 questions. Unless there is a clinical trial demonstrating a 70% reduction in DVT I will not consider that there is any evidence supporting the use of a device. The electrical stimuli used in the old studies were strong and painful. They could only be used under GA.

Reply 3: Dr John Mosley (Received 22nd of August 2013)

I agree with Gerard though a medical device that increases venous blood flow may reduce the incidence of VTE without a controlled trial it would be speculative. It should be pretty easy to undertake a trial if the device was randomly place on one leg and subsequently both were scanned.

I remember many years ago having a peripheral involvement in a trial of pneumatic compression applied to the arms that reduced the incidence of VTE in the legs. Often things are more complex than they initially appear.

Reply 4: Prof Charles McCollum (Received 22nd of August 2013)

1. No

2. Increased venous flow is a help, reducing venous transit time and venous volumes is more important.

3. No

4. No

Reply 5: Dr John Scurr (Received 28th of August 2013)

1. I do not think one can assume similar prophylactic effects from similar devices. The efficacy of the devices will vary depending on the stimulus and the position on the legs. Whilst I think it is reasonable to compare prophylactic effects using physiological parameters i.e increase blood flow etc. The ideal way of comparing these devices would be a clinical trial.

2. Yes, depending the substantial trial in due course.

3. Both geko and IPC have an effect on venous blood flow and there is good scientific evidence to suggest the effective in reducing the risk of thromboembolism. On that basis I think it is fair to assume a positive effect from geko.

4. I think this is a reasonable assumption.

Appendix 8

Questions Posed to Expert Advisers via Email on 23rd of August 2013

Please find KITEC's questions in black and Expert Advisers' replies in red

We have been asked to discuss, using your expert opinion, the extent of the effect walking/mobility has on the risk of DVT. I believe of particular interest is why mobile patient is considered a low/no risk when they are not continuously walking.
Additionally, it has been asked whether peroneal nerve stimulation could be considered as a surrogate for exercise in reducing the risk of DVT.

Reply 1: Prof Charles McCollum (Received 28th of August 2013)

There is no doubt that walking stimulates both arterial flow in the leg (and thereby venous flow) and calf muscle pump (improving venous return, reducing venous volumes and reducing venous transit times). Patients do not develop DVT whilst walking! Immobility (long journeys by coach and aeroplane particularly) are known to be risk factors for DVT. Immobility in bed for hospital inpatients are in the same category but surgery, trauma and cancer all produce hypercoagulability states that combine immobility with hypercoagulability to increase the frequency of DVT.

Appendix E: Sponsor's factual check of the assessment report and the External Assessment Centre's responses

