KING'S College LONDON

Assessment Report

The geko™ electro-stimulation device for venous thromboembolism prophylaxis

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Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

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Abbreviations

CE	Conformité Européenne
CI	Confidence Interval
CT	Computed Tomography
DVT	Deep Vein Thrombosis
EAC	External Assessment Centre
FID	Foot Impulse Device
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
ICU	Intensive Care Unit
IPC	Intermittent Pneumatic Compression
IQR	Inter Quartile Range
KITEC	King's Imaging Technology Evaluation Centre
LMWH	Low Molecular Weight Heparin
MEST	Muscular Electrical Stimulation
NA	Not Applicable
NCU	Normal Clinical Use
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMES	Neuromuscular Electrical Stimulation
PE	Pulmonary Embolism
PPG	Photoplethysmography
PSSRU	Personal Social Services Research Unit
PTS	Post-Thrombotic Syndrome
RCT	Randomised Controlled Trial
RR	Relative Risk
SD	Standard Deviation
SR	Systematic Review

SPG	Strain Gauge Plethysmography
TED	Thromboembolism Deterrent
TS	Threshold Setting
UK	United Kingdom
USA	United States of America
VAS	Visual Analogue Scale
VTE	Venous Thromboembolism

1 Summary

1.1 Scope of the sponsor's submission

The sponsor has submitted clinical and economic evidence in support of the use of the geko™ device for VTE prophylaxis. The sponsor included evidence relating to the efficacy of other forms of mechanical prophylaxis (NMES/MEST and IPC) which is claimed to demonstrate a relationship between increased blood flow and VTE prophylaxis. This was included in the absence of any current clinical evidence relating directly to the geko™ device and VTE prophylaxis. The sponsor's evidence centres on the assertion that IPC devices work by increasing venous blood flow, therefore reducing VTE incidence. The sponsor claims that the effect of the geko™ device in terms of increasing blood flow has been compared to that of IPC devices in trials submitted in evidence, and that the geko™ device is at least as effective as IPC, therefore concluding that the geko™ will reduce VTE incidence.

The cost analysis has assessed the impact of the technology (geko™ device) and comparator (no mechanical prophylaxis) in the patient population. This matches with the cost analysis specified in the final scope. The modeling structure is appropriate along with most of the parameters, although there are issues related to one major assumption used in the cost model.

1.2 Summary of clinical evidence submitted by the sponsor

The sponsor has submitted all the available evidence related to geko™, including internal post-market surveillance and an interim report. Seven studies related directly to the use of the geko™ device. Of these, all were descriptive studies, a combination of published and unpublished manuscripts, and all recruited only healthy volunteers. Three of these studies were considered by the EAC as providing a suitable comparator as defined in the final scope (no mechanical prophylaxis); Jawad (coagulation) (2012), Jawad et al (vs. IPC) (2012) and Williams et al (unpublished) (2013). Outcome measurements varied substantially between the geko™ studies and so no meta-analysis or synthesis was conducted by the sponsor or the EAC. The sponsor also provided several studies using NMES and IPC devices as clinical evidence, several of which included a suitable comparator as defined in the scope.

1.3 Summary critique of clinical evidence submitted by the sponsor

The EAC considers that the sponsor has submitted all of the evidence related to the geko™ device. However, in all the geko™ studies submitted as clinical evidence, blood flow and velocity were the only two outcome measures documented that are within the scope. The EAC concludes that there are two reasons for this. Firstly, there is currently limited clinical evidence regarding the geko™ device, so that the sponsor has included NMES/MEST and IPC studies to support a link between increased blood flow and VTE prophylaxis. Secondly, the sponsor failed to include certain outcome terms in their systematic review. The EAC conducted its own systematic review to address this. Whilst the EAC did identify additional relevant NMES/MEST and IPC studies, they did not add to or alter the EAC's opinion that there is currently little direct clinical evidence that geko™ prevents VTE, and that such evidence as there is depends on an unproven relationship between blood flow measurements and VTE risk.

1.4 Summary of economic evidence submitted by the sponsor

The sponsor conducted a systematic review to retrieve relevant health economics studies from published and unpublished literature related to geko™ and NMES/MEST devices. Based on the review, the sponsor did not find any economic evidence and concluded that none is available for either geko™ or NMES/MEST devices. In the absence of published economic evidence, the sponsor has submitted a de novo cost model.

The patient group considered in the cost model is patients for whom current mechanical methods of prophylaxis are impractical or contraindicated. The sponsor submitted a decision tree model, an amended version of that used in NICE venous thromboembolism (VTE) guidelines, from the NHS and personal social services perspective. The technology (geko™) and comparator (no mechanical prophylaxis) are as specified in the scope.

The model, and all subsequent estimated cost impacts relating to geko™ and the comparator, is built on the assumption that patients who have an underlying risk of DVT and who are subsequently administered the geko™ device will experience a reduction in their baseline risk of DVT. Subsequently, a proportion of them may have

pulmonary embolism, asymptomatic or symptomatic DVT. A proportion of patients are also assumed to experience post-thrombotic syndrome (PTS), a permanent comorbidity which can generate lifetime costs. Cost estimates were based on the NICE VTE guidelines, NHS reference costs, annual Personal Social Services Research Unit cost compendium and literature.

The results of the base case analysis and the sensitivity analysis show that geko™ is a cost saving option compared to no prophylaxis.

Sub group analysis was performed on an option that combines pharmacological prophylaxis with geko™ and an option involving the use of pharmacological prophylaxis alone. The results showed that geko™ in combination with pharmacological prophylaxis (for six days of prophylaxis) was not a cost saving option with an incremental cost of £69 over and above the use of pharmacological prophylaxis alone. The geko™ device in combination with pharmacological prophylaxis is cost saving only for the first two days of combined prophylaxis and cost neutral if used for three days. Additional sub group analysis on stroke patients was also performed and the results showed that the geko™ device would result in savings of £146 per patient compared to no prophylaxis.

1.5 Summary critique of economic evidence submitted by the sponsor

The EAC believes that the systematic review could include the HTA database (this is excluded from the sponsor's search strategy). Regarding the sponsor's cost model, it is the view of the EAC that, while the overall structure of the economic model provides a sound representation of the clinical pathways of relevance for estimating the cost implications of geko™, the core modeling assumption that geko™ will reduce the risk of DVT within the relevant patient population, and the estimated cost savings that follow from this, is unreliable. The sponsor builds the case for geko™ based on the hypothesis that the relative risk reduction in DVT obtained with the geko™ device would be at least equivalent to that achieved with IPC. This assumed equivalence of IPC and geko™ is based on a comparison of their effect on venous blood flow. The geko™ device is assigned a relative risk value appropriate for other NMES/MEST devices, which falls within the range of values for IPC devices. However, the EAC is of the view that this does not provide a robust basis for assuming that geko™ is an

effective prophylaxis, given that the effect of IPC on the risk of DVT includes other factors either independently of, or in combination with, improvements in blood flow. This conclusion has been confirmed by the nominated experts. Evidence in the literature that IPC devices reduce DVT incidence only via effects on blood flow is poor or non-existent. The EAC believes that new evidence needs to be generated for geko™ with respect to its impact on the risk of DVT within the patient population, and where there is evidence of an impact this could then be applied in the submitted cost model.

With the submitted cost model, the EAC does not agree with a cost parameter for nurse time. The EAC feels that a rate of £100 per hour for nurse time should have been used instead of £41. Although a re-estimation was done by the EAC for completeness, the EAC feels that it does not add value to the economic evidence since the major assumption on which the cost model is built is not reliable.

1.6 External Assessment Centre commentary on the robustness of evidence submitted by the sponsor

The clinical evidence provided by the sponsor relating directly to the geko™ device was a combination of both published and unpublished evidence. All studies relating to NMES and IPC devices were published evidence. The large variation of design methodologies in all these studies meant that it was not possible to synthesize the evidence. Furthermore, the sponsor's evidence centres on the assertion that IPC devices work by increasing blood flow, thereby reducing incidence of DVT. However, the EAC concludes that the evidence provided by the sponsor does not support this assertion, given the conflicting evidence regarding IPC devices and related changes in blood flow. There is also uncertainty about the impact of increasing blood flow on VTE prophylaxis. Expert advice was received by the EAC to the effect that evidence demonstrating that a device increases venous blood flow is relevant, but not sufficient to conclude that it can prevent VTE. Therefore, it is the EAC's opinion that the clinical evidence provided by the sponsor is not robust.

The systematic review and the cost model structure along with key model parameters are robust. The base case analysis and sensitivity analysis have been well performed. However, the major assumption regarding the relative risk of DVT for geko™ compared to no prophylaxis used in the cost model is not robust. It is based on a

NMES/MEST device, which falls within in the relative risk range for IPC devices. Assuming equivalence based on blood flow is a weak assumption; a conclusion supported by expert opinion and literature. It is the view of the EAC that new clinical evidence for the impact of geko™ on the relative risk of DVT needs to be generated, and where there is evidence of an effect, this could then be applied in the submitted cost model.

1.7 Summary of any additional work carried out by the External Assessment Centre

The sponsor failed to include certain outcome measures in its systematic review. Furthermore, the sponsor excluded studies that used a pharmacological intervention, which the EAC considers inappropriate given that patients receiving pharmacological prophylaxis are listed as a subgroup in the scope. Therefore, the EAC conducted a further systematic review, using all outcome terms listed in the scope, including studies with a pharmacological intervention. A total of thirty-eight studies were identified for full-paper review, some of which were already identified by the sponsor. Of these, the EAC accepted five studies as providing clinical evidence relevant to the scope (Broderick et al [2011a], Broderick et al [2010a], Broderick et al [2010b], Katz et al [1987] and Lindstrom et al [1982]). Evidence synthesis and meta-analysis of the available evidence was not conducted by either the sponsor or the EAC given the heterogeneity of the available studies (across all devices: geko™, NMES and/or IPC).

The EAC additionally searched the HTA database using the search strategy provided by the sponsor and did not find any additional economic evidence, confirming the conclusions that no economic evidence is available for geko™ or other NMES/MEST devices.

For completeness, the EAC re-estimated the cost savings of geko™ in the base case analysis with a cost of £100 per hour instead of £41 for nurse time. This resulted in a change in cost savings of geko™ from £206 to £197.

2 Background

2.1 Overview and critique of sponsor's description of clinical context

The geko™ device is a single-use, electrostimulation device that is intended to reduce the risk of venous thromboembolism (VTE). The sponsor describes the clinical context for the device in Section 3 of the submission, beginning with a description of VTE. The EAC is in agreement with the majority of the sponsor's comments, but there are some points on which the EAC's view differs from that of the sponsor:

- In the description of VTE, complications arising from clots travelling to the brain and heart have been included. Infarction is a complication associated with arterial and not venous thrombosis (Previtali et al [2011]), so only pulmonary embolism is of concern in this context.

- The description of morbidity associated with non-fatal VTE uses treatment costs from the USA, which may differ from those in the UK.

The submission continues, on page 14, by describing current methods of thromboprophylaxis, which are divided into pharmacological and mechanical forms. Currently NICE Clinical Guideline 92 recommends three forms of mechanical prophylaxis for VTE; antiembolism stockings, foot impulse devices and intermittent pneumatic compression (IPC) devices. The sponsor describes geko™ as a mechanical form of prophylaxis intended for patients who are contraindicated for the other recommended forms of mechanical prophylaxis.

As stated in the sponsor's submission, there are other Muscular Electrical Stimulation (MEST) and Neuromuscular Electrical Stimulation (NMES) devices that have been shown to be effective in reducing the incidence of VTE. These devices were considered for inclusion in the previous NICE clinical guideline (CG46). The high level of discomfort associated with some of these devices, usually restricting their use to anaesthetised patients, is thought to have excluded them from CG46 and also from the current version of this guidance (CG92).

Other NMES and MEST devices use transcutaneous stimulation, usually applied in the vicinity of the muscles to be stimulated (Table 3.3 provides further details for the specific studies concerned) rather than the more indirect application of geko™ at a

point higher on the neural pathway. It is this unique stimulation pathway[1] that makes geko™ innovative and potentially less discomforting to patients than previous NMES/MEST devices. However, the EAC notes that the pathway introduces an additional uncertainty, as the type of muscle contractions caused by geko™ will need to be shown to be effective in reducing the incidence of DVT. The expert opinions that the EAC has received agrees with this. Some types of NMES/MEST devices have been found to be ineffective in preventing VTE in the past (Moloney et al [1972]), so the clinical evidence cannot be assumed to be applicable to all NMES/MEST devices.

The sponsor quotes HES data showing there were 9.5 million admissions for surgical procedures in 2011 (sponsor submission page 15). The EAC notes that the numbers of surgical admissions includes 5.6 million day cases that would be considered low risk and are unlikely to be prescribed mechanical VTE prophylaxis other than anti-embolism stockings. The remaining 3.9 million would normally (as per standard clinical practice) have their risk of VTE assessed and be provided with prophylaxis if considered to be at risk.

NICE Clinical Guideline 92 recommends that surgical patients receive both forms of prophylaxis, but that pharmacological prophylaxis will be contraindicated if there is a high risk of bleeding. The guideline also recommends that general medical patients are only given mechanical VTE prophylaxis if pharmacological prophylaxis is contraindicated.

geko™ is intended as an option for patients who have been assessed as requiring mechanical prophylaxis, but for whom all the current recommended forms are contraindicated. 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. The EAC team contributing to this report includes the Senior Medical Advisor to the national VTE prevention programme. In his opinion, in the absence of patient outcome data, and given the proportion of the population for whom thromboprophylactic methods

[1] FirstKind (sponsor) have stated that the stimulation pathway used is covered by patent.

currently available in the UK are suitable, there is no clear clinical indication for the use of the geko™ device.

2.2 Overview of sponsor's description of on-going studies

The sponsor lists eight on-going trials, which are expected to be completed by July 2014. These studies are all based in the UK. Seven of these studies use a patient population. Patient studies will be a valuable addition to the evidence in this submission, which is solely based on studies involving healthy volunteers. One of the seven patient studies, aiming to recruit 40 patients, will use incidence of DVT as an outcome. This is the first time that impact on the relevant clinical condition is being studied directly, rather than relying on the assumption that prevention of venous stasis leads to the prevention of DVT. The remaining studies will use a measure of blood flow as the outcome.

Overall, the EAC believes that while on-going studies will contribute to the evidence, additional clinical studies, preferably including randomised controlled trials with DVT or VTE as an outcome, would be a better way of building a strong case for the clinical efficacy of geko™.

2.3 Critique of sponsor's definition of the decision problem

Population

The population is defined in the scope as:

> *'People at risk of VTE and for whom current methods of prophylaxis are impractical or contraindicated. The device is most likely to be initiated in a hospital setting'*

The sponsor has estimated that between 95,000 and 475,000 patients per year would be eligible for treatment with geko™. This is based on 2011-2012 HES data that the sponsor reports as returning 9.5 million hospital admissions for surgical procedures. In the absence of further data, the sponsor has estimated that 1% of patients would be

contraindicated to all current methods of prophylaxis and 5% would be contraindicated to current forms of mechanical prophylaxis.

In contrast to this, the evidence submitted by the sponsor consists entirely of studies that recruited healthy volunteers, aged 18-65 years. Subjects with a known risk factor for VTE were excluded. The EAC considers that the population included in these studies differs substantially from the population defined in the scope. Specifically, subjects with conditions that may impair the effectiveness of geko™ (such as oedema, chemical or physical muscle paralysis, venous insufficiency and adipose tissue insulating the stimulation area) are included within the scope but excluded in the sponsor's evidence. 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. Moreover, this position has been shown to influence both blood flow and incidence of VTE.

Intervention

The technology described in the sponsor's submission relates to the geko™ device. In most of the studies submitted as evidence, the geko™ device was used as described in the scope. The sponsor also provides clinical evidence on other technologies (NMES and IPC) in relation to outcome measurements not captured in the geko™ studies.

The geko™ device received a CE mark as a Class IIa medical device in October 2010, to increase blood circulation and for the prevention of venous thrombosis. This CE mark was extended in 2012 to include preventing and treating oedema, promoting wound healing and treating venous insufficiency and ischemia.

Comparator(s)

The comparator listed in the scope is 'no mechanical prophylaxis'. The interventions and comparators for studies included in the submission are summarised in table 2.1 below.

Table 2.1: Summary of study design, interventions and comparator for sponsor included clinical evidence.

Reference (sponsor reference)	Technology/ Intervention	Comparator
Tucker et al (2010) (45)	geko™	Baseline measure and dorsiflexions.
Jawad (cardiac) (2012) (62)	geko™	No mechanical device at baseline measure.
Jawad (coagulation) (2012) (62)	geko™	No mechanical device.
Williams et al (published) (2013) (60)	geko™	Baseline measure and IPC.
Jawad et al (vs IPC) 2012 (63)	geko™	Baseline measure and IPC.
Warwick et al (2013) (64)	geko™	Plaster cast and patient positions
Williams et al (unpublished) (2013) (61)	*	[redacted]
Corley et al (2012) (35)	NMES	No mechanical device.
Czyrny et al (2010) (38)	NMES	IPC
Faghri et al (1997) (13)	NMES	IPC
Lindstrom et al (1982) (24)	NMES	Pharmacological prophylaxis or no mechanical device.
Rosenberg et al (1975) (42)	NMES	Pharmacological prophylaxis or no mechanical device.
Velmahos et al (2005) (46)	MEST	No mechanical device.
Broderick et al (2013) (21)	NMES	No mechanical device in contralateral leg.
Broderick et al (2011b) (49)	NMES	Contralateral leg.
Browse & Negus (1970) (23)	NMES	No mechanical device in contralateral leg.
Griffin et al (2010) (22)	NMES	No mechanical device at baseline measure.
Izumi et al (2010) (39)	NMES	IPC, electrical muscle stimulation, and patient's movements in variety of positions.
Kaplan et al (2002) (20)	NMES	No mechanical device in contralateral leg.
Nicolaides et al (1972) (74)	NMES	No mechanical device.
Nicolaides et al (1983) (37)	IPC and NMES	Pharmacological prophylaxis
Pitto et al (2004) (47)	IPC	Pharmacological prophylaxis
Santori et al (1994) (43)	FID	Pharmacological prophylaxis
Sobieraj-Teague et al (2012) (44)	IPC	Standard VTE prophylaxis care
Warwick et al (2002) (48)	FID	Pharmacological prophylaxis
Kurtoglu et al (2005) (40)	IPC	No mechanical device.
Pitto et al (2008) (41)	IPC	Stockings and no mechanical device.

NMES: Neuromuscular electrical stimulation
MEST: Muscular electrostimulation
FID: Foot Impulse Device

The EAC notes that there are two situations to consider with regard to the interpretation of the comparator defined in the scope. Firstly, if the study outcome is a clinical endpoint, such as VTE, then the comparator corresponds to 'usual care/do nothing'. This is applicable to the NMES and IPC studies. However, a different situation arises when the study outcome is a measured physiological parameter such as blood flow and/or blood velocity, when it is critical that the measurements are made

in the same way in all study groups. This is relevant when assessing the geko™ studies, as they do not include the outcome measure of VTE. A full evaluation of the comparators used in the above studies is in section 3 of this report.

Outcomes

There are seven outcomes listed in the scope. Only one of these outcomes, 'venous transit time, blood flow and blood velocity', is considered in the geko™ studies included by the sponsor.

