National Institute for Health and Care Excellence

Medical Technologies Evaluation Programme

MT196 – The geko device for reducing the risk of venous thromboembolism
Consultation Comments table for MTCD1

MTAC date: 23rd January 2014

This is the first of 2 consultation comments tables. There were 56 consultation comments from 8 consultees (6 NHS professionals, 1 emeritus professor and 1 sponsor). The comments are reproduced in full in Table 1. In addition to the comments, further evidence and information submitted, or prepared in response to consultation (and referenced in individual comments) and is attached as follows:

- two supporting documents (attached as Appendices 1 and 2) and 20 comments about the assessment report overview (ARO) (Appendix 6) submitted by consultee 6 (the sponsor);
- responses prepared by the External Assessment Centre attached as Appendix 3 (the External Assessment Centre response to Appendix 1), and Appendix 4, (the External Assessment Centre response to Appendix 2);
- a summary of additional input sought from expert advisers, attached as Appendix 6;
- a conference abstract which became available after the meeting at which the Committee developed its original provisional recommendations for consultation, and a short critique prepared by the External Assessment Centre (attached as Appendix 7).

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1.	6. Sponsor	1	The Sponsor remains convinced that it has presented a credible clinical and economic case for positive guidance and adoption of the geko™ device for the narrow population of patients currently defined within the MTEP196 scope. To substantiate this view the Sponsor would like to highlight the following At the centre of the Sponsor's clinical rationale was the assurance that its basic scientific and clinical argument (see Appendix 2 sections 1 and 2) was universally accepted by the MTAC; namely that the prevention of venous stasis in the veins of the leg, as delivered by their technology, would reduce VTE risk in patients where other forms of VTE prophylaxis are contraindicated. This hypothesis was at the very foundation of the resulting MTEP196 scope. The Sponsor took further confidence from the fact that the MTAC had selected the technology knowing that the only clinical data currently available was blood volume flow and velocity and that the technology was superior in this respect to other mechanical VTE prophylactic devices	Thank you for your comment. This comment and comments 43 and 47 refer to the Committee's considerations in selecting and routing the technology for evaluation. The Committee carefully considered this comment and decided not to change the guidance in response to this specific comment. The MTEP Methods guide (section 3) states that MTAC 'makes decisions on selecting and routing technologies by discussing the case for adoption and applying the selection and routing criteria to specific technologies'. The Committee does not consider the evidence in detail at the selection stage. The Committee's reasons for selection (as stated in Section 2 of the scope) included: "The Committee considered that there was evidence to indicate that using the geko device could lead to an increase in venous return, arterial flow and microcirculation in the lower limb." Guidance recommendations are based on the clinical and economic evidence and informed by contributions from expert advisers and patient and carer organisations (see MTEP methods

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				guide Section 8).
2.	5. NHS Professional (Expert adviser)	**1**	I maintain my opinion that increasing blood flow does reduce the risk of VTE. I believe that it is clear from the consultation document that this view is shared by the majority of advisors. There are patients for whom we currently provide no form of VTE prophylaxis as they are contraindicated for both pharmaceutical and mechanical prophylaxis and are at risk of VTE. As the geko device increases blood flow I believe it should be an available option when nothing else can be used. An alternative would be to recommend that the Sponsor provides blood flow data in patients at risk of VTE, before we provide guidance. I am aware the Sponsor is currently the sponsor of comparative blood flow studies in patients at risk of VTE. Currently about to start a study to that effect	Thank you for your comment. This comment and comments 8, 18, 19, 45 and 46 refer to the use of venous blood flow as a surrogate outcome, particularly for patients at risk of VTE who are unable to have current mechanical methods of prophylaxis. The Committee considered these comments, together with the additional evidence and additional expert advice (Appendix 5) presented at the consultation and decided to change section 3.16 to reflect its acceptance that the available data on measurements of blood flow provide some support for the claim that the device reduces the risk of VTE. This change was also reflected in revisions to section 1 of the guidance.
3.	6. Sponsor	1	The Sponsor remains convinced that it has presented a credible clinical and economic case for positive guidance and adoption of the geko™ device for the narrow population of patients currently defined within the MTEP196 scope. To substantiate this view the Sponsor would like to highlight the following The agreed MTEP196 scope was to justify the adoption of the technology for use in patients in whom other forms of mechanical prophylaxis are unsuitable. Sub-populations also included those where no form of prophylaxis was considered an option. However, the provisional recommendations make reference to a broader population of patients suggesting the technology could be used more widely. In conclusion the MTAC found there was insufficient evidence to justify routine use. Two issues concern the Sponsor in the use of “broader” and “routine” as such language	Thank you for your comment. The Committee’s consideration in section 3.20 was based in part on expert advice received about the practical difficulties of conducting studies in patients who cannot receive current methods of VTE prophylaxis. The Committee also judged that information on the comparative effectiveness of the geko device would be easier to obtain and would be

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			suggests that the current “draft” guidelines have been reviewed against a vision significantly beyond the current MTEP196 scope. Furthermore, there is real concern that the reasons for MTAC technology selection are significantly different from the reasons stated in the consultation document by the MTAC for not supporting immediate technology adoption. The current MTEP196 scope investigates justifying adoption of the technology in a very narrow patient group justified by surrogate endpoint data. However, the MTAC have declined the case for adoption based on there being “insufficient evidence on its clinical effectiveness” and rather than the envisaged adoption in a narrow population, MTAC alludes to the unsuitable use of the device in a broader population. This is rather a mixed message and appears to the Sponsor to be falling outside of the boundary of the agreed scope Whilst the Sponsor is motivated by the MTAC potentially widening the scope in the future, the Sponsor did not seek approval for technology use in a broader population mainly because, and on this point the Sponsor agrees, it cannot at this time be clinically justified. As such, the Sponsor is worried that the original scope has been superseded (in a positive way) by a more complicated review that could never have been substantiated and was one that the Sponsor did not request or agree to. It wishes for the technology to be reviewed as per the MTEP196 scope and no other because it believes the clinical rationale can be supported with credibility.	valuable. The Committee considered these comments, together with the additional evidence and expert clinical advice presented at consultation and decided to change section 1.1 (and associated sections 3.18-3.20, 4.3, 5.12 and 6.1) of the guidance to recommend the use of the geko device in a limited population for whom other methods of DVT are unavailable or contraindicated.
4.	4. NHS Professional	**1**	Whilst there is insufficient evidence to support routine adoption in the NHS, it would be reasonable on the basis of reduction in venous stasis to consider its use in selected patients for whom other forms of prophylaxis are not suitable.	Thank you for your comment. Please refer to the response to comment 2.
5.	3. NHS Professional (Expert adviser)	**1**	It is very unlikely that a placebo or no-prophylaxis study will be allowed by an ethics committee. Equivalence trials, assuming a reasonably similar efficacy between GEKO and the comparator, would require a very large sample size which may not be pragmatically and financially viable. VTE research with mechanical devices has routinely assumed that an increase in femoral vein velocity translates into a reduction in DVT due to flushing of vein valves and stimulation of fibrinolytic venous endothelial factors. Several mechanical devices are available already and used in the Health Service in UK and abroad based on this surrogate basis given the difficulties of randomised trials. The	Thank you for your comment. Please refer to the responses to comment 33 (further studies), 11 (devices used with FDA approval) and 2 (use in scope population on basis of blood flow data).

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			GEKO has a theoretical role for cases where traditional mechanical methods are unsuitable such as broken lower legs; in these patients chemical prophylaxis may also be contraindicated. Adoption of the device based on the flow surrogate would be a reasonable option for NICE to support rather than waiting for evidence of clinical effectiveness	
6.	7. NHS Professional (Expert adviser)	**1**	The research in section 1.2 needs to be done. No small company (SME) could undertake RCTs with the outcome of "clinical venous thromboembolic events". Access to the market facilitates RCTs on DVT detected by imaging, which could address the other outcome measures you identify. Blocking adoption where no other mechanical prophylaxis is available is a major obstacle to the development of this promising technology. GEKO increases venous flow and reduces transit time through the calf; not merely due to increased inflow through the microcirculation (which is important) but also by reducing calf volume confirming calf muscle pump stimulation. These are well-established surrogate markers for DVT prevention. These mechanisms are similar to elastic stockings and intermittent pneumatic pumps, but with no risk of pressure ulceration. The NHS cost of GEKO for DVT prophylaxis when other mechanical prophylaxis cannot be used would be small but would stimulate the necessary clinical research. The ability to increase venous flow and reduce transit times justifies immediate adoption limited to patients with no alternatives.	Thank you for your comment. This comment and comments 15, 38 and 51 refer to the link between adoption in a narrow population and further research. The options available to the Committee in making research recommendations are set out in Section 8.3 of the published MTEP Methods Guide. The Committee considered these comments and changed sections 1.1 and 6.2 to recommend the geko device in a population who cannot use any other form of prophylaxis. The Committee also changed the recommendation for further research to encourage strongly further data collection to demonstrate the size of the risk reduction associated with using geko (see sections 3.16 and 6.2) in other patient populations (see section 3.20 and 6.2)**.**
7.	2. NHS Professional	**1**	Mechanical prophylaxis is today an acceptable option for the prevention of DVT especially in those who are at high risk for bleeding or when used in combination with anticoagulant prophylaxis to improve efficacy (Grade 2A). Mechanical methods of prophylaxis, which includes GCS, IPC and electro-stimulation devices increase venous	Thank you for your comment. This comment and comments 11, 12, 21, 30, 40, 44, 52 and 53 refer to the relationship between geko and other

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			outflow and reduces stasis within the leg veins and Geko stimulation device is no different. In fact Geko device has demonstrated a significantly more venous flow return and higher peak systolic flow than any IPC, leading to DVT risk reduction where other mechanical devices are not suitable. Virchow's triad describes the three main factors responsible for the development of thrombosis: hypercoagulability, stasis & endothelial injury. The Geko is a non-invasive device, pain-free stimulating the Peroneal nerve, leading to increase venous flow return through activation of the calf muscle pump. It has demonstrated a 4 fold increase in blood flow volume, therefore significantly enhancing venous blood flow return and reducing venous stasis when compared to control group. It has also demonstrated a significant reduction in the tPA antigen levels.	mechanical devices and the validity of using a risk reduction based on other mechanical devices in the geko cost analysis. The External Assessment Centre stated that the unique mode of action of the geko device introduces uncertainty about the association between the type of muscle contractions generated and a reduction in the incidence of deep vein thrombosis compared with those generated by using either neuromuscular electrostimulation or intermittent pneumatic compression. Expert advice to the Committee was divided about the generalisability of results from neuromuscular electrostimulation studies to the geko device. The Committee considered these comments and changed sections 1.2 and 6.2 to recommend the geko device in a population who cannot use any other form of prophylaxis, while noting there was no direct evidence for the size of the relative risk reduction. The Committee also changed their recommendations to strongly encourage further data collection to demonstrate the size of the risk

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				reduction associated with using geko (see sections 3.16 and 6.2) in other patient populations (see section 3.20 and 6.2)**.**
8.	6. Sponsor	1.1	The Sponsor believes that there is a deviation of views between the External Assessment Centre, MTAC and the Sponsor in the following key areas: The validity of enhanced blood volume flow and velocity being a surrogate endpoints in the patients defined in the scope. This is examined in Appendix 2, Section 4.1. Feedback made here and in the assessment overview report has addressed these areas in the hope that the MTAC can be fully informed prior to the creation of final guidance.	Thank you for your comment. Please refer to the response to comment 2 on the use of venous blood flow as a surrogate outcome.
9.	6. Sponsor	1.1	The Sponsor believes that there is a deviation of views between the External Assessment Centre, MTAC and the Sponsor in the following key areas: Lack of patient data. This is addressed in Appendix 1. Feedback made here and in the assessment overview report has addressed these areas in the hope that the MTAC can be fully informed prior to the creation of final guidance.	Thank you for your comment. This comment and comments 20, 24, 28 and 48 refer to the new evidence submitted by the sponsor from on-going studies in patients (rather than in healthy volunteers). The Committee considered these comments carefully in combination with the External Assessment Centre analysis of the further clinical data submitted (see Appendices 1 and 7 for the data and Appendices 4 and 7 for the External Assessment Centre critiques) and expert clinical advice. The Committee decided to change section 1.1 of the guidance to recommend the use of the geko device in patients who have a high risk of venous thromboembolism and for whom other mechanical and pharmacological methods of

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				prophylaxis are impractical or contraindicated.
10.	6. Sponsor	1.1	The Sponsor believes that there is a deviation of views between the External Assessment Centre, MTAC and the Sponsor in the following key areas: The suggestion that the original MTEP196 scope has been superseded by a wider review. Feedback made here and in the assessment overview report has addressed these areas in the hope that the MTAC can be fully informed prior to the creation of final guidance.	Thank you for your comment. Please refer to the response to comment 3
11.	6. Sponsor	1.1	The Sponsor remains convinced that it has presented a credible clinical and economic case for positive guidance and adoption of the geko™ device for the narrow population of patients currently defined within the MTEP196 scope. To substantiate this view the Sponsor would like to highlight the following There is a deviation of views between the External Assessment Centre, MTAC and the Sponsor in the relationship between mechanical devices and the legitimacy to align their risk reduction and economic impact. The Sponsor believes that there is an inherent misunderstanding. The literature is strongly suggestive that mechanical devices; old style NMES, old style IPC and new style IPC are efficacious because (like the geko™ device) they prevent venous stasis, how they prevent stasis is not the central issue and clinical extrapolation with appropriate sensitivity analysis is therefore very credible. The MTAC may wish to consider that the FDA has approved new NMES devices based upon the technical equivalence to previous NMES devices and this is documented further in Appendix 2 Section 5. Further the External Assessment Centre suggest that old NMES or mechanical devices cannot be aligned to the geko™ device or assumed to be the same. However the Sponsor has shown that this assumption is already happening on a significant scale within the NHS as new mechanical compression devices from new suppliers are being adopted that may or may not be the same as their predecessor and do not have VTE end point data. The Sponsor suggests that their adoption is based on the assumption that these new devices prevent venous stasis and that this surrogate end point is the commonality and justification for their introduction into clinical pathways that are far wider than those being reviewed here. The Sponsor cites two new entrants into this market,	Thank you for your comment. Please refer to the response to comment 7. The External Assessment Centre has stated that it considers that the precise method by which stasis is prevented is important and has explained this further in its response to the additional information provided by the sponsor (see Appendix 4). The objectives, processes and methods used by device regulators (such as the FDA) and health technology assessment programmes (such as MTEP) are different. NICE clinical guideline 92 advises that the choice of mechanical VTE prophylaxis should be based on individual patient factors including clinical condition, surgical procedure and patient preference. The Committee

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			namely the foot compression system from Vadoplex (http://www.vadoplex.com/de-en/thromboseprophylaxe.html) and the calf compression system from G&N medical (http://www.gandn.com/medical/products/deep-vein-thrombosis-dvt-prevention/pnuemapress-intermittent-compression-system/. This VTE endpoint clinical assumption is being made even though device cycles, calf/foot pressures, blood flow rates and patient compliance of these new entrants may be different to any other previous mechanical devices. In terms of economic modelling the Sponsor again used a very simple premise that it was credible to align the relative risk (RR) of other clinically proven mechanical devices (with the same primary endpoint of increasing blood flow velocity in the veins of the leg) to create a credible RR band from which to financially model (see Appendix 2 section 4).. The Sponsor logically aligned the RR from clinically proven neuromuscular electro stimulation (NMES) and intermittent pneumatic compression (IPC) devices and robustly modelled the assumptions for the geko™ device in patients where no other VTE prophylaxis could be prescribed. This justification was made even more relevant and valid because the geko™ device had shown superior blood flow velocity to that of IPC so the expected reduction in VTE can be anticipated on this basis.	noted that NMES devices are not currently recommended in the clinical guideline. The adoption of other new mechanical devices in the NHS is outside the scope of this evaluation The Committee carefully considered these comments together with the additional evidence and expert advice presented at the consultation, and decided to change the recommendations and sections 3.18-3.20, 4.3, 5.12 and 6.1 of the guidance.
12.	6. Sponsor	1.1	The Sponsor believes that there is a deviation of views between the External Assessment Centre, MTAC and the Sponsor in the following key areas: The clinical relationship between mechanical devices and the legitimacy to align their risk reduction and economic impact. This is examined in Appendix 2, Section 4.2 Feedback made here and in the assessment overview report has addressed these areas in the hope that the MTAC can be fully informed prior to the creation of final guidance.	Thank you for your comment. Please refer to the response to comment 7.
13.	6. Sponsor	1.1	The Sponsor remains convinced that it has presented a credible clinical and economic case for positive guidance and adoption of the geko™ device for the narrow population of patients currently defined within the MTEP196 scope. To substantiate this view the Sponsor would like to highlight the following A further deviation of views between the External Assessment Centre and the sponsor concerns the stimulation of fibrinolysis. The External Assessment Centre believes this is a standalone phenomenon that is triggered by IPC independent of blood flow, The External Assessment Centre state references to substantiate their point which simply do	Thank you for your comment. The Committee carefully considered this comment, and the External Assessment Centre's response (see Appendices 3 and 4) and decided not to change the guidance.