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 1.1 page 6, line 6 Section 1.3 page 7, final line Section 1.5 page 8, line 12-21 Section 1.6 page 9, line 6 and 13 Section 1.6 page 9, 2nd Paragraph, line 3-10 Section 2.2 page 13, line 8 Section 3.10 page 82, 3rd Paragraph lines 5-9 Section 3.10 page 83, 2nd Paragraph lines 5-7 Outcomes. page 16, 3rd Paragraph Outcomes page 16, 4th Paragraph Outcomes page 17 5th Paragraph Section 4.2 page 89, Paragraph after 2nd bullet point Subgroup analysis page 98, 4th Paragraph lines 2-4. Section 4.4, page 99 line15-	The primary reason for the employment of mechanical compression devices such as IPC and FID is to increase lower limb venous blood flow, thereby preventing venous stasis, enhance pro-fibrinolytic activity and therefore creating the conditions to reduce the risk of VTE. These additional benefits of enhanced blood flow would clearly not be created if it were not for the on-going enhancement of venous blood flow that is delivered by these compression modalities. As such, the sponsor believes that the clinical hypothesis is valid in that the geko ™ device increases lower blood flow (and thereby reduces stasis) to at least the equivalent level of IPC and therefore the associated benefits of this blood flow enhancement is expected to be at least equivalent to that of IPC. Given that the sponsor believes that the reduction of stasis will reduce VTE risk it asks for the highlighted factual errors to be more reflective of the generally accepted view that stasis prophylaxis as delivered by mechanical compression will reduce VTE risk.	As written, the resulting inference is that the geko™ device, which increases blood flow as effectively as IPC, has no credible clinical attributes in respect to reducing VTE risk. In addition because this content a cited as a conclusion rather than an opinion the tone is unnecessarily negative given that the sponsor has positively positioned the technology as a potential form of stasis prophylaxis within an area of unmet need. In support of correcting this inaccuracy the sponsor cites the following as taken from the NICE clinical guidelines (CG92), pg 146 **Intermittent pneumatic compression (IPCD) devices** "…. It combats VTE through its haemodynamic effect on reducing venous stasis and by stimulating fibrinolytic activity. This fibrinolytic mechanism is involved in the dissolution of clot and prevention of thrombus formation". **Foot impulse devices (FID)** "Foot impulse devices (or foot pumps) increase venous outflow and reduce stasis in immobilized patients….The pulsatile flow produced by walking reduces the risk of thrombus formation. It is within this physiological mechanism that the foot impulse device is designed to stimulate the venous pump artificially by compressing the	The EAC has noted throughout the report that venous stasis has long been considered a risk factor for VTE. However, it is not considered the only risk factor. The EAC could not find clinical evidence to support the view that efficacy in VTE prophylaxis could be proven by demonstrating an effect on venous stasis alone. Therefore, while prevention of venous stasis is a plausible mechanism by which geko™ could have a prophylactic effect on VTE, this hypothesis has not yet been tested. The EAC's concludes that it is not possible to say whether preventing venous stasis in patients, will, on its own, have a significant effect on the occurrence of VTE. This is reflected in the current NICE clinical guidelines (CG92) cited by the sponsor, which refer to stimulation of fibrinolytic activity in addition to reducing venous stasis. This stimulation is independent of

17. The EAC suggest throughout the document that it is an assertion on the part of the sponsor (and other community stakeholders) that IPC devices work by increasing blood flow. This is not an assertion but it is a fact that IPC devices do work by increasing blood flow. Furthermore The EAC suggests throughout the report that the relationship between blood flow and stasis reduction upon VTE risk is unproven but do not substantiate this view. The sponsor believes that this is not factually accurate nor is it the view of the community or indeed NICE. In addition the EAC suggests that IPC devices work through factors other than increasing blood flow but do not substantiate this view. The sponsor believes all the associated VTE prophylactic benefits are a consequence of venous blood flow enhancement.		venous plexus and mimicking normal walking and reducing stasis in immobilized patients". Morris and Woodcock [2004] conclude: "Intermittent compression prevents DVT and prevents venous stasis. The precise way in which that stasis is prevented appears to be of much less relevance than ensuring that systems are applied properly". Virchow's Triad (Martinelli et al. [2010]). EAC experts as cited within this review which suggests the clinical hypothesis of the sponsor is "strongly suggestive" (page 89 final paragraph) and "reasonable" (page 90) both comments would appear to contradict the conclusion of the EAC. Warwick [2013] as submitted (www.bjr.boneandjoint.org.uk/content/2/9/179.full) discusses "Therefore, reliance on a venous flow surrogate is generally regarded as reasonable proof of concept" Warwick [2008] http://www.ncbi.nlm.nih.gov/pubmed/22477449 Concludes "Pulsatile impulse calf compression (A-VI) more closely mimics PFV of normal ambulation than slow-squeeze sequential compression (SCD). Pulsatile calf compression may provide superior protection against thrombosis in immobile patients".	effects on venous stasis, and occurs via a different mechanism (the production of tissue-type plasminogen activator (t-PA) by the vascular endothelium) (Christen et al 1997).