This outcome is a surrogate, in terms of the claimed clinical benefit of the device, i.e. prevention of VTE. Its relevance relies very much on how strongly blood velocity changes are correlated with VTE risk. The sponsor also included several NMES and IPC studies as part of their clinical evidence, to show an association between blood flow and DVT, but did not draw a conclusion as to the strength of this relationship.

The EAC notes that the location where venous stasis occurs is important. The literature highlights the valve cusps and soleal sinuses as areas with a higher probability of thrombosis (Nicolaides et al [1971]). The increased blood flow demonstrated in the evidence is not measured at these sites. There is therefore a tacit assumption in the submission that an increase in flow measured at one location translates to adequate increases in other parts of the venous system where VTE risk is greater. Expert opinion on this point is summarised in Section 3.9.

The submission considers other forms of mechanical prophylaxis, which have been shown clinically to reduce the incidence of VTE and have also been shown to increase blood flow. The sponsor's conclusion is that, by implication, geko™ will reduce the incidence of VTE. The EAC is not convinced that this inference is sound. The EAC provides a more detailed discussion of these issues in section 3.

A further note of caution is provided in a clinical comparison of five different IPC devices (Proctor et al [2001]). This study found that the IPC devices that were the least effective in preventing DVT were the ones that caused the largest increases in blood velocity. The EAC acknowledges that this single finding is not conclusive, but notes that this study highlights the difficulties in assuming that an increase in venous blood flow leads to a reduction in risk of VTE. A low rate of blood flow (venous stasis)

has long been considered one of three main risk factors for thrombosis, as defined in Virchow's Triad (Martinelli et al. [2010]). But there appears to be insufficient evidence to conclude that thrombosis cannot occur in the absence of stasis (Morris and Woodcock [2004]). IPC devices have other effects, such as changes to venous volume that can reduce the shear stresses on the vessel walls and prevent damage to the endothelial linings, another part of Virchow's Triad. Because of this, it cannot be assumed that increasing the blood flow alone is sufficient to prevent VTE. This position was echoed in expert advice received by the EAC.

The EAC believes that, in order to investigate patient compliance, possible adverse effects and complications, such as muscle fatigue and impact on sleep patterns, it is necessary to conduct trials in which geko^{TM} is used over a similar time period and with the same duty cycle anticipated in clinical practice.

On page 85 of the submission, the sponsor has included post-market surveillance data consisting of 215 responses to questionnaires *'assessing post-wear feedback on the ergonomics and comfort of the geko^{TM}'*. The results show that in a majority of the cases the application, operation and comfort of the device were described in positive terms. The subject group is described as "mainly post-operative vascular, post-operative orthopaedic (and) non-surgery vascular".

One of the expert advisors was able to comment further on the results and stated 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'*

The sponsor did not include outcome terms in the systematic review; therefore the EAC conducted a revised systematic review (described in section 3).

Cost analysis

The cost analysis has assessed the impact of the technology (geko™ device) and comparator (no mechanical prophylaxis) in the patient population, as specified in the scope. The EAC concludes that the sponsor has appropriately included the technology and comparator with regards to the cost analysis. The time horizon for the analysis is also sufficient to reflect differences in costs and consequences between the technology and comparator. This matches with the cost analysis specified in the final scope, although there are issues related to some of the major assumptions used in the model.

Subgroups

The scope refers to two subgroups; 'those in whom pharmacological prophylaxis is contraindicated' and 'those in whom pharmacological prophylaxis is indicated and prescribed'. All of the evidence supplied relates to healthy volunteers, so neither of the two subgroups is represented. Furthermore, pharmacological prophylaxis was an exclusion term in the literature review, so it is to be expected that the subgroups are excluded.

Special considerations, including issues related to equality

The sponsor has declared that the device may not be suitable for those with:

- Fragile skin, burns, and skin conditions within the area of application.
- An inaccessible common peroneal nerve or device application site.
- Impaired function of the common peroneal nerve.

Representatives of the sponsor stated to the EAC that bariatric patients may fall into the inaccessible common peroneal nerve category, as adipose tissue may insulate the nerve from the device.

3 Clinical evidence

3.1 Critique of the sponsor's search strategy

The search strategy provided by the sponsor for geko™ was divided into three sections. The first search strategy relates specifically to studies that used the geko™ device. The second and third search strategies related to data on non-pharmacological comparators (neuromuscular electrostimulation [NMES] and intermittent pneumatic compression [IPC]). The sponsor states that the studies using NMES and IPC devices were included 'as evidence on the association between increased blood flow and a reduction in DVT'. The EAC considers that all three search strategies are to be regarded as clinical evidence.

The sponsor's search identified 31 published papers of which 21 were considered relevant by the sponsor. Of these 21 papers, one related to geko™ (non-RCT[2]), 13 related to NMES (7 RCT, 6 non-RCT), and 7 related to IPC (5 RCT, 2 non-RCT). The sponsor conducted a search for unpublished studies (within the sponsors own database) of the geko™ device: of which three were identified (all were non-RCT). Furthermore, a search for unpublished studies related to NMES and IPC was not conducted by the sponsor.

The EAC replicated the sponsor's search strategy and considers that it was lacking important search terminology. The EAC therefore conducted a revised systematic review with additional search terms related to outcomes (see section 3.8) as defined in the scope. Furthermore, the EAC's systematic review removed the two exclusions listed in the sponsor's search strategy.

The EAC notes that there were discrepancies in the description of the sponsor's systematic review methodology. Clarification was sought from the sponsor (dated 29th July 2013). The sponsor responded that table 6 of the submission refers to geko™ devices exclusively, and table 7 refers to other forms of mechanical prophylaxis. The sponsor's search, although performed to address three different questions as described above, was conducted as a single entity, hence the single flow diagram. The sponsor also corrected a discrepancy between tables 6 and 7 and corresponding tables in appendix 9.1.6, as 'included population' should read 'DVT' and not 'VTE'.

[2] RCT: randomized controlled trial

3.2 Critique of the sponsor's study selection

The sponsor's selection criteria (table 6 of the sponsor's submission) excluded two interventions. The first exclusion was: 'non-mechanical prophylaxis devices such as compression stockings'. The EAC considers that this is inappropriate because compression stockings are mechanical. The sponsor's submission does not detail further what is considered 'non-mechanical'. The sponsor responded to this query (29th July 2013):

> *'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[3]'*

The sponsor also stated in their response that the exclusion criteria as listed in table 6 of their submission should state 'anti-embolic stockings' and not 'non-mechanical prophylaxis devices such as compression stockings'. However, in keeping with the comparator group 'non-mechanical methods' as listed in the final scope, the EAC disagrees and has therefore included 'anti-embolic stockings' in the systematic review described later (section 3.8).

The second excluded intervention listed in the sponsor's search strategy referred to: 'pharmacological interventions such as LMWH[4]'. However, one of the comparator groups listed in the final scope listed 'those in whom pharmacological prophylaxis is indicated and prescribed'. The sponsor later clarified this (29th July 2013):

> *'Pharmacological agents are non-mechanical and were also excluded'*

The EAC considers that studies comparing pharmacological with mechanical prophylaxis provides useful evidence (as per the revised search criteria in section 3.8). However, the EAC does agree with the sponsor's decision to exclude studies that assess pharmacological prophylaxis alone (as per the sponsor excluded studies [appendix 3.1]).

The sponsor identifies that the Williams unpublished (2013) study is based on data presented in the published poster by Williams (2013) and that Jawad (cardiac) (2012)

[3] SR: systematic review
[4] LMWH: low molecular weight heparin

and Jawad (coagulation) (2012) are both chapters of the same thesis by Jawad (2012). The EAC notes that the unpublished study identified by the sponsor, Jawad (vs. IPC) (2012), is based on another chapter of the same thesis by Jawad.

3.3 Included and excluded studies

Table 3.1 provides a summary of all published (geko™, NMES and IPC) and unpublished (geko™) studies, with their key findings. Appendix 3.1 provides a summary of all ten excluded studies (the sponsor did not exclude any unpublished studies). The EAC considers that the exclusion of eight of these papers was appropriate. The sponsor excludes Moloney et al (1972), stating that it is a letter. However, the EAC rejects the reason for this exclusion as it is not a letter, and it is included as a relevant study (as per the sponsors search criteria) in table 1a.

In the studies included by the sponsor, measurements are performed with subjects in a variety of positions, some of which could potentially mimic the medical setting. For example, Izumi et al (2010) has subjects positioned prone, whilst Tucker et al (2010) and Jawad (coagulation) (2012) both have subjects positioned in airline seats. However, the sponsor excludes Morita et al (2006) (58) due to the outcome related to patient positioning. Using the sponsor's inclusion criteria, the EAC determined that the sponsor should have included this study; therefore it is described further in table 1a (although the EAC search criteria ultimately excluded this study). It is worth noting that the scope does not mention patient/subject positioning. Furthermore, patient positioning has the potential to influence both blood flow and incidence of VTE (Hitos et al [2007]).

The sponsor excluded three papers as they involved a pharmacological intervention. This exclusion is considered appropriate. These studies were also excluded from the EAC systematic review. The EAC notes that one NMES sponsor-identified study (Rosenberg et al [1975]) includes a comparator of pharmacological prophylaxis (of note given the sponsor exclusion criteria of no pharmacological interventions). The EAC assumes that the sponsor included this study as it also has a comparator group of no prophylaxis.

geko™ studies:

- Comparators used to assess the geko™ device varied. Three studies (Jawad [vs. IPC] [2012], Williams [published] [2013], and Williams [unpublished] [2013]) [redacted]. Tucker et al (2010) compared the geko™ device with baseline measures in addition to voluntary dorsiflexions, whilst Warwick et al (2013) compared the geko™ device in subjects with and without a plaster cast and in different positions. Jawad (coagulation) (2012) compared measurements at baseline, during and after geko™ device application. Jawad (coagulation) (2012) used a second visit with no geko™ device as the comparator. This is the only geko™ study that included subject follow-up.

- All geko™ studies reported by the sponsor were descriptive; there were no RCT studies. All studies were within single centres.

- geko™ studies were all performed with healthy volunteers. There were no medical or surgical subjects.

- Age range for all studies was 18 to 65 years, and all studies were conducted in the United Kingdom.

- Application period of the geko™ device varied by study. The longest application period was four hours in Tucker et al (2010). Jawad (cardiac) (2012), Williams et al (published) (2013), Williams et al (unpublished) (2013) and Jawad (vs. IPC) (2012) [redacted]. Jawad (coagulation) (2012) used a 15-minute device protocol (also with interlaced recovery/equilibrium periods). Warwick et al (2013) did not report the time period of geko™ device application. Current management of VTE risk as per NICE Clinical Guideline 92 recommends the use of prophylaxis continually 'until the risk of VTE recedes with recovery and mobilization, generally 5 to 7 days'. Therefore, the EAC queries the appropriateness of the geko™ related studies submitted by the sponsor, given that none assessed the device over a time period similar to that used in the relevant clinical setting.

NMES studies including two sponsor excluded studies (Moloney et al [1972] and Morita et al [2006]):

- The NMES studies reported by the sponsor vary in study design. They range from: single to multi-centre studies, RCT and non-RCT, and blinded and non-blinded.

- NMES studies were conducted amongst both healthy volunteers (six studies) and medical/surgical patients (nine studies).

- The age ranges for the NMES studies varied. Five studies reported subject ages to be 40 years or over (Czyrny et al [2010], Lindstrom et al [1982], Rosenberg et al [1975], Browse & Negus [1970] and Kaplan et al [2002]). Three studies reported mean age (60.7, 69.5 and 56 [control group] vs. 52 [test group]) (Faghri et al [1997], Broderick et al [2013], and Nicolaides et al [1972]). Broderick et al (2011b) did not state age characteristics of subjects. All other studies reported an age from ten years upwards to 81 years of age.

- The studies were from several countries (Ireland n=3, USA n=4, Sweden n=1, Japan n=2 and UK n=5).

- Of the RCT studies, the sample sizes ranged from 30 to 295 subjects. Of the observational studies, the sample size ranged from 11 to 116 subjects.

IPC related evidence:

- Of the IPC studies reported by the sponsor, five were RCTs, and two were observational prospective studies.

- All IPC studies were conducted amongst surgical patients. The type of surgery varied, including abdominal surgery, hip/knee replacement, cranial neurosurgery and other non-specified surgery.

- All studies reported a mean age. These were between 49.7 and 73 years of age. Most IPC studies reported a mean age for each intervention group.

- The studies were from several countries (UK n=2, New Zealand n=2, Italy n=1, Canada n=1 and Turkey n=5).

- Five IPC studies had a sample size between 150 and 229 patients. Pitto et al (2008) had a large sample size of n=846, whilst Kurtoglu et al (2005) had a sample size of n=38.

The EAC includes five studies as additional clinical evidence identified through the EAC's own systematic review. The selection of these studies is detailed below in section 3.9.

Table 3.1: Summary of key points from sponsor-included published geko™ (n=4), NMES (n=15), IPS (n=7), and unpublished geko™ studies (n=3). Two additional NMES study initially excluded by sponsor are included (Moloney et al [1972] and Morita et al [2006]).

Reference (sponsor reference)	Study	Patient population	Intervention and/or Comparator	Country	Age	Study design	Comments
geko™ studies							
Tucker et al (2010) (45)	Evaluation of novel transdermal neuromuscular device applied to the common peroneal nerve on blood flow in the lower limb.	Healthy volunteers (n=30).	geko™. The device was fitted unilaterally with baseline measures and voluntary dorsiflexions used as comparators.	UK	Not reported, although inclusion criteria = 18 to 65 years.	Single arm, single centre, unblinded. Patients were seated in an economy airline seat and a stimulation programme of 15 sequences was conducted. This sequence was reversed in a second visit two weeks later. Changes in measurements were compared to baseline values (at rest), and voluntary muscle action (10 dorsiflexion's), during the 5 min stimulation period and/or during 5 min recovery phase. Measurements taken at four hourly intervals 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.	**Sponsor systematic review identified** Several measures of blood flow were used 'geko™' not named in study. Medical patients do not sit in airline seats. Device was turned on and off every 5 minutes, which would not happen in medical patients. Unclear if second visit reversed leg sequence used with device. No CIs for estimates. Timing of dorsiflexion protocol not given
Jawad (cardiac) (2012) (62)	Investigation of effectiveness in increasing venous	Healthy volunteers (n=9).	geko™. Device was	UK	Aged between 18-65	Single arm, single centre, unblinded. Measurements of arterial volume	**Sponsor internal identified.**

Reference (sponsor reference)	Study	Patient population	Intervention and/or Comparator	Country	Age	Study design	Comments
	return of lower limb with use of novel neuromuscular device, with particular reference to enhancing cardiac performance.		fitted bilaterally to the common peroneal nerve. Comparisons of blood flow changes were compared at baseline, during and after application of device.		years.	flow, peak velocity, femoral vessel diameter, microcirculation, and echocardiography were taken.	CIs given in figures. Short application/duration of devices (30 minutes) does not mimic medical setting.
Jawad (coagulation) (2012) (62)	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.	Healthy volunteers (n=10).	geko™. Two visits were required, with repeat measurements, and no device used on the second visit (control study).	UK	Aged between 18-65 years.	Single arm, single centre, unblinded. Measurements of arterial and venous blood flow were made using colour flow duplex ultrasound and laser Doppler flowmetry. Not all outcomes reported/analysed across the different interventions.	**Sponsor internal identified.** CIs given in figures. Device applied for five minutes every 15 minutes, with a 10 minutes recovery phase. Subjects placed in airline seating for four hours. Does not mimic medical setting.
Williams et al (published) (2013) (60)	Assessment of efficacy using haemodynamic measure changes with the use of neuromuscular	Healthy volunteers (n=10).	geko™ and IPC. Devices were fitted to patient, with	UK	Mean age 27.1.	Interventional crossover single centre trial. Measurements of venous velocity and flow were taken at baseline and after	**Sponsor internal identified.** No CIs given. Alternating and short application/duration of devices (30

Reference (sponsor reference)	Study	Patient population	Intervention and/or Comparator	Country	Age	Study design	Comments
	electrical stimulation (geko™ device) and intermittent pneumatic compression.		baseline values compared to bilateral programme with each of the two devices applied.			each device. The first device was applied for 30 minutes, followed by 20 minutes rest, and then the second device was applied for 30 minutes.	minutes) does not mimic medical setting. Several measures of blood flow and volume.
Jawad et al (vs IPC) 2012 (63)	Comparison of geko™ device with two IPC devices (Huntleigh Flowtron Universal and Kendall SCD Express) in enhancing lower limb blood perfusion.	Healthy volunteers (n=10).	geko™ and IPC. Devices were fitted bilaterally to subject's legs in a sequential manner. The geko™ device was compared to the two IPC devices.	UK	Aged between 18 and 65 years.	Single arm, single centre, unblinded. Ordering of devices were applied to subjects using a pre-set randomisation schedule. Each device was active for a period of 30 minutes followed by a 10 minutes recovery phase. 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. Measurements were made using colour flow duplex ultrasound and laser Doppler fluxmetry.	**Sponsor internal identified.** Several measures of blood flow and volume. Subjects lay supine during experiment. Alternating and short application/duration of devices (30 minutes) does not mimic medical setting. No CIs for estimates.
Warwick et al (2013) (64)	To investigate the characteristics of deep venous flow, as a potential for thromboprophylaxis	Healthy volunteers (n=10).	geko™. The device was fitted to the back of	UK	Between 18 and 65 years.	Single arm, single centre, unblinded trial. One leg of subject was fitted with a	**Sponsor internal identified.** One CI reported in text.