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			not make the same conclusion as the External Assessment Centre (see Appendix 2, Section 6). The Sponsor agrees the literature is inconclusive but is strongly suggestive that if fibrinolysis is stimulated by IPC then it is a consequence of blood flow and the resulting shear stress within the vessel (see Appendix 2 section 3). This again is a significant point because the External Assessment Centre used this unfounded conclusion to undermine the clinical and economic hypothesis of the Sponsor. To this point the Sponsor commissioned a review by one of the Authors cited by External Assessment Centre in support of their argument this is included in Appendix 1, Section 4 (statement by Dr. Rhys Morris) . The Sponsor has defended its clinical hypothesis throughout this consultation feedback process (both here and elsewhere). The Sponsor has, during the consultation, seen for the first time the questions and answers from the nominated experts in respect to the specific clinical rationale that is being examined. The Sponsor believes that an analysis from expert responses shows that only 29% of experts rejected the hypothesis when the relevant clinical questions that are central to the debate were asked of them. There is, it seems, overwhelming evidence within the assessment overview document that the majority of opinion supports the clinical hypothesis of the Sponsor and the creation of positive MTAC guidance. Consequently, the Sponsor believes that the External Assessment Centre has wrongly undermined the Sponsor's clinical and scientific hypothesis and has not represented expert opinion in respect to the critical clinical questions accurately for the Sponsor believes it has shown that expert opinion is on their side on this central clinical argument. Furthermore the External Assessment Centre cited references to support their specific scientific arguments that the Sponsor strenuously believes do not substantiate the points they were making. This is documented in Appendix 2, Section 6.	
14.	6. Sponsor	1.2	The Sponsor's view is as follows: The enhanced venous flow and velocity data presented in the manufacturer's submission, further supported by the additional coagulation data presented in Appendix 1, Section 3 response provides the scientific basis for use of the geko™ device to reduce the risk of VTE in patients where other VTE prophylaxis modalities are contraindicated. In order to satisfy the research proposals made by the MTAC in this Section of the	Thank you for your comment. This comment refers to the difficulties of VTE end point studies. An assessment by the External Assessment Centre of the new information in Appendix 1 is in

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			medical technology consultation document, we propose that: Patient volume flow and velocity data is sufficient for use in patients where other VTE prophylactic modalities are contraindicated If practically possible a VTE endpoint data study is completed before guidance is extended for use beyond the current patient scope The Sponsor would like to highlight to the MTAC the challenges and the number of patients required to power a randomised controlled study to demonstrate equivalence between IPC and the geko^{TM} device in terms of DVT outcomes. The number of patients can be calculated, based on the following assumptions: Suppose 'equivalence' means a clinically acceptable margin of equivalence, say +/- 10%. Note that this margin is arbitrary, but that exact equivalence is always impossible to prove. In equivalence studies, it is always necessary to define an acceptable margin of equivalence. We want the study to have 80% power (i.e. an 80% chance that the question posed by the study will be answered by the study) i.e. Beta =0.2 We select a level of significance which we shall deem convincing to be Alpha=0.05, i.e. 95% confidence) Actual DVT incidence in chosen patient population when prophylaxed with IPC = 10% i.e. (Ps=0.1) Actual DVT incidence in chosen patient population when prophylaxed with the gekoTM device = 10% ± 1% (Pn=0.1). The hypothesised difference, D, is 10% of Pn, i.e. D=0.01) Based on these assumptions, a sample size calculation was conducted using the following equation: N=(Z0.95+ Z0.80)*2*[Ps(1-Ps) + Pn(1-Pn)] / (Ps-Pn-D)2 Where Z is the Z-distribution value for the given probability: Z0.95=1.96 and Z0.80=0.84 So: N = (1.96 +0.84) x 2 x [0.1*0.9 + 0.1*0.9]/ (0.01)2 = 10,080 per leg of the study	Appendix 4. The options available to the Committee in making research recommendations are set out in Section 8.3 of the published MTEP Methods Guide. The Committee carefully considered this comment, together with the additional evidence and expert advice presented at consultation and decided to change section 1.1 of the guidance to recommend the use of the geko device in patients who have a high risk of venous thromboembolism and for whom other mechanical and pharmacological methods of prophylaxis are impractical or contraindicated. The Committee also changed their original research recommendation to a more general considerations for further research to demonstrate the size of the risk reduction associated with its use (see sections 3.16 and 6.2) and to investigate the use of geko in other patient populations (see section 3.20 and 6.2).

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			N=20,160 patients in total Stipulating a smaller margin of equivalence would increase the required numbers, e.g. 5% would multiply the numbers required by 4. Alternatively, if the geko™ device was actually superior to IPC, and the actual incidence of DVT in the population prophylaxed with the geko™ device was 7.5% as opposed to 10% for IPC, it would take 2,200 patients to demonstrate this. The above demonstrates the challenge for a suitably powered standalone study which, as far as the Sponsor can ascertain, has not yet been delivered for an equivalent mechanical compression device even though these devices are entrenched and in routine use throughout the NHS. As referred elsewhere new supplier entrants are bringing new mechanical IPC compression devices to market today and the NHS is adopting these devices without the above evidence but is justifying adoption based on the surrogate end point commonality with older IPC devices. These new devices maybe different in their functionality but the commonality of surrogate end point is presumably seen as the justification for their adoption.	
15.	6. Sponsor	1.3	The Sponsor understands this point but remains hopeful, given the support of expert opinion leaders, that the surrogate end point data will be sufficient for adoption guidelines to be issued for patients within MTEP 196 scope who are contraindicated for other methods of VTE prophylaxis. There is a strategic issue in that the Sponsor's vision was always to complete a clinical study to support wider adoption than that outlined in the current scope and felt that a limited adoption of the technology in the NHS would aid and accelerate the timing of this study. There is a concern that the required VTE end point data could require a significant change of direction and the timing of when this technology could become available to the NHS.	Thank you for your comment. Please refer to the response to comment 6.
16.	7. NHS Professional (Expert adviser)	**2**	The GEKO device should be recommended for mechanical prophylaxis in patients where elastic stockings and intermittent pneumatic compression devices cannot be used as outlined in NICE Clinical Guideline 92. This would facilitate the much-needed research on the efficacy of this device on the primary clinical outcome measure of clinical venous thromboembolism or asymptomatic DVT detected by duplex imaging	Thank you for your comment. Please refer to the response to comment 2.

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17.	2. NHS Professional	**2**	The Geko is a non-invasive device, pain-free and well tolerated by patient, therefore better compliance with potential use in wound care, other vascular arterial disorders and sports medicine	Thank you for your comment.
18.	5. NHS Professional (Expert adviser)	**3**	It is clear that increased blood flow reduces the risk of VTE – that is why we use compression. When I examined the paper referenced by the External Assessment Centre, to support their opinion that compression pumps have some other mechanism of action as well as increasing blood movement, the paper describes that the mechanism of action of pumps is ONLY increased blood flow. The blood flow then goes on to have the anti-coagulant effects (Christen et al). The paper concludes that: "the present study indicates that the antithrombotic effect of mechanical prophylaxis is probably mainly due to its ability to increase venous peak velocity and flow, especially under venous stasis conditions." Christen Y, Watschert R, Weimer D, de Moerloose P, Kruithof EK, Bounameaux H. (1997). Effects of intermittent pneumatic compression on venous haemodynamics and fibrinolytic activity. Blood Coagul Fibrinolysis. 8(3):185-90. As far as I am aware the evidence is that increased blood flow reduces the risk of VTE.	Thank you for your comment. Please refer to the response to comment 2 on the use of venous blood flow as a surrogate outcome.
19.	7. NHS Professional (Expert adviser)	**3**	Although venous flow and transit time studies were in healthy volunteers, requiring DVT prophylaxis are not different. There is no more appropriate group. GEKO adopting by NICE for patients where there are no other options for mechanical prophylaxis is the way to ensure that research on patients, with DVT as the outcome, can be done. With respect to paragraph 3.14 and 3.15, generating increased venous flow and reducing transit times are clearly surrogates for DVT prevention, but well-established surrogate addressing the primary causes of DVT in hospital patients. Immobilization and venous stasis (aeroplanes or plaster casts) are powerful causes of DVT. Even in patients with a hypercoagulable response to injury or surgery, DVT will not develop in the absence of venous stasis. It matters not how GEKO achieves increased venous flow and reduced transit times, what matters is that it clearly does and therefore has immense potential. How does a small British SME undertake this research if it is effectively barred from the market in an indication where there is no other option for mechanical prophylaxis?	Thank you for your comment. Please refer to the response to comment 2 on the use of venous blood flow as a surrogate outcome.
20.	6. Sponsor	3	Section 3 overview comments The Sponsor strongly defends the surrogate endpoint hypothesis to justify MTAC guidance for technology adoption as defined within the MTEP196 scope. However, the	Thank you for your comment. Please refer to the response to comment 9.

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			Sponsor does acknowledge that even if the MTAC becomes convinced of this argument the Sponsor does concur, based on comments within the consultation document, that MTAC will require some additional data from the patient setting, The Sponsor has been focusing on the following areas: There would be a need for the Sponsor to demonstrate blood flow velocity outcome in hospitalised patients at risk of VTE and not just in healthy volunteers. To this point, during recent weeks the Sponsor has been determined to extract as much patient blood flow velocity data from current patient studies as has been possible, so to give the MTAC as much information prior to final guidance. This new clinical evidence is included in Appendix 1, Sections 1 and 2, and for the sample size reported does show the geko™ device achieving the expected increased blood flow volumes and velocity outcome in the patient studies outlined. The Sponsor also positions additional evidence is respect to the capability of the technology to stimulate fibrinolysis. Whilst we differ in opinion with the External Assessment Centre about how this process is initiated, the Sponsor believes this evidence will remove any doubt that IPC and the gekoTM device prevent VTE risk via the same processes. This evidence was within the Sponsor's clinical submission but not referred to as it was not an outcome identified in the MTEP196 scope. This evidence can be found within Appendix 1, Section 3 of the Sponsor's submission. Finally, the Sponsor has re-submitted elements of the PMS data which clarifies patient wear of the device. This issued was identified by the External Assessment Centre and for the avoidance of doubt this included in the Appendix 1, Section 2 of the Sponsor's submission.	
21.	2. NHS Professional	**3**	Mechanical methods of prophylaxis, which includes GCS, IPC and electro-stimulation devices increase venous outflow and reduces stasis within the leg veins and by extrapolation, Geko stimulation device is no different	Thank you for your comment. Please refer to the response to comment 7.
22.	3. NHS Professional (Expert adviser)	**3.4**	The paper by Warwick et al (2013) is criticised above (section 3.4) as not having a proper control arm I would ask the External Assessment centre to reconsider. It does have a proper control arm - the subjects' own resting venous velocity. This is the ideal control. The study should be repeated in due course in patients with pathology rather	Thank you for your comment. The Committee carefully considered this comment and decided not to change the guidance in response to

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			than controls.	this specific comment. The External Assessment Centre noted that this study was rejected due to the presence of a plaster cast on the subjects and thus did not have a suitable comparator. The Committee was advised by the External Assessment Centre that this study did not have an appropriate comparator and thus did not fit inside the scope.
23.	6. Sponsor	**3.4**	The Sponsor deals with the External Assessment Centre rejection of the studies below by individual Author: Tucker et al (2010) was rejected by the External Assessment Centre because the comparators were baseline measures and voluntary muscle action (dorsiflexions). The Sponsor considers that this is not a legitimate reason to reject the study. Self-control (as used within the study) is not only a valid form of control, but more statistically powerful and sensitive than un-paired controls. On this basis the Sponsor believes the evidence should not have been rejected Warwick et al (2013) was rejected by the External Assessment Centre because the External Assessment Centre felt there was a lack of a proper control. The sponsor again believes that this study included self- and contralateral controls, which are more statistically powerful, sensitive, and valid than non-paired controls. The experimental design has been peer-reviewed, accepted, and published. On this basis the Sponsor believes the evidence should not have been rejected. Jawad (Cardiac) (2012) was rejected by the External Assessment Centre because the use of cardiac outcomes did not fit within the scope. The Sponsor would like to highlight that this paper included data for lower limb venous volume, venous velocity, arterial velocity, and lower limb capillary blood flow which all seem to be extremely relevant within the comparators agreed within the agreed MTEP scope. On this basis the Sponsor believes the evidence should not have been rejected.	Thank you for your comment. This relates to Section 4.1 of the Assessment Report Overview, pages 8-14. The Committee carefully considered this comment and decided not to change the guidance in response to this specific comment. Please see comment 22 for a discussion of Warwick et al. (2013). The Committee was advised by the External Assessment Centre that these studies were not specifically designed to provide evidence of increased venous blood flow: Jawad was excluded on the basis that the cardiac outcomes measured were outside of the scope; and Tucker on the basis of inappropriate comparator (voluntary muscle action). The Committee noted the External Assessment Centre

Comment no	Consultee number and organisation	Section No.	Comments	Response
			Williams (published 2013) was rejected by the External Assessment Centre because insufficient details were provided of how baseline measurements were obtained The Sponsor would like to highlight that the Williams study is a crossover study comparing the effects of the geko™ device and IPC and the methodology is fully explained. On this basis the Sponsor believes the evidence should not have been rejected.	accepted other studies which provide evidence of venous blood flow which was outside their stated scope and that the excluded studies were on small populations of healthy volunteers. The Committee agreed with External Assessment Centre judgment that inclusion of the studies cited in the comment would have provided no relevant additional evidence.
24.	6. Sponsor	**3.9 1st Bullet**	The Sponsor accepts this point and has been determined to extract as much patient blood flow velocity data from current patient studies as has been possible, so to give the MTAC as much information prior to final guidance. This new clinical evidence is included in Appendix 1, Section 1 and for the sample size reported does show the geko™ device achieving the expected increased blood flow volumes and velocity outcome in the patient studies outlined.	Thank you for your comment. Please refer to the response to comment 9
25.	6. Sponsor	**3.9 2nd Bullet**	No single seated, supine, or otherwise recumbent position 'mimics the medical setting'. Patients are nursed in a wide variety of different positions, including sitting, elevated backrest, and with knee-break on profiling beds. Indeed, tissue viability guidelines indicate that the patient position should be changed at least once every two hours. The origin of the seat is of no importance. For valid experimental control, it is essential that a reproducible stationary position is established, and this is the purpose of the aircraft seat	Thank you for your comment. The Committee carefully considered this comment and decided not to change the guidance in response to this specific comment. The Committee considered the External Assessment Centre's comments on the limitations of the studies were made in the context of the generalizability of the evidence in healthy volunteers to the clinical use of the technology.
26.	6. Sponsor	**3.9 3rd**	The studies referred to were not DVT outcomes studies. Therefore, the duration of wear is of no relevance. The objective here is the extent to which geko ™ device augments flow relative to no device. Repeated measurements of short duration are entirely	Thank you for your comment. The Committee carefully considered this comment and decided not to

Comment no	Consultee number and organisation	Section No.	Comments	Response
		Bullet	appropriate	change the guidance in response to this specific comment. The Committee considered the External Assessment Centre's comments on the limitations of the studies were made in the context of the generalisability of the evidence in healthy volunteers to the clinical use of the technology.
27.	6. Sponsor	3.11	The primary outcome of previous clinically proven NMES devices is the same as the technology under review and as such they are related. In simple terms, both the geko™ device and previous NMES devices engage muscle groups and achieve augmentation of venous flow in the lower leg (prevent venous stasis) and in doing so reduce the risk of VTE. How these previous NMES devices specifically engaged muscle groups to achieve this outcome is not the central point. What is relevant is the fact that (like the geko ™ device) these previous devices did deliver this venous outcome which was the primary reason why they were seen to be efficacious. The Sponsor agrees that the extent upon which risk reduction can be compared between the geko™ device and previous NMES examples is debatable but this aspect is robustly examined within the economic model by extensive sensitivity analyses. It should be noted that the general model approach was approved by the External Assessment Centre The Sponsor would highlight to the MTAC that the NHS has already made this association through its adoption of new mechanical devices and the geko™ device must logically be seen in the same context. This is especially relevant as the Sponsor only seeks guidance for adoption in patients within scope who are contraindicated to other forms of VTE prophylaxis	Thank you for your comment. The Committee carefully considered this comment and decided not to change the guidance in response to this specific comment. The Committee noted that NMES devices are not currently recommended in the clinical guidelines. The adoption of other new mechanical devices in the NHS is outside the scope of this evaluation.
28.	6. Sponsor	3.13	The Sponsor accepts this point but hopes, that with expert opinion support, the MTAC will issue positive guidance for adoption as per MT196 scope. It does realise that the latest data from studies would be helpful and has been determined to extract as much patient blood flow velocity data from current patient studies as has been possible, so to give the MTAC as much information prior to final guidance. This new clinical evidence in	Thank you for your comment. Please refer to the response to comment 9.

<table>
<tr><th>Comment no</th><th>Consultee number and organisation</th><th>Section No.</th><th>Comments</th><th>Response</th></tr>
<tr><td></td><td></td><td></td><td>patients is included in Appendix 1, Sections 1 and 2 of the consultation feedback document and for the sample size reported does show the geko™ device achieving the expected increased blood flow volumes and velocity outcome in the patient studies outlined.</td><td></td></tr>
<tr><td>29.</td><td>6. Sponsor</td><td>3.14</td><td>The Sponsor refers the MTAC to the following analysis extracted from the assessment overview report which it believes is supportive of the surrogate marker end point hypothesis:
The data can be found in Appendix 7 where the following questions were tabulated by the External Assessment Centre:
Question 2: Would a medical device’s demonstration of increasing venous blood flow be enough for you to consider it to have a prophylactic effect on VTE? and
Question 3: Can the same efficacy be assumed for geko™ device and IPC devices based on a comparison of their effects on venous blood flow alone?
The sponsor would like to stress to the MTAC that these questions were posed to experts without any further qualification (such as an option of confirming any response through a clinical trial).
These questions are at the very centre of the clinical hypothesis submitted by the Sponsor that supports adoption of the technology for the scope in question.
Question 2 is asking whether the surrogate end point of venous blood flow would reduce risk and
Question 3 is asking whether the alignment and risk reduction of IPC is valid based on blood flow alone

For clarity the responses are tabulated below:
<table>
<tr><th>Responder</th><th>Question 2</th><th>Question 3</th></tr>
<tr><td>Prof. Gerald Stansby</td><td>It would be an important finding</td><td>Strongly suggestive</td></tr>
<tr><td>Prof Andrew Nicolaides</td><td>No</td><td>No</td></tr>
</table>
</td><td>Thank you for your comment.
The Committee carefully considered this comment and decided not to change the guidance in response to this specific comment.
The Committee noted that the External Assessment Centre has confirmed that it is satisfied that the summary presented in the assessment report accurately reflects the replies that it received.</td></tr>
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<tr><th>Comment no</th><th>Consultee number and organisation</th><th>Section No.</th><th>Comments</th><th>Response</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Mr John Mosley</td><td>I agree with Gerald “it would be an important finding”</td><td>Did not respond</td></tr>
<tr><td>Prof Charles McCollum</td><td>Increase venous flow would help</td><td>No</td></tr>
<tr><td>Dr John Scurr</td><td>Yes</td><td>This is a fair to assume a positive effect from the geko.</td></tr>
</table>

Of those who responded only 3/10 replies were dismissive of the hypothesis tabled by the External Assessment Centre.
Therefore 67% agreed with the proposition as questioned by the External Assessment Centre.
In addition, questionnaire feedback from experts (page 36) suggested that 9/12 would support the production of guidance (presumably based on the current MTEP scope).
This suggests that the relevant question has been asked of the experts’ 22 times with 21 responses
6 or 29% rejected the clinical hypothesis
15 or 71% did not reject the clinical hypothesis
The Sponsor believes this is indicative that expert opinion supports its clinical hypothesis that would justify the positive guidance for this technology within scope and use of the device in patients who cannot be given and other form of VTE prophylaxis
The Sponsor concludes that the above data is supportive of the MTAC issuing adoption guidance for use as per the current MTEP scope and if it were to do so the MTAC would appear to have the backing of expert and peer reviewed opinion.</td><td></td></tr>
<tr><td>30.</td><td>6. Sponsor</td><td>3.15</td><td>The primary outcome of previous clinically proven NMES devices is the same as the technology under review and as such they are related by mode of action and by extrapolation their clinical outcome. In simple terms, both the geko™ device and previous NMES devices engage muscle groups and achieve augmentation of venous</td><td>Thank you for your comment.
Please refer to the responses to comments 2 and 7.</td></tr>
</table>

Comment no	Consultee number and organisation	Section No.	Comments	Response
			flow in the lower leg (prevent venous stasis) and in doing so reduce the risk of VTE. How these previous NMES devices specifically engaged muscle groups to achieve this outcome is not the central point. What is relevant is the fact that (like the geko ™ device) these previous devices did deliver this venous outcome which was the primary reason why they were seen to be efficacious. The Sponsor agrees that the extent upon which risk reduction can be compared between the geko™ device and previous NMES examples is debatable but this aspect is robustly examined within the economic model by extensive sensitivity analyses. It should be noted that the general model approach was approved by the External Assessment Centre	
31.	6. Sponsor	3.16	The Sponsor discusses the practicalities and strategic challenges of VTE end point studies are discussed in 1.2 above and highlights that this has never been delivered by any other VTE prophylaxis device.	Thank you for your comment. Please refer to the response to comment 14.
32.	6. Sponsor	3.17	As 3.17 but the Sponsor asks the MTAC not to lose sight of the MTEP scope which was purposely limited and well defined	Thank you for your comment. Please refer to the response to comment 3.
33.	3. NHS Professional (Expert adviser)	4	The group is small but there is an unmet need here; use of the device for these people will provide a reasonable expectation of efficacy against DVT based on flow studies, pending confirmation or otherwise of clinical effectiveness in due course by appropriate studies.	Thank you for your comment. Please refer to the response to comment 2.
34.	5. NHS Professional (Expert adviser)	4	There are patients who cannot get any form of VTE prophylaxis at the moment and it may not be ethical to leave them with no form of VTE prophylaxis when the geko has been shown to increase blood flow. The patient population may not be large, but guidance here will benefit patients who have no other option and do need VTE prevention. As an exemplar centre I am aware of a study in the UK recently that shows that 8% of all patients were contraindicated for pharmaceutical prophylaxis and there are a good percentage of patients who I see and are unsuitable for compression due to PAD. This is not an insignificant number of NHS patients who are at risk of VTE and are contraindicated for both pharmaceutical and mechanical prophylaxis. We should be looking to provide geko to these patients as a first step. Then look to increase patient groups when more data becomes available. I am aware that the Sponsor is currently	Thank you for your comment. Please refer to the response to comment 2.