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The EAC suggest throughout the document that the sponsor suggests that the geko™ device **is as** effective as IPC. Section 1.1 Page 6, Line 10 Section 1.4 page 7, 3rd Para, 3rd line Section 1.5 Page 8, line 9 This is not the language that the sponsor used in the submission and the sponsor is concerned that this assertion on the part of the EAC has steered their approach and overriding negative conclusions.	To use the language as originally submitted by the sponsor in the context that this technology has the potential of delivering VTE prophylaxis to groups of patients who currently receive no VTE protection. Please amend to the following throughout: *The geko™ device is expected to result in a reduction in DVT that is at least equivalent to IPC*	Factually incorrect and a distortion of the original submission and the sponsor would be grateful for this correction.	The EAC agrees that. Section 1.1 Page 6, Line 10 does not accurately reflect the sponsor's opinion and has changed the report to reflect this. The other sections mentioned do reflect the sponsor's opinion, as given in the submission.

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 2. Page 13, last sentence The EAC concludes that "there is no clear indication for the use of the geko™ device".	The sponsor believes that this could be represented in a more balanced way and in doing so represent the factual opportunity as recognised by MTAC.	The sponsor believes the clinical indication is very clear. The geko offers an anti-stasis device for a group of patients (as defined within the scope) who may be at an increased risk of VTE due to	The quote given of the EAC's conclusion is not correct. This comment does appear, but it is not the EAC's conclusion, and is not presented as such. The last paragraph on page 12 states

		prolonged immobilization and where other compression modalities or means to prevent stasis or reduce VTE are contraindicated.	the EAC's conclusion: "The EAC considers this group to consist of: patients with lower limb plaster casts (if thromboprophylaxis is required and chemical prophylaxis is contraindicated; geko™ may also be contraindicated if the lower limb requires complete immobilisation), those with external fixation in place, those with peripheral vascular disease and those with localised conditions or injuries that do not impact on the geko™ application site (e.g. burns or ulcers). It is difficult to estimate how many patients this is likely to be, but the EAC believes it to be a small number." In other words, we accept that the device may be useful (although this has not been proven), but if so in only a small number of patients. The quote provided is the opinion of the Senior Medical Advisor to the national VTE prevention programme, based in part on the small number of patients not already well served by alternative forms of prophylaxis. MTAC is likely to be interested in the number of patients indicated by the scope, but as explained in the preceding paragraphs, there is difficulty in defining a number for this. In the absence of this we felt we should show them the range of opinions on what that number could be.

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 2.3 page 14 Line 10. The EAC infers that the sponsor did not submit evidence that was "representative of a typical hospital setting".	The sponsor believes that this could be represented in a more balanced way.	This is factually incorrect as further acknowledged on page 22 where Jawad data is collected from subjects likely to represent a hospital setting It ignores the fact patients in the hospital setting may indeed be positioned in a seated position for prolonged periods It ignores the fact the post-market surveillance data was submitted in contrast to this EAC statement	The EAC's statement is factually correct. The full sentence says "A further difficulty in the sponsor's evidence is that, in *some* of the studies, subjects were positioned in economy-style airline seating which is not representative of a typical hospital setting." The EAC has not stated that *all* of the studies are not representative of a hospital setting. Tucker et al. 2010 and Jawad (coagulation) 2012, state that their subjects are seated in economy-style airline seating.

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Outcome section, page 16 1st line. The EAC suggests that "Only one of these outcomes, 'venous transit time, blood flow and blood velocity', is considered in the geko™ studies included by the sponsor". Outcomes section. Page 16, 2nd Paragraph relates to the outcome as being surrogate.	Three outcomes are considered and submitted by the sponsor: venous transit times, blood flow and blood velocity. If the above is corrected this will need amending appropriately.	Factually incorrect and a misrepresentation Given that some experts (as cited by the EAC) believe that, as an example, increased blood flow is a reasonable surrogate marker from which to build a credible hypothesis around VTE risk.	In the scope venous transit time, blood flow and blood velocity are listed together as one outcome. While we agree the sponsor has submitted evidence that considers each of the three aspects listed, and have stated as much in the report, under the outcomes specified by the scope they count together as one outcome.