Reference (sponsor reference)	Study	Patient population	Intervention and/or Comparator	Country	Age	Study design	Comments
	in the leg encased in a cast with use of a wearable neuromuscular stimulator (geko^{TM}), and to examine participant's tolerance of the stimulator.		subject's leg. This was measured with and without a plaster cast, and with subjects in different positions.			plaster cast. The same leg acted as control when measured without a plaster cast. Measurements were taken whilst subject was supine, with lower leg elevation, and whilst 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. Ultrasound measurements of superficial femoral veins assessed blood flow velocity, volume, and average velocity using Doppler ultrasound and vessel diameter.	No time period was given for application/duration of device, or for duration of different subject positions, Measurements taken every 10 minutes. The measurements taken in different positions do not necessarily mimic medical patient experience.
Williams et al (unpublished) (2013) (61)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Reference (sponsor reference)	Study	Patient population	Intervention and/or Comparator	Country	Age	Study design	Comments
						[redacted]	
NMES studies							
Corley et al (2012) (35)	To investigate changes of blood flow due to NMES to the calf muscles, and secondly to evaluate subject compliance to the protocol.	Healthy volunteers (n=24).	NMES. Two groups, with one group receiving NMES, whilst the control groups had no NMES.	Ireland	Aged between 20 to 26 years.	Randomised single centre, unblinded. Compression stockings were worn to cover electrodes. Both NMES group and control group wore the stockings continuously throughout duration of trial. NMES group received 30 minutes of NMES daily, Measurements of popliteal venous velocity and vein diameter were taken at various intervals of the stimulation programme. These included ejected venous volume, peak venous velocity, and stimulation intensity (NMES group only), Measurements of compliance were taken.	**Sponsor systematic review identified.** Measurements taken over a period of seven days.
Czyrny et al (2010) (38)	Comparison venous blood flow velocity with mild electrical	Healthy volunteers (n=40).	NMES vs. IPC. Two sessions,	USA	Aged 50-80 years.	Randomised cross over trial, unblinded.	**Sponsor systematic review identified.**

Reference (sponsor reference)	Study	Patient population	Intervention and/or Comparator	Country	Age	Study design	Comments
	stimulation of the plantar foot muscles with IPC.		with each subject receiving either IPC or electric foot stimulation (NMES). Subjects received both therapies in either session. Order of therapy was random.			Subjects seated, and were allowed to use bathroom twice during the four hour stimulation programme. Measures of compliance were taken. Measure of popliteal and femoral venous flow velocities were taken at several times during the four hour programme.	CIs in figures.
Faghri et al (1997) (13)	Comparisons of venous return in total hip and knee arthroplasty patients using either sequential compression device or electrical stimulation techniques.	Total hip and knee arthroplasty patients (n=30).	NMES vs. IPC. Patients received either NMES or IPC during their respective surgery. Device application discontinued after completion of surgery.	USA	Mean age 60.7 ± 9.7 years.	Randomised, single centre blinded study. Both groups received standard pharmaceutical prophylaxis and were wearing compression stockings throughout the study. Measures of hemodynamic data (cardiac output, stroke volume, blood pressure, heart rate, and total peripheral resistance) were taken every 15 minutes during surgery, including a baseline measure before surgery. The last measure was taken 15 minutes after completion of surgery.	**Sponsor systematic review identified.** Standard errors were listed.
Lindstrom et	Compare effects of	Patients of	NMES vs.	Sweden	All above	Randomised study. Unclear if	**Sponsor systematic review**

Reference (sponsor reference)	Study	Patient population	Intervention and/or Comparator	Country	Age	Study design	Comments
al (1982) (24)	calf muscle stimulation with groups of impulses with established prophylactic (Dextran 40).	major abdominal surgery (n=112).	Dextran. Patients were assigned randomly either to NMES, Dextran 40, or control group (who received standard routine).		40 years.	blinded, as NMES only applied during surgery. Incidences of DVT and PE during the first 4-6 postoperative days were recorded.	**identified.** CIs included.
Rosenberg et al (1975) (42)	Comparison of incidence of leg vein thrombosis in patients with malignant disease with the use of intermittent electrical calf muscle stimulation or heparin calcium 5000.	Patients of major general surgery (n=295).	NMES. Patients were assigned randomly to NMES, Heparin, or no specific prophylaxis.	UK	All above 40 years.	Randomised study. Unclear if blinded, as NMES only applied during surgery, and Heparin given post-surgery. Incidences of both minor and major venous thrombosis were measured daily for seven days, using the Fibronogen-uptake test.	**Sponsor systematic review identified.** No CIs of estimates. Comparison is made between minor and major DVT, and for patients of benign and malignant disease.
Velmahos et al (2005) (46)	To assess the prevention of deep vein thrombosis in patients with major trauma using electrostimulation.	Major trauma patients (n=47).	NMES. Subjects either received NMES or no NMES (control group).	USA	All subjects over 18 years,	Randomised prospective unblinded multi-centre study. NMES was applied twice daily for 30 minutes over a period of up to 14 days (minimum of seven days). Incidence of DVT and measures of venous flow velocity and diameter	**Sponsor systematic review identified.** No CIs for estimates.

Reference (sponsor reference)	Study	Patient population	Intervention and/or Comparator	Country	Age	Study design	Comments
						were recorded. Subject inclusion required contraindication for prophylactic heparin.	
Broderick et al (2013) (21)	Evaluation of the use of NMES to the calf muscles in the immediate hospitalised recovery period following total hip arthroplasty to increase venous return.	Total hip replacement patients (n=11).	NMES. Patients contralateral limb used as control, with NMES applied to both legs. Measurements were taken from both the operated and un-operated limbs.	Ireland	Mean age of 69.5 ± 8.1 years.	Observational, single centre unblinded study. Measurements of lower limb haemodynamic output, venous velocity, and popliteal vein diameter. Device applied for four hours. Patient's tolerance of the NMES device was also assessed.	**Sponsor systematic review identified.** No CIs included. Patients lay supine.
Broderick et al (2011b) (49)	To assess patient tolerance of NMES in the presence of orthopaedic implants and associated venous outflow.	Total hip and total knee arthroplasty patients (n=20).	NMES. Patients contralateral limb used as control, with NMES applied to both legs.	Ireland	Not stated.	Observational, single centre unblinded study. NMES application conducted 3 weeks post-surgery. NMES applied to both legs, and contralateral leg used as control. A five-minute stimulation protocol was followed. Measurements were taken	**Sponsor systematic review identified.** No CIs included. Patients lay supine.

Reference (sponsor reference)	Study	Patient population	Intervention and/or Comparator	Country	Age	Study design	Comments
						at before and during NMES use. Measurements included Visual Analogue Scale (VAS), blood flow, velocity, and vein cross-sectional area.	
Browse & Negus (1970) (23)	Evaluation of effectiveness of NMES application in post-operative patients in terms of preventing postoperative deep vein thrombosis.	Patients of major surgery (n=110).	NMES. Each patient acted as own control, as only one leg given NMES.	UK	Aged between 40 to 81 years.	Observational prospective single centre blinded study, NMES device applied/activated during surgery. I-fibronogen uptake test post-operation was used to detect DVT. Patients of leg surgery excluded.	**Sponsor systematic review identified.** No CIs included.
Griffin et al (2010) (22)	To determine the effect of NMES application on popliteal vein blood velocity and blood volume, and to evaluate other aspects of efficacy of the device.	Healthy volunteers (n=24).	NMES. Comparisons of baseline measurements were taken. Only one leg (randomly chosen) per volunteer was tested.	UK	Aged between 18 to 61 years.	Pilot study in multi-centres, unblinded. Ultrasound of popliteal veins was used to take measures of blood velocity and volume flow. Measure of calf circumference was also obtained. An initial 15 minutes of rest/equilibrium was then followed the activation of the device. Maximum tolerance level of the device was obtained.	**Sponsor systematic review identified.** Patients placed in semi-recumbent position. CIs given in figures/graphs.
Izumi et al	Investigation of	Healthy	NMES vs.	Japan	Aged	Observational single centre	**Sponsor systematic review**

Reference (sponsor reference)	Study	Patient population	Intervention and/or Comparator	Country	Age	Study design	Comments
(2010) (39)	effect of NMES and other mechanical methods of thromboprophylaxis on venous blood flow.	volunteers (n=10).	other mechanical methods (electrical muscle stimulation, IPC, active ankle motion and calf squeeze).		between 22 and 48 years.	unblinded study. Measures of blood flow included peak venous velocity and flow volume. After initial five minute rest, baseline measurements were taken. Each subject received all mechanical methods, during which three measures were taken and the average value used in analysis. A rest period was included between each mechanical method.	**identified.** EAC exclude given patient position. Patients in prone position. No CIs for estimates.
Kaplan et al (2002) (20)	Investigation of effect of mild electrical stimulation of the plantar foot and calf muscles, on venous blood flow velocity in the femoral and popliteal veins.	Healthy volunteers (n=49).	NMES. Subjects own contralateral leg (without NMES) acted as control (randomly assigned).	USA	Aged between 51 and 76 years.	Observational unblinded single centre study. NMES device activated for four hours, and patients were allowed to use the toilet twice. Four measurements of popliteal and femoral venous blood flow velocities were taken during the study. One at baseline, two during application of device, and one at the end of the study. Subjects	**Sponsor systematic review identified.** Subjects seated for four hours. No CIs for estimates.
Nicolaides et al (1972) (74)	To determine the most effective electrical stimulus	Surgical patients (n=116).	NMES. Split into two	UK	Mean age for control group: 56 ±	Observational blinded study of two parts.	**Sponsor systematic review identified.**

Reference (sponsor reference)	Study	Patient population	Intervention and/or Comparator	Country	Age	Study design	Comments
	in preventing DVT.		groups: a test group received NMES during operation, the control group, no NMES.		12.4 years. Mean age for test group: 52 ± 13.8 years.	Firstly, blood velocities in the femoral veins were measured to obtain optimal stimulation to prevent venous stasis. Secondly, I-fibronogen uptake test was used to detect DVT. Both test and control groups followed standard DVT prevention methods postoperatively.	No CIs of estimates. No measures of femoral blood velocities were provided.
Moloney et al (1972) (57)	To evaluate the effect of electrical stimulation of the legs on postoperative thrombosis.	Surgical patients (n=285).	NMES. Split into two groups, with the test group receiving NMES during operation, and the control group, no NMES.	UK	Aged from 10 to over 80 years.	Randomised blinded single centre study. Although authors note some discrepancy in randomisation protocol. Incidence of thrombosis post operation was measured based on clinical symptoms. Whilst measures of blood flow were collected, they were not reported in paper.	**Excluded by sponsor systematic review based on study design – letter.** No CIs of estimates.
Morita et al (2006) (58)	Aimed to evaluate the effects of sitting posture on lower limb venous flow and to explore the beneficial effects of NMES and an ottoman-type seat on the venous flow.	Healthy volunteers (n=21).	NMES. Subjects own contralateral leg (without NMES) acted as control (randomly	Japan	Aged from 20 to 50 years.	Observational unblinded single centre study. Subjects lay in horizontal prone position and in seated position using ottoman. Measurements of blood flow velocity	**Excluded by sponsor systematic review based on outcome – patient position.** No CIs of estimates. Three treatment groups: non-NMES (whilst in prone position),

Reference (sponsor reference)	Study	Patient population	Intervention and/or Comparator	Country	Age	Study design	Comments
			assigned). Comparison was also made with subjects positioning, either lying down or using ottoman style seating,			(peak. mean and volume), and cross-sectional areas were taken at 30, 60, 90 and 120 minutes.	NMES (in prone position) and Ottoman (with NMES). No measurement of non-NMES device in Ottoman seating was recorded.
IPC studies							
Nicolaides et al (1983) (37)	Intermittent sequential pneumatic compression of the legs and thromboembolism-deterrent stockings in the prevention of postoperative deep venous thrombosis.	Patients who had undergone major abdominal operation (n=150).	IPC and NMES. Group A: Electrical calf stimulation (NMES). Group B: Low-dose subcutaneous heparin Group C: Intermittent sequential compression /TED stockings using a sequential	UK	Patients aged over 30 years. Age mean (SD) by prophylactic group: Group A: 59.2 (16.6) years Group B: 58.6 (13.3) years Group C: 57.3 (13.4)	Randomized clinical trial. Patients were stratified into four groups based on level of risk of DVT as estimated from an equation derived from a multivariate analysis of risk factors in previous studies (i.e. low, moderate, high and extremely high). Patients were then randomised to one of three prophylactic groups using sealed envelopes.	**Sponsor systematic review identified.** Duration of study period is not clear. No CIs for reported estimates. Flowchart of trial process not presented.

Reference (sponsor reference)	Study	Patient population	Intervention and/or Comparator	Country	Age	Study design	Comments
			compression device. Device was used during the entire period of the operation and for 72 hours post – op. Maximum period of continuous use was 2 weeks.		years		
Pitto et al (2004) (47)	Mechanical prophylaxis of deep vein thrombosis after total hip replacement.	Patients admitted with osteoarthritis of the hip for uncemented total hip arthroplasty. Number of males who completed study n=62/200 (31%) (n=216).	IPC. A-V Impulse System foot pump fitted to both feet. These were activated when the patient was not bearing weight the pneumatic compression cycle set at 20 seconds with applied pressure of 130 mmHg for one second	New Zealand	Age mean (SD) by randomised group: Foot-pump group: 57.3 (12), LMWH group: 58.1 (11).	Randomised clinical trial. All patients wore thigh high anti-thromboembolic stockings. On 2nd day post-operation, physiotherapy exercises and mobilisation with partial weight bearing for six weeks post operation. DVT was investigated by serial duplex ultrasonography.	**Sponsor systematic review identified.** It is not clear whether the patients who found the foot-pump uncomfortable completed the regime. Analysis should have been based on intention to treat. Reported only characteristics of patients who completed the trial (n=200) and excluded those who were randomised but stopped using the foot pumps after three to ten days post-operative (n=16). Flowchart of trial process not

Reference (sponsor reference)	Study	Patient population	Intervention and/or Comparator	Country	Age	Study design	Comments
							presented.
Santori et al (1994) (43)	Prophylaxis against deep-vein thrombosis in total hip replacement.	Patients undergoing total hip replacement between June 1990 and December 1991 (n=132). Males: n=15 (23%)	Foot Impulse Device (FID). Patients were randomly assigned to receive either mechanical or pharmacological prophylaxis.	Italy	Age mean (SD) by randomised group: Heparin: 69.8 (6.2) years, A-V Impulse system: 72.4 (6.65) years	Randomised controlled trial Post-operative follow up period: six weeks. Mechanical prophylaxis involved fitting of A-V Impulse system to both feet immediately after surgery. Pharmacological prophylaxis was 5000 IU of calcium heparin administered subcutaneously starting on the day before surgery, three times a day for ten days.	**Sponsor systematic review identified.** No confidence intervals for estimated proportion of patients who experienced adverse reactions or events. It is assumed that all patients completed the trial study. Odds ratio (with 95% CI for major and minor DVT are not reported). Flowchart of trial process not presented.
Sobieraj-Teague et al (2012) (44)	Randomized controlled trial of a new portable calf compression device (Venowave) for prevention of venous thrombosis in high-risk neurosurgical patients.	Neurosurgical patients aged ≥18 years admitted to Hamilton General Hospital for cranial or spinal neurosurgery between May 2009 and November 2010 (n=150).	IPC. Patients were assigned to Venowave devices or VTE prophylaxis (usual care as determined by surgeon).	Canada	Patients aged ≥18 years Randomised group (mean [SD]): Venowave group: 61.9 (10) years Control: 62.1 (11.8)	Randomised controlled trial. Venowave devices were applied to both calves within 4 hours of surgery or within 24 hours of admission to hospital in patients who didn't have surgery. The device was worn continuously (except at bath time) and its use was only discontinued if the patient developed symptomatic venous thromboembolism.	**Sponsor systematic review identified.** It is not clear if there were any differences between surgical patients and non-surgical patients with respect to comfort and compliance in using device. Unclear if differences in compliance at night time had any effect on blood flow.

Reference (sponsor reference)	Study	Patient population	Intervention and/or Comparator	Country	Age	Study design	Comments
					years		
Warwick et al (2002) (48)	A randomised comparison of a foot pump and low molecular –weight heparin in the prevention of deep-vein thrombosis after total knee replacement.	Patients undergoing primary total knee replacement in a regional orthopaedic centre between September 1996 and March 1999 (n=229). Males: n=80 (35%)	Foot Impulse Device (FID). Foot pumps were applied while patients were in the recovery room post-op.	UK	Age mean (SD) by randomised group: Foot pump: 73 (9) years. LMWH: 71 (10) years.	Randomised clinical trial Follow up period: three months. The foot pump was activated every 20 seconds at pressure of 130mmHg for one second whenever the patient was not bearing weight until discharge from hospital.	**Sponsor systematic review identified.** CIs for difference in proportions were reported.
Kurtoglu et al (2005) (40)	Intermittent pneumatic compression in the prevention of venous thromboembolism in high-risk trauma and surgical ICU patients.	Surgical ICU patients who used IPC devices for prophylaxis of venous thromboembolism between October 2001 and June 2002 (n=38). Males: n=27 (71%)	IPC. Calf IPC devices was applied to the lower extremities of the patients and were each inflated for 90seconds up to 40 mmHg and then applied for 30 seconds.	Istanbul, Turkey	Mean (SD): 49.7 (18.6) years	Prospective cohort study. Follow up period: nine months. To detect DVT, venous duplex ultrasonography of lower extremities was performed at day three, day seven and time of discharge. Spiral thorax CT scanning for PE was performed during the first few weeks.	**Sponsor systematic review identified.** The time schedule for the spiral thorax CT scan is unclear. Also the frequency of application of IPC device is unclear. No CIs for reported estimates. No comments were made on compliance.

Reference (sponsor reference)	Study	Patient population	Intervention and/or Comparator	Country	Age	Study design	Comments
Pitto et al (2008) (41)	Foot pumps without graduated compression stockings for prevention of deep-vein thrombosis in total joint replacement: efficacy, safety and patient compliance.	Patients with degenerative osteoarthritis of the hip or knee for total hip or total knee replacement between January 2003 and December 2005 (n=846).	IPC. A-V Impulse System foot-pump units were used in all patients (n=846). 46 patients discontinued use of foot pump. 400 patients received foot pumps in combination with GCS and 400 patient received foot pumps alone.	New Zealand	Patients Mean (SD) Stocking group: 67 (10) years. Non – stocking group: 65 (9) years.	Prospective comparative study Study duration: three years (Jan 2003 – Dec 2005). Foot pumps were activated when patients were not bearing weight. The pneumatic compression cycle was set at 20 /second with pressure of 130mmHg applied per second. Patients with clinical signs of DVT were screened in serial bilateral duplex studies with 5-7.5 MHz linear transducers.	**Sponsor systematic review identified.** No confidence intervals for reported estimates. Did not report specific number (percentage) of males and females. Not clear what criteria/strategy was used in allocating patients to stocking or no stocking group.

3.4 Overview of methodologies of all included studies

The geko™, NMES and IPC studies vary in study design, subject selection and comparator. The EAC reviewed the methodologies of these studies separately based on type of mechanical device:

geko™ studies (n=7):

- Only Jawad (coagulation) (2012), Jawad et al (vs. IPC) (2012) and Williams et al (unpublished) (2013) are considered by the EAC to have used the specified comparator in their measurement of an outcome listed in the scope (described further in section 3.6).

- Jawad (cardiac) (2012) and Jawad (coagulation) (2012) document CIs within figures/graphs and not in tables or in the text. Warwick et al (2013) documents one overall CI.

- Five of the studies had a relatively small sample size of nine or ten subjects. Tucker et al (2010) had a larger sample size of n=30.

- The majority of the geko™ studies assessed the outcome measures of blood flow (except Warwick [unpublished] [2013]) and blood velocity. However, these reported measures are not comparable between studies. For example, Tucker et al (2010) uses both baseline and dorsiflexion measures as comparators, whilst Jawad (cardiac) (2012) and Jawad (coagulation) (2012) use baseline measures.

- Jawad (cardiac) (2012) only measures arterial blood flow, so is not comparable to the other geko™ studies, which included venous and/or arterial outcome measures.

- Some studies used the geko™ 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 geko™ as described in the sponsor's submission.

- The EAC notes that Jawad (cardiac) (2012) and Jawad (coagulation) (2012) use the Thrive device, not the geko™. As stated in these studies, Thrive uses

a different current, frequency and pulse length to geko™. For example, the studies using Thrive document a current of 25mA, frequency of 3Hz and pulse width of 600 μs, whilst the geko™ is markedly different with a current of 27mA, frequency of 1Hz and maximum pulse width setting of 560 μs.