Comment no	Consultee number and organisation	Section No.	Comments	Response
			gaining blood flow data in patients who are at risk of VTE	
35.	7. NHS Professional (Expert adviser)	4	I hope that the NHS would wish to encourage the development of simple devices such as this with real potential to prevent DVT. The device is not expensive and its application in patients who do not currently have access to mechanical DVT prophylaxis (a limited number of patients) is the obvious way to support the research that is needed. Almost inevitably, this limited population of patients where no other mechanical DVT prophylaxis is available, will also benefit from the use of GEKO. In my view, the use of this device post discharge would be part of the clinical trials that are so desperately needed.	Thank you for your comment. Please refer to the response to comment 2.
36.	6. Sponsor	4.1	The Sponsor remains convinced that the scientific and economic case for adoption has been made for patients within MTEP196 who are contraindicated for other forms of VTE prophylaxis. It is the narrow population within the current scope and no extension of this scope that the Sponsor wishes the MTAC to consider.	Thank you for your comment. Please refer to the response to comment 3.
37.	6. Sponsor	4.3	The Sponsor has invested time in trying to help the MTAC get a stronger indication of the size of the patient group represented by the current MTEP196 scope. Hitherto neither NICE, the MTAC, the External Assessment Centre, individual hospital trusts or the literature could assist in this matter. The Sponsor would like to bring to the MTAC's attention a recent publication which assessed VTE risk assessment and prophylaxis across four UK hospitals, including two VTE exemplar centres, following the implementation of NICE clinical guideline (CG92) (4,5). The study reported that 8.5% of patients were documented to have a contraindication pharmaceutical VTE prophylaxis. Also, 15% of patients received low molecular weight heparin despite having a contraindication, thus putting those patients at increased risk of bleeding. In addition to the study above, the Sponsor has used published data in an attempt to further quantify the size of the potential population suitable for treatment with the geko™ device (using the MTEP scope as a guide). The assessment focuses on three populations; stroke patients, patients with major trauma and patients with peripheral arterial disease (PAD). Hospital Episode Statistics (6) report that in 2012–13 there were 11.7 million ordinary Finished Consultant Episodes (FCEs) of which 41.5% require a procedure or intervention equating to 4,836,101 FCEs. If we assume that 8.5% of these FCEs will be	Thank you for your comment. Section 4.3 describes the Committee consideration of the patient population. The External Assessment Centre has assessed the study by Bateman and has concluded that there remains significant uncertainty about the size of the patient population for whom mechanical methods of VTE prophylaxis are indicated but are impractical or contraindicated. The proportion estimated by the sponsor in its submission was 1% compared with 8.5% in the study by Bateman. The aim of the Bateman study was to investigate the effect of NICE clinical guideline implementation, not primarily to audit patient admissions, and their data show

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contraindicated to current pharmacological methods of prophylaxis (5) this equates to 411,069 patients. Of these patients approximately 65% are aged over 65 (7), and of those, according to NICE guidelines (8), 20% will have some form of peripheral arterial disease (PAD) and will therefore also be contraindicated to mechanical methods of prophylaxis. This equates to approximately 53,439 patients who are contraindicated to both pharmacological and mechanical methods of prophylaxis who would therefore be suitable for prophylaxis with the geko™ device.

This will include a proportion of 28,880 stroke patients (152,000 strokes per annum of which; 15% will be haemorrhagic and 4% of which will be ischemic with increased risk of bleeding both groups therefore contraindicated to current methods of prophylaxis (9). The Sponsor believes this number to be approximately 3,700 patients [20% of 65% = 13% of 28,800]) and a proportion of the 20,000 major trauma cases that occur annually each year would be eligible for prophylaxis with the geko™ device.

The analysis provided in the original submission demonstrated that the use of the geko device as a prophylaxis could result in savings to the NHS of £206 per patient. Applying this saving to the 53,439 patients identified above could results in total savings to the NHS of over £11 million per annum and even allowing for the adjustment made by the External Assessment Centre, a saving to the NHS of £10.5 million per annum

<table>
<tr><th></th><th>% affected</th><th>Number of patients</th><th>Source</th></tr>
<tr><td>Total ordinary Finished Consultant Episodes (FCEs)</td><td></td><td>11,653,256</td><td>(6)</td></tr>
<tr><td>Proportion with a procedure or intervention</td><td>41.50%</td><td>4,836,101</td><td>(6)</td></tr>
<tr><td>Contraindicated to VTE</td><td>8.50%</td><td>411,069</td><td>(5)</td></tr>
<tr><td>Proportion of FCEs with a procedure or intervention aged over 65</td><td>65.0%</td><td>267,195</td><td>(9)</td></tr>
<tr><td>Proportion aged over 65 with PAD</td><td>20.0%</td><td>53,439</td><td>(8)</td></tr>
</table>

The Sponsor sees this as the beginning of a more constructive debate on the size of this population represented by the current MTEP196 SCOPE. In partnership with all
</td><td>
significant uncertainty – the largest group of the patients stated as being contraindicated for pharmaceutical prophylaxis (33%) had no reason for the contraindication documented.

The Committee considered the Consultee's comments and decided to change section 4.3 of the guidance to further clarify the uncertainty in the size of the population covered by the scope. The Committee considered the disparity in the estimates of the population from different sources and concluded that the size of the population could not be accurately estimated.
</td></tr>
</table>

Comment no	Consultee number and organisation	Section No.	Comments	Response
			stakeholders within this process the Sponsor looks forward to expanding this approach to help justify the positive MTAC guidance for technology adoption for patient groups that do exist and have a clinical need. Whatever the size of this population the Sponsor stresses to the MTAC that its commitment to serving these patients remains absolute.	
38.	6. Sponsor	4.4	The sponsor is motivated by the MTAC's vision of using of the geko™ device post-discharge within the home setting and this is embedded in the strategic plan for this technology. However the Sponsor believes that the limited adoption of the geko™ device is a logical place to begin any wider use both within and outside of the hospital setting. There are many advantages to this including a gradual but progressive awareness of the device for appropriate clinicians and a rolling programme of product training. It is the Sponsor's vision that this would subsequently create a launch pad for wider use, wherever that may be within the clinical pathway(s) chosen as dictated by future MTAC guidance.	Thank you for your comment. Please refer to the response to comment 6.
39.	6. Sponsor	5	Section 5 overview comments The External Assessment Centre have been positive about the methodology of the Sponsor's health economic modelling and all of the associated sensitivity analysis. However, the External Assessment Centre believe that the assumptions made by the Sponsor in respect to surrogate blood flow velocity end point data and the subsequent alignment and use of RR from clinically proven mechanical devices who have the same primary end point is a flawed extension of this rationale. The Sponsor and the External Assessment Centre have opposing views on this issue but do agree that the extent to which risk reduction will occur is unknown and can only be categorically proven via an appropriately powered RCT. Therefore, on the basis that the surrogate end point data is a valid foundation to model risk reduction then the Sponsor (in the absence of end point data) aligned the known clinical efficacy of devices which are efficacious due to the exact same surrogate end point of augmenting venous flow of the leg. It is the Sponsor's view that it credible to take the known relative risk (RR) of a device which has the same primary outcome of reducing venous stasis by augmenting venous flow in the leg and using this as a bench	Thank you for your comment. Please see response to comment 42.

Comment no	Consultee number and organisation	Section No.	Comments	Response
			mark from which to conduct an economic model. However, the Sponsor was more conservative as it created a band of RR from a variety of sources. This included older style NMES devices and newer IPC devices and it is again emphasised that these devices are related because of their impact on preventing venous stasis. How they specifically prevent stasis is not this issue it's the fact that they do that matters. Further confidence was provided in that the geko™ device is superior in augmenting venous flow than IPC which again provided reassurance of the approach. In an attempt to clarify the Sponsor's position further details are provided to answer section 5.5 where the External Assessment Centre's objection is registered.	
40.	2. NHS Professional	**5**	Extrapolation of risk reduction with other devices that prevent stasis is justifiable and acceptable	Thank you for your comment. Please see response to comment 7.
41.	7. NHS Professional (Expert adviser)	**5**	It is important that the cost evidence suggests that there would be a cost-benefit through the adoption of GEKO. I entirely accept that without good evidence on the proportion of DVTs that will be inhibited by GEKO, there are assumptions in this cost benefit analysis that need to be confirmed by future research. Limited adoption by NICE would achieve the NHS objective that this device be rapidly assessed in research where the primary outcome is DVT	Thank you for your comment. Please see responses to comment 2 and 6.
42.	6. Sponsor	**5.5**	Both IPC and NMES are clinically proven to prevent stasis, thereby reducing the risk of VTE. In order to assess the economic impact of the geko™ device, the Sponsor created a credible RR band from which to assume a RR for the geko™ device. With a baseline risk of 29.1% for every 100 patients at risk without any form of prophylaxis there would be an estimated 26 symptomatic DVTs and associated sequelae. Using a RR of 0.39 the gekoTM device would reduce the number of symptomatic DVTs to 10 This RR has been taken from the Browse and Negus NMES study	Thank you for your comment. The Committee carefully considered this comment and decided not to change the guidance in response to this specific comment. The Committee accepted that, while there remained significant uncertainties in the principal assumptions used in the sponsor's cost model, the scenarios – as revised by the External Assessment Centre based on expert clinical advice -

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It is a much more conservative risk to use than that observed by Nicolaides et all (0.08)
It falls within the range specified with the NICE VTE guidelines (0.31 to 0.58).

The following table is a simplification of the relative risk for VTE prophylaxis devices

<table>
<tr><th>Assumed equivalence to:</th><th>Relative Risk</th><th>Source</th><th>No. of symptomatic DVT per 100 pts</th><th>No. of symptomatic DVT avoided (vs no prophylaxis)</th><th>Cost difference vs no prophylaxis per 100 pts given geko</th></tr>
<tr><td>No prophylaxis</td><td>1.00</td><td>NICE VTE guidelines (1)</td><td>26.0</td><td>0.0</td><td>£13,815 Incremental</td></tr>
<tr><td>NMES (basecase)</td><td>0.39</td><td>Browse and Negus, 1970 (2)</td><td>10.2</td><td>15.8</td><td>£20,586 saved</td></tr>
<tr><td>NMES</td><td>0.37</td><td>Nicolaides et al, 1972 (Test vs control) (3)</td><td>9.7</td><td>16.3</td><td>£21,602 saved</td></tr>
<tr><td>NMES</td><td>0.08</td><td>Nicolaides et al, 1972 (Stimulated vs not) (3)</td><td>2.2</td><td>23.8</td><td>£37,935 saved</td></tr>
<tr><td>IPC/FID</td><td>0.31</td><td>NICE VTE guidelines (1) (Table 9: NMA results for IPC/FID for the general surgery group [Gastrointestinal, gynaecological, laparoscopic, thoracic and urological surgery])</td><td>8.1</td><td>17.9</td><td>£25,181 saved</td></tr>
<tr><td>IPC/FID</td><td>0.58</td><td>NICE VTE guidelines (1) (Table 12.75: NMA results for IPC/FID for the hip fracture surgery group)</td><td>15.1</td><td>10.9</td><td>£9,922 saved</td></tr>
<tr><td>Sponsor’s scenario analysis to achieve cost neutrality</td><td>0.76</td><td>Calculated using the Excel cost-consequence model</td><td>20.0</td><td>6.0</td><td>£0
(Cost neutral)</td></tr>
</table>
</td><td>were reasonable.</td></tr>
</table>

Comment no	Consultee number and organisation	Section No.	Comments	Response
			This threshold analysis demonstrates that the reduction in DVT/VTE only needs to be relatively small, especially when compared with other mechanical methods of prophylaxis, to achieve cost-neutrality. We would argue that in a high risk cohort of patients, who should be receiving VTE prophylaxis in line with current NICE guidance but who cannot receive current methods of mechanical or pharmacological prophylaxis, the gekoTM device offers potential clinical advantages to patients while also offering potential financial savings to the NHS.	
43.	6. Sponsor	5.11	The MTAC state here that two factors are driving the current guideline position Lack of direct VTE end point data The Sponsor feedback to these points: At the centre of the Sponsor's clinical rationale was the assurance that its basic scientific and clinical argument was universally accepted by the MTAC; namely that the prevention of venous stasis in the veins of the leg, as delivered by their technology, would reduce VTE risk in patients where other forms of VTE prophylaxis are contraindicated. This hypothesis was at the very foundation of the resulting MTEP196 scope. The Sponsor took further confidence from the fact that the MTAC had selected the technology knowing that the only clinical data currently available was blood volume flow and velocity and that the technology was superior in this respect to other mechanical VTE prophylactic devices. Accordingly, the Sponsor has worked on the orthodoxy that increasing blood flow velocity in unprotected patients was desirable, with a key debate being the consequent extent that the geko^{TM} device would reduce VTE risk and drive the resulting economic case for adoption. As such there is real concern (and disappointment) that the reasons for the MTAC technology selection are significantly different from the reasons stated in the consultation document for the MTAC not supporting immediate technology adoption. The current MTEP196 scope investigates justifying adoption of the technology in a very narrow patient group with surrogate endpoint evidence. However, the MTAC have declined the case for adoption based on there being" insufficient evidence on its clinical effectiveness" and rather than the envisaged adoption in a narrow population MTAC alludes to the unsuitable use of the device in a broader population. This is rather a mixed message and appears to the Sponsor to be falling outside of boundary of the agreed scope.	Thank you for your comment. Please refer to the response to comment 1 on MTAC considerations in selecting and routing the technology for evaluation.

Comment no	Consultee number and organisation	Section No.	Comments	Response
			The Sponsor remains hopeful that with expert opinion support that the surrogate end point hypothesis can be accepted during the consultation stage. The Sponsor has shown that 71% of responses to the related question supported the surrogate end point rationale.	
44.	6. Sponsor	5.11	The MTAC state here that two factors are driving the current guideline position 2. It did not consider it appropriate to use a risk reduction (RR) based on the RR of older style NMES devices The Sponsor feedback to these points: The Sponsor has addressed this point throughout. The primary outcome of previous clinically proven NMES devices is the same as the technology under review and as such they are related. In simple terms, both the geko™ device and previous NMES devices engage muscle groups and achieve augmentation of venous flow in the lower leg (prevent venous stasis) and in doing so reduce the risk of VTE. How these previous devices specifically engaged muscle groups to achieve this outcome is not the central point. What is relevant is the fact that (like the geko ™ device) these previous devices did deliver this venous outcome which was the primary reason why they were seen to be efficacious. While it is acknowledged that older NMES and muscle electro stimulation (MEST) devices use transcutaneous stimulation, usually applied in the vicinity of the muscles to be stimulated, rather than the more indirect application of the gekoTM device at a point higher on the neural pathway, the physical consequence of both is the contraction of the lower limb muscle groups to activate the venous valve pumps, reduce stasis and therefore reduce the risk of DVT	Thank you for your comment. Please see response to comment 7.
45.	3. NHS Professional (Expert adviser)	**6**	See comments in Section 4 - flow studies are a reasonable surrogate for clinical effectiveness and on this basis the device could be justified for those with a current unmet need. I agree that clinical studies, if feasible and affordable, should be encouraged	Thank you for your comment. Please refer to the response to comment 2.
46.	5. NHS Professional (Expert adviser)	**6**	The surrogate marker of increased blood flow should be sufficient for immediate guidance, for patients who have no other VTE prophylactic option available as per scope. This group of patients is contraindicated for both mechanical and pharmaceutical prophylaxis. . Further research should be undertaken before extending beyond this	Thank you for your comment. Please refer to the response to comment 2.