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Within the document the EAC suggest some issue and major assumptions in the cost model submitted by the sponsor. Please see section 1.1, page 6, 2nd paragraph final sentence	Please consider removing this inaccuracy	Factually incorrect and a distortion of the original submission. Given that this comment only relates to a small EAC amendment to the Nurse cost which has no significant impact on the conclusion of the economic submission this statement is a gross exaggeration.	This comment does not refer to the minor amendment to the nurse cost, which we accept and state has negligible impact. The sponsor considers that the use of the geko™ device is expected to result in a reduction in DVT at least equivalent to that demonstrated with IPC. However, the EAC believes that this assumption

			lacks adequate justification in the form of clinical evidence. As the subsequent economic model is based on this major assumption, the EAC considers that there are issues related to this key parameter. The EAC recognises that the sentence might be misleading as the small amendment to the nurse cost has only minor impact (around £9) on the overall savings. The EAC has revised the sentence to reflect this.

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.3, page 23, 5th bullet point final sentence. The EAC do not acknowledge the post-market surveillance data which indicates device wear over longer and more relevant periods.	To acknowledge the post-market surveillance data as relevant in this respect.	To offer a more balanced critique.	In the post-market surveillance data submitted, no indication is provided of how long the device had been worn. Therefore, the EAC was unable to consider the data in this context.

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.4, page 42, 6th bullet point.	The submitted evidence did contain studies conducted with the geko™ device. The sponsor	Inaccurate and not reflective of the sponsor's submission	The EAC agrees that the statement it has made is incorrect. Some of the studies did indeed use the geko™

The EAC states that "Each study used the gekoTM device with differing currents, frequencies and pulses. For example, in Tucker et al (2010), both the amplitude and frequency of the electric stimulation was varied according to 15 predetermined programs. None of these programs matched those available with gekoTM as described in the sponsor's submission.	suggests removal of this paragraph.		device on settings that match those detailed in the submission. The EAC has amended the report to reflect this more accurately.

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.4, page 43, 9th bullet point. The EAC state... "The EAC considers that the population defined in the scope would include subjects with conditions that may impair the effectiveness of geko™ device, (for example, oedema, chemical or physical muscle paralysis, venous insufficiency and adipose tissue insulating the stimulation area)"	This sponsor made note of this potential exclusions within the clinical submission and as such this reference is not valid and should be removed.	Inaccurate and not reflective of the sponsor's submission	The EAC is required by NICE to compare the population included in the evidence with the expected patient population stated in the scope.

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.4, page 43, 11th bullet point. The EAC states…" However, in the submitted evidence, the longest period of time for which the device was continuously active was 30 minutes. The longest study period in the supplied evidence was four hours, but the device was only active for five minute intervals in that study".	This ignores the post-market surveillance data which show device wear for longer periods and the sponsor request that this is acknowledged.	To reflect more accurately the facts of the sponsor's submission.	As stated above under issue 7, the sponsor provided no data on how long the device had been worn for the post-market surveillance. Therefore the EAC could not include the post-market surveillance evidence in considering duration of usage.

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.6, page 47, final paragraph The EAC states..."The EAC considers that the use of a plaster cast as a comparator in the Warwick et al (2013) study and the use of cardiac outcomes in Jawad (cardiac) (2012) do not fit within the scope".	This is incorrect - the plaster cast is not a comparator (i.e. application of a plaster cast is not for the prevention of VTE). Therefore this paper should not have been excluded as patients with a plaster cast were within the scope	To reflect more accurately the facts of the sponsor's submission.	The EAC's comment in the original report is not very clearly expressed. The EAC believes that this study is not valid as a means of establishing the effects of geko on blood flow, because measurements at baseline and with geko in place were not taken under comparable conditions. The baseline measurement was taken after 30mins supine rest, but the measurements made with the geko™ device active were

			made shortly after the subject had moved and used the legs to bear their weight. This makes blood flow comparison to the baseline invalid, as the weight bearing would have increased the blood flow. Therefore, this study cannot be used to show that geko™ affects blood flow. However, the study does show that geko™ can be used with a plaster cast in place. Although, not specified in the scope, the EAC thought this was a relevant point as patients with plaster casts could form part of the population under consideration. The EAC has altered the comment to reflect this.