- All studies included only healthy volunteers, so are potentially not generalizable to a patient population. These studies used exclusion criteria and/or performed prior screening of their subjects to exclude any subjects presenting with a known risk factor for VTE. The EAC considers that the population defined in the scope would include subjects with conditions that may impair the effectiveness of geko™, (for example, oedema, chemical or physical muscle paralysis, venous insufficiency and adipose tissue insulating the stimulation area). These factors would have been screened out by the exclusion criteria used in the submitted evidence. Therefore, the EAC considers the population used in the evidence to differ considerably from the population defined in the scope.
- Some baseline characteristics were documented for Jawad (cardiac) (2012), Jawad (coagulation) (2012), Williams (published) (2013) and Williams (unpublished) (2013).
- Application period of the geko™ device varied between studies, making it harder to interpret and compare the results. The EAC's understanding of the geko™ device is that in order to function as a VTE prophylaxis, the device would need to be in situ for a minimum of 24 hours, without interruptions. 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.
- Methodology for the baseline comparators was not always adequately described, and it is not always possible to determine whether the subject's blood flow and velocity were at equilibrium/stabilization before stimulation using the geko™ device.
- Several studies used verbal rating scores and verbal acceptance scores to assess tolerability, which the EAC suggests could be a surrogate for patient adherence (as listed in the scope).

NMES (n=15):

- The sponsor provided several studies: a combination of RCT and observational design. Six studies included only healthy volunteers and nine medical/surgical patients.

- Some studies only reported arterial measures. The EAC does not consider this a suitable outcome measure of blood flow and/or velocity, because outcomes of cardiac function and arterial flow are not among those specified in the scope.

- Only two NMES studies directly investigated incidence of DVT alongside measures of blood flow: Nicolaides et al (1972) and Velmahos et al (2005).

IPC studies (n=7):

- The sponsor included seven IPC studies: five RCTs and two observational prospective studies, recruiting a combination of healthy volunteers and medical/surgical patients. Two of these studies used a Foot Impulse Device (FID) (Santori et al [1994] and Warwick et al [2002]) rather than IPC.

- Most studies compared IPC or FID with a pharmacological intervention. The EAC did not consider this relevant to the scope, and therefore subsequently excluded these studies.

3.5 Overview and critique of the sponsor's critical appraisal

The sponsor conducted a critical appraisal of all geko™, NMES and IPC studies that were identified in the systematic review. The critical appraisal of the NMES and IPC studies were placed within Appendix 5 and 6 of the sponsors submission, whilst the critical appraisal of the geko™ studies was included within section 7.5 'Critical Appraisal of relevant studies'.

geko™ appraisal:
The critical appraisal of geko™ studies answered many questions regarding bias and confounding factors. However, the sponsor failed to explain adequately how each study's reported outcomes were controlled to minimise bias. For example, the

sponsor only lists the methods used to obtain measurements of outcome, rather than discussing the methods in relation to bias minimization.

Whilst the sponsor provides an interpretation of the clinical evidence in section 7.9, there is no discussion of the strengths and weaknesses of the studies. The sponsor does not offer or document any synthesis of the studies. However, this may be due to the varying nature of the outcome measures, study designs and range of comparators and interventions between the studies.

NMES/IPC appraisal:
The sponsor's critical appraisal of the observational NMES and IPC studies were presented in a similar format to the geko™ critical appraisal. Therefore, there are similar issues. Firstly, there is no explanation of how bias was minimised in relation to outcome measures. Secondly, there is no discussion of the overall strength and weaknesses of the studies. Finally, there is no overall synthesis of the studies. The sponsor correctly used a separate critical appraisal structure for assessing the RCT NMES and IPC studies. However, similar to the observational studies, the sponsor did not provide an overview or summary of strengths and weaknesses of these RCT studies.

3.6 Results

In table 3.2, the EAC provides a summary of the outcomes of all sponsor-included published (n=4), and unpublished (n=3) geko™ studies. Three of the sponsor-identified geko™ studies were considered by the EAC to contain comparators and outcomes that fitted within the scope and the EAC search criteria (detailed below), These studies were Jawad (coagulation) (2012), Jawad et al (vs. IPC) (2012) and Williams et al (unpublished) (2013). The EAC notes that, in addition to outcomes that are within the scope, these three studies also included measures of arterial flow/velocity, which the EAC does not consider an appropriate outcome measure as it is not listed in the scope.

Jawad (coagulation) (2012) measured several different blood flow-related outcomes using a variety of methodologies and settings. One of the main findings (applicable to the scope) during the geko™ stimulation sessions was that venous blood flow and velocities significantly increased (P≤0.001 and P≤0.001 respectively) when compared

to baseline (in the same leg). The highest increase was found after three hours in both measures (+326% and +181% respectively) during the four-hour stimulation session. However, Jawad does not compare these results in the contralateral (unstimulated) leg during either session; therefore, it is difficult to ascertain the clinical significance of these values.

The EAC make the following comments regarding Jawad (coagulation) (2012):

- Whilst Jawad collects data for blood flow, velocity and vessel wall diameter during two sessions (stimulation and control) and displays the mean results in figures and tables, no direct statistical analysis comparing these two sessions is made.

- Jawad does not directly compare the stimulated leg and contralateral leg for blood flow and/or velocity. Whilst it appears that this data was collected, no analysis of this potential comparison is reported. Comparison is only made to baseline.

- Comparisons are made for skin microcirculatory assessments (for both stimulated and unstimulated legs) and in measures of blood coagulation. However, none of these measurements relate to the outcomes listed in the scope.

Jawad et al (vs. IPC) (2012) is based on a chapter of Jawad's PhD thesis. Jawad also documents a significant increase in both venous blood flow and venous blood velocity (both P≤0.001) using two settings of the geko™ device (normal clinical use and threshold setting) in comparison to two IPC devices at baseline. As all subjects received all three devices in one session, it is not possible to directly compare the percentage changes in these measures to other studies identified by the sponsor. The EAC note that both IPC devices demonstrated an average percentage change in comparison to baseline for venous blood flow of -4%. However, the sponsor's evidence centres on the assertion that IPC devices work by increasing venous blood flow.

Williams et al (unpublished) (2013)

[redacted]

[redacted] Similar to Jawad et al (vs. IPC) (2012), the subjects in Williams [redacted] However, the results of these studies cannot be combined due to the different design methodologies, such as application times, ordering and settings.

Four of the geko™ studies identified by the sponsor were rejected using the EAC search criteria. Tucker et al (2010) was rejected as the comparators were baseline measures and voluntary muscle action (dorsiflexions), neither of which are listed comparators in the scope. The EAC considers that the lack of a proper control in the Warwick et al (2013) study and the use of cardiac outcomes in Jawad (cardiac) (2012) do not fit within the scope. The study by Williams (published) (2013) did not provide sufficient detail of how baseline measurements were obtained, therefore, the EAC could not determine if this baseline measurement was suitable as a comparator as defined in the scope.

Table 3.2: Summary of outcomes from sponsor-included published geko™ (n=4) and unpublished geko™ studies (n=3).

Reference	Study	Subjects	Outcome 1 Blood Flow	Outcome 2 Blood Velocity	Outcome 3 Skin Microcirculatory Assessments	Outcome 4 Acceptance and Tolerability	Outcome 5 Other Outcomes
geko™ **studies**							
Tucker et al (2010) (45) **Subsequently rejected by EAC.**	Evaluation of novel transdermal neuromuscular device applied to the common peroneal nerve on blood flow in the lower limb.	Healthy volunteers (n=30), of which the baseline measures and voluntary dorsiflexions used as comparators. There were no separate treatment arms. Two visits, with stimulation programme reversed.	Venous flow showed significant increase in all stimulations (P<0.01). Higher stimulations also associated with increase in venous blood flow with both amplitude (R^2=0.55) and frequency (R^2=0.82).	Venous velocity showed significant increase in all stimulations (P<0.01). Higher stimulations also associated with increased venous velocity with both frequency (R^2=0.72) and current (R^2=0.74).	Microcirculatory flux was significantly associated (P<0.01) with frequency and current. Only frequency had a strong positive correlation (R^2=0.86). Skin temperature was found to significantly increase in stimulated leg compared to the unstimulated leg (P=0.04).	Patient discomfort rating increased with higher stimulation. No P-values available.	No significant changes in oxygen saturation or heart rate. No significant differences found in relation to mean vessel diameter. Venous emptying (as measured by PPG) significantly associated with higher amplitude (P=0.0004, R^2=0.56). Calf circumference change (as measured by SPG) significantly associated with frequency (P<0.001, R^2=0.84).
Jawad (cardiac) (2012) (62) **Subsequently rejected by EAC.**	Investigation of effectiveness in increasing venous return of lower limb with use of novel neuromuscular device, with particular reference	Healthy volunteers (n=9), of which there were no separate treatment arms. One visit.	Arterial flow showed significant increase, using device at different pulse widths (400 µs and 600 µs) compared to	Arterial velocity showed significant increase, using device at different settings compared to	Significant increase in microcirculation (measured in Flux units) when using device at different settings compared to	NA	No significant change in mean vessel diameter and area.

Reference	Study	Subjects	Outcome 1 Blood Flow	Outcome 2 Blood Velocity	Outcome 3 Skin Microcirculatory Assessments	Outcome 4 Acceptance and Tolerability	Outcome 5 Other Outcomes
	to enhancing cardiac performance.		baseline (P≤0.05). mL/min, mean ± SD Baseline 174.1±39.2 400µs 258.8±65.6 600µs 273.1±97.1	baseline (P≤0.05). Cm/sec, mean ± SD Baseline 81.19±13.62 400 µs 101.60±22.43 600 µs 100.90±26.37 Cardiac output significantly increased with device at different pulse widths compared to baseline (P≤0.05). Left ventricular outflow tract velocity time interval, mean ± SD Baseline 59.89±3.72 400 µs 60.33±4.44	baseline (P≤005). Flux units, mean ± SD Baseline 7.71±3.39 400µs 107.5±68.1 600µs 117.9±67.8		

Reference	Study	Subjects	Outcome 1 Blood Flow	Outcome 2 Blood Velocity	Outcome 3 Skin Microcirculatory Assessments	Outcome 4 Acceptance and Tolerability	Outcome 5 Other Outcomes
				600 µs 62.56±4.80			
Jawad (coagulation) (2012) (62) **Accepted by EAC.**	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.	Healthy volunteers (n=10), of which there were no separate treatment arms. Two visits. The second visit (termed control) had no device.	In the control session, no significant changes were found in venous measurements of blood flow. Arterial measures of blood flow were found to be significant when compared to baseline (P≤0.05): One hour: -25% Two hours: -10% Three hours: -20% Four hours: -11% In the stimulation session, both venous and arterial measures of blood flow were significant when compared to baseline (P≤0.001 and P≤0.05	In the control session, no significant changes were found in venous or arterial measurements of blood velocity. In the stimulation session, only venous measures of blood velocity was significant when compared to baseline (P≤0.001): One hour: +125% Two hours: -+150% Three hours: +181% Four hours: +140%	There was no significant increase in microcirculation (measured in Flux units) in the control session, in either leg. During the stimulation sessions, a significant increase in mean microcirculation in the stimulated leg, compared to the passive leg (P≤0.001).	No significant difference in discomfort using visual analogue score or verbal rating score was measured during the stimulation session.	No significant change in mean vessel diameter. Range of clotting time assessments and coagulation factors were measured, with varying results.

Reference	Study	Subjects	Outcome 1 Blood Flow	Outcome 2 Blood Velocity	Outcome 3 Skin Microcirculatory Assessments	Outcome 4 Acceptance and Tolerability	Outcome 5 Other Outcomes
			respectively). Venous (stimulation): One hour: +293% Two hours: -+278% Three hours: +326% Four hours: +275% Arterial (stimulation): One hour: +64% Two hours: +34% Three hours: +47% Four hours: +43%				
Williams et al (published) (2013) (60) **Subsequently rejected by EAC.**	Assessment of efficacy using haemodynamic measure changes with the use of neuromuscular electrical stimulation (geko™ device) and intermittent pneumatic	Healthy volunteers (n=10). Unclear ordering of interventions were randomised. One visit as part of the wider Williams	Overall comparison of flow measures between IPC and geko™ was statistically significant (P=0.02), with higher % change associated with	Overall comparison of velocity measures between IPC and geko™ were not statistically significant. However, peak velocity % change was significantly higher during	NA	NA	NA

Reference	Study	Subjects	Outcome 1 Blood Flow	Outcome 2 Blood Velocity	Outcome 3 Skin Microcirculatory Assessments	Outcome 4 Acceptance and Tolerability	Outcome 5 Other Outcomes
	compression.	(unpublished) (2013) study (see below).	geko™. Blood flow % rate change was only significantly increased during the geko™ application when IPC was first applied in the sequence (P<0.01).	geko™ stimulation when applied first in the sequence then followed by IPC (P>0.01). Other measures of velocity change were not significant.			
Jawad et al (vs IPC) (2012) (63) **Accepted by EAC.**	Comparison of geko™ device with two IPC devices (Huntleigh Flowtron Universal [HF] and Kendall [Kendall] SCD Express) in enhancing lower limb perfusion.	Healthy volunteers (n=10), of which there were no separate treatment arms as volunteers received all three devices in a sequential manner. There were two geko™ settings used: NCU (normal clinical use) and TS	A significant difference in both venous and arterial blood flow was found between the devices (P≤0.001). Median (IQR[5]) (average % change) venous volume flow (mL/min): Baseline: 123.5 (73.4) (na)	A significant difference in both venous and arterial blood velocity was found between the devices (P≤0.001). Median (IQR) (average % change) venous velocity (cm/sec): Baseline: 13.8 (5.4) (na) geko™ (NCU):	Significant difference in microcirculation (measured in Flux units) between devices (P≤0001). Flux units, median (IQR) Baseline: 9.45 (7.61) geko™ (NCU): 27.13 (24.92) geko™ (TS): 27.13 (24.92) HF: 6.67 (7.89)	No significant differences were found using visual analogue score. Using the verbal rating score, a significant difference was found between the devices (P≤0.05). Use of the geko™ (NCU) was rated as 'mild	Safety assessments had no significant reported differences between devices. No significant differences were found in measurements of mean vessel diameter.

[5] IQR: Inter Quartile Range

Reference	Study	Subjects	Outcome 1 Blood Flow	Outcome 2 Blood Velocity	Outcome 3 Skin Microcirculatory Assessments	Outcome 4 Acceptance and Tolerability	Outcome 5 Other Outcomes
		(threshold setting). One visit.	geko™ (NCU): 163.0 (105.3) (+33%) geko™ (TS): 129.0 (42.7) (+14%) HF: 118.0 (72.7) (-4%) Kendall: 115.0 (60.2) (-4%) Median (IQR) (average % change) arterial volume flow (mL/min): Baseline: 197.5 (135.8) (na) geko™ (NCU): 244.5 (125.0) (+30%) geko™ (TS): 170.0 (107.5) (-7%) HF: 181.5 (70.5) (-9%) Kendall: 158.0 (73.0) (-16%)	38.3 (10.35) (+174%) geko™ (TS): 22.0 (12.75) (+73%) HF: 14.7 (8.35) (+166%) Kendall: 12.6 (5.2) (+143%) Median (IQR) (average % change) arterial velocity (cm/sec): Baseline: 83.15 (24.23) (na) Geko (NCU): 98.25 (27.70) (+24%) Geko (TS): 84.75 (22.1) (+2%) HF: 81.90 (20.40) (-4%) Kendall: 80.30 (17.85) (-1%)	Kendall: 6.71 (12.58)	discomfort' compared to other devices, which were rated as minimal sensation.	
Williams et al (unpublished)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Reference	Study	Subjects	Outcome 1 Blood Flow	Outcome 2 Blood Velocity	Outcome 3 Skin Microcirculatory Assessments	Outcome 4 Acceptance and Tolerability	Outcome 5 Other Outcomes
(2013) (61) **Accepted by EAC.**	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
Warwick et al (2013) (64) **Subsequently**	To investigate the characteristics of deep venous flow, as a potential for	Healthy volunteers (n=10), of which the volunteers	NA	In all postural positions, both with and without plaster cast, peak	NA	Using visual rating score, median discomfort was	No statistically significant difference was found in measurements of the femoral vein cross

Reference	Study	Subjects	Outcome 1 Blood Flow	Outcome 2 Blood Velocity	Outcome 3 Skin Microcirculatory Assessments	Outcome 4 Acceptance and Tolerability	Outcome 5 Other Outcomes
rejected by EAC.	thromboprophylaxis in the leg encased in a cast with use of a wearable neuromuscular stimulator (geko^{TM}), and to examine participant's tolerance of the stimulator.	own contralateral leg used as control. There were no separate treatment arms. One visit.		venous velocity was significantly higher when geko^{TM} was active (P<0.05, 95%CI: 17.6% - 131%). Posture alone (without geko^{TM} active) had an effect on venous velocity, with higher flow in elevated limb (P=0.015) and lower in standing position (P=0.02). There was no significant difference between weight bearing and non-weight bearing positions. With an active geko^{TM}, wearing a plaster cast or postural position		lower when using an active geko^{TM} and in a plaster cast. No significance levels were provided in text. Using visual analogue score, active geko^{TM} in all positions was associated with less discomfort when wearing a plaster cast (P<0.0001).	sectional area.

Reference	Study	Subjects	Outcome 1 Blood Flow	Outcome 2 Blood Velocity	Outcome 3 Skin Microcirculatory Assessments	Outcome 4 Acceptance and Tolerability	Outcome 5 Other Outcomes
				had no significant effect.			

The EAC search criteria (as further described in section 3.8) excludes several of the NMES and IPC studies included by the sponsor (detailed further in appendix 3.2). Therefore, in table 3.3, the EAC provides a summary of studies that were later accepted using the EAC's search criteria. The EAC includes (from the sponsor submitted evidence) eleven NMES studies and one IPC study.

Corley et al (2012) documents outcomes and results of both the NMES stimulation and control group: both between groups and compared within group from baseline (day one) to the seventh day. The study found a significant increase of venous peak velocity and ejected volume over the seven days with the use of NMES. The authors cite possible low power in the study to detect differences in haemodynamic outcomes between groups on any given day. It is worth noting that the study design involved use of compression stockings in conjunction with NMES in both groups, and that stimulation was only applied three times daily for 30 minutes.

Czyrny et al (2010) compared NMES to IPC, concluding that NMES is at least as effective as IPC in increasing venous blood flow velocity in both the popliteal and femoral veins during the study period. However, there was no significant difference in the overall blood flow velocity between the contralateral control leg and the stimulated leg (for either type of device).

Broderick et al (2013) assessed three outcome measures in the popliteal veins of eleven patients who had undergone unilateral total hip replacement surgery, by applying NMES stimulation to both the operated and unoperated limb and comparing with the resting state. These measures included: peak venous velocity, mean velocity and volume flow. The study concluded that applying NMES to the calf muscle post-operation resulted in increased popliteal blood flow as assessed by all three measures. Broderick et al (2011a) also reported increased popliteal blood flow using the same three measures in post-operative patients following total hip and knee arthroplasty, as did Kaplan et al (2002) who used two different stimulation sites (calf and foot plantar) compared to the unstimulated limb.

Lindstrom et al (1982) directly investigated the incidence of pulmonary embolism (PE) and deep vein thrombosis (DVT). Study participants were patients having major abdominal surgery. The study found that either the NMES stimulation or pharmacological interventions, when compared to the control (standard care), significantly reduced the incidence of PE. The study only found a reduction in incidence of DVT with patients who had a malignant disease and received NMES

(54% [control] vs. 15% [NMES]). Conversely, Rosenberg et al (1975) found no significant difference in incidence of minor or major DVT amongst surgical patients with malignant disease between NMES (46.2% and 15.4%) and a control group (46.9% and 46.9%); whilst the heparin group had a significant decrease in incidence of minor DVT (4.8%) ($P<0.01$).