Comment no	Consultee number and organisation	Section No.	Comments	Response
			scope	
47.	6. Sponsor	6	The MTAC was notified at the time of selection that only the surrogate end point clinical argument could be made at this time, so for the MTAC to decline adoption because direct VTE evidence was lacking is somewhat surprising	Thank you for your comment. Please refer to the response to comment 1 on MTAC considerations in selecting and routing the technology for evaluation.
48.	6. Sponsor	6	The Sponsor accepts that with hindsight that surrogate blood flow velocity data was needed in patients (but again the technology was selected by the MTAC in the knowledge that data was only available in healthy subjects) and has worked tirelessly to extract data from ongoing studies so that the MTAC can make an informed final guidance decision in respect to the surrogate end point rationale for risk reduction in patients within scope.	Thank you for your comment. Please refer to the response to comment 9.
49.	7. NHS Professional (Expert adviser)	**6**	I agree with the Committee that the GEKO device shows considerable promise. It is immensely difficult for small SMEs such as the manufacturers of GEKO to undertake clinical studies in NHS patients when the product has not been adopted by the NHS or NICE. This is a clear example of an opportunity for our NHS and NICE to achieve their research and development objectives by supporting the British SME and limited adoption of this device in patients who would almost certainly benefit as they have no other option for mechanical DVT prophylaxis	Thank you for your comment. Please refer to the response to comment 3.
50.	6. Sponsor	6	The Sponsor is motivated that the MTAC is positive about the technology and its future potential in a broader population. However, this avoids the immediate opportunity for use which was carefully and specifically identified as a suitable launch of the technology into the NHS. Therefore, the Sponsor is surprised and disappointed that the narrow focus of the agreed MT196 scope and been superseded. This extension of use (broader population) was not a request of the Sponsor and until sufficient clinical data is available the Sponsor would not approach MTAC with such a proposal. The Sponsor would like to re-iterate that the adoption of the geko™ device is sought in a population of patients who are currently unable to receive other forms of VTE prophylaxis. Threshold analyses have demonstrated that the reduction in DVT/VTE only	Thank you for your comment. Please refer to the response to comment 3. The relevant system consideration is described in the response to comment 42.

Comment no	Consultee number and organisation	Section No.	Comments	Response
			needs to be relatively small (24%), to achieve cost-neutrality. We would argue that in a high risk cohort of patients, who should be receiving VTE prophylaxis in line with current NICE guidance but who cannot receive current methods of mechanical or pharmacological prophylaxis, the geko™ device offers potential clinical advantages to patients while also offering potential financial savings to the NHS.	
51.	6. Sponsor	**6**	The sponsor has highlighted the practical and strategic difficulties of delivering the further research without first issuing MTAC guidance on a restricted and low risk introduction of this technology into the NHS.	Thank you for your comment. Please refer to the response to comment 6.
52.	6. Sponsor	**6**	Whilst the Sponsor is hopeful that, with the help of expert opinion the surrogate data hypothesis can be accepted the Sponsor would like to highlight that even if the gekoTM device is assumed to be only 60% as efficacious as IPC or older versions of NMES, the economic model is still favourable	Thank you for your comment. Please see responses to comment 7 and 42.
53.	2. NHS Professional	**6**	NICE guidance on the use of Geko stimulation device can be issued on the basis of its effectiveness in improving venous outflow and the cost when compared to other IPC technologies.	Thank you for your comment. Please see response to comment 7.
54.	Emeritus Professor (Expert adviser)	**General**	I have always followed the deliberations on the prevention of VTE by NICE and their resulting clinical guidance with great interest and have over many years enjoyed making an International contribution to this important debate. I am writing this letter to make a number of clarifications in respect to my invited input to the NICE geko device evaluation. My input into this review is now in the public domain (Appendix 7 of the Assessment report overview document) and some aspects of my response need to be clarified because I believe that my short answers to your questions might have been misleading. I would like to make the following points: 1. Many RCTs performed in the last 30 years have confirmed that any method that reduces blood hypercoagulability (LDUH, LMWH, warfarin) and any method that increases blood flow or velocity (passive muscle compression by IPC or active muscle compression by electrical stimulation) will reduce the incidence of DVT to a certain extent. However, the magnitude of this reduction can only be shown by RCTs. 2. RCTs are necessary for a grade A or B recommendations, but not for a grade C	Thank you for your comment. Please refer to the responses to comments 27 (NMES devices) and 11 (FDA approval). The Committee considered this comment together with the other consultation comments, the additional evidence and expert advice obtained during consultation and decided to change section 1.1 (and associated sections 3.18-3.20, 4.3, 5.12 and 6.1), The Committee decided to recommend the use of the geko device in a limited population for whom other methods of

Comment no	Consultee number and organisation	Section No.	Comments	Response
			recommendation where clinical justification for limited use can legitimately be made by extrapolation from related RCTs in different populations or from related devices that have the same mode of action or primary outcome (in this case blood flow velocity). 3. You have asked me 4 questions: a. (a) Would it be fair to assume that prophylactic effects from one device would be similar to another? b. (b) Would a medical device's demonstration of increasing venous blood flow be enough for you to consider it to have a prophylactic effect on VTE? c. (c) Can the same efficacy be assumed for geko and IPC devices based on a comparison of their effects on venous blood flow alone? d. The sponsor has used the relative risk of NMES device (Browse and Negus 1970) for geko in their cost model, due to lack of evidence. Is this reasonable?" My previous negative responses to all of these questions referred to the required level of evidence (i.e. the incidence of DVT) that would need to be demonstrated by the geko device to clinically justify NICE guidance for a grade A or B recommendation (i.e. to replace current methods). In this context my responses were accurate. However, it does not mean that the geko device cannot be used immediately with a C recommendation meaning that in situations where current VTE prophylactic methods are contraindicated and patients have no other form of prophylactic treatment. A good example in the patient with multiple trauma and a fractured leg with external fixation where LMWH is contraindicated because of the risk of bleeding and IPC or other compression cannot be applied. My recommendation for the use of the geko device is based on extrapolation from four previous NMES RCTs which have shown that different electrical stimuli of calf muscle groups reduced the incidence of DVT. These devices, whilst all different, were efficacious because they all increased blood velocity in the veins of the lower leg and the geko device is no different in this respect. The extrapolation of these RCTs (including Browse and Negus) to the geko device is therefore clinically justified because the geko device has been shown to increase blood velocity and this will reduce VTE risk. Whether the reduction in the incidence of DVT in practice will be 40% or 70% is irrelevant in this situation. Ultimately, this question will be answered in due	DVT are unavailable or contraindicated (as described in the response to Comment 2).

Comment no	Consultee number and organisation	Section No.	Comments	Response
			course by RCTs. Until then the assumed efficacy of the geko device can legitimately be modelled using previous risk reduction outcomes from any of the published NMES studies I refer to. In this respect I do not agree with 3.11 (page 9 of 22) of the consultation document. The above is the logical justification for a C recommendation for the geko device in specific situations where no other method of prevention would be applicable given in International Guidelines on the prevention of VTE published on both sides of the Atlantic in March 2013. You may be interested to know that the same reasoning was applied by the FDA who gave approval to the Veinoplus device (electrical calf muscle stimulator) to be used in the prevention of VTE even though there has not been any RCT demonstrating its efficacy. I hope the above will clarify my previous answers and will prevent the absolute dismissal of a potentially useful device for which there is currently a place, however small, in our clinical practice particularly where no other method can be used (Grade C recommendation).	
55.	5. NHS Professional (Expert adviser)	**General**	About to start a study using the Geko in different patient groups eg: Patients with PVD, stroke patients and patients with arterial and venous ulcers. The study is funded by Firstkind medical.	Thank you for your comment
56.	8. DH	**General**	I wish to confirm that the Department of Health has no substantive comments to make regarding this consultation	Thank you for your comment.
	6. Sponsor	**Comment on Assessment Report**	Appendix 6 contains comments on the Assessment Report Overview and responses from the External Assessment Centre	Thank you for your comments. The Committee considered these comments and decided not to make any further changes to the guidance in response to these comments and responses.

Comment no	Consultee number and organisation	Section No.	Comments	Response
		Overview		

1. National Institute for Health and Clinical Excellence. NICE CG92. Venous thromboembolism - reducing the risk. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital.
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3. Nicolaides AN, Kakkar VV, Field ES, Fish P. Optimal electrical stimulus for prevention of deep vein thrombosis. Br Med J. 1972 Sep 23;3(5829):756-8
4. National Institute for Health and Clinical Excellence. NICE CG92. Venous thromboembolism - reducing the risk. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. Available at: http://www.nice.org.uk/CG092. (Last accessed 28 Mar 2013). Jan 2010.
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6. Office for National Statistics - Health and Social Care Information Centre. Hospital Episode Statistics. Admitted Patient Care, 2012-13. Available at: https://catalogue.ic.nhs.uk/publications/hospital/inpatients/hosp-epis-stat-admi-pati-care-eng-2012-13/hosp-epis-stat-admi-summ-rep-2012-13-rep.pdfhttps://catalogue.ic.nhs.uk/publications/hospital/inpatients/hosp-epis-stat-admi-pati-care-eng-2012-13/hosp-epis-stat-admi-summ-rep-2012-13-rep.pdf (last accessed 10th Dec 2013). 5 Nov 2013.
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9. Royal College of Physicians. Hospitals on the edge? The time for action. Available at: http://www.rcplondon.ac.uk/sites/default/files/documents/hospitals-on-the-edge-report.pdf (last accessed 10 Dec 2013). Sept 2012.

not endorsed by NICE, its officers or Advisory committees."

geko MTCD consultation comments table Appendix 1 (new data from sponsor)

This Appendix was submitted by the Sponsor to support consultation comments on the Medical Technologies Consultation Document and the Assessment Report Overview. It contains new evidence and information.

1. Patient blood flow data for the geko™ device

Two studies are currently ongoing to assess the effectiveness of the geko™ device in patient populations:

- The geko™ device vs IPC of the foot in patients following elective total hip replacement (THR) surgery (25)
- The geko™ device vs TEDS in patients following elective THR surgery (26).

The interim reports have been supplied in the accompanying reference pack.

1.1.1. The geko™ device vs IPC of the foot following elective THR

An overview of the study methodology is provided in Table 1.

Table 1: Summary of methodology for study vs IPC of the foot

Study name (acronym)	Interim analysis, vs IPC of the foot in patients following THR
Objective	IPC of the foot versus the geko™ device: comparison of lower limb circulation following elective THR
Location	UK
Design	Single centre, randomised, intra-patient comparison
Duration of study	1 visit
Population	Patients scheduled for elective THR surgery
Sample size	10 patients planned, 7 included in this interim analysis
Inclusion criteria	• Aged 18 and over • Good general health and fitness other than the clinical requirement for a planned hip replacement • No history or signs of drug abuse (including alcohol), licit or illicit
Exclusion criteria	• Requiring hip revision surgery • Previous or current diagnosis of DVT or PE • History or signs of significant haematological disorders (especially in relation to clotting or coagulation) or thrombophlebitis • Peripheral arterial disease, clinically significant varicose veins or lower limb ulceration or ischemia • Recent surgery within the last 3 months (such as abdominal, gynaecological, hip or knee replacement) • Recent trauma to lower limb • Chronic obesity (BMI>40 kg/m^2) • Pregnancy • Significant history of following diseases o Cardiovascular: Recent MI (<6 months) o PCI with stent (<3 months for BMS and <12 months for DES) o Moderate to severe CCF, uncontrolled AF o Neurological: Stroke, hemiplegia/paraplegia, myopathies o Renal: Moderate to severely impaired renal function o Hepatic: Moderate to severely impaired hepatic function o Psychiatric disorders o Dermatological conditions affecting lower limbs • On LMWH/Heparin (prophylactic/therapeutic doses) or warfarin or warfarin stopped recently and replaced by LMWH/ Heparin • Long term steroid use with dermatological changes • A pulse rate of less than 40 bpm • A sitting SBP >180 and <100 mmHg and/or a sitting diastolic pressure of >100 mmHg • Participation in any clinical study during the 8 weeks preceding the screening period • THR for hip fracture • Pacemaker
Intervention(s) (n =) and comparator(s) (n =)	**After surgery** • Baseline measurement • After 10 minutes, activation of either the geko™ device or foot pump • Rest period (30 mins) without device (return to baseline) • After 10 minutes, activation of the alternate device All measurements to be carried out in triplicate
Baseline differences	N/A

Study name (acronym)	Interim analysis, vs IPC of the foot in patients following THR
Statistical tests	• Comparison of blood flow and velocity in femoral artery and femoral vein using Student's t-test • Tolerability and acceptability questionnaire data compared with Mann-Whitney u-test
Outcomes (including scoring methods and timings of assessments)	• Duplex ultrasound of superficial femoral vein and femoral artery. Bilateral assessment of blood flow velocity, volume, vessel diameter • Evaluation of the tolerability of the devices by patient rated questionnaire • Evaluation of the ease of use (acceptability) of the devices rated by the person responsible for fitting the device • Evaluation of the safety of the device by recording AEs and vital signs

Abbreviations: AE, adverse event; AF, atrial fibrillation; BMI, body mass index; BMS, bare metal stent; CCF, congestive cardiac failure; DBP, diastolic blood pressure; DES, drug eluding stent; DVT, deep vein thrombosis; IPC, intermittent pneumatic compression; LMWH, low molecular weight heparin; MI, myocardial infarction; N/A, not applicable; PCI, percutaneous coronary intervention; PE, pulmonary embolism; SBP, systolic blood pressure; THR, total hip replacement.

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1.1.2. The geko™ device vs TEDS following elective THR

An overview of the study methodology is provided in Table 2.

Table 2: Summary of methodology for study vs TEDS

Study name (acronym)	Interim analysis, vs TEDS in patients following THR
Objective	Comparison of the incidence of asymptomatic and symptomatic DVT between the geko™ device and TEDS in post-operative patients recovering from elective THR surgery
Location	UK
Design	Multicentre, randomised, open label, adaptive design
Duration of study	Minimum of 4 days in hospital, follow-up at 6 weeks
Population	Patient scheduled for elective total hip replacement surgery
Sample size	20 patients per arm; n=40 16 included in this interim analysis: • n=7 randomised to TEDS • n=9 randomised to the geko™ device
Inclusion criteria	• Aged 18 years of age and over • Free of significant abnormal findings as determined by medical history (specifically an absence of DVT or haematological disorders) • Has not used any medications (prescribed or over-the-counter including herbal remedies) judged to be significant by the Principal Investigator during the ten (10) days preceding enrolment

Exclusion criteria	• Requiring hip revision surgery
	• History or signs of previous deep or superficial vein thrombosis/PE
	• Evidence of asymptomatic DVT by Duplex Ultrasound.
	• Peripheral arterial disease (ABPI < 0.8)
	• Significant varicose veins, phlebitis or lower limb ulceration or ischemia. CEAP Grade 4-6
	• Recent surgery within the last 3 months (such as abdominal, gynaecological, hip or knee replacement)
	• Recent trauma to lower limb
	• Chronic obesity (BMI>40 kg/m^2)
	• Pregnancy
	• Significant history of following diseases
	  ○ Cardiovascular: Recent MI (<6 months)
	  ○ PCI with stent (<3 months for BMS and <12 months for DES)
	  ○ Moderate to severe CCF, uncontrolled AF
	  ○ Neurological: stroke, hemiplegia/paraplegia, myopathies
	  ○ Significant dermatological conditions affecting lower limbs resulting in broken or inflamed skin particularly at the site where the device is to be fitted
	  ○ Clinically significant haematological conditions i.e. coagulation disorders, sickle cell disease
	  ○ Psychiatric disorders
	• On LMWH/Heparin (prophylactic/therapeutic doses) or warfarin or warfarin stopped recently and replaced by LMWH/ Heparin
	• Long term steroid with dermatological changes
	• A pulse rate of less than 40 bpm
	• A sitting SBP >180 and <100 mmHg and/or a sitting DBP of >100 mmHg
	• Any significant illness during the 4 weeks preceding the hip replacement surgery
	• Participation in any clinical study during the 8 weeks preceding the screening period

Intervention(s) (n =)	The geko™ device (acting on the lateral popliteal nerve) and TEDS used

Study name (acronym)	Interim analysis, vs TEDS in patients following THR
and comparator(s) (n =)	continually post-surgery for 48 hrs and then a minimum of 4 hrs/day until discharge
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patients followed-up 6 weeks post-surgery using Duplex ultrasound
Statistical tests	• Rates of DVT (asymptomatic or symptomatic) compared at Day 2, discharge and Week 6 using Fisher's Exact test • Oedema: graphs will be plotted of leg circumference versus time and gradients compared • Peak velocity and volume flow in femoral vein measured for each subject. Values calculated relative to an initial baseline before surgery and then compared using Student's t-test • Discharge time for each group recorded, and Mann-Whitney u-test performed to identify any significant difference between groups. Patients kept in hospital for a minimum of 4 days • Tolerability data for each intervention collected on discharge, measured using a Likert 1-5 scale. Interventions subsequently compared with Mann-Whitney u-test
Outcomes (including scoring methods and timings of assessments)	• Duplex ultrasound of both legs to identify asymptomatic DVT and blood flow at Day 2, discharge and Week 6. Baseline scan conducted immediately prior to surgery • Blood flow measurements by Duplex ultrasound carried out pre-operatively, Day 2 (with and without the geko™ device or TEDS in place), discharge and Week 6 • All blood flow measurements to be carried out in triplicate • Evaluation of the acceptance and tolerability of both TEDS and geko™ by administration of the questionnaire (Verbal Rating Scores)

Abbreviations: ABPI, ankle brachial pressure index; AF, atrial fibrillation; BMI, body mass index; BMS, bare metal stent; CCF, congestive cardiac failure; CEAP, Clinical severity etiology anatomy pathophysiology; DBP, diastolic blood pressure; DES, drug eluding stent; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; MI, myocardial infarction; PCI, percutaneous coronary intervention; PE, pulmonary embolism; SBP, systolic blood pressure; TEDS, thromboembolism deterrent stockings; THR, total hip replacement.

This study is intended as a pilot of 40 patients, using the DVT outcomes data to provide rate estimates to power a larger randomised controlled trial of DVT outcomes.