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.9. Page 81, 3rd line. The EAC states..."whether the 1Hz frequency of geko™ device would lead to this effect within the expected treatment period, if it does, this may affect the patient's rehabilitation".	The sponsor believes this is an unnecessary negative extension, until proven, of a valid point which creates an inaccurate perception. It would be more reasonable to conclude that "it may or may not affect the patient's rehabilitation" or indeed remove it completely.	Unproven extension. The sponsor's submission attempts to position a prophylactic solution to for an unmet need and this should be viewed in this way.	This was an opinion received from the nominated expert replies. It does state that it is "not known whether the 1Hz frequency of geko™ would lead to this effect" and it does not seem that any undue weight has been given to this point.

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.9 Page 83, 2nd line. The EAC states … "The geko™ device is being considered by MTAC because it is a device using an innovative method of applying the electrical stimulation".	The geko ™ device It is being considered by MTAC as a means to prevent stasis in patients who are contraindicated for other forms of mechanical VTE prophylaxis.	To reflect more accurately the facts of the sponsor's submission.	MTEP considers innovative devices. This statement is to explain why geko™ is different to previous NMES devices and therefore should be considered by MTAC. This is an additional reason to considering its effect on VTE.

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 4.2, Page 91 1st Paragraph, The EAC states…"Given these weakness in the major clinical parameter used in the cost model and with the assumptions being confirmed as not appropriate by most of the NICE expert advisors, it falls short of credibility as a basis for estimating the cost of the geko™ device"	As stated the sponsor believes that the assertion made by the EAC is not accurate and the sponsor's view is supported by the reasons for IPC use as cited in CG92 guidelines As cited the sponsor believes the anti-stasis comparison is a valid clinical hypothesis. As cited, some but not all of the EAC experts agree with the sponsor's clinical assumptions and therefore by association they would concur with the health economic model as presented, a model that the EAC found to be robust in every other respect.	The sponsor strongly believes that the hypothesis that drives the economic model is valid and as such it is credible. The sponsor rejects the assertion that expert opinion obtained gives any unanimous foundation for the EAC's conclusion.	As highlighted above in issue 6, the EAC believes the hypothesis that drives the economic model is not valid as it lacks suitable clinical justification. The EAC believes it has reflected fairly the opinions of the nominated experts (who are not EAC experts, but independent expert advisers to NICE). The EAC's conclusions agree with the majority of replies. The sentence quoted by the sponsor from the EAC's report shows that the EAC indicated that opinion was not unanimous.

Issue 15

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 92. **Technology and comparators' costs** The cost of the technology (geko™ device) is £22 per pair exclusive of VAT. The cost per	The cost of the technology (geko™ device) is £22 per pair exclusive of VAT. The cost per course of six days prophylaxis is £132. Please highlight as above.	The cost of geko™ device is commercially confidential and should be highlighted as such, similarly any figures reported which would allow for its estimation should also be highlighted accordingly	The EAC has amended this point to reflect the proposed amendment, but has highlighted in turquoise as this is commercial confidential rather than academic confidential.

course of six days prophylaxis is £132. This is based on the information from the company and is therefore reasonable for inclusion in the model. Further, the administration time for gekoTM by a nurse is estimated to be around 1.5 minutes per day. The cost per administration is £1.02 and for a course of six days is £6.15. This is based on an hourly cost of £41 for a ward nurse (Curtis, 2012). However, the EAC does not agree with this cost estimate of £41, since it does not refer to the cost of patient contact. The unit cost of £100 (Curtis, 2012) should have been used to estimate administration time, which now works out to be £2.50.			

Issue 16.