Velmahos et al (2005) includes outcome measures for both DVT and blood flow amongst patients with major trauma. However, no direct statistical comparison of the two measures is made. Velmahos did not find any significant evidence of a reduction in DVT rates with the use of NMES compared to no NMES. However, there is evidence of a significant increase of venous flow velocity in the left superficial femoral vein and left popliteal vein during the second duplex scan.

Nicolaides et al (1972) also describes the use of measures of both DVT and blood flow amongst surgical patients. However, analysis of blood flow was only used to optimise use of the NMES device. There are no reported measures of blood flow. Nicolaides 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]), as did Rosenberg, with a significant decrease in the incidence of major DVT using NMES amongst surgical patients when compared to no NMES (12.3% [control] vs. 0% [NMES]). Browse & Negus (1970) also assessed DVT incidence and found a reduction in incidence in NMES stimulated legs in a surgical population. However, Moloney et al (1972) found no significant reduction in DVT incidence amongst a sample of surgical patients (25% [control: no NMES] vs. 20% [NMES]). The EAC notes that Nicolaides et al (1983) found that the use of IPC with TED stockings was just as effective as receiving low-dose subcutaneous heparin in reducing the incidence of DVT, whilst electrical calf stimulation (NMES) was not as effective (4%, 9% and 18% respectively).

With regards to the outcome measure of venous transit time listed in the scope, the sponsor cites an unpublished interim report by Khanbhai et al (2013), [redacted] This is an interim report, and hence not included by the sponsor as direct clinical evidence. The EAC agrees with the exclusion of this report from the clinical evidence. However, the sponsor does cite some initial outcomes.

[redacted]

[redacted]

Several studies assessed subjects' tolerance of the geko™ and NMES with varying results. Tucker et al (2010) documented increased discomfort at the highest amplitude and frequency settings of the geko™ device. Jawad (vs. IPC) (2012) and Williams (unpublished) (2013) [redacted] Warwick et al (2013) reported that the geko™ device was more tolerable when subjects were wearing a plaster cast. Jawad (coagulation) (2012) reported no significant difference in patient discomfort levels with the use of geko™. Corley et al (2012) reported patient tolerability, and found a significant decrease in discomfort levels over time with the use of the NMES device, similar to Broderick et al (2013). Czyrny et al (2010) reported that subjects were more tolerant of the IPC device than the NMES device, and both Broderick et al (2011b) and Kaplan et al (2002) indicated that patients were generally tolerant of NMES stimulation. The sponsor also cites their own post-market surveillance data of 215 patients (reported as mainly post-operative vascular, post-operative orthopedic, and non-surgical vascular patients) (Firstkind Ltd. DOF_005. 2013.), stating that 85.1% (n=183) of patients assessed the geko™ device as comfortable or very comfortable to wear once applied.

The EAC also makes the following comments:

- None of the geko™ studies identified by the sponsor used pharmacological comparators. Three of the NMES/IPC studies include pharmacological prophylaxis as a comparator. Rosenberg et al (1975) and Nicolaides et al (1983) both included a test group receiving Heparin. Lindstrom et al (1982) included a test group receiving Dextran 40; however, this is not recommended as a thromboprophylaxis modality by NICE Clinical Guidance 92.

- Four of the studies, Moloney et al (1972), Lindstrom et al (1982), Browse & Negus (1970) and Rosenberg et al (1975), used an older style of NMES device, which could only be used while patients were under general anaesthesia. As the EAC has noted in table 3.2, these devices use different methodologies, so the findings are potentially less applicable to later studies

and devices. The expert opinion received by the EAC agrees that these devices are not readily comparable.

- None of the geko™, NMES and IPC studies included by the sponsor specifically analysed any potential statistical association between changes in blood flow and/or velocity in relation to incidence of DVT or PE/VTE.

- Neither the sponsor nor the EAC identified any comparator studies that included fondaparinux (one of the current standard treatments for venous thromboembolism in the UK [as listed in the scope]).

- No reported studies assessed the outcomes of post-thrombotic syndrome or length of hospital stay that are listed in the scope.

- Only three studies directly measured VTE, through measures of DVT and PE.

- There are significant differences in both the method of application and type of electrical stimulation used by the various MEST and NMES devices used in the studies. Any information presented in the studies on electrode type and placement, the pulse characteristics and duration, and the muscles being stimulated have been summarised in the study column of the table. The EAC believes that these differences make cross comparisons between effects of the devices problematic. The EAC consulted the nominated experts on this matter. Their opinions were that either comparison cannot be made, or that it cannot be made without demonstrating that there was an equivalent contraction of the calf muscles.

The sponsor implies that efficacy in VTE prophylaxis can be assessed for geko™ by comparing its effect on venous blood flow volume with that of IPC devices. The EAC is not convinced that this inference is sound. It has been shown that IPC devices exert additional prophylactic effects to that of increasing blood flow (Dai et al [1999]). Furthermore, 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]). The EAC asked the nominated experts for their opinion on the validity of assuming the same efficacy in VTE prophylaxis for geko™ 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.

Table 3.3: Summary of outcomes from sponsor identified published NMES (n=11) and IPC (n=1) studies that fitted the EAC search criteria.

Reference	Study	Subjects	Outcome 1	Outcome 2	Outcome 3	Outcome 4
Corley et al (2012) (35)	To investigate changes of blood flow due to NMES to the calf muscles, and secondly to evaluate subject compliance to the control. Duo-STIM stimulator used to stimulate calf muscles with a frequency of 36 Hz. Two round 5cm diameter neurostimulation electrodes placed over soleus motorpoints on subject's right calf. Balanced biphasic waveform with a pulse width of 350 µs and inter-pulse interval of 100 µs.	Healthy volunteers (n=40). Half group received NMES, second group, no NMES.	No significant difference in popliteal peak venous velocities and ejected venous volumes due to resting and NMES between groups on day 1 (P>0.05) or at baseline stimulation intensities (P>0.05).	Significant increase in peak venous velocities due to NMES over seven days (P<0.05): Stimulation group: 92±106% Controls: 39±40%.	Ejected venous volumes only increase significantly due to NMES in the stimulation group compared to baseline (P<0.01): Stimulation group: 100±122%. Controls: 27±28%.	Significant difference (P<0.05) in VASs scores at baseline (27.9±8.6) when compared to day seven (18.5±7.7). Compliance: mean compliance rate was 100±31% (% of unsupervised hours in which subject performed NMES).
Czyrny et al (2010) (38)	Comparison venous blood flow velocity with mild electrical stimulation of the plantar foot muscles	Healthy volunteers (n=40). Two sessions, with each subject receiving either IPC or	Before adjustment for baseline values, noninferiority of NMES device was achieved in the femoral vein	No statistical significant differences between control and stimulated	No statistical significant differences between devices and different groupings patients	Questionnaire of patient tolerance concluded that both treatments (NMES and IPC) were

Reference	Study	Subjects	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	with IPC. Focus Neuromuscular Stimulation System (NMES) provided stimulation via surface electrodes placed on sole of the foot over the plantar muscle group. 50 pulses per second, with a phase duration of 300 milliseconds was applied until slight twitch of muscle was visible. Kendall Novamedix A-V impulse system (IPC) was used with a 130 mm Hg impulse pressure with three second impulse duration.	electric foot stimulation (NMES).	(P=0.005) at time 120 minutes, and in the popliteal vein at times 120 minutes (P=0.004) and 240 minutes (P=0.055). After adjustment of baseline values, noninferiority of NMES device achieved in femoral vein at 120 minutes (P=0.008) and for the popliteal vein at times 120 minutes (P=0.018) and 240 minutes (P=0.043).	NMES leg and blood flow velocity.	based on body-mass index.	uncomfortable, 92.5% for IPC, and 82.5% for NMES.
Broderick et al (2013) (21)	Evaluation of the use of NMES to the calf muscles in the immediate hospitalised recovery period following total hip arthroplasty to	Total hip replacement patients (n=11). Patients contralateral limb used as control, with NMES applied	In the operated limb, NMES produced significantly increased peak venous velocities compared to resting (12±5.9 versus 22.5±16.8 cm/s, P=0.006).	Mean venous velocity was significantly higher in NMES stimulated operated limb compared to resting (2.3±1.4 versus 7±5.7 cm/s,	No significant differences between resting volume flow of operated and unoperated limbs (P=0.342). NMES stimulated	VAS scores used to assess comfort. No significant differences were found between baseline, start and end VAS scores (P=0.211).

Reference	Study	Subjects	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	increase venous return. Duo-STIM NMES device applied using two surface electrodes (5cm x 5cm) over motor points of the soleus muscles of both legs. NMES applied with a biphasic square-wave with a 350 µs pulse width, an interpulse interval of 100 µs and a frequency of 36 Hz.	to both legs. Measurements were taken from both the operated and un-operated limbs.	In the unoperated limb, NMES also produced significantly increased peak venous velocities compared to resting (13.8±7.6 versus 43.9±13.7 cm/s, P=0.018). Percentage increase in peak velocity produced by NMES in unoperated was significantly larger than operated limb (P=0.02). No significant differences between the resting velocities of the operated and unoperated limbs (P=0.892).	p=0.003). In the unoperated limb, NMES also produced significantly higher mean venous velocity compared to resting (3.7±2 versus 12.9±4.3 cm/s, P=0.018). No significant differences produced between operated and unoperated limbs when both at rest, with and without stimulation.	venous volume flow was significantly increased in operated limb (78.7±61.1 versus 230.4±215.2 ml/min, P=0.003) and in unoperated limb (112.6±69.5 versus 457.6±215 ml/min, P=0.018). No significant increase in volume flow between operated and unoperated limb.	
Broderick et al (2011b) (49)	To assess patient tolerance of NMES in the presence of orthopaedic implants and associated venous outflow. Duo-STIM NMES	Total hip and total knee arthroplasty patients (n=20). Patients contralateral limb used as control, with NMES applied to both legs.	No significant difference found between peak venous velocity (P=0.44) or mean velocity flow (P=0.54) and type of surgery. NMES stimulation	No significant difference between control limb and operated limb in unstimulated measures of peak venous velocity, mean velocity flow and volume flow in	VAS scores (not statistically assessed) reported five patients considered NMES stimulation ‘very comfortable’, 13 as ‘comfortable’ and two as ‘bearable’.	

Reference	Study	Subjects	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	device applied using electrodes placed over calf muscles of both legs. Electrodes used were four 5cm x 5cm with a pulse width of 350 μs, with a frequency of 36 Hz.		resulted in significantly higher mean velocity flow compared to resting (P<0.001).	both patient groups (P=0.647, 0.983, 0.744 respectively).		
Browse & Negus (1970) (23)	Evaluation of effectiveness of NMES application in post-operative patients in terms of preventing postoperative deep vein thrombosis. Two NMES devices used (mains operated SS Electronics Diagnostic Stimulator Type V MkIII or battery-operated Medelec TS2 stimulator). Direct calf muscle stimulation was applied every two seconds by two electrodes to the	Patients of major surgery (n=110).Each patient acted as own control, as only one leg given NMES.	NMES stimulation resulted in significantly reduced incidence of DVT when controlling for stimulated and unstimulated leg, and right and left leg (0.001<P<0.01).	No significant difference in DVT incidence between left and right unstimulated and stimulated leg (P>0.05 for both).	DVT was reported in one or both legs of 25 patients (incidence of 23%).	

Reference	Study	Subjects	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	back of the calf muscle, just below the lower border of the popliteal fossa and the other to the posterior surface of the lower third of the lower leg. Stimulating voltage adjusted to produce brisk plantar-flexion of foot without violent movement, with a pulse width of 30 milliseconds (15 to 45 V).					
Kaplan et al (2002) (20)	Investigation of effect of mild electrical stimulation of the plantar foot and calf muscles, on venous blood flow velocity in the femoral and popliteal veins. The Focus™ Neuromuscular Stimulation System was used to stimulate the calf and foot plantar	Healthy volunteers (n=49). Subjects own contralateral leg (without NMES) acted as control (randomly assigned).	NMES stimulation of calf muscles resulted in significantly increased femoral (P<0.035) and popliteal (P<0.003) blood flow.	NMES stimulation of foot plantar muscles resulted in significantly increased femoral (P<0.0.0001) and popliteal (P<0.009) blood flow.	There were no significant differences in magnitude of blood flow of either femoral or popliteal between the different muscle stimulation groups.	Patient tolerance during calf and foot plantar stimulation was found to be significantly significant with most patients describing the stimulation as comfortable.

Reference	Study	Subjects	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	muscles. Pulse widths of 50 per second, phase duration of 300 microseconds.					
Lindstrom et al (1982) (24)	Compare effects of calf muscle stimulation with groups of impulses with established prophylactic (Dextran 40). Bilateral calf muscle stimulation with electrodes applied preoperatively. Stimulation strength of 40-50 mA, impulse duration of 50 ms.	Patients of major abdominal surgery (n=112). Patients randomised to NMES, Dextran 40 or control group (standard routine only).	Significant decrease in incidence of pulmonary embolism in stimulation (NMES) and Dextran 40 group when compared to control (P<0.05): Stimulation: 16%. Dextran 40: 11%. Control: 35%. No significant difference in incidence of DVT.	Significant lower incidence of DVT in patients with malignant disease (no p value specified): Stimulation: 54%. Dextran 40: 15%. Control: 36%.	No significant difference in mean values for measures of coagulation.	
Rosenberg et al (1975) (42)	Comparison of incidence of leg vein thrombosis in patients with malignant disease with the use of intermittent electrical calf muscle stimulation or heparin calcium 5000.	Patients of major general surgery (n=295). Randomly assigned to NMES, heparin or no specific prophylaxis group.	Amongst surgical patients, there was a significant reduction in incidence of major DVT for both heparin calcium and NMES group compared to control (P<0.01 & P<0.001). NMES: 4% Heparin: 0%	Patients with benign disease had significant reduction in incidence of major DVT for both heparin calcium and NMES group compared to control (P<0.05 and P<0.05).	Patients with malignant disease had significant reduction in incidence of minor DVT in only the heparin calcium group compared to control (P<0.01). Minor DVT:	Majority of DVT occurrences occurred within the first day after operation for all three groups: NMES 62.5% Heparin: 35.7% Control: 65.3%. Only heparin group compared to control

Reference	Study	Subjects	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	Thrombophylactor device used, delivering interrupted direct current to 50 milliseconds duration every five seconds. Each pulse automatically reversed in polarity to avoid tissue ionization. Voltage applied caused calf muscle contraction without affecting thigh muscles. Electrodes strapped to two locations: one of upper calf, and other above the ankle.		Control: 20.2%. Only significant reduction in heparin calcium for minor venous thrombosis (P<0.05). NMES: 24% Heparin: 7.3% Control: 23.6%.	Minor DVT: NMES: 16.2% Heparin: 8.8% Control: 22.8%. Major DVT: NMES: 0% Heparin: 0% Control: 12.3%.	NMES: 46.2% Heparin: 4.8% Control: 46.9%. Major DVT: NMES: 15.4% Heparin: 0% Control: 12.5%.	was significantly different (P<0.05).
Velmahos et al (2005) (46)	To assess the prevention of deep vein thrombosis in patients with major trauma using electrostimulation. Lymphavision stimulator used,	Major trauma patients (n=47). Randomly assigned to either MEST or no MEST group.	No significant differences found in rates of DVT Proximal DVT: MEST: 11.5% Control: 14%. Peripheral DVT: MEST: 15% Control: 14%.	The majority of measures of venous flow velocity (cm/min) were not significant. However, the MEST group had significantly increased velocity	No significant differences in venous diameter between groups.	

Reference	Study	Subjects	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	with electrodes placed on calves and medial thighs of both extremities. Voltage gradually applied (0-120 V), until slight visible titch of the muscles. Stimuli were three milliseconds long at frequency of 1.75 Hz (105 /minute). Inversion of polarity every 5 seconds.		Total DVT: MEST: 27% Control: 28.5%.	compared to control in two measures in the second duplex. Left superficial femoral vein (P=0.02): Mean (SD): MEST: 21±6 Control: 16±5 Left popliteal vein (P=0.03): Mean (SD): MEST: 22±10 Control: 15±9		
Nicolaides et al (1972) (74)	To determine the most effective electrical stimulus in preventing DVT. Thrombophylactor used when patient anaesthetized. Two padded electrodes (6 by 15 cm) applied to upper and lower part of the posterior aspect of one calf, 50 millisecond square wave current applied every five seconds. Alternative	Surgical patients (n=116). Split into NMES or no NMES group.	Significant decrease in indigence of DVT in stimulated (NMES) leg of test group when compared to right or the left leg of control group (p=0.00028): NMES: 1.6% Control right leg: 23% Control left leg: 21% Study reports a 92% reduction in the incidence of DVT in stimulated leg. No significant difference in incidence of DVT in unstimulated	Incidence of DVT occurring on day of operation was significantly lower in the unstimulated leg (n=0) when compared to either leg of the control group (both n=6) (P=0.011).	No values or measures of blood velocities were reported.	

Reference	Study	Subjects	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	pulse automatically reversed in polarity to avoid tissue ionization.		(NMES) leg of test group when compared to right or the left leg of control group.			
Moloney et al (1972) (57)	To evaluate the effect of electrical stimulation of the legs on postoperative thrombosis. Purpose built machine (Rank Precision Industries Ltd) used to deliver surged alternating current, lasting 3 seconds, every 7.5 seconds. Peak output voltage (100-200 V) applied to anaesthetized patient. Voltage adjusted until visible stimulation of calves, thighs, buttocks and feet.	Surgical patients (n=285). Randomly assigned to either NMES or no NMES group.	Incidence of leg-vein thrombosis was not statistically significant difference between stimulated (NMES) (20%) and unstimulated groups (25%).	Patients of emergency admission or waiting list admission had no significant difference in DVT incidence when NMES group compared to no NMES group.	Majority of DVT occurred within nine days of operation.	Age distribution was found to be comparable between groups. Incidences of pulmonary embolism were too small for analysis.
Nicolaides et al (1983) (37)	Intermittent sequential pneumatic compression of the legs and thromboembolism-	Major abdominal operation patients (n=150). Patients randomly assigned to NMES, heparin or IPC/TED	Significant reduction in DVT incidence in heparin group (9%) compared to NMES group (18%) (P<0.05).	Significant reduction in DVT incidence in IPC/TED stockings group (4%) compared to NMES	No significant difference between heparin group and IPC/TED stockings group (P>0.05).	

Reference	Study	Subjects	Outcome 1	Outcome 2	Outcome 3	Outcome 4
	deterrent stockings in the prevention of postoperative deep venous thrombosis. Powley Doran Electronic Gaiter applied stimulation to anesthetized patients. A galvanic stimulus delivered to the gastrocnemius-soleus muscle group at a rate of 12 per minute. Adjustment was made until brisk plantar flexion of the foot was produced with only slight movement at the knee.	stockings group.		(18%) (P<0.0025).		

3.7 Description of the adverse events reported by the sponsor

The sponsor reports that the only known adverse incidents were thirteen events of skin irritation or inflammation, thought to be from the use of hydrogel electrodes. The frequency of this event is reported as 0.1%. The EAC views this as a normal incidence rate for hydrogel use, and it does not raise an undue safety concern.