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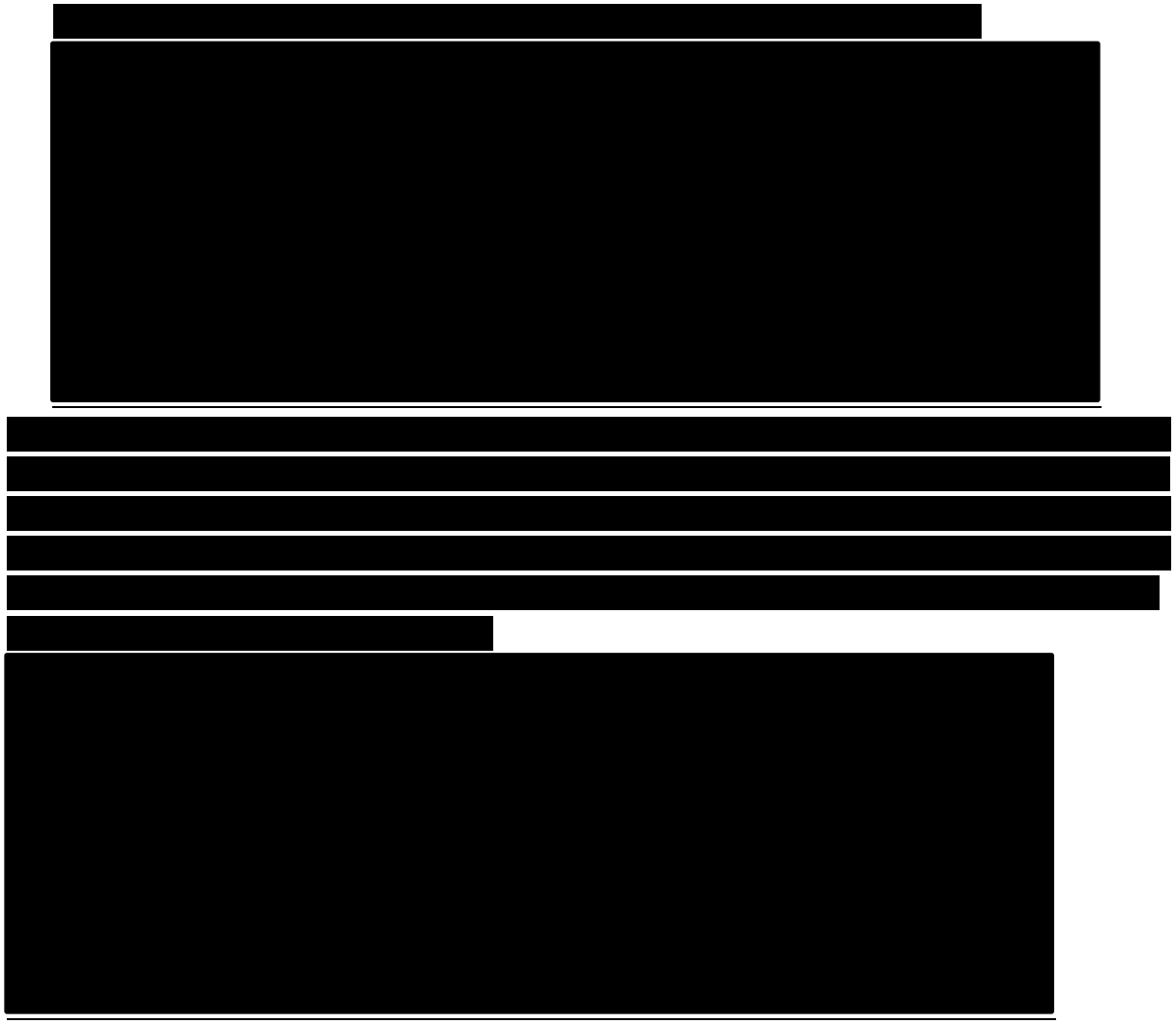

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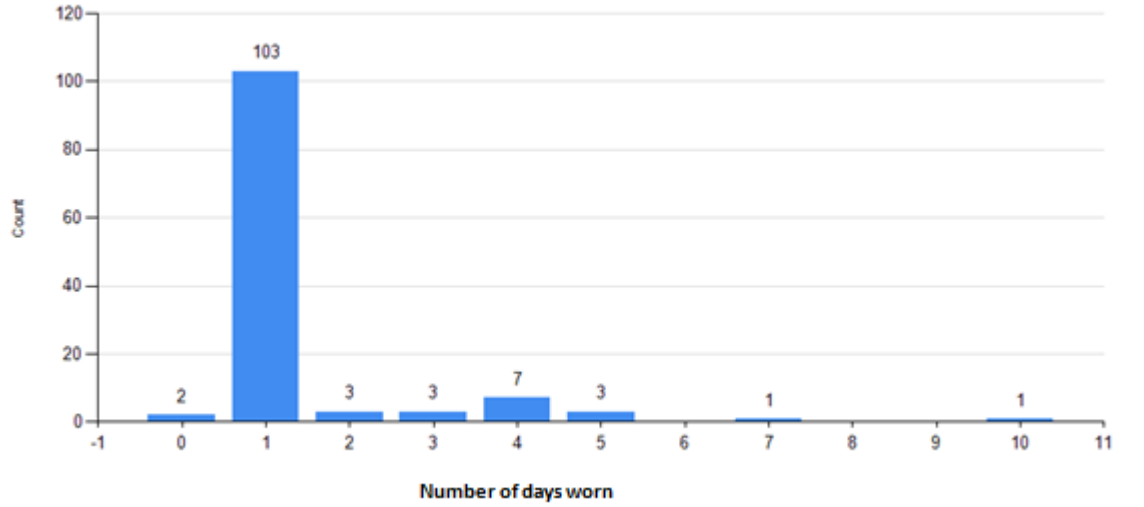
2. Clarification of PMS wear time

Post market surveillance (PMS) data of 216 patients was collected across a 24–48hr period of patient wear. Of the 216 patients surveyed, 184 (85.2%) assessed the geko™ device as comfortable or very comfortable to wear once applied.

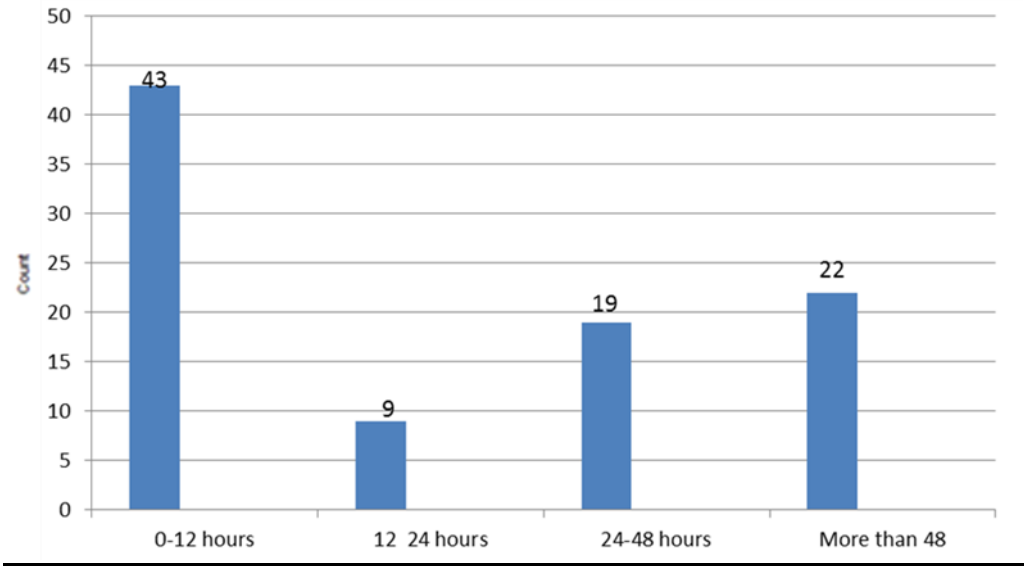
During PMS data collection, the question around length of time worn was amended. In response to the question 'How many days was the device worn in total?', 121/123 patients (98%) wore the geko™ device for 1 or more days (Figure 5). The maximum number of days worn was 10 days (1 patient).

Figure 5: Number of days the geko™ device was worn in total, n=123



Is response to the question 'How long was the device worn?', 41/93 patients (44%) wore the geko™ device for 24 or more hours (Figure 6).

Figure 6: Duration of device wear, n=93



3. Evidence to show that the geko™ device does stimulate fibrinolysis

Evidence for fibrinolysis was not included in the manufacturer's submission as it was not listed as an outcome in the NICE scope, but the geko™ device has been shown to affect fibrinolysis. The evidence for the effect of the geko™ device on fibrinolysis comes from Jawad 2012 coagulation study (blood flow data was originally submitted in the manufacturer's submission) (16).

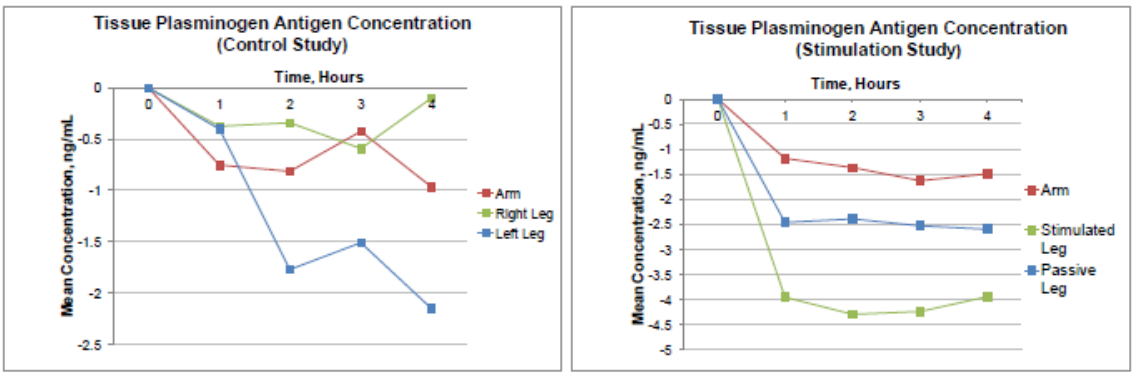
Measurements were made using the same subjects over two sessions:

1. One session with the geko™ device on one leg only for a 4 hour period, to compare the geko™ device leg with control (A) leg
2. Second session without the geko™ device, as control (B) for a four hour period, to compare with session 1 to check for systemic effects of the geko™ device.

The geko™ device is exactly analogous to THRIVE device used in this study, with the same printed circuit in a different casing. This study utilised a current of 25mA (within the manufactured range of the geko™ device), pulse width 600 µs (within range of the geko™ device) and frequency of 3Hz (vs 1Hz with the geko™ device).

In the control study a significant drop in tissue plasminogen activator antigen (t-PA) levels over time was observed in the left leg ($p \leq 0.001$), but no significant difference was observed in either the right leg or arm, $p>0.05$. In the stimulation study, significant reductions were observed in both the arm and stimulated leg, $p \leq 0.001$ (no significant change was observed in the passive leg; $p>0.05$) (Figure 7).

Figure 7: Jawad, unpublished (coagulation), adjusted mean tissue plasminogen activator antigen concentration



Adjusted percentage change from baseline displayed a fall in tissue plasminogen activator antigen levels by 14% in the stimulated leg vs 10% in the arm and 1% in the left leg (Table 3).

Table 3: Jawad, unpublished (coagulation), tissue plasminogen activator measurements

Mean (SD)	Arm		Right/stimulated leg		Left/passive leg	
	ng/mL	p value	ng/mL	p value	ng/mL	p value
Control Study						
Baseline	4.29 (4.44)	p>0.05	6.79 (3.92)	p>0.05	8.26 (5.61)	p ≤ 0.001
1 hour	3.54 (3.44)		6.42 (3.93)		7.86 (5.27)	
2 hours	3.48 (2.80)		6.45 (3.61)		6.49 (4.63)	
3 hours	3.87 (3.20)		6.21 (4.32)		6.75 (4.83)	
4 hours	3.33 (3.66)		6.69 (4.10)		6.11 (4.22)	
Stimulation Study						
Baseline	7.65 (4.29)	p ≤ 0.001	11.43 (8.21)	p ≤ 0.001	11.67 (8.53)	p>0.05
1 hour	6.47 (3.11)		7.47 (3.07)		9.21 (3.64)	
2 hours	6.28 (2.98)		7.13 (2.80)		9.28 (3.73)	
3 hours	5.45 (2.74)		7.19 (2.50)		9.14 (3.29)	
4 hours	5.15 (3.41)		7.49 (3.01)		8.67 (4.58)	

Abbreviations: SD, standard deviation.

The main finding was that the geko™ device had an effect in reducing tPA. A deficiency in tPA can result in a reduction of the capacity to degrade a clot, predisposing to thrombosis. Levels of tPA antigen were significantly reduced throughout the stimulation and control study. In the stimulation study, the geko™ device reduced tPA in the geko™ device leg by 14% compared with the control leg (control A) and there was also an observable systemic reduction in the control study (control A relative to control B with no geko™ device). Thus, the geko™ device has both a local and a systemic effect at reducing tPA. tPA antigen levels reflect both tPA and tPA bound to PAI-1 (it does not represent tPA levels alone); and that most of the circulating tPA is bound to PAI-1 (17, 18). A direct relationship exists between tPA antigen and PAI-1 levels and decreased fibrinolytic activity is associated with increased levels of PAI-1. Therefore, the drop in plasma tPA concentration suggests increased fibrinolytic activity.

4. The physiological actions of mechanical deep vein thrombosis prophylaxis, a statement obtained from Dr Rhys Morris, co-author of Morris and Woodcock, 2004

Mechanical Deep Vein Thrombosis (DVT) prophylaxis systems have two methods of action: they can be passive or active. Graduated compression stockings are passive and aim to act by reducing the diameter of deep veins, thereby increasing resting venous blood flow velocity. Their major effect may, however, be to prevent venous distension, which will reduce the pooling of blood (15). Intermittent pneumatic compression and electrical stimulation systems are active as they cause the deep veins to be compressed periodically, which ejects venous blood back towards the heart. The effectiveness of these mechanical methods in DVT prophylaxis is well established (8). What is less well established is how their different actions produce the prophylactic effect. If a device prevents thrombosis, it must counteract one or more of the causes of thrombosis. It is an examination of these that provides our current understanding of the physiological actions of active mechanical DVT prophylaxis, and particularly the role of blood flow velocity.

Thrombogenesis

The triad of causes of DVT described by Virchow in 1856 (30) (vessel damage, hypercoagulability and stasis) is still regarded as the basis for the understanding of the pathophysiology of the condition (7). Where there is still debate is around the relative importance of each cause, and their interactions with each other.

Vessel damage or abnormality is considered a factor in DVT formation as it produces a site for forming thrombus to adhere. It is, of the three causes, the lesser target for prophylaxis (31): it can be difficult to avoid after some surgical procedures. However, while observed after orthopaedic surgery and trauma, no microscopic wall damage has been found in patients who develop DVT after other surgical procedures (32). Exposure of the subendothelial matrix in this manner is known to be a significant part of arterial thrombosis formation (33), yet the evidence is that venous thrombus can form in the absence of any damage (3).

The most prevalent approach both to the prophylaxis and treatment of DVT is to change blood coagulability. Indeed, it can be the main focus of care for patients at increased risk. Deep vein thrombosis is, though, localised, and blood coagulability is not. If systemic changes were the only abnormality there would be disseminated intravascular coagulation (1). If only 30% of patients with DVT or pulmonary embolism have inherited haematological conditions (factor V Leiden, antithrombin III deficiency, etc.) that would produce hypercoagulability (34), the remainder must have some other causal factors. Reducing blood coagulability, while important, does not necessarily address the whole root of the problem.

While aspects of blood coagulability can be defined quantitatively, venous ‘stasis’ is poorly defined (27). The literal meaning is ‘unmoving’, but may more normally be assumed to mean ‘slow’ blood flow in the context of thrombogenesis. The formation of thrombus by stasis is not a purely mechanical effect: completely static blood does not immediately solidify (27). Stasis is therefore the slowing of blood sufficient to allow thrombus to form, rather than the process of thrombus formation itself. Leucocytes have been shown to be more likely to bind to endothelia under these slow flow conditions (35). Indeed, it is known that induced stasis alone will initiate thrombus formation (3). Valve pockets are considered the most likely location for the thrombus to form (36) because the regions behind the leaflets in the valve sinus experience slow flow with low oxygen tension, and would allow cell accumulation (37).

The natural process to avoid the slow flow around valve leaflets is for the deep veins to be compressed by the muscle pumps of the legs when walking. The accelerated flow will not only increase the velocity around the valve, but the higher velocity disturbed flow may strip out nascent thrombi (38). It is further contended (27) that the reduction or lack of pulsatility of blood, rather that its velocity alone that provides the condition for thrombus to form. Resting lower limb venous blood flow is naturally modulated by changes in abdominal pressure during respiration. Muscle pump action, or active mechanical prophylaxis will restore or augment pulsatility lost during periods of immobility or restriction of venous outflow.

Stasis and Shear Stress

Mechanical prophylaxis devices were designed to prevent venous stasis. However, it was established early in development that intermittent pneumatic compression also caused haematological changes (39). Not only are clotting factors reduced, but inhibitors of clotting factors are increased, as is

thrombolytic activity (40). There is clearly therefore some way in which the mechanical effects are causing these changes in coagulability. While it is possible that intermittent pneumatic compression devices could have some direct effect on blood vessels during compression, haematological changes have also been demonstrated with electrical stimulation (41) and graduated compression stockings (42) which have different physical actions. Since the objective of all mechanical systems is to change blood flow, the most plausible explanation for the haematological effects is that they are mediated by the flowing blood itself (43).

These known physiological effects lead to the prophylactic mechanism of mechanical devices to be divided into two distinct, if related parts. Firstly, prevention and elimination of stasis itself will prevent thrombus formation. Secondly, the acceleration of blood caused by this process stimulates release of substances in the body that reduce coagulability.

The avoidance of stasis must, at a minimum, ensure blood is not static, but there is little understanding of how much it should be accelerated. Clinical evidence does not suggest that the faster the flow velocity the lower the DVT rate (44). The faster the velocity produced by an intermittent compression system, for instance, the faster the inflation rate, and the higher the pressure of the garment has to be (15). This has inevitable consequences for patient comfort and acceptance of the method. Defining the velocity required to overcome stasis will ultimately have real clinical consequences.

One factor that does increase with venous blood flow velocity is the shear stress caused to the venous endothelium. Shear stresses in normal laminar flow are greatest at the edges of the vessel where there is drag on the vessel wall. This is of fundamental importance because shear stress is known to cause the endothelium to release substances that are both pro- and anticoagulant (45-47). Moreover leucocytes and platelets will tend to be displaced by erythrocytes from the centre of the vessel, and therefore will have higher concentrations at those regions undergoing shear (7).

Increased shear stress has been shown to increase the secretion of tPA (tissue plasminogen activator) in cultured endothelial cells, and to increase tPA messenger RNA levels (48). Prostacyclin release has been increased in a similar manner (49), as has nitric oxide (NO) synthase activity (50)27 and nitric oxide synthase mRNA (51, 52). Intermittent compression has been shown to increase general tPA levels in vivo (40). Since both prostacyclin and NO inhibit platelet aggregation, there is a reasonable conclusion that all mechanical methods provide prophylaxis by increasing shear stress (7, 53, 54).

A dysfunctional endothelium will increase von Willebrand factor, tissue factor and plasminogen activator factor (46), increasing blood coagulability. Mechanical prophylaxis has also been associated with measured decreases in all of these. The evidence therefore indicates that not only does the increased flow from mechanical devices stimulate the venous endothelium to produce substances that reduce blood coagulability, but may counteract increased coagulability caused by an endothelium that is not functioning in its normal antiplatelet, fibrinolytic manner due to trauma, sepsis or other disruption (46).