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The EAC make strong and understandable reference to expert opinion from which they suggest universal opinions which then drive the EAC conclusions: 3.10, page 82 paragraph 3. The EAC states..."The EAC considers	The sponsor would like to highlight that opinion was often not unanimous and suggests that opinion, rather than conclusive, was mixed. This is not reflected throughout the EAC report and the sponsor is concerned that this mixed expert opinion is not reflected in a fair and balanced way and the conclusions are	To ensure that any conclusions reflect expert opinion more factually as the sponsor rejects the assertion that expert opinion obtained gives any unanimous foundation for the EAC's conclusion. In addition the sponsor would like to	The EAC believes it has reflected the opinions of the nominated experts fairly. Any inconsistencies reflect the responses given by experts to the various questions posed The EAC's conclusions agree with the majority of replies, and the EAC has

the outcome of venous blood flow to be a surrogate for that of preventing VTE, and note the conclusions of a review on the use of surrogate comparisons (Ciani et al [2013]). This study demonstrated that when compared with equivalent trials that have used true clinical endpoints, surrogates give over-optimistic results, as they are more likely to report larger treatment effects. The EAC therefore suggests that the sponsors argument that 'the enhanced blood flow observed during the treatment with the geko™ device is expected to equate to a reduction in the incidence of VTE' may not be justified based on the available evidence. **Consultation with the nominated experts agreed with this".** Furthermore in Section 4.6 page 101 the EAC states that… "**Experts also confirm** that same efficacy for geko™ device and IPC devices cannot be assumed, based on a comparison of their effects on venous blood flow alone".	misrepresented. As such the sponsor requests amendment as appropriate to both the clinical and economic conclusions as outlined. .	cite all the justification outlined in Issue 1 above to substantiate this key point. In addition inconsistencies to the EAC conclusions are highlighted: The sponsor cites Page 60-61 "The EAC asked the nominated experts for their opinion on the validity of assuming the same efficacy in VTE prophylaxis for geko™ device as that for IPC devices, based on comparison of their effects on venous blood flow alone. Five experts replied, four were strongly of the view that this assumption is not valid, but **one felt that the assumption was fair".** Page 89 where the EAC states "The sponsor uses clinical evidence to infer that if geko™ device improves venous flow by the same amount as IPC, it can be assumed to have the same efficacy as IPC in preventing VTE. The EAC believes that this is not a valid assumption. This is due to the fact that although IPC devices have been shown clinically to reduce the incidence of VTE, they have also been shown to have additional prophylactic effects (Dai et al [1999]) independent of increasing venous blood flow. **Two of the nominated experts**	indicated when opinion was not unanimous.

		expressed the opinion that venous volume and venous distension factors may play important roles. It is not known which of these effects, or combination of effects, has the greatest impact on VTE prophylaxis (Dai et al [1999] and Morris & Woodcock [2004])". Page 90 where the EAC states "The EAC sought the opinion of NICE experts on the validity of the assumption. The responses received from four NICE experts indicated that it was not appropriate to assume the same efficacy for gekoTM and IPC devices based on a comparison of their effects on venous blood flow alone, **although it was strongly suggestiv**e. However, one expert (who was an expert advisor to the sponsor for the development of the cost model) was of the opinion that it might be **reasonable to make this assumption".** Page 79 where the EAC states "The EAC requested the opinions of the nominated expert advisors, as to whether the mild dorsal flexion and increased venous blood flow, created by geko ™ device, could be expected to translate throughout the	

		lower limb and prevent VTE. Five replies were received which are summarised below: **Two respondents did not claim first-hand experience with geko™ device, but felt that if geko™ device increased venous flow sufficiently, then there would be a rationale to expect that it might prevent VTE.**	

Reference

Christen Y, Wütschert R, Weimer D, de Moerloose P, Kruithof EK, Bounameaux H. (1997). Effects of intermittent pneumatic compression on venous haemodynamics and fibrinolytic activity. Blood Coagul Fibrinolysis. 8(3):185-90.