The EAC would like to highlight that, to date, the device has been studied on a small number of healthy subjects and that there are no completed studies involving patients. In view of this, the EAC does not believe that any conclusions can be drawn regarding adverse incidence caused by the use of this device in clinical practice.

One of the expert advisers reported that the device did not appear to work if the limb was oedematous and that they had trouble keeping the device attached to the leg.

The EAC did not consider that the post market surveillance as reported by the sponsor assessed adverse incidents.

3.8 Description and critique of evidence synthesis and meta-analysis carried out by the sponsor

No meta-analysis or evidence synthesis was conducted for the geko™ studies. The sponsor states that this is due to the *'high degree of heterogeneity between study methodologies'*. Specifically, the sponsor notes that there were variations in geko™ device settings used, that only two outcome measures (as listed in the scope) were reported, that outcome measures were reported differently between studies, that the comparators varied, and that all trials were non-blinded.

The sponsor provides an overview of each geko™ study separately in section 7.9. However, this is hard to interpret given the different outcome measures and the listed clinical benefits, which do not all fit within the outcomes listed in the scope.

The sponsor provides no evidence synthesis or meta-analysis of the NMES and IPC studies. However, there is a summary of these studies in section 7.9, under the heading 'Increased blood flow results in reduction in DVT'. In this section, the

sponsor also refers to several studies and publications not identified in the sponsor's own systematic review.

3.9 Additional work carried out by the External Assessment Centre in relation to clinical evidence

The EAC had the following concerns regarding the effectiveness of the sponsor's search strategy:

- The systematic review excluded any studies involving a pharmacological intervention. This prevented the subgroups specified in the scope from being investigated.
- The included intervention was specified as "geko™ OnPulse™ technology device" but it is not possible to identify this as the device used in several of the included studies.
- Terms referring to venous blood velocity and flow, one of the outcomes included in the scope, had not been included in the search strategy.

The EAC decided that this should be addressed by conducting an additional systematic review to ensure that all available evidence had been considered.

The EAC determined that this review could be limited to those that include a NMES or MEST device, including geko™, among the interventions. This differs from the sponsor's search strategy because the EAC is not convinced of the applicability to geko™ of studies using *only* IPC or foot impulse devices. The EAC has no reason to exclude MEST studies from its own SR (given the scope), and notes that the sponsor also included a MEST study (although incorrectly reported as a NMES study [Velhamos et al {2005}]). No interventions were excluded, so this allowed the inclusion of studies that *compared* the efficacy of NMES or MEST devices with other forms of thromboprophylaxis including IPC and pharmacological interventions.

Table 3.4 lists the revised EAC systematic review search terms. The search method (including the search terminology) used is presented in appendix 3.3.

Table 3.4: Selection criteria used to identify NMES and MEST published studies.

Inclusion criteria	
Population	Patients and volunteers
Intervention	NMES/MEST[6]
Outcomes	Incidence of DVT/VTE Incidence of pulmonary embolism Postthrombotic syndrome Blood flow velocity Blood circulation Venous insufficiency Venous transit time
Study design	RCTs, non-RCTs
Language restrictions	• English language only • Foreign language papers with English abstracts could be included
Search dates	No restriction
Exclusion criteria	
Population	Patients undergoing treatment of DVT
Study design	Case studies, editorials, letters, reviews
Interventions	No restriction

NMES: Neuromuscular electrical stimulation
MEST: Muscular electrostimulation
DVT: Deep vein thrombosis
VTE: Venous thrombosis

A total of thirty-eight studies were selected for full paper review (see appendix 3.4 for all papers). Thirteen of these had been present in the sponsor's systematic review and so did not receive further critique. Of the remaining twenty-five, twenty were rejected. The EAC's findings from the five accepted papers are now summarised and an overview of each study presented in table 3.5.

[6] NMES devices include the geko^{TM} device

Table 3.5: Summary of key points from additional accepted EAC systematic review studies (n=5).

Title and Author(s)	Publication	Study design, and duration/follow up	Subjects, age, gender, and country	Duration of study	Intervention/comparator	Outcomes
Hemodynamic performance of NMES in the early post-operative period following orthopaedic surgery. Broderick BJ, Breathnach O, Masterson E, Breen PP and OLaighin G.	Medicine & Biology Society. 2011: 7630-7633.	Pilot study, four hours, no follow up.	Five (but one did not complete) post-operative THA patients. One male and five female. Unstated age. Republic of Ireland.	Four hours of NMES.	NMES (Duo-Stim)/ compared to baseline.	Final peak venous flows all higher than baseline (between 18% and 78%) (P<0.05) but venous flow not significantly different from baseline (P=0.19). Three increased, one decreased, and one had problems with measurement so abandoned.
A pilot evaluation of a neuromuscular electrical stimulation (NMES) based methodology for the prevention of venous stasis during bed rest. Broderick BJ, O'Briain DE, Breen PP Kearns SR and OLaighin G	Medical Engineering & Physics. 32 (4): 349-355, 2010.	Pilot study, four hours, no follow up.	Ten healthy volunteers. 22-36 years. Six male and four female. Republic of Ireland.	Four hours.	Duo-Stim/rest protocol	Four hours of rest decreased popliteal vein flow by 47%. Four hours of NMES increased popliteal vein flow by ~301%.
Venous emptying from the foot: Influences of weight bearing, toe curls, electrical stimulation, passive compression, and posture. Broderick BJ, Corley GJ,	Journal of Applied Physiology. 109 (4): 1045-1052, 2010.	Pilot study. No follow up.	Ten healthy volunteers. Unstated age. Five male and five	Three repetitions of each comparator.	Weight-bearing/ toe-curling exercises/ foot IPC/ NMES.	Weight-bearing and toe curls expel more blood from the leg than IPC or NMES. Flow measured in popliteal vein was greater than post tibia and peroneal veins.

Title and Author(s)	Publication	Study design, and duration/follow up	Subjects, age, gender, and country	Duration of study	Intervention/comparator	Outcomes
Quondamatteo F, Breen PP, Serrador J and OLaighin G.			female. Republic of Ireland.			Note: foot muscles of participants start to cramp with NMES.
Functional electric stimulation to enhance systemic fibrinolytic activity in spinal cord injury patients. Katz RT, Green D, Sullivan T & Yarkony G.	Archives of Physical Medicine & Rehabilitation . 68 (7): 423-426, 1987.	Pilot study. Full article not available online - from abstract.	Ten spinal cord injury patients. Age, gender and country unavailable.	60 minutes of stimulation, 160 minutes study period.	Before NMES/ 60minutes after NMES/ 100 minutes after NMES.	Significant increase in plasma fibrinolytic activity was noted using whole blood and platelet-rich plasma clot lysis assays. A mild to moderate increase in flow was achieved. FES was not as successful as manual compression in promoting venous emptying of the lower extremity. FES may be a useful tool in the prevention of DVT in SCI patients due to a significant increase in fibrinolytic activity and a mild to moderate increase in venous blood flow. FES merits full-scale clinical evaluation for this purpose.
Prediction and prophylaxis of postoperative thromboembolism--a comparison between peroperative calf muscle stimulation with groups of impulses and dextran 40. Lindstrom B, Holmdahl C, Jonsson O, Korsan-Bengtsen K, Lindberg S, Petrusson B,	British Journal of Surgery. 69 (11): 633-637, 1982.	Clinical prospective trial, patients randomly placed into three groups, including a control.	112 patients. 30-86 years. 65 males and 45 females. Sweden.	Stimulation applied during operation only. Dextran 40 given post operatively and then on day one	Stimulation / Dextran 40 / Control Group	A significant reduction in the incidence of DVT and PE was seen in the stimulation and Dextran 40 groups compared to the control. ($P<0.05$). There was no significant difference between Dextran 40 and stimulation groups.

Title and Author(s)	Publication	Study design, and duration/follow up	Subjects, age, gender, and country	Duration of study	Intervention/comparator	Outcomes
Pettersson S, Wikstrand J & Wojciechowski J.		Final assessment for VTE was done four to six days post operation.		and three post-operation.		

FES: Functional Electrical Stimulation

Three of the accepted studies (Broderick et al [2011a], Broderick et al [2010a], and Broderick et al [2010b]) detail preliminary work on the Duo-Stim NMES device by the same group associated with the study included by the sponsor (Broderick et al [2013]).

The first of these pilot studies (Broderick et al [2010a]) used ten healthy volunteers and found that performing simple weight bearing or toe curl exercises was more effective in raising venous blood velocity than either Duo-Stim or an IPC device. There were reported incidents of the NMES device causing cramping of the foot muscles during this study.

The second of these studies (Broderick et al [2010b]) also used ten healthy volunteers as subjects, positioned in an elevated supine position, typical of a hospital bed. The effect on blood flow in the popliteal vein was compared for four hours of rest and four hours of Duo-Stim application. The outcomes of this study were that rest decreased blood flow in the popliteal vein by 47% on average, and that Duo-Stim reversed this trend, increasing peak venous flow by approximately 301% at the end of the four-hour study period.

The third study (Broderick et al [2011a]) used five post-operative patients (total hip arthroplasty) and compared venous blood velocity and flow measurements, before, during and after four hours of Duo-Stim application. Blood velocity measurements were found to have increased significantly, but blood flow was reported not to have changed significantly from baseline. This was due to one patient's blood flow decreasing over the study period. One patient reported muscle fatigue at the end of the study.

The EAC considers the Duo-Stim to be a different type of NMES device to the geko^{TM}. The method of application is directly to the muscle motor points and the electrical stimulation is delivered in 'packets of pulses' lasting two seconds at a time with 30 second rest intervals in between. The frequency of stimulation during the pulse packet differs from that of geko^{TM} (38 Hz versus 1 Hz). The EAC concludes that it is difficult to relate the outcomes from the studies using Duo-Stim to geko^{TM}, as the type of muscle contraction they produce could be very different.

Katz et al (1987) applied 60 minutes of electrical stimulation to a group of ten spinal injury patients and compared it to the use of an IPC device. A mild to moderate increase in flow was reported with the use of electrical stimulation, but it was not as

successful as IPC in venous emptying of the leg. The application method and type of stimulation used is also different to that of geko™ as shown in table 3.5.

Lindstrom et al (1982) conducted a prospective clinical trial involving 112 post-operative patients. Three groups were formed, one receiving electrical stimulation during the operation, one receiving Dextran 40 (a pharmacological form of prophylaxis) and one control group who received no prophylaxis. Incidents of VTE were actively investigated four to six days post operation, using a fibrinogen uptake test, pulmonary perfusion scintigraphy, and x-ray examinations. The Dextran 40 and stimulation groups are both reported as having significantly less incidence of VTE than the control group. There was no significant difference between the Dextran 40 and stimulation groups. This is the only study with a pharmacological comparator, and as mentioned previously, Dextran 40 is not recommended as a thromboprophylaxis modality in NICE Clinical Guidance 92. Furthermore, the application, duration and type of electrical stimulation are quite different to that of geko™.

The EAC believes that this additional literature review has not added any significant clinical evidence that would change its earlier conclusions. The varying results found in the studies, and differences between the various NMES devices used, has confirmed the EAC's opinion that the evidence for one type of device may not apply to another. Furthermore, there is a high degree of heterogeneity between these studies; therefore, the EAC does not consider that a meta-analysis and/or evidence synthesis would be useful.

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™, 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™, but felt that if geko™ increased venous flow sufficiently, then there would be a rationale to expect that it might prevent VTE, but However, both added that prospective, randomised, controlled trials with DVT as an endpoint would be needed to demonstrate this conclusively.

- The three remaining respondents had first-hand experience of the geko™ device:

  '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 vein'

  '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'

- The sponsor was able to show the ultrasound clips to the EAC. The EAC agrees that the extent of the effect that was apparent from these clips looks promising in demonstrating that geko™ is capable of preventing venous stasis throughout the lower limb. If the completed study was to show this level of clearance is achievable in patients, then the EAC believes that this would demonstrate a possible mechanism by which geko™ may be expected to reduce the risk of thrombosis.
- The next respondent provided details from a study they had conducted using geko™. These details were provided academic in confidence as the study is not yet published. The study is included in the clinical evidence submitted by the sponsor and the EAC has already made comment on this study in sections 2 and 3 of this report.
- The final respondent commented on their experience of using the device on patients:

'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 off and is difficult to keep attached to the leg'

The EAC feels this experience helps to highlight why studies involving patients should be necessary, as the experience of the device can be quite different to that with healthy volunteers.

The EAC requested the opinion of the expert advisors as to why mobile patients are deemed to be at low risk of DVT. The following reply was received:

'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.

3.10 Conclusions on the clinical evidence

All of the evidence regarding geko™ concerns its use on healthy volunteers. The EAC believes that conditions present in a typical patient population could impair the efficacy of geko™.

The only outcome listed in the scope which is considered in the evidence regarding geko™ is impact on venous blood flow. The EAC believes that the location in which the blood flow is found to improve is important. Increasing the peak venous flow in the middle of a major vein may have little impact on preventing venous stasis in other areas, where the probability of thrombosis is thought to be higher. However, some of the expert opinion did state that they felt it was reasonable to expect the increase in flow to translate throughout the lower limb and that investigation of this effect may already be underway.

The EAC considers 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. Many of the NMES/IPC studies did not find that stimulation necessarily resulted in decreased incidence of DVT. Only two studies included measures of both DVT and PE incidence. Furthermore, it is recognised that the exact mechanism, or combination of mechanisms, by which these devices prevent VTE is not understood (Roberts et al [1970], Morris & Woodcock [2004], Nicolaides et al [1971] and Dai et al [1999]).

The literature shows that venous thrombosis has long been believed to have three major risk factors, known as Virchow's Triad. While the EAC agrees that venous stasis is a risk factor, it does not believe the literature shows it is essential for venous thrombosis (Morris & Woodcock [2004]). Therefore, the efficacy of VTE prevention cannot be proven by venous stasis prevention alone. The EACs consultation with the nominated experts agreed with this.

The sponsor has made an association between geko™ and other NMES devices that have shown efficacy in preventing VTE in patients. The geko™ is being considered by MTAC because it is a device using an innovative method of applying the electrical stimulation. This allows the device to use a significantly lower electrical output, applied across a smaller area. This has the potential to eliminate the discomfort associated with other NMES devices, some of which can only be administered under general anaesthetic. However, the EAC believes that the evidence pertaining to one NMES device cannot be assumed to be applicable to another, as the devices can produce very different types of muscle contractions. Furthermore, some NMES devices have not been shown to be effective in preventing VTE. The EACs consultation with the nominated experts agreed with this.

The effect of geko™ on venous blood flow has been compared to that of IPC devices. The inference being made is that if geko™ improves venous flow by the same amount as IPC, it can be assumed that geko™ is as efficacious as IPC in preventing VTE. The sponsor's evidence centres on the assertion that IPC devices work by increasing venous blood flow, therefore reducing VTE incidence. However, the EAC does not consider this inference to be valid given that there is conflicting evidence for the relationship between IPC use and VTE prophylaxis. Whilst some studies documented in this report found a reduction in the incidence of VTE with the use of IPC, it is not clear whether it is due to increased venous blood flow or other prophylactic effects. Some of the nominated experts expressed the opinion that venous volume and venous distension factors may play important roles. Therefore, it is not known presently which of these effects, or combination of effects, has the greatest impact on VTE prophylaxis. Furthermore, one of the sponsor's identified studies found a reduced venous blood flow with IPC use: Jawad (vs. IPC) (2012) documents an average percentage change to baseline for venous flow of -4%.

Overall, it is the EAC's opinion that there is little to link efficacy of VTE prevention in patients to the evidence submitted.

4 Economic evidence

4.1 Published economic evidence

Critique of the sponsor's search strategy

The sponsor submitted a search strategy designed to retrieve relevant health economics studies from published and unpublished literature. The following databases were searched: NHS EED database in the Cochrane Library, Medline and Medline In-Process, Embase and Econlit. The searches combined terms for the conditions (VTE), the treatment (geko™ and electrical stimulation) and economic search terms. Electronic searches were supplemented by searching manufacturer databases and the Cost-Effectiveness Analysis Registry.

In total, 27 publications were identified and titles and abstracts were reviewed for full text assessment. However, none of them were found to be relevant, and all were excluded. The sponsor thus concluded that no economic evidence was available for geko™ or other NMES/MEST devices.

The EAC reviewed the search strategy and considered it appropriate. However, the EAC felt that the Health Technology Assessment (HTA) Database should also have been searched. The EAC performed this additional search using the strategy provided by the sponsor to search the NHS EED database. No further useful publications were found, substantiating the conclusions reached by the sponsor that no economic evidence is available for geko™ or other NMES/MEST devices.

Critique of the sponsors study selection

Not applicable as the sponsor has not included any economic studies.

Included and excluded studies

Not applicable as the sponsor has not included any economic studies.

Overview of methodologies of all included economic studies

Not applicable as the sponsor has not included any economic studies.

Overview and critique of the sponsor's critical appraisal for each study

Not applicable as the sponsor has not included any economic studies.

Does the sponsor's review of economic evidence draw conclusions from the data available?

Not applicable as the sponsor has not included any economic studies.

4.2 De novo cost analysis

Since no economic evidence was available for geko™ and NMES/MEST devices, the sponsor has submitted a cost model. In summary, it is the view of the EAC that, while the overall structure of the economic model provides a sound representation of the clinical pathways of relevance for estimating the cost implications of geko™, the core modeling assumption that geko™ will reduce the risk of DVT within the relevant patient population, and the estimated cost savings that follow from this, is unreliable. In the remainder of this section a more detailed assessment and critique of the economic modeling presented by the sponsor is provided. The discussion of clinical parameters and variables in this section deals specifically with the EAC's concerns regarding the core assumption that geko™ will reduce the incidence of DVT.

Patients

The patient group considered in the cost model is patients for whom current mechanical methods of prophylaxis are impractical or contraindicated. This could potentially include a diverse range of patients with comorbidities like stroke, obesity, severe leg deformity, plaster casts, bilateral lower extremity trauma, severe or critical lower limb ischaemia, swelling of the legs, recent operative leg vein ligation, local leg

conditions in which other mechanical prophylactic devices may cause damage or pain, or a known allergy to materials used in current methods of mechanical prophylaxis. This is consistent with the patient group (people at risk of venous thromboembolism and for whom current mechanical methods of prophylaxis are impractical or contraindicated) covered by the scope. The cost analysis also considers the sub groups mentioned in the scope. Subgroup analysis related to the use of pharmaceutical prophylaxis (i.e. combined prophylaxis); and stroke patients has been considered.