Stasis is then itself two different phenomena. It is the slowing and pooling of blood cells, but also the lack of shear stress. Both of these will favour thrombus formation. Esmon & Esmon (55) have proposed a more detailed refinement to this mechanism whereby the pooling of cells is in the large blood vessels, and does not reach anticoagulant molecules that are abundant in the

microvasculature. In the large vessels the ratio of blood to endothelial surface is increased, increasing the ratio of procoagulants to anticoagulants. Increasing flow reduces the time blood cells are present in the large vessels, and the likelihood of clotting.

Yet, shear stress remains an initiator of clotting (45, 47). High shear will activate platelets, and increase cell adhesion (56). This may partially explain the lack of a link between higher flow velocities and reduced rates on DVT in clinical trials (44). Shear is a desirable effect of increased flow to restore the procoagulant/anticoagulant balance in the blood by releasing tPA, NO and other substances from the endothelium. However, if the velocity is increased beyond a certain level, perhaps beyond that which is normal during ambulation, the shear-induced effects may be counterproductive.

Preventing DVT

A summary of our current understanding of DVT formation would be that the process begins with the deactivation of the limb muscle pump by prolonged rest or general anaesthesia, together with a reduction in the flow pulsatility and possibility volume (27). Clotting factors accumulate, and coagulation inhibitors are consumed in the slowest flow regions such as venous valves (37), muscular venous sinuses (32) or where there is venodilatation during surgery (57). The 'ishaemic-hypoxic' hypothesis claims that this slow or non-pulsatile flow around venous valves causes oxygen to be consumed by the endothelial cells without normal blood exchange (27). This, in turn, will cause hypoxic injury to the endothelial cells of the valve leaflets giving sites of leucocytes and platelets from any later flow to accumulate and begin the process of thrombogenesis. Flow will be restricted beginning the process of thrombus growth.

As this process indicates an interaction between the parts of Virchow's triad, it leads to the 'multiple hit hypothesis' where an interaction between two or more increases risk. In cancer, for instance, tumours shed tissue factor and other particles that increase procoagulant activity (1), but may also increase blood viscosity and potentially compress veins, leading to reduced flow rates/stasis. The rational approach to DVT prevention must then be to reduce as many parts of this process that are factors in a particular at-risk group.

The role of stasis in deep vein thrombosis is sometimes neglected where the emphasis of hospital prophylaxis is on anticoagulants. However, the available scientific evidence is that the reduction of stasis by increased venous flow velocity is an effective method of preventing thrombus formation by preventing cell adhesion and aggregation, by reducing blood coagulability, and by favouring thrombolysis. The primary objective of mechanical prophylaxis should therefore be the increase of venous blood flow velocity to a level that prevents cell accumulation and adhesion, and promotes the release of anti-clotting factors from the venous endothelium.

Rhys Morris, December 2013

geko MTCD consultation comments table Appendix 2 (Other information from Sponsor)

This Appendix was submitted by the Sponsor to support consultation comments on the Medical Technologies Consultation Document and the Assessment Report Overview.

5. Why the elimination of stasis will reduce risk

5.1. The aetiology of DVT; Virchow's triad

The simplicity of the Sponsor's clinical rationale for immediate guidance and NHS adoption is represented by the risk factors identified in "three corners" of Virchow's triad (1). These three risk factors remain accepted as the basic aetiological model (1) and are:

1. reduced blood flow
2. coagulability of blood
3. damage to blood vessel endothelium.

Mechanical interventions (like the geko™ device and intermittent pneumatic compression [IPC]) are aimed at reducing venous stasis within the veins of the leg (increasing blood flow) whereas pharmaceutical interventions for prophylaxis are aimed at reducing blood coagulability.

It has been pointed out that "hypercoagulability" is not necessary for thrombus formation: under static conditions, blood of normal coagulability will clot (2). The aim of pharmaceutical interventions is to reduce coagulability below normal levels, with the attendant risk of haemorrhage that that entails.

5.2. The relationship between risk factors

It has been established that there is interaction between these factors (blood flow, coagulability and endothelial damage). Variations in one factor will influence others, for example: blood vessel damage will affect the chemical composition of the blood with respect to coagulation factors, and increased, reduced, or altered patterns of blood flow will affect coagulability (2, 3).

5.3. Removal of stasis will reduce risk

It has been shown in the literature that both these approaches (reducing stasis by mechanical means; reducing coagulability by pharmaceutical means) are individually successful in reducing DVT incidence.

Patient groups within the MTEP scope will have thrombotic risks (stasis or coagulability) that will not be clinically managed due to their contraindicated state. As such the Sponsor believes its clinical rationale to be credible in that the use of the geko™ technology to reduce stasis is a robust clinical basis for assuming that VTE risk will be reduced in patients where no other form of VTE prophylaxis can be prescribed.

5.4. Additional terms of reference

Stasis: The literal meaning of stasis is 'unmoving', but may more normally be assumed to mean 'slow' blood flow in the context of thrombogenesis. The formation of thrombus by stasis is not a purely mechanical effect: completely static blood does not immediately solidify. Stasis is therefore the slowing of blood sufficient to allow thrombus to form, rather than the process of thrombus formation itself.

Peak velocity: The maximum velocity of the blood in a vessel, for example at systole in pulsatile arterial flow, or during muscle contraction in venous flow. Units of (distance/time) e.g. cm/s.

Volume flow: Sometimes referred to as simply 'flow' or 'volume'. Units of volume/time e.g. ml/min. This may be related to TAMV by a simple arithmetic function, by multiplying by the cross-sectional area of the vessel.

Time averaged mean velocity (TAMV): The velocity of blood in the vessel, averaged over a period of time, for example 1 minute. Units of distance/time e.g. cm/s.

Transit time: The time taken for a bolus of blood to move from one point to another as measured by ultrasound.

Fibrinolysis: The breakdown of thrombi by agents in the bloodstream. Plasmin is responsible for cutting the fibrin mesh within the thrombus, resulting in clot fragmentation. Plasmin is produced in the inactive form, plasminogen, and converted to plasmin by tissue plasminogen activator (t-PA) and urokinase.

Shear stress: A consequence of blood flow against the vascular endothelium (4-7). It is a function of the velocity and viscosity of the blood, and the diameter of the blood vessel. Units of N/mm^2.

Shear stress = 8 x viscosity x velocity/ vessel diameter

Risk reduction: The reduction in risk between one group and a comparator group. Usually expressed as a percentage or ratio.

6. Mechanical compression devices, primary mode of action and primary outcome

6.1. Mechanical devices cause intermittent activation of the venous pumps of the leg to enhance blood flow and reduce VTE risk

Mechanical interventions for the prophylaxis of VTE are aimed at reducing stasis (increasing blood flow) and their effectiveness is well established (8). Active mechanical systems cause the deep veins to be compressed periodically, thereby ejecting venous blood back towards the heart. Examples of mechanical compression devices are intermittent pneumatic compression (IPC) and neuromuscular electrostimulation (NMES) (including the geko™ device). IPC works by externally compressing the limb (generally the foot or lower leg) periodically. NMES (including the geko™ device) triggers muscular contraction in the leg. Both modalities engage the venous valve pumps in the leg to reduce stasis and enhance blood flow and velocity. By reducing venous stasis, these mechanical devices reduce the risk of VTE.

6.2. Credibility of using relative risk from these devices for modelling the clinical effect of the geko™ device

Given the above clinical context and the relative risk of the related devices, combined with the fact that the geko™ device is superior in volume flow and velocity when compared with IPC, the Sponsor believes that the clinical hypothesis that underpins the economic modelling to be robust and credible.

While it is acknowledged that older NMES and muscle electrostimulation (MEST) devices use transcutaneous stimulation, usually applied in the vicinity of the muscles to be stimulated, rather than the more indirect application of the geko™ device at a point higher on the neural pathway, the physical consequence of both is the contraction of the lower limb muscle groups to activate the venous valve pumps, reduce stasis and therefore reduce the risk of DVT. The Sponsor agrees that the extent upon which risk reduction can be compared between the geko™ device and previous NMES examples is debatable but this aspect is robustly examined within the economic sensitivity modelling which was otherwise approved by the EAC (Section 8.2 and Section **Error! Reference source not found.**). Notably, even if the geko™ device is assumed to be only 60% as efficacious as IPC or older versions of NMES, the economic model is still favourable.

7. Mechanical compression devices and secondary prophylactic outcomes

7.1. Fibrinolysis, a secondary benefit of enhanced blood flow

Outcomes for fibrinolysis were introduced by the EAC in their assessment report, but were not included in the final MTEP scope issued by NICE. Therefore, this consequential effect of enhancing volume flow and velocity was not included in the manufacturer's submission.

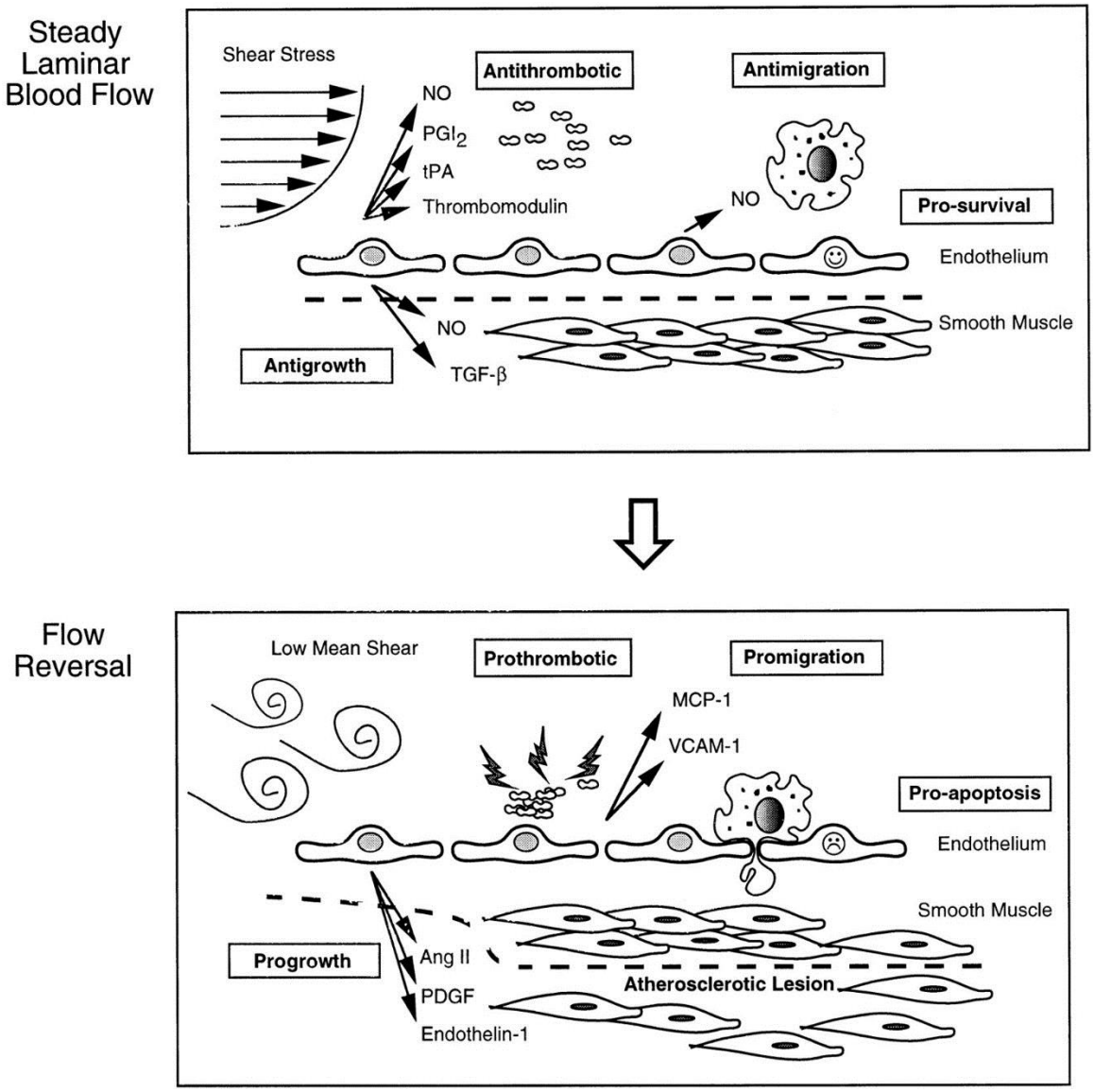
The Sponsor and EAC have different views of how or if fibrinolysis is stimulated by mechanical compression. The EAC believes it is independent of blood flow whilst the Sponsor believes it is a consequence of blood flow.

Fibrinolysis is the body's natural process by which blood clots are prevented from increasing in size and becoming problematic. It is a secondary effect of enhanced blood flow which results in shear stress, triggering fibrinolysis and thereby reducing VTE risk. It has been shown to be better promoted by pulsatile (regular, intermittent) flow than by continuous flow (2).

7.2. How is fibrinolysis stimulated

The Sponsor believes that shear stress is a consequence of blood flow against the vascular endothelium (4-7) and is the mechanism by which bioactive agents are delivered to and from the blood vessel walls (endothelia) (Figure 8). Traub et al (5) state that "Steady laminar shear stress promotes release of factors from endothelial cells that inhibit coagulation, migration of leukocytes, and smooth muscle proliferation, while simultaneously promoting endothelial cell survival. Conversely, low shear stress and flow reversal shift the profile of secreted factors and expressed surface molecules to one that favours the opposite effects". Therefore shear stress from enhanced blood flow triggers fibrinolysis, thereby reducing VTE risk.

Figure 8: Endothelial cell biology and shear stress



Abbreviations: Ang II, angiotensin II; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; PDGF, platelet-derived growth factor; PGI_2, prostacyclin; TGF-b, transforming growth factor-b; tPA, tissue plasminogen activator; VCAM-1, vascular cell adhesion molecule-1.
Source: Traub 1998 (5).

7.3. The fibrinolysis argument stipulated by the EAC

The EAC assessment report argued that the prophylactic effect of NMES could not be considered to be equivalent to that of IPC on the basis that both work by increasing blood flow. The report stated that IPC provided an additional protective mechanism, namely fibrinolysis, which it believed was separate from increased blood flow.

The EAC assessment report (Column 4, page 64/65) cites Christen et al as a reference for this argument (9) which they interpret as saying that the induced fibrinolytic effect is “independent of effects on venous stasis, and occurs via a different mechanism (the production of tissue-type plasminogen activator [t-PA] by the vascular endothelium)”.

7.4. Critique of the reference used by the EAC regarding fibrinolysis

Christen et al actually says the opposite, and in fact concludes: “In conclusion, the present study indicates that the antithrombotic effect of mechanical prophylaxis is probably mainly due to its ability to increase venous peak velocity and flow, especially under venous stasis conditions.”

This conclusion is found consistently in the scientific literature. A review by Lipi et al finds that the fibrinolytic effect with IPC is unproven (10). Killewich et al (11) and Cahan et al (12) similarly find no separate fibrinolytic effect with IPC, and conclude that blood flow is the essential benefit.

Although there is no consistent evidence for the fibrinolytic effect of IPC, it is clear from the science that if there is such an effect , it is caused by blood flow. Kawai et al (13) confirmed *in vitro* that the mechanical effects of blood flow caused fibrinolysis and Diamond et al (14) found that fibrinolytic factors were produced by shear stress resulting from blood flow. Therefore, a direct consequence of enhancing venous volume flow and velocity is the mediation of the additional benefit of fibrinolysis via the shear stress effects of moving blood against the venous endothelium.

In **Error! Reference source not found.**1section 4, Rhys Morris (co-author of Morris and Woodcock, 2004 (15)) confirms that the likely cause behind the effectiveness of mechanical compression is increased blood flow.

Evidence to show that the geko^{TM} device does stimulate fibrinolysis is described in Appendix 1 section 3.

8. MTEP196 scope: modelling the geko^{TM} device vs no treatment

8.1. Validity of blood flow velocity as surrogate endpoint

The Sponsor agrees with the EAC that the degree of VTE risk reduction achieved with the geko^{TM} device is yet to be determined empirically. In modelling the potential relative risk (RR), it is credible to associate the geko^{TM} device with clinically proven devices that have the same primary outcome of augmenting venous flow in the leg and through this action have been shown to reduce VTE risk. There are two related and clinically proven technologies from which to extrapolate a credible RR range and model the efficacy and health economic impact. The relevant devices are intermittent pneumatic compression (IPC) and previous examples of neuromuscular electro stimulation (NMES). A publication by Morris and Woodcock (15) concluded: “All the major types of intermittent compression systems are successful in emptying deep veins of the lower limb and preventing stasis in a variety of subject groups. The most important factors in selecting a mechanical prophylactic system, particularly during and after surgery, are patient compliance and the appropriateness of the site of compression.”

The primary outcome in studies of previous NMES devices is the same as that used in studies of the geko^{TM} device, i.e. blood flow. Both the geko^{TM} device and previous NMES devices engage muscle groups and achieve intermittent or pulsatile augmented venous flow in the leg and in doing so reduce the risk of VTE. It is the ability of these devices to achieve venous emptying, rather than the exact physiology involved (although all these devices work by stimulating muscular contraction) that is key in why NMES devices are considered efficacious in enhancing blood flow.

Whilst a recent review by Ciani (19) cited by the EAC to question this hypothesis concluded that surrogate outcomes give over-optimistic results, they also discuss the numerous limitations of their study:

The study is very susceptible to latent selection bias. They randomly select studies from high impact general medical journals. These journals demand a high level of 'newsworthiness' for a study to be publishable. Since primary endpoint studies are de facto considered to be more publishable, a higher standard of newsworthiness (i.e. bigger effect finding) is applied to the surrogate studies. Thus, it is inevitable that the average published surrogate study will have a larger reported effect than the average published direct outcome study.

Multiple study subject areas were included, and there may be poor matching between study subject areas for the surrogate and direct groups.

The findings were not generalisable, i.e. the findings could not be extrapolated to subject areas outside their original scope, such as to DVT prophylaxis.

8.2. Applicability of use of a VTE risk reduction derived from IPC or NMES data

The geko™ device facilitates the same primary outcome as other mechanical compression devices, i.e. the regular augmentation of venous flow in the leg (preventing venous stasis in these veins). This primary outcome is a well-established factor in reducing the risk of VTE. The patients considered within the MTEP scope are high risk patients who are contraindicated for currently available forms of VTE prophylaxis.

As discussed in Section 5.1, the main clinical evidence for adoption of the geko™ device within the NHS in England is the ability of the device to disrupt Virchow's triad, namely in preventing blood stasis by enhancing blood flow.

The older generation NMES devices and the geko™ device all work by contracting the muscle groups in the leg responsible for activation of the venous valve pumps (whether they are direct muscle stimulators or they stimulate via the nerve). The endpoint of relevance is that they all move blood and prevent stasis and therefore reduce the risk of VTE. The older NMES devices have been proven to enhance blood flow and reduce the risk of DVT, but were generally used under anaesthesia as they were intolerable to the patient (20). The geko™ device has also been proven to enhance blood flow to an equivalent extent, but has vastly improved patient tolerability and has been used without anaesthesia in the clinical trials reported.

The Sponsor agrees that the extent upon which risk reduction can be compared between the geko™ device and previous NMES examples is debatable but this aspect is robustly examined within the economic sensitivity modelling which was otherwise approved by the EAC.

Given the above clinical context and the RR of the related devices, combined with the fact that the geko™ device is superior in volume flow and velocity when compared to IPC, the Sponsor believes that the clinical hypothesis that underpins the economic modelling to be robust and credible.

9. Outstanding critical points for further consideration

9.1. Approval of devices by the American Food and Drug Administration (FDA)

The FDA provide pre-marketing approval in the USA for devices for DVT prevention due to their ability to increase blood flow. This is evidenced by multiple pre-marketing approvals for devices approved by the FDA for DVT prevention as recently as July 2013 and the FDA's statement on the indication for use for each device (Table 4).

Table 4: FDA approval of IPC devices for DVT prevention

Device	Approval number Approval date	FDA public notification of indications for use
Cirona	K131743 1st July 2013	"to be used preventatively to increase venous blood flow in patients at risk of deep vein thrombosis"
DVTCARE CA5	K1301074 2nd May 2013	"to help prevent the onset of DVT in patients by stimulating blood flow in the legs"
DVT-2600	K112677 Jan 13th 2012	"to prevent DVT (Deep Vein Thrombosis) by improving the blood velocity of patients"
Restep DVT System	K090308 May 1st 2009	"to stimulate blood flow in the deep veins of the legs and is intended for use in Preventing Deep Vein Thrombosis"

THE FDA approves new NMES devices as equivalent to older NMES devices

The FDA approves NMES devices for VTE prevention based upon technical equivalence to previously FDA approved NMES devices (as far back as 1997). The Sponsor provides examples below where FDA provides approval of new NMES devices for VTE prevention based on equivalence to devices approved by the FDA as far back as 1999 with links to FDA documents of public record (Table 5).

Table 5: FDA approval of NMES devices for DVT prevention, based on equivalence to previous NMES device

Device	FDA Device Approval number Approval date	Equivalence to: (previous NMES device and approval date)
Mettler Electronics Corp ME 940 For VTE prevention	K071137 Aug 1st 2007 http://www.accessdata.fda.gov/cdrh_docs/pdf7/K071137.pdf	K984142 Feb 9th 1999 http://www.accessdata.fda.gov/cdrh_docs/pdf/k984142.pdf
AdRem Technology Veinoplus For VTE prevention	K072252 Jan 30th 2008 http://www.accessdata.fda.gov/cdrh_docs/pdf7/K072252.pdf	K022175 Sept 9th 2002 http://www.accessdata.fda.gov/cdrh_docs/pdf2/k022175.pdf
Bio-Medical Research Ltd Neurotech Plus, Type 413 For VTE prevention	K112258 Jan 9th 2012 http://www.accessdata.fda.gov/cdrh_docs/pdf11/K112258.pdf	K082011 Nov 28th 2008 http://www.accessdata.fda.gov/cdrh_docs/pdf8/K082011.pdf
Famidoc Technology ED401 For VTE prevention	K113010 Dec 21st 2012 http://www.accessdata.fda.gov/cdrh_docs/pdf11/K113010.pdf	K093138 Feb 12th 2010 http://www.accessdata.fda.gov/cdrh_docs/pdf9/K093138.pdf

9.2. International consensus statement position

The International Union of Angiology (24) recommends that “Electrical stimulation of the calf muscles may be considered in patients in whom pharmacological prophylaxis is contraindicated because of multiple injuries and IPC cannot be applied because of external fixation to a leg fracture”.

10. Critique of key references cited by the EAC

Table 6: Summary of EAC assessment of references

Reference	EAC cite reference as saying	Reference actually says
Christen et al, 1997	"fibrinolytic effect is independent of effects on venous stasis, and occurs via a different mechanism" Page 65 of assessment overview report	"the present study indicates that the antithrombotic effect of mechanical prophylaxis is probably mainly due to its ability to increase venous peak velocity and flow, especially under venous stasis conditions"
Dai et al, 1999	"IPC devices have been shown to exert additional prophylactic effects to that of increasing blood flow, including changes to venous volume that can reduce the shear stresses on the vessel walls and prevent damage to the endothelial linings" Page 17, table 3 of assessment overview report	Dai et al makes no such finding. It is a mechanical engineering paper, using a computer model to examine flow of a viscous fluid representing blood in a flexible tube representing a blood vessel being compressed. They find that different modalities of compression have a different effect on blood flow, and thus shear stress. It appears that the EAC misunderstand shear stress to mean some phenomenon externally acting on the vessel, whereas it is in fact, as explained by Dai et al, merely a manifestation of laminar flow in the vessel. The venous volume referred to is volume FLOW, i.e. ml/min. It IS blood flow, not an "additional benefit to that of increasing flow" as EAC state.. Dai actually says that compression INCREASES the shear stress, by virtue of increasing flow. Dai et al make no pronouncements about prophylactic effects.
Morris & Woodcock, 2004	EAC cite this paper as saying that DVT prophylaxis from IPC is achieved by means other than blood flow. "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" Page 17 table 3 of assessment overview report	Morris and Woodcock actually finds: "All the major types of intermittent compression systems are successful in emptying deep veins of the lower limb and preventing stasis in a variety of subject groups. The most important factors in choosing between mechanical prophylactic systems, particularly during and after surgery, are patient compliance and the appropriateness of the site of compression."
Ciani et al, 2013	"Ciani et al (2013) demonstrated, when compared with equivalent trials, surrogates give over-optimistic results. the EAC has concluded that this [that an increase in blood flow is a credible surrogate for reduction in risk of VTE] is a flawed assumption" Page 28 of assessment overview report	Ciani et al have a 500 word section in the paper in which they discuss the numerous limitations of their study. Among these, are: 1) The study is very susceptible to latent selection bias. They randomly select studies from high impact general medical journals. These journals demand a high level of 'newsworthiness' for a study to be publishable. Since primary endpoint studies are de facto considered to be more publishable, a higher standard of newsworthiness (i.e. bigger effect finding) is applied to the surrogate studies. Thus, it is inevitable that the average published surrogate study will have a larger reported effect than the average published direct outcome study.

		2) They included multiple study subject areas, and acknowledged that there may be poor matching between study subject areas for the surrogate and direct groups. 3) They highlighted that their findings were not generalisable, i.e. the findings could not be extrapolated to subject areas outside their original scope. For example, to DVT prophylaxis, The authors warn that their findings need to be checked. In any case, even if the point were true that reported effect sizes for surrogate markers (e.g. blood flow) were larger than those for direct outcomes (e.g. DVT), since we are simply establishing relative efficacy to another intervention using the SAME surrogate, this would make no difference to the result.
Proctor et al, 2001	"Proctor et al. [2001]), highlighted the difficulties in assuming that an increase in venous blood flow leads to reduction in the risk of VTE" Page 28 of assessment overview report	In fact, Proctor et al is a non-randomised study, which compares five different IPCs with different sleeve lengths. No difference in VTE outcomes is found between different sleeve lengths, "We were unable to show a difference in DVT incidence based on the length of the device or the method of compression. Randomized studies are needed to confirm our findings" Given the relatively small numbers in this non-randomised trial, it is unsurprising that statistically significant differences were not observed, and in any case the basis for comparison is sleeve length, not venous velocity.

The Sponsor has commissioned a report from Rhys Morris (co-author of Morris and Woodcock, 2004 (15)), explaining in detail physiology behind thromboembolism and the relationship between blood flow, shear stress and fibrinolysis (see **Error! Reference source not found.**).

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geko MTCD consultation comments table Appendix 3 (EAC review of sponsor evidence in Appendix 1)

During the draft guidance consultation, the sponsor provided interim results of two studies using the geko™ device in patient populations. The sponsor also provided updated results from their own Post Market Surveillance (PMS) data in a patient population. The EAC reviewed this new information to determine whether it adds anything significant to the evidence provided in the original submission from the sponsor and the additional evidence identified by the EAC, described in the EAC report. Interim results of the two patient population based studies are detailed in table 1.

Study 8.1.1: The geko™ device vs Intermittent Pneumatic Compression (IPC) of the foot following elective Total Hip Replacement (THR)

The first study provided is listed in section 8.1.1 of the sponsor's consultation response document ('Interim analysis, vs IPC of the foot in patients following THR'). This study provided the interim results of a single centre randomised comparison study comparing geko™ and IPC in a patient population following elective total hip replacement (THR). The study is described as 'intra-patient', however, the EAC concludes that this is a typo as no 'intra'-patient comparison is planned in the study protocol or described in the interim results. The EAC would describe the study as a 'inter'-patient comparison study.

- The interim analysis is based on a sample of n=7 patients, whilst the full study will have n=10.
- Patients were randomly assigned to one of two treatment arms (with the ordering of devices alternating). [redacted]
- All patients received both geko™ and IPC, both of which were activated for a ten minute period, followed by a 30 minute rest period between devices.
- The control is defined as ultrasound measurements taken at baseline.
- Comparison of each device is made to baseline, which fits the scope.
- Comparison to IPC is not applicable, as IPC is not listed as a comparator in the scope.
- [redacted]
- No assessment of reduction in DVT incidence is planned.

[redacted]

[redacted]

Study 8.1.2: The geko™ device vs TEDS following elective THR

The second study, listed in section 8.1.2 ('Interim analysis, vs TEDS in patients following THR), documents the interim results of a multicentre randomised unblinded study comparing geko™ and 'TEDS' in a patient population following elective total hip replacement (THR).

- The interim analysis is based on a sample of n=16 patients, whilst the full study will have n=40 (n=20 in each trial arm).
- The full study (n=40) is described in the study protocol as a phase one study, which will inform the sample size calculation of the phase two study.
- Patients were randomly assigned to one of two treatment arms (receiving either geko™ or TEDs). Seven patients were assigned to receive geko™, and nine received TEDs in the interim analysis.
- The geko™ device (activated) and TEDs were used continuously for 48 hours post-surgery before effects were assessed by ultrasound.
- Comparison was made to baseline, which fits the scope.
- Comparison to TEDs is not applicable, as TEDs is not listed as a comparator in the scope.
- The control is defined as ultrasound measurements taken at baseline (immediately prior to surgery).

[redacted]

The report describes the graduated compression stockings used as 'TEDs'. To avoid potential confusion with the brand name 'TEDs', the EAC would like to note that the manufacturer in this present study is Saphena Medical.

[redacted]

Additional Post-Market Surveillance (PMS) data

The sponsor has also provided additional post-market surveillance data, mainly related to patient wear time of the geko™ device. The patients surveyed were a post-surgical population.

Results:

- Of the patients surveyed (n=216), 85.2% (n=184) assessed the geko™ as comfortable or very comfortable to wear.
- In total n=123 patients responded to the question: "how many days was the device worn in total?" n=121 (98%) wore the geko™ device for 1 or more days.
- The maximum number of days for which the geko™ device was worn was 10 days (1 patient).
- In total n=93 patients responded to the question: "how long was the device worn?" n=41 (44%) wore the geko™ device for 24 hours or more. N=43 patients (46%) wore the geko™ device for 12 hours or less.
- Clinicians were instructed in the use/application of the geko™ device on patients and how to confirm that the device was active ('foot twitch'). Instructions for the use of the geko™ device were provided to clinicians in the product packaging.
- The PMS data did not provide detailed information regarding how long the geko™ device was activated. However, the EAC concludes, given the clinicians' instructions, that it is reasonable to assume that the geko™ device was activated for at least part of the period of wear.
- The PMS data did not provide sufficient information to clarify whether the degrees of patient acceptability and tolerability were related to the period for which the geko™ device was activated.
- Furthermore, no data was provided on the number of patients for whom use of geko™ was discontinued, or the rationale for discontinuing.

EAC Summary of Appendix 1 sections 1 and 2

Student's t-test was used to assess blood flow/velocity changes in both the studies described in 8.1.1 and 8.1.2. The EAC notes that the use of a t-test for comparing changes in two groups is not the correct statistical method. For example, in each study, when estimating the change from baseline to any device, the appropriate method of analysis to use is a regression model. This would then test the treatment effect of the device(s) with baseline measurement included as a covariate. As the EAC considers that the only relevant result in terms of the scope is the comparison of geko™ with baseline (and not IPC or TEDs), the results of both of these studies are potentially invalid given the incorrect choice of statistical analysis. Furthermore, it is not advisable to conduct analyses on interim data as it increases the type 1 error (concluding that there is a difference between the groups in the target populations when in fact there is not).

The EAC considers that this new evidence (although interim) is promising, as both studies have been conducted in a patient population with an activated geko^{TM} device. Notably, the intention of the study described in 8.1.2 is to assess asymptomatic DVT, although the interim report only includes results for blood flow. However, there are significant limitations in both the study methodology (in general and in terms of the scope) and the level of information provided, which casts serious doubt on the reliability and interpretation of these interim study results in their present form. Therefore, the EAC considers that the conclusions that were presented in the original EAC report remains valid and appropriate at the present time.

Table 1: Overview of the study design and interim results of additional evidence related to the geko™ device provided by Sponsors December 2013

Reference	Study and Design	Patient Population	Intervention/Comparator	[redacted]	[redacted]	[redacted]
Study One: 8.1.1 The geko™ device vs IPC of the foot following elective Total Hip Replacement (THR)	Single centre, randomised, non-blinded inter-patient comparison. Single visit.	THR patients. Interim results based on n=7. Planned for entire study n=10.	geko™ vs IPC. geko™ vs baseline. IPC vs baseline.	[redacted]	[redacted]	[redacted]
Study Two: 8.1.2 The geko™ device vs TEDS following elective THR.	Multicentre, randomised, open label, non-blinded design.	THR patients. Interim results of n=16 based on n=7 (TEDS) and n=9 (geko™). Planned for entire study n=40, with n=20 in each trial arm.	geko™ vs TEDs. geko™ vs baseline. TEDs vs baseline.	[redacted]	[redacted]	

				[redacted]	[redacted]	

EAC reply to Appendix 1 sections 3 and 4.

The sponsor has provided additional information on the mechanism of thrombosis and the factors that influence its occurrence in Appendix 2. This includes a statement from Dr Rhys Morris on the subject of physiological actions of mechanical deep vein thrombosis. Of particular interest to the EAC is the relationship between shear stress and the release of substances from the vessel wall endothelium.

The EAC has noted that in the studies submitted by the sponsor, geko is shown to increase venous blood velocity while not significantly affecting the vessel diameter. Therefore, the EAC considers it reasonable to expect the shear stress between the vessel wall and the blood flow to increase. Although the EAC was aware that this can cause anticoagulant substances to be released, it was also aware that pro-coagulant effects can occur. This is confirmed in the statement by Dr Morris. The EAC has concluded that there is an uncertainty as to what would be the overall effect on thrombosis.

Dr Morris explains that although both pro- and anticoagulant substances are released, the overall effect of increased flow from mechanical devices is of an anticoagulant nature.

Dr Morris's statement concerns mechanical prophylaxis systems in general and he explicitly mentions intermittent pneumatic compression (IPC) and graduated compression stockings (GCS) in his statement. He states that there is "reasonable conclusion that all mechanical methods provide prophylaxis by increasing shear stress." a position he supports with references that concern IPC and GCS devices. It is not stated whether Dr Morris includes the geko™ device in his statement. But as the statement was written in December 2013 on a commission from the sponsor, it may be reasonable to assume Dr Morris is aware of, and includes geko™ in this statement.

Dr Morris concludes his section on stasis and shear stress with the following paragraph:

> "Yet, shear stress remains an initiator of clotting. High shear will activate platelets, and increase cell adhesion. This may partially explain the lack of a link between higher flow rate velocities and reduced rates on DVT in clinical trials. Shear is a desirable effect of increased flow to restore the pro-coagulant/anticoagulant balance in the blood by releasing tPA, NO and other substances from the endothelium. However, if the velocity is increased beyond a certain level, perhaps beyond that which is normal during ambulation, the shear-induced affects may be counterproductive."

This is the original question the EAC raised, as we do not know what levels of shear stress can be associated with the geko™ device. Dr Morris has suggested the rate achieved during ambulation as a threshold. The EAC would agree that this would be an intuitively sensible level to set in the absence of direct evidence.

The application method specified by the sponsor for geko™ results in the production of a slight visible twitch of the foot. This is below the full movement associated with ambulation. The full movement of ambulation causes intermittent compression and expansion of the lower limb veins, creating the emptying and refilling of the venous system and changing the vessel diameter. This adds complexity to the task of comparing the shear stress. No comparison of shear stress or coagulation properties of the blood has been made between that caused by ambulation and that caused by geko™ stimulation.

Three of the studies compare the performance of geko™ with IPC devices [Williams 2013, Jawad (vs IPC) 2012, Williams (unpublished) 2013]. As presented in the discussion regarding Christen et al. (1997) the EAC would consider IPC devices to have levels of shear stress that are not believed to be pro-coagulant. This is supported by substantial RCT

evidence that shows that IPC's overall effect is to prevent VTE and concurs with the statement of Dr Morris.

Comparisons between geko™ and IPC are not straight forward. As the sponsor has explained, IPC devices can create a more pulsatile effect on blood flow due their lower frequency of operation. The studies originally submitted by the sponsor give indication that shear stress on the vessel wall may be higher with the geko™ device. This is due to the velocity of the blood increasing while the vessel diameter did not significantly change. Although it is important to note that, due to the pulsatile nature of IPC, this higher shear stress may only arise when average or instantaneous values are compared. It is possible that IPC devices, if only momentarily, exceed the shear stress present with geko™. Without a measurement of shear stress achieved by each device the EAC cannot gain more insight from these three studies.

In its comments made on the draft recommendation, the sponsor has highlighted one of the studies by Jawad [(coagulation), 2012) for reconsideration.

It should be noted that the study uses a slightly different version of the geko™ device known as THRIVE to produce the stimulation, although the sponsor has stated that the specifications of this device are within the range of parameters available with geko™.

In section 3.5 of the sponsor's comments on the draft recommendation, the sponsor states the finding of this study to be a reduction in tPA when stimulation was used (page 12). The sponsor also states that "a deficiency in tPA can result in the reduction of the capacity to degrade a clot, predisposing to thrombosis" (page 12). This last statement would concur with the EAC's understanding, the statement of Dr Morris and the study by Christen et al. This statement would appear to contradict the sponsor's later assertion that "the drop in plasma tPA concentration suggests increased fibrinolytic activity" (page 12).

In an attempt to understand this inconsistency in the sponsor's statement, the EAC took an alternative approach and examined the comparison of clotting time measurements presented in the original submission. This found a significant ($p \leq 0.05$) drop in clotting time measured when stimulation was used compared to no stimulation. Although, all values were within the normal range (100 to 240 seconds).

The reduction in clotting time and the drop in tPA level would appear to indicate that the overall effect of stimulation by geko™ is to activate a greater proportion of pro-clotting substances into the plasma. This would seem contradictory to the sponsor's explanation of the mechanisms at work. It may be that the additional effect that blood flow has on thrombosis in the main flow of the blood would be more than that capable of counteracting this suggested pro-thrombotic effect, but the EAC can see no evidence that demonstrates this. It would therefore appear to support the EAC's opinion, that for the geko™ device, a confident expectation of VTE prophylaxis cannot be made based on blood flow measurements alone.

geko MTCD consultation comments table Appendix 4 (EAC review of sponsor evidence in Appendix 2 section 6)

In Appendix 2 section 6 the sponsor provided a critique of the EAC assessment of key references. The EAC response to their comments is as follows:

Christen et al. 1997

The sponsor's original comment would be valid if the study had said that the antithrombotic effect of mechanical prophylaxis was *entirely* due to its ability to increase venous peak velocity and flow, but it does not say this. As the sponsor has quoted, the study uses the phrase "…*probably mainly due….".* The EAC is attempting to highlight that an increase in venous flow may not always lead to an antithrombotic effect. This point is also made in the statement from Dr Morris provided by the sponsor.

The study by Christen et al. was not able to exclude a favourable effect for IPC from fibrinolysis. As quoted by the sponsor the authors maintain that the effect of IPC on the "stimulation of endogenous fibrinolytic activity" is probably not as great as its effect on "haemodynamic action (increase of blood flow velocity)". They have not said that the endogenous fibrinolytic activity does not occur.

Even if IPC devices were to be subsequently shown to not have any stimulation effect on the endothelial linings, this may be beneficial in terms of prevention of VTE, because too much stimulation of the endothelial lining may activate factors that promote thrombosis. As stimulation of the endothelial lining increases with shear stress and this is in turn increases with blood velocity, the EAC considers it fair to say that increasing blood flow cannot be considered alone as prophylactic. The EAC believes that, in addition, there should be confidence that shear stress, acting on the inside of the endothelial lining of the vessel, is at a level where either the effects that are anticoagulant in nature dominate or where no stimulation occurs. Due to the additional anti-coagulant effects of blood flow within the vessel, the EAC would then feel confident that the overall effect would be to prevent VTE.

The Christen et al. study is referenced because it demonstrates that the shear stress created by IPC devices is within the range where the cumulative effect of all the effects of increased blood flow are thought to be antithrombotic. This finding is supported by the clinical trial evidence for IPC devices that use VTE or DVT as an endpoint.

The EAC considers it important to ensure that the enhancement to blood flow observed when using the geko device is still within the range where the overall effect is VTE prevention. This point is discussed further in our reply to Appendix B.

Dai et al. 1999

It is shear stress on the inside of the blood vessel wall as exerted by the flow of blood that is of interest to the EAC. The EAC agrees with the sponsor's quotation from the paper that "different modalities of compression have different effects on blood flow, and thus shear stress."

It is fair to say that the prophylactic effects are interdependent, but sheer stress is not solely dependent on peak venous velocity; the vessel diameter will also have an effect. Likewise, blood flow is dependent on both blood velocity and vessel diameter. From the information submitted by the sponsor, it is clear that geko achieves its increase in venous blood flow by altering the determinant factors of velocity and vessel diameter in different proportions from those achieved by IPC. The EAC was attempting to divide the mechanisms into those which the EAC and the sponsor agree are reasonable expectations for geko and those which the

EAC believes there is considerable uncertainty about. In hindsight the EAC could have made this point clearer.

Morris and Woodcock, 2004

Both quotes are present in the paper. As the EAC has stated previously, we agree that it is reasonable to expect an increase in blood flow to reduce the risk of thrombosis from one part of Virchow's Triad. For mechanical devices such as IPC, the clinical trial data with VTE as an endpoint allows us to go further and conclude that the overall effect of the IPC device is to reduce incidence of VTE.

The uncertainty with geko arises because there is a difference in how blood flow is affected as compared to IPC, and we do not know how this different mechanism affects other parts of Virchow's Triad. In the absence of clinical trial data with VTE as an endpoint for geko, we cannot conclude that the overall effect will be to prevent VTE. There is more discussion on this issue in our replay to Appendix B.

Proctor et al. 2001

The EAC agrees with the sponsor that there are limitations with the Proctor et al. study. However, the study has been referenced in this context before and required consideration by the EAC.

When initially assessing this study the EAC felt that the findings of this study were not sufficiently evidenced to provide a reasonable confidence, due to a small sample sizes. In light of this, the EAC limited its comment to a note of caution, and stated that it found this single finding inconclusive.

In transferring the EAC's comments to the overview report these qualifying statements have not been included, although a reference back to the original comment has been provided.

Ciani et al. 2013

Response to (1): The generally accepted structure of a peer-reviewed scientific paper is that any potential limitations (whether observed or not) should be discussed. Therefore, Ciani et al's '500 word section' discussing the limitations of the study can be considered highly appropriate.

In Ciani et al's '500 word section' the authors describe how they sought to minimise potential limitations in the study design. For example, whilst Ciani et al do acknowledge that there is the potential for selection bias, they also go on to state that:

"We observed higher methodological quality of trials in our sample compared with a representative sample of trials indexed in PubMed, therefore it could be argued our findings are less likely to be susceptible to confounding by other aspects of trial methodology".

Therefore, the EAC does not consider it unreasonable to reference this peer-reviewed study from a high-impact medical journal.

Response to (2): Ciani et al's methodological approach was to compare the treatment effects of matched RCT studies reporting surrogate primary outcomes and final primary outcomes across 'a range of medical conditions and interventions'. Therefore, restricting their inclusion criteria to homogenous RCTs (or to a 'within trial' comparison) would not have addressed the study purpose. Furthermore, as Ciani et al state:

'trials with surrogate primary outcomes may be underpowered for final patient relevant outcomes and thus lead to imprecision in the estimation of the comparative treatment effect of surrogate and final outcomes'.

The study design also sought to maximise comparability between studies by matching on the basis of four key criteria: intervention clinical area, clinical population, journal and publication year. Adjustment was also made for each of these criterions as covariates in the

metaregression model. The EAC has considered the degree of matching and this methodological approach to be sufficiently close to provide reliable estimates of comparisons between studies.

Response to (3): Ciani et al do not highlight 'that their findings were not generalisable' as the sponsor states. Ciani et al in fact suggest that given that their search criteria were limited to 'six high impact general medical journals over two specific consecutive calendar years, the findings may lack generalisability'. Therefore, the EAC considers that the sponsor's conclusion that the findings are not generalisable goes beyond the the limitation as stated by the authors. The EAC therefore does not agree that the results are not generalizable 'for example, to DVT prophylaxis' and considers that this is a misunderstanding of the limitations stated by the authors.

Response to final point made by sponsor: '…. Since we are simply establishing relative efficacy to another intervention using the SAME surrogate, this would make no difference to the result'. As the EAC has previously described, 'the evidence for one type of device may not apply to another', due to potential differences in the mechanisms through which the devices work in VTE prevention. Therefore, the EAC does not consider that the sponsor has established relative efficacy (i.e. of the geko) to another intervention (i.e. IPC or NMES) with the SAME surrogate.

geko MTCD consultation comments table Appendix 5 (Additional expert advice on responses to consultation comments)

To provide further clarification on the main issues raised by consultees, the NICE MTEP team asked Expert Advisers to answer 3 specific questions; the questions and responses received are tabulated below.

Questions	Nicolaides	Scurr	McCollum	Stansby	Mosley
1. Blood flow as a surrogate outcome measure (section 3.14 of the MTCD). Consultees argued that the impact of geko on blood flow, as shown in studies on healthy volunteers, was a valid predictor of reduction in risk of VTE events. Do you think that the evidence of blood flow measurements obtained for Geko in healthy volunteers is generalisable to patients at risk of VTE who are unable to receive current mechanical methods of VTE prophylaxis ?	Yes. I agree with the consultation comments as they are now worded.	Increasing blood flow has been used in other mechanical devices to assess their efficacy . On that basis I believe the Geko device does enhance blood flow, and this we know is important for reducing VTE. On that basis i believe the GEKO device does enhance blood flow and this we know is important for reducing the VTE.	I do consider that the augmentation in venous flow seen in healthy volunteers is generalizable to patients at risk of VTE. These are not necessarily patients who have had a previous VTE or who have signs of chronic venous insufficiency. Nor are there necessarily patients with impaired mobility of the foot or ankle. There is absolutely no reason why the GEKO device should not be affective in patients who have allergies to elastic stockings, diabetes or most of the general contraindications to wearing elastic stockings. The GEKO device may even be appropriate for patients with peripheral arterial disease although it is possible that some patients may experience symptoms resembling claudication. Under these circumstances the patient would not suffer any harm but would merely complain of pain in the calf such that the GEKO would have to be discontinued. This latter example of a symptom that might be experienced by patients using GEKO is an excellent example of what we might learn should this device be licensed for the limited indication of patients where no other mechanical prophylaxis is possible.	Probably if done under the same conditions. However it is not clear that is the case. Prolonged bed rest was not in the studies	Yes

Questions	Nicolaides	Scurr	McCollum	Stansby	Mosley
2. The case for adoption in a small selected population (sections 1.1 and 3.13 of the MTCD). Consultees argued that the strength of the evidence for geko on blood flow was sufficient to allow NICE to recommend its use in patients who would otherwise be offered mechanical prevention but where existing methods are impractical or contraindicated. Do you think that the results of geko studies showing a measured increase in blood flow represents sufficient relevant evidence to support the case for adoption in patients at risk of VTE who are unable to receive current mechanical methods of VTE prophylaxis?	Yes	I think the available evidence of the Geko device does support the case for its adoption in patients at risk of VTE. I think it is particularly helpful in those patients who cannot receive current mechanical methods.	I do consider that studies showing that GEKO increases venous return and reduces venous transit time are relevant evidence to support adoption of GEKO as a mechanical prophylaxis against VTE.	Yes on the basis that it is unlikely to harm and may be better than nothing. However it should be clear that these are relatively few patients.	Yes

Questions	Nicolaides	Scurr	McCollum	Stansby	Mosley
3. The use of baseline risk and risk reduction data from other mechanical methods (section 5.11 of the MTCD). Consultees argued that the estimates used in the sponsor's cost modelling both for the baseline risk of DVT incidence in patients unable to receive current mechanical methods (29.1%) and the relative risk reduction (0.39, from the Brown and Negus NMES study) were valid. In particular, consultees argued that the assumptions were valid because both geko and previous NMES devices engage muscle groups and achieve augmentation of venous flow in the lower leg and in doing so reduce the risk of VTE, and that the relative risk reduction value falls within the range (0.31 to 0.58) identified for IPC in the NICE VTE guideline. What is your view of the generalisability of risk reductions (for VTE events) shown in older studies of NMES or IPC devices to the geko device for the purpose of estimating a relative risk in the economic modelling to support the case for adoption in patients at risk of VTE who are unable to receive current mechanical methods of VTE prophylaxis ?	Yes	The older studies showing risk reductions for VTE and mechanical devices increase blood flow remain valid. The best studies will of course use VTE as an end point and ultimately I am sure we can do that. It would be a great pity not to use the Geko device, particularly in patients were current mechanical methods are indicated but not suitable	I do not think that the old neuromuscular electrical stimulation (NMES) or intermittent pneumatic compression (IPC) data are directly relevant to the efficacy of GEKO. The research shown to your Committee is that GEKO does significantly increase venous return and reduce calf transit times. However venous flow is augmented, we would expect that the consequence was a reduced risk of DVT. Licensing this product for use in those patients where no other mechanical prophylaxis is possible would enable the manufacturer of GEKO to explore the risk reductions that are achieved. The available evidence suggests that patients who are not able to use other mechanical prophylaxis will benefit. There is no evidence that the use of GEKO will result in unwanted side effects. If any patient suffers discomfort or pain as a result of GEKO, the devise can simply be removed and there are unlikely to be any subsequent consequences. It is also important to recognise that routine pharmaceutical DVT prophylaxis using low molecular weight heparins can be used in patients fitted with a GEKO without any known risk.	I feel this is unsafe - partly that is a "gut" feeling, partly because they are old and fairly small studies, partly becuase I haven't seen that equipment in action (does it produce contractions in the same muscles for example?). And anyway if such a risk reduction is possible it would be nice to have a Geko study showing similar results. Also I think it is hard to recommend anything strongly just on first principles - there are so many examples in medicine where that has been subsequently shown to be wrong	Unable to express an opinion

geko MTCD consultation comments table Appendix 6 (Sponsor's comments on ARO)

The sponsor submitted 20 comments on the assessment report overview (ARO) during the geko MTCD consultation. NICE requested the EAC to provide responses. These comments were discussed by MTAC in January 2014.

Comment No.	Section No. (of ARO document)	Comments
1	**2.3**	**3rd paragraph, page 4** The EAC notes " that it is difficult to estimate how many people geko is likely to be suitable for, but believes it to be a small number " The Sponsor as stated above agrees with this, this is not in dispute, but it was a known fact when the technology was selected onto the programme. These patient groups were then defined within the MTEP scope and as such the Sponsor presumes that all parties believe this list to be credible. These patients therefore do exist and the Sponsor maintains the view that these patients would benefit from positive guidance for an initial phase of technology adoption based on the clinical and economic hypothesis presented.

2	**4.1**	**Table 1 col 4 page 8** **EAC consideration in respect to Jawad coagulation 2012** **1) This study used the THRIVE device** The geko™ device is exactly analogous to THRIVE, with the same printed circuit in a different casing. In this study THRIVE was set at 25mA (within the permitted variance of the geko ™ device) and 600µs (within geko ™ device range) and 3Hz (the geko™ device is 1Hz). The Sponsor accepts that while the settings used in the THRIVE device do not exactly match those in the geko device, they are within the permitted range and thus the results obtained using the THRIVE device would be strongly indicative of the efficacy of the geko device. **2) Subjects placed in airline seating for 4 hours. Does not mimic medical setting.** No single seated, supine, or otherwise recumbent position 'mimics the medical setting'. Patients are nursed in a wide variety of different positions, including sitting, elevated backrest, and with knee-break on profiling beds. Indeed, tissue viability guidelines indicate that the patient position should be changed at least once every two hours. The origin of the seat is of no importance. For valid experimental control, it is essential that a reproducible stationary position is established, and this is the purpose of the aircraft seat. **3) Not all outcomes reported across the different interventions.** The Sponsor does not agree, all outcomes were reported and as such this comment is unfounded.
3	**4.1**	**EAC consideration in respect to Jawad vs. IPC 2012:** 1) **Alternating and short application/duration of devices (30 minutes) does not mimic medical setting**. This study is not a DVT outcomes study. Therefore, the duration of prophylaxis is of no relevance. The objective here is the extent to which geko™ device augments flow relative to no device. Repeated measurements of short duration are entirely appropriate. If the EAC is concerned about whether this study represented patient tolerance in the medical setting as opposed to investigating comparative blood flow then this is a different point of discussion which in any event is dealt with by the Sponsor later in this section. 2) **No confidence intervals for estimates.** No confidence intervals were presented, however inter-quartile ranges were presented.

4	**4.1**	**EAC consideration in respect to Tucker et al 2010.** 1) **Used a prototype device: the programs did not match geko™ device** This was a dose-ranging study and the resulting geko settings are directly derived from this and within the range of this study so are clinically relevant. 2) **Airline seats.** No single seated, supine, or otherwise recumbent position 'mimics the medical setting'. Patients are nursed in a wide variety of different positions, including sitting, elevated backrest, and with knee-break on profiling beds. Indeed, tissue viability guidelines indicate that the patient position should be changed at least once every two hours. The origin of the seat is of no importance. For valid experimental control, it is essential that a reproducible stationary position is established, and this is the purpose of the aircraft seat. 3) **Device turned on/off every 5 minutes.** This study is not a DVT outcomes study. Therefore, the duration of prophylaxis is of no relevance. The measure here is the extent to which geko™ device augments flow relative to no device. Repeated measurements of short duration are entirely appropriate. If the EAC is concerned about whether this study represented patient tolerance in the medical setting as opposed to investigating comparative blood flow then this is a different point of discussion which in any event is dealt with by the Sponsor later in this section 4) **No confidence intervals for estimates.** This is incorrect as standard error of difference was presented for every parameter.

5	**4.1**	**EAC consideration in respect to Jawad (Cardiac) 2012** 1) **This study used the THRIVE device** The geko™ device is exactly analogous to THRIVE, with the same printed circuit in a different casing. In this study THRIVE was set at 20mA (less than the geko™ device) and 400 & 600us (within geko ™ device range) and 3Hz (the geko™ device is 1Hz). The Sponsor accepts that match is not 100% between the THRIVE and the resulting production device but any study outcome would be strongly indicative. 2) **Short application/duration of devices (30 minutes)** This study is not a DVT outcomes study. Therefore, the duration of prophylaxis is of no relevance. The measure here is the extent to which geko™ device augments flow relative to no device. Repeated measurements of short duration are entirely appropriate. If the EAC is concerned about whether this study represented patient tolerance in the medical setting as opposed to investigating comparative blood flow then this is a different point of discussion which in any event is dealt with by the Sponsor later in this section 3) **Only measures arterial blood flow (not venous)** This is incorrect and the Sponsor would like to highlight that this paper included data for lower limb venous volume, venous velocity, arterial velocity, and lower limb capillary blood flow which all seem to be extremely relevant within the context of the agreed MTEP scope and the clinical hypothesis therein.
6	**4.1**	**EAC consideration in respect to Warwick et al (2013)** 1) **No time period was given for application/duration of device for different subject** It is clearly stated in the method that a biostabilisation period of 30 minutes is given in each position prior to measurement 2) **The measurements taken in different positions do not necessarily mimic medical patient experience** The Sponsor would like to highlight to the MTAC that: Four different positions were used, and the respective and relative effects of position, plaster cast, and geko™ device, are discussed at length. As such the Sponsor cannot agree with the EAC's position because as discussed what would mimic a patient position in this context? The study covers a reasonable variety of patient positions which is more likely than not to represent medical reality. Furthermore, it was found that the effect of position on haemodynamic parameters was less pronounced than that of intervention; a point which hjas some bearing on the discussion of Tucker et al above.

7	**4.1**	**EAC consideration in respect to Khanbhai et al (2013)** 1) **This is an interim report. The EAC agreed with the Sponsor's exclusion of this report** The Sponsor included this interim report because it supports the clinical hypothesis for adoption. It was marked academic confidential but did not mean for the EAC and the MTAC