Technology & Comparator(s)

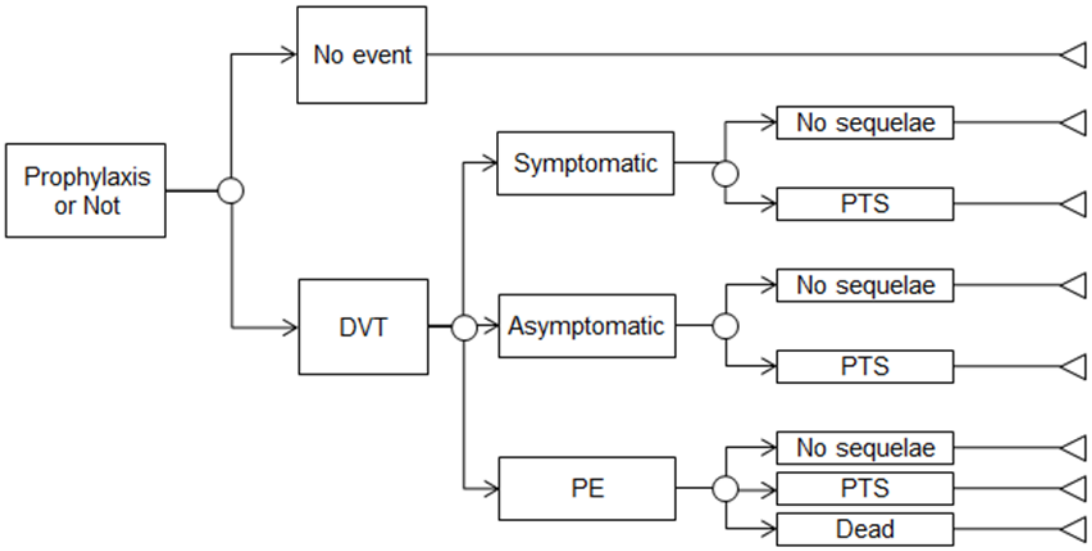
The cost model has assessed the impact of geko^{TM} in the patient population mentioned in the scope. For this evaluation, the comparator as per the scope is no mechanical prophylaxis. The EAC believes that the sponsor's submitted model has appropriately included the technology and a relevant comparator and provided results for them in this evaluation.

Model structure

The sponsor submitted a decision tree model from the NHS and personal social services perspective, for estimating the cost associated with geko^{TM} along with the comparator. The decision tree structure is an amended version of that used in the NICE venous thromboembolism (VTE) guidelines (NICE 2010).

The model, and all subsequent estimated cost impacts relating to geko^{TM}, is built on the assumption that patients who have an underlying risk of deep vein thrombosis (DVT), and who are subsequently administered the geko^{TM} device, will experience a reduction in their baseline risk of DVT. The model then assumes that a proportion of those patients who experience DVT will progress to pulmonary embolism (PE), while the remainder will have either asymptomatic or symptomatic DVT. Subsequently, a proportion of patients are also assumed to experience post-thrombotic syndrome (PTS), a permanent comorbidity which can generate costs over the patient's lifetime. Further, it is also assumed that the PE patients also have a risk of death. A diagrammatical representation of the model structure is presented in Figure 4.1.

Figure 4.1: Model structure



The time horizon for the decision tree is one year, where most of the costs associated with prophylaxis, DVT and PE treatment are assumed to occur. However, PTS can generate lifetime cost and the model includes the lifetime (15 years) cost of PTS. The primary aim of the prophylaxis is to prevent DVT and its sequelae, and the decision tree structure reflects the impact of prophylaxis and the clinical pathways. The EAC believes that 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 VTE NICE model and the sponsor's model is that NICE considers DVT and PE as separate arms in the model, whereas the sponsor models PE to commonly occur as a result of DVT, which the EAC believes is a reasonable amendment to make. The EAC did not find any areas for improvement and is of the view that the model structure with its assumptions, pathways and health states is sound. The model also has added credibility as it is an amended version of that used to develop existing NICE guidelines.

Clinical parameters and variables

There are a number of assumptions around the clinical parameters and variables used in the model, which are described and critiqued below. The sponsor used three experts (one of them is a NICE nominated expert adviser) to check the validity of the model structure, inputs and assumptions:

- The underlying risk of DVT with no prophylaxis used in the base analysis is 29.1%, based on the average risk of DVT for all surgical patients as per the NICE VTE guidelines. The sponsor also uses the underlying risk of DVT for general medical patients (23.8%) as per the NICE VTE guidelines in a sensitivity analysis of changes to the baseline risk of DVT.

- The proportion of DVTs that are symptomatic is assumed to be 20%. This assumption is based on literature estimates, but the sponsor does not clearly indicate how they arrived at the 20% rate, which seems rather arbitrary. The EAC considers that use of arbitrary assumptions to be valid in the absence of data, provided that a clear explanation and justification is given. Even though this assumption is arbitrary, the EAC note that it has been subjected to sensitivity analysis by the sponsor to reflect the uncertainty in this parameter.

- The proportion of DVT progressing to a PE is assumed to be 10.5%, and the sponsor states that this is based on the NICE VTE guidelines. The guidelines report the incidence of symptomatic PE at 3.1% and the sponsor states that, assuming PEs occur as a result of a DVT (with an underlying risk of 29.1%), the proportion of DVTs that must progress to a PE can be approximated to 10.5%. It not clear from the sponsor's submission how exactly the approximation of 10.5% was estimated from the underlying risk and incidence of PE, making it difficult for the EAC to ascertain whether the approximation of 10.5% is reasonable. However, uncertainty in relation to this variable has been handled both through deterministic and probabilistic sensitivity analysis, which is considered reasonable.

- The death rate resulting from PE is assumed to be 6%, based on the NICE VTE guidelines for general surgery patients, which the EAC considers as reasonable. It has also been subjected to sensitivity analysis to explore the uncertainty.

- PTS is assumed to occur in 25% of patients with symptomatic DVT and PE and in 15% of patients with asymptomatic DVT. This assumption is based on the NICE VTE guidelines and is considered reasonable by the EAC. Further, uncertainty surrounding these estimates has been explored in the sensitivity analysis undertaken by the sponsor.

- The base case analysis does not include pharmacological prophylaxis, and therefore the risk of bleeding is not relevant for the modelling. The EAC considers this assumption to be appropriate.

- The sponsor recognizes that there are no clinical trials demonstrating a direct relative risk (RR) reduction associated with the use of the geko^{TM} device as a prophylaxis. The sponsor builds the case for geko^{TM} based on the hypothesis that the RR reduction in DVT obtained with the geko^{TM} device would be at least equivalent to that achieved with IPC. The equivalence of IPC and geko^{TM} is assumed based on the clinical evidence that simulation with the geko^{TM} device results in significantly greater increases in blood flow compared with IPC. A relative risk of 0.39 based on incidence of DVT following use of NMES as reported in Browse & Negus (1970) is used in the base-case analysis, on the conservative assumption that the geko^{TM} device would achieve the same RR reduction as that reported by Browse & Negus (1970). This is further justified with reference to the fact that the RR value falls within the range (0.31 to 0.58) identified for IPC in the NICE VTE guidelines.

  The EAC believes that this is a weak assumption to make in the absence of clinical evidence that directly links the use of geko^{TM} with a reduction in the risk of DVT. The sponsor uses clinical evidence to infer that if geko^{TM} 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 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]).

  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 geko^{TM} and IPC devices based on a comparison of their effects on venous blood flow alone, although it was strongly suggestive. 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. All experts agreed that there is a need to demonstrate the clinical effectiveness of geko™ in reducing DVT/VTE in clinical trials.

Further, the relative risk pertaining to NMES/MEST devices cannot be assumed to apply to geko™ device, since the EAC believes that the evidence related to one NMES device cannot be assumed to be applicable to another, as the devices can produce very different types of muscle contractions. The EAC also sought expert opinion from NICE nominated experts on using the evidence of NMES/MEST devices for geko™ device. Responses from four NICE experts clearly indicated that it was not appropriate to use the NMES/MEST evidence, especially from old studies since the electrical stimuli used in the old studies were strong, painful and need to be used under general anaesthesia. One expert also said that the relative risk for the NMES/MEST device might be too high and not appropriate to be used for geko™. However, one expert (who was an expert advisor to the sponsor for the development of the cost model) expressed the opinion that it is a reasonable assumption to make. Further, experts have also confirmed that different NMES/MEST devices can produce very different type of muscle contractions.

Morris & Woodcock (2004) published a review of published scientific evidence for the venous flow effects of mechanical devices, particularly IPC, and the relation to prevention of deep vein thrombosis. The authors conclude that:

'there are clearly flow implications to the particular type of compression used, but evidence for the clinical influences of those differences in flow patterns (peak velocity, duration, etc.) are poor or nonexistent. There is no reason to believe that any particular compression is more or less effective in preventing DVT than any other system. This is particularly true when peak velocities are considered, which are a very popular measure among some manufacturers of the 'efficacy' of their systems. There is no evidence that intermittent compression systems that produce higher velocities on compression yield lower DVT rates. High peak velocity does not equal better DVT protection. Indeed, one recent study by Proctor et al (2001) would suggest the opposite'

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. Although the general model structure is sound, the basic assumption around the expected impact of the geko™ device on the risk of DVT makes the overall analysis and economic conclusions weak. If more robust clinical evidence for geko™ can be generated in the future and applied in this model, the results would offer a firmer basis for quantifying any cost savings from the model.

Resource identification, measurement and valuation

A number of assumptions on resource identification, measurement and valuation have been used to estimate costs used in the model, which are described and critiqued as below:

- A systematic review was not conducted to identify resource data from literature, but instead the estimate was based on NICE VTE guidelines, which the EAC believes was a credible way to estimate costs.

- The cost of symptomatic DVT is £1,718 and is equal to the non-elective inpatient (long stay) NHS reference cost (QZ20Z) for DVT, which the EAC considers appropriate as an estimate of the additional cost generated through the incidence of DVT.

- The cost of managing a DVT is considered to be the same irrespective of the patient's underlying condition. The sponsor recognizes that this is a conservative assumption and that the cost could vary with underlying comorbidities. This uncertainty has been explored through sensitivity analysis by the sponsor, which the EAC considers to be reasonable.

- The cost of PE arising in consequence of DVT is assumed to be £2,022 and is 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 EAC

considers this estimate to be reasonable. The sponsor has also allowed for uncertainty in relation to the cost of PE through sensitivity analysis.

- No direct cost has been estimated for asymptomatic DVT because, by definition, the patient does not know they have DVT and will not present for treatment. The EAC considers this assumption to be reasonable.

- Lifetime costs for PTS are included in the model. A mean life expectancy of 15 years from interim life tables for the mean age based on VTE guidelines 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 literature estimate is, however, from a USA study including only direct medical costs in both the inpatient and the outpatient setting. A limitation with this is that there could be differences between the approaches to clinical management of PTS in the USA and the UK. In the absence of UK-based estimates, the EAC considers the USA estimate to be reasonable and notes that it has been appropriately converted from USA$ to UK£ using purchasing power parities and inflated to 2012 using relevant inflation indices. The EAC believes that these estimates would have benefited from further validation with UK-based experts in the management of PTS before using in the model. Uncertainty concerning the life-time cost of PTS has also been addressed by the sponsor through sensitivity analysis.

Technology and comparators' costs

The cost of the technology (geko^{TM}) is £22 per pair exclusive of VAT. The cost per 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 geko^{TM} 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.

The comparator in the base-case analysis is no mechanical prophylaxis, and there is consequently no cost associated with it. The cost of pharmacological prophylaxis is considered in the sub group analysis and the average cost per day is £2.95 which is a cost based on the British National Formulary, weighted based on quantity dispensed, as reported in the Prescription Cost Analysis 2012. Again, the cost per administration is based on the hourly cost of £41 and is underestimated because medication administration to the patient should be considered as a patient contact task and therefore valued at £100.

Sensitivity analysis

In order to explore the uncertainty surrounding parameters used in the cost model, sensitivity analysis was performed. One-way sensitivity analysis was performed on all model parameters using confidence intervals/ranges (table 4.1). Two-way scenario analysis was conducted varying the RR of DVT following use of the geko™ device and the proportion of symptomatic DVTs (table 4.2). In addition, probabilistic sensitivity analysis (with 10,000 iterations) was also performed using confidence intervals/ranges and the associated distributions (table 4.3). The EAC considers all the sensitivity analysis to be reasonable and a valid approach to test for uncertainty surrounding the parameters. Only the staff nurse cost per hour of £41 is not appropriate for the reasons mentioned in the previous sections. However, this cost is based on the annual Personal Social Services Research Unit (PSSRU) unit cost compendium (Curtis [2012]) and the EAC does not expect any variation in assumptions used in relation to this value to have a large effect on the cost savings for geko™.

Table 4.1: Variables used in one-way scenario-based deterministic sensitivity analysis

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

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

Table 4.2: Variables used in multi-way scenario-based sensitivity analysis

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

DVT: deep vein thrombosis
RR: relative risk

Table 4.3: Variables used in probabilistic sensitivity analysis

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

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

4.3 Results of de novo cost analysis

Base-case analysis results

The cost per patient estimated within the decision model for the technology (geko™) is £359 and for the comparator (no prophylaxis) is £565, resulting in a cost saving for geko™ of £206 per patient. An hourly cost of £41 for nurse time was used in the cost model. While the EAC considers that the appropriate rate of £100 should have been used, the EAC would not expect this to have any major implications for cost savings if the model is re-estimated. Since the EAC believes that basic assumptions on the expected impact of the geko™ device on the risk of DVT makes the overall analysis and economic conclusions weak, re-estimation of the model would add little value to the economic evidence. However, the EAC has re-estimated the cost savings of geko™ device with the new parameter for completeness.

Sensitivity analysis results

Univariate sensitivity analysis showed that with changes in model parameters, the cost savings conclusion for geko™ does not change. The sponsor also notes from the univariate analysis that the top three drivers are 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 to no prophylaxis. In order for geko™ to be cost neutral:

- The cost of PTS would need to be as low as £1,242, which is more than an 80% reduction from the base assumption.
- Relative risk of DVT when using the geko™ device needs to increase to 0.76, which is outside the range observed in the NICE VTE guidelines for IPS.
- 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 to the base 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/managing symptomatic DVT) need to be negative (implausible) for geko™ to be cost neutral with no prophylaxis.

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

a saving of £154 per patient compared to no prophylaxis with the simple tree structure.

Two-way sensitivity analysis was performed, varying the relative risk of DVT through the use of geko™ and the proportion of DVTs that are symptomatic. The results showed that, for each point estimate of the relative risk of DVT when using geko™, the proportion of DVTs that are symptomatic 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, where 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 cost saving conclusion for the geko™ device to change.

Probabilistic sensitivity analysis also showed that geko™ 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 concludes that both univariate and probabilistic sensitivity analysis show that geko™ is cost saving compared to no prophylaxis. The EAC also agrees that the sensitivity analysis has covered all the uncertain variables, was well performed and that the results support the conclusions regarding cost savings from the submitted model.

Subgroup analysis

The scope listed two patient sub group analyses to be considered:

1) Those in whom pharmacological prophylaxis is contraindicated.

2) Those in whom pharmacological prophylaxis is indicated and prescribed.

The EAC considers the main base case analysis to have covered the first sub group. The sponsor has further presented the sub group analysis for the second sub group by adding pharmacological prophylaxis to the technology and comparator. As suggested in the scope, sub group analysis was performed on an option that combines pharmacological prophylaxis with geko™ and an option involving the use of pharmacological prophylaxis alone.

As there was no evidence available for the effectiveness of geko™ used in combination with pharmacological prophylaxis, evidence for IPC from a Cochrane review was used. The 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 to pharmacological prophylaxis alone, geko™ in combination with pharmacological prophylaxis was not estimated to be a cost saving option with an incremental cost of £69. The geko™ device in combination with pharmacological prophylaxis is cost saving for the first two days of combined prophylaxis and cost neutral if used for three days.

As noted earlier, the cost of pharmacological prophylaxis has been estimated using an hourly cost of £41 for a nurse, which is an underestimate. The EAC believes that the appropriate value for hourly cost per patient contact should be £100. However, since both the options in the sub group analysis include pharmacological prophylaxis, the extra cost will cancel out and will not have any impact on the results.

Apart from that, the sub group analysis has the same flaw as the base case analysis. Evidence on IPC is being extrapolated to geko™ which the EAC believes is not valid for reasons mentioned earlier. There is a need to generate clinical evidence on the combination of pharmacological prophylaxis with geko™ before attempting to model the costs.

The sponsor also performed a sub group 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 to no prophylaxis.

Model validation

The sponsor has also submitted results of validation of the economic model in section 10.11. The electronic version of the model presented (the Microsoft Excel file) seems to be robust and the EAC did not detect any further validity issues with the model.

4.4 Interpretation of economic evidence

The sponsor concludes that currently there is no published literature comparing the technology and comparators, and that the cost model analysis shows that geko™ has cost savings compared to no prophylaxis. Both univariate and probabilistic sensitivity analysis support this conclusion. Whilst the model structure is robust, the EAC believes that the basic assumption of clinical effectiveness of geko™ on which the whole cost modelling is built is unreliable. There is no direct evidence that geko™ can prevent DVT. The sponsor builds the case for geko™ based on the hypothesis that the RR reduction in DVT obtained with the geko™ device would be at least equivalent to that achieved with IPC. The equivalence of IPC and geko™ is assumed based on the clinical evidence that simulation with the geko™ device results in significantly greater increases in blood flow compared with IPC. However the EAC is of the view that this does not provide a sufficiently reliable basis for assuming that geko™ is an effective prophylaxis given that the effect of IPC on the risk of DVT includes other factors, either independently of or in combination with improvements in blood flow. Experts' opinion also confirms that geko™ and IPC devices cannot be assumed to have the same efficacy based on a comparison of their effects on venous blood flow alone. There is a need to generate new clinical evidence for the impact of geko™ on DVT incidence so that a more robust economic assessment can be carried out using the modelling structure presented by the sponsor.

4.5 Additional work undertaken by the External Assessment Centre in relation to economic evidence

The systematic review and general structure of the cost model presented is good. Since the sponsor did not include the HTA database, the EAC additionally searched the HTA database using the search strategy provided by the sponsor to search the NHS EED database. The EAC did not find any additional evidence from the HTA database, confirming the conclusions reached by the sponsor that no economic evidence is available for geko™ or other electrostimulation devices.

The EAC does not agree with one parameter used in the sponsor's model, the cost of nurse time (£41), and considers that a cost of £100 per hour is more appropriate. The EAC used this cost to re-estimate the cost savings of geko™ in the base case

analysis. Based on this change, the cost of geko™ device prophylaxis is £147 instead of the £138.2. The total cost per patient for geko™ prophylaxis is £368 (instead of £359) against £565 for the 'no prophylaxis' strategy. This changes the cost savings of geko™ from £206 to £197.

Though the EAC has re-estimated the cost savings of geko™ with a new cost parameter for completeness, it is reiterated that the EAC believes that the basic assumption of clinical effectiveness of geko™ on which the whole cost modelling is built is unreliable, and the re-estimated costing savings add little value to the overall economic evidence.

4.6 Conclusions on the economic evidence

The sponsor conducted a search for published economic evidence on the geko™ device and concluded that no published evidence was available. The EAC confirmed the conclusions, after running the search additionally on the HTA database. As no published evidence was available, a cost model was subsequently submitted by the sponsor. The model, and all subsequent estimated cost impacts relating to the geko™, is built on the assumption that patients who have an underlying risk of DVT, and who are subsequently administered the geko™ device, will experience a reduction in their baseline risk of DVT. The model is an adapted version of that used in the NICE VTE guidelines. The EAC thinks that the model structure with its assumptions, pathways and health states is reasonable and needs no further improvement. Most of the clinical and cost parameters used in the model are also appropriate. The base-case analysis and sensitivity analysis are also well performed. The results show that geko™ is a cost saving option compared to no prophylaxis. The EAC had concerns with the cost estimate used for nurse time, and re-estimated the cost savings of geko™ with a new cost parameter. The results still showed a cost saving for geko™.

Whilst the EAC thinks that the cost modelling has been well performed, it believes that the basic assumption on which the cost model is built is unreliable. The sponsor has used a relative risk for geko™ based on evidence from NMES devices, which falls within the range for IPC devices. The sponsor used clinical evidence to infer that geko™ has the same efficacy as IPC in preventing VTE, since both improve venous flow at least by the same amount. The EAC believes that this is a weak assumption

to make since IPC methods have shown additional prophylactic effects, independent of increasing venous blood flow. It is not known which of these prophylactic effects has the greatest impact on VTE prophylaxis. The literature also points out that there is no evidence that intermittent compression systems that produce higher velocities on compression yield lower DVT rates. Experts also confirm that same efficacy for geko™ and IPC devices cannot be assumed, based on a comparison of their effects on venous blood flow alone.

In view of these issues, the EAC is of the opinion that further evidence needs to be generated for geko™ device's prophylactic effects on DVT/VTE and the evidence should be used in this sound model structure along with the parameters to reach more robust economic conclusions on the cost saving resulting from the use of geko™.

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

The total cost per patient for geko™ prophylaxis is £368 (instead of £359) against £565 for the 'no prophylaxis' strategy. The cost savings of geko™ changes from £206 to £197.

5 Conclusions

The EAC concludes that there are a number of weaknesses that would need to be addressed in order to demonstrate the efficacy of geko™ in the prophylaxis of VTE.

In the absence of clinical evidence showing VTE/DVT prevention, the sponsor has provided evidence of the effect that geko™ has on venous blood flow. Further evidence has been provided demonstrating the effects of MEST, other NMES and IPC devices on both venous blood flow and VTE prophylaxis. The sponsor has made comparisons between the effects of geko™ and IPC on venous blood flow and has based their economic model on the assumption that the prophylactic effect of geko™ is equivalent to that of IPC.

There is little discussion concerning the validity of comparing geko™ to MEST, other NMES and IPC devices in the sponsor's submission. Review of the literature by the EAC found that the MEST and other NMES devices used significantly different methods of application and stimulation. IPC devices have been shown to exert additional prophylactic effects to that of increasing venous blood flow, and these have not been demonstrated by geko™. It is not known how much of a contribution the increase in venous blood flow makes to the overall prophylactic effect of IPC devices. The EAC would therefore conclude that the efficacy of these devices in preventing VTE cannot be assumed to apply to geko™.

The EAC believes that the proposed mechanism by which geko™ would prevent VTE has not been clearly demonstrated in the evidence submission. It is not evident how the increases in venous blood flow observed in particular locations would translate to other areas at risk of thrombosis. However, some of the nominated experts did feel that that there was reason to expect the venous blood flow to increase throughout the leg.

There are a number of conditions present in a typical patient population, which would not have been present in the healthy volunteer study populations included in the submitted studies that could impair the function of geko™. There are potential complications, raised with us by the nominated experts, such as muscle fatigue and weakness, which would not have had time to manifest in the short study times used. It is the EAC's opinion that these are uncertainties that need to be addressed.

Although the cost model structure along with its assumptions, pathways and health states are appropriate, the basic assumption that geko™ will reduce the relative risk of DVT is unreliable. There is no direct clinical evidence to support this. The EAC thinks that there is an opportunity to generate newer clinical evidence on the impact of geko™ on DVT/VTE incidence, where evidence of an effect exists, could be used to support further economic analysis using the cost model structure developed by the sponsor.

6 Implications for research

The EAC considers that evidence to demonstrate efficacy for the geko™ device should ideally come from a carefully designed randomised controlled trial in patients, with a suitable comparator or inferiority assessment defined by the specific measured outcome. This trial would need to be adequately powered to detect a meaningful difference in VTE between geko™ and its comparator. Several NICE expert advisors support this view. However, the EAC does appreciate that the small intended population may restrict the practicality of this ideal approach, and that other, less rigorous, forms of evidence are acceptable within MTEP.

The three main weaknesses are the absence of studies that (1) are performed using patients rather than healthy volunteers, (2) are conducted using geko™ for an appropriate time period (days instead of hours), and (3) use DVT or VTE as the endpoint.

The chain of reasoning that has been used to imply that the geko™ device can prevent VTE would benefit greatly from studies that addressed these three current weaknesses.

Of the on-going studies listed by the sponsor, only one of these is thought to address these three points. The intention of this study is to recruit 40 patients, so additional studies would be required to provide sufficient statistical power.

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Appendix 3.1 - Summary of key points from sponsor-excluded published studies (based on sponsor submission and sponsor response (29th July 2013).

Reference	Sponsor submission reason for exclusion	Sponsor response dated 29th July 2013	EAC comments
Dejode et al (1973) (50)	Study design	Study design – review, no clinical data.	NMES study. The EAC agree with exclusion of this paper based on study design.
Hardwick et al (2011) (55)	Pharmacological intervention	Pharmacological intervention.	IPC vs. pharmacological intervention. The EAC agree with exclusion of this paper based on pharmacological intervention.
Khouli et al (2006) (56)	Study design	Pharmacological intervention, some patients received heparin, however results are not stratified by pharmacological group and device.	IPC vs. pharmacological intervention. The EAC agree with exclusion of this paper based on pharmacological intervention, not study design.
Moloney et al (1972) (57)	Study design - letter	Study design – letter.	NMES study. This study is not a letter, therefore the EAC do not agree with the sponsor's exclusion. The EAC include this paper as relevant.
Morita et al (2006) (58)	Outcomes - patient position	Outcomes – patient position.	NMES study. This study uses contralateral leg as control. Based on the sponsor's selection criteria, this study should have been included. However, the EAC selection criterion excludes this paper due to study design.
Norgren et al (1998) (59)	Pharmacological intervention	Pharmacological intervention.	IPC vs. pharmacological intervention. The EAC agree with exclusion of this paper based on IPC and pharmacological intervention.
Pollock (1977) (51)	Study design - review	Study design – review, no clinical data.	The EAC agree with exclusion of this paper based on study design – review.
Pollock (1978) (52)	Study design - review	Study design – review, no clinical data.	The EAC agree with exclusion of this paper based on study design – review.
Powley & Doran (1973) (53)	Study design - review	Study design – review, no clinical data.	The EAC agree with exclusion of this paper based on study design – review.
Turpie et al (2007) (54)	Pharmacological intervention	Pharmacological intervention. IPC/fondaparinux vs. IPC. As IPC is in both groups cannot determine efficacy of	IPC vs. pharmacological intervention. The EAC agree with exclusion of this paper based on IPC and pharmacological intervention.

Reference	Sponsor submission reason for exclusion	Sponsor response dated 29th July 2013	EAC comments
		IPC.	

Appendix 3.2 Summary of EAC rejected NMES and IPC studies initially included by the sponsor (note inclusion of Morita et al [2006])

Reference	EAC comments
Faghri et al (1997) (13)	The EAC exclude this study as outcomes used hemodynamic measures of cardiac and arterial measures.
Griffin et al (2010) (22)	The EAC excludes this study, as study methodology is inconsistent.
Izumi et al (2010) (39)	The EAC excludes as baseline values are not valid (five minute stabilisation not sufficient), patient positioning, and no 'non mechanical' comparator.
Morita et al (2006) (58)	The EAC exclude this study, as intervention does not fit scope (patient positioning and NMES device).
Pitto et al (2004) (47)	The EAC exclude this study as it compares IPC and pharmacological intervention.
Santori et al (1994) (43)	The EAC exclude this study as it compares FID and pharmacological intervention.
Sobieraj-Teague et al (2012) (44)	The EAC exclude this study as it compares IPC and pharmacological intervention.
Warwick et al (2002) (48)	The EAC exclude this study as it compares FID and pharmacological intervention.
Kurtoglu et al (2005) (40)	The EAC exclude this study as NMES not included as comparator.
Pitto et al (2008) (41)	The EAC exclude this study as NMES not included as comparator.

Appendix 3.3: EAC systematic review search terminology.

Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; Searched on 25th July 2013, and Embase 1974 to 25th July 2013.

1	exp thromboembolism/	370651
2	*embolism/	15603
3	((venous or vein) adj (thrombosis or thrombus or thromboembolism)).mp.	142676
4	(dvt or vte).mp.	26315
5	exp deep vein thrombosis/	78442
6	exp thrombophlebitis/	38204
7	or/1-6	439567
8	electrostimulation/	73164
9	Electric stimulation therapy/	27992
10	Electric stimulation/	181326
11	(electrical muscle stimulation or EMS).mp.	18204
12	(electric$ adj5 stimulat$).tw.	117434
13	(electromyostimulation.mp.	235
14	Electr$ therapy.tw.	14858
15	Geko.mp.	25
16	(pulse adj2 tech$).mp.	3302
17	Nmes.mp.	1183
18	Neuromuscular electrical stimulation.mp.	1426
19	Or/8-18	293459
20	Exp blood flow velocity/	86145
21	Exp blood circulation/	341628
22	Exp venous insufficiency/	14245
23	Haemodynam$.mp.	59779
24	((venous or vein) adj5 (stasis or pooling)).mp.	5466
25	(blood adj5 velocity).mp.	97878
26	((venous or vein) adj5 (flow or velocity)).mp.	29638
27	Or/20-26	496130
28	7 and 19 and 27	154

The Cochrane Library, to present; searched on 25th July 2013.

1	Thromboembolism
2	Embolism
3	(venous or vein) near (thrombosis or thrombus or thromboembolism)
4	dvt or vte
5	deep vein thrombosis
6	thrombophlebitis
7	#1 or #2 or #3 or #4 or #5 or #6
8	electrostimulation
9	electric stimulation therapy
10	electric stimulation
11	electrical muscle stimulation or EMS
12	Electric* near stimulat*
13	electromyostimulation
14	Electr* therapy
15	geko
16	pulse near tech*
17	nmes
18	neuromuscular electrical stimulation
19	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
20	blood flow velocity
21	blood circulation

22	venous insufficiency
23	Haemodynam*
24	(venous or vein) near (stasis or pooling)
25	blood near velocity
26	(venous or vein) near (flow or velocity)
27	#20 or #21 or #22 or #23 or #24 or #25 or #26
28	#7 and #19 and #27

Appendix 3.4: Summary of all EAC systematic review identified studies (n=38).

Title and author(s)	Publication	Decision
Hemodynamic performance of NMES in the early post operative period following orthopaedic surgery. Broderick BJ, Breathnach O, Masterson E, Breen PP and OLaighin G.	Medicine & Biology Society. 2011: 7630-7633.	The EAC include this study.
A pilot evaluation of a neuromuscular electrical stimulation (NMES) based methodology for the prevention of venous stasis during bed rest. Broderick BJ, O'Briain DE, Breen PP, Kearns SR and Olaighin G	Medical Engineering & Physics. 32 (4): 349-355, 2010.	The EAC include this study.
Venous emptying from the foot: Influences of weight bearing, toe curls, electrical stimulation, passive compression, and posture. Broderick BJ, Corley GJ, Quondamatteo F, Breen PP, Serrador J and OLaighin G.	Journal of Applied Physiology. 109 (4): 1045-1052, 2010.	The EAC include this study.
Functional electric stimulation to enhance systemic fibrinolytic activity in spinal cord injury patients. Katz RT, Green D, Sullivan T & Yarkony G.	Archives of Physical Medicine & Rehabilitation. 68 (7): 423-426, 1987.	The EAC include this study.
Prediction and prophylaxis of postoperative thromboembolism--a comparison between peroperative calf muscle stimulation with groups of impulses and dextran 40. Lindstrom B, Holmdahl C, Jonsson O, Korsan-Bengtsen K, Lindberg S, Petrusson B, Pettersson S, Wikstrand J & Wojciechowski J.	British Journal of Surgery. 69 (11): 633-637, 1982.	The EAC include this study.
Electrical stimulation of acupoint combinations against deep venous thrombosis in elderly bedridden patients after major surgery. Hou L, Chen C, Xu L, Yin P & Peng W.	Journal of Traditional Chinese Medicine. 33 (2): 187-193, 2013.	The EAC exclude as study method involves traditional Chinese medicine.
Preventive effect of electrical acupoint stimulation on lower-limb thrombosis: A prospective study of elderly patients after malignant gastrointestinal tumor surgery.	Cancer Nursing. 36 (2): 139-144, 2013.	The EAC exclude as study method involves traditional Chinese medicine.

Title and author(s)	Publication	Decision
Hou LL, Yao LW, Niu QM, Xu L, Yu QH, Sun WQ, Yin PH & Li Q.		
Haemodynamic performance of neuromuscular electrical stimulation (NMES) during recovery from total hip arthroplasty. Broderick BJ, Breathnach O, Condon F, Masterson E & Olaighin G.	Journal of Orthopaedic Surgery. 8:3, 2013.	The EAC includes this study as contralateral leg used as control. The sponsor also identified this study.
Hemodynamic effects of habituation to a week-long program of neuromuscular electrical stimulation. Corley GJ, Breen PP, Birlea SI, Serrador JM, Grace PA & Olaighin G.	Medical Engineering & Physics. 34 (4): 459-465, 2012.	The EAC include this study. The sponsor also identified this study.
Patient tolerance of neuromuscular electrical stimulation (NMES) in the presence of orthopaedic implants. Broderick BJ, Kennedy C, Breen PP, Kearns SR & OLaighin G.	International Journal of Angiology. 19 (1): e31-37, 2011.	The EAC includes this study as contralateral leg used as control. The sponsor also identified this study.
The efficacy of a new stimulation technology to increase venous flow and prevent venous stasis. Griffin M, Nicolaides AN, Bond D, Geroulakos G & Kalodiki E.	European Journal of Vascular and Endovascular Surgery. 40 (6): 766-771, 2010.	The EAC excludes this study, as study methodology is inconsistent. The sponsor also identified this study.
Electrical foot stimulation: A potential new method of deep venous thrombosis prophylaxis Czyrny JJ, Kaplan RE, Wilding GE, Purdy CH & Hirsh J.	Vascular. 18 (1): 20-27, 2010.	The EAC includes this study as it uses contralateral leg as control. The sponsor also identified this study.
Prevention of venous stasis in the lower limb by transcutaneous electrical nerve stimulation. Izumi M, Ikeuchi M, Mitani T, Taniguchi S & Tani T.	European Journal of Vascular & Endovascular Surgery. 39 (5): 642-645, 2010.	The EAC excludes as baseline values are not valid (five minute stabilisation not sufficient), patient positioning, and no 'non mechanical' comparator. The sponsor also identified this study.
A hemodynamic study of popliteal vein blood flow: the effect of bed rest and electrically elicited calf muscle contractions. Broderick BJ, O'Briain DE, Breen PP, Kearns SR	Medicine & Biology Society. 2009: 2149-2152.	The EAC exclude, as it is a report. The sponsor also identified this study.

Title and author(s)	Publication	Decision
& Olaighin G.		
Neuromuscular electrical stimulation and an Ottoman-type seat effectively improve popliteal venous flow in a sitting position. Morita H, Abe C, Tanaka K, Shiratori M, Oguri M & Shiga T.	Journal of Physiological Sciences. 56 (2): 183-186, 2006.	The EAC exclude this study, as intervention does not fit scope (patient positioning and NMES device). The sponsor also identified this study.
Electrostimulation for the prevention of deep venous thrombosis in patients with major trauma: a prospective randomized study. Velmahos GC, Petrone P, Chan LS, Hanks SE, Brown CV & Demetriades D.	Surgery. 137 (5): 493-498, 2005.	The EAC include this study. The sponsor also identified this study.
Electrical foot stimulation and implications for the prevention of venous thromboembolic disease. Kaplan RE, Czyrny JJ, Fung TS, Unsworth JD & Hirsh J.	Thrombosis & Haemostasis. 88 (2): 200-204, 2002.	The EAC includes this study as contralateral leg used as control. The sponsor also identified this study.
The arteriovenous impulse system in total hip arthroplasty. Eidner G, Pohlmann G, Anders J & Grohmann G.	Vasa. 28 (2): 112-116, 1999.	The EAC exclude as study is in German and due to patient position comparator.
Strain gauge plethysmography and duplex ultrasound study of venous blood flow changes during application of the A-V Impulse System(TM) foot pump and T.E.D.(TM) anti-embolism stockings Abu-Own A, Sommerville K, Scurr JH & Coleridge Smith PD.	International Angiology. 1996.	The EAC exclude as cannot find a full version of this paper: conference proceedings only.
Venous stasis during laparoscopic cholecystectomy. Jorgensen JO, Lalak NJ, North L, Hanel K, Hunt DR & Morris DL.	Surgical Laparoscopy & Endoscopy. 4 (2): 128-133, 1994.	The EAC exclude as investigates particular complication in blood flow and doesn't involve NMES.
Transcutaneous muscle stimulation - A 'new' possibility of prophylaxis for thrombosis. Klecker N & Theiss W.	Vasa - Journal of Vascular Diseases. 23 (1): 23-29, 1994.	The EAC exclude as in German and not enough information in English abstract.
Etiology, incidence, and prevention of deep vein thrombosis in acute spinal cord injury.	Archives of Physical Medicine and Rehabilitation. 74 (11): 1199-1205, 1993.	The EAC exclude as used pharmacological and IPC intervention only, and no NMES.

Title and author(s)	Publication	Decision
Merli GJ, Crabbe S, Paluzzi RG & Fritz D.		
Hemodynamic effects of electrically stimulated leg muscles. Rattan SN, Glaser RM & Collins SR.	Federation Proceedings. 44 (5): no. 5666, 1985.	The EAC exclude as cannot find a full version of this paper: conference proceedings only.
Electrically induced short-lasting tetanus of the calf muscles for prevention of deep vein thrombosis. Lindstrom B, Korsan-Bengtsen K, Jonsson O, Petruson B, Pettersson S & Wikstrand J.	British Journal of Surgery. 69 (4): 203-206, 1982.	The EAC include this study. The sponsor also identified this study.
The prevention of deep vein thrombosis, with particular reference to mechanical methods of prevention. Cotton TL.	Surgery. 81 (2): 228-235, 1977.	The EAC exclude, as is a review.
Prevention of venous thromboembolism. Gallus AS & Hirsh J	Seminars in Thrombosis & Hemostasis. 2 (4): 232-290, 1976.	The EAC exclude, as is a review.
The prevention of deep vein thrombosis after surgery. Calnan JS & Allenby F.	British Journal of Anaesthesia. 47 (2): 151-160, 1975.	The EAC exclude, as is a review.
The prevention of postoperative deep vein thrombosis. Joffe SN.	South African Medical Journal. Suid-Afrikaanse Tydskrif Vir Geneeskunde. 49 (5): 153-156, 1975.	The EAC exclude, as is a review.
The incidence of postoperative venous thrombosis of the legs. A comparative study on the prophylactic effect of dextran 70 and electrical calf-muscle stimulation. Becker J & Schampi B.	Acta Chirurgica Scandinavica. 139 (4): 357-367, 1973.	The EAC exclude as not available online.
Post-operative venous thrombosis. A clinical and experimental study with special reference to early diagnosis, prophylaxis, course and some haematological findings. Becker J.	Acta Chirurgica Scandinavica - Supplementum. 431: 1-38, 1972.	The EAC exclude as not available online.
Venous stasis and deep-vein thrombosis. Nicolaides AN, Kakkar VV, Field ES & Fish P.	British Journal of Surgery. 59 (9): 713-717, 1972.	The EAC include this study. The sponsor also identified this study.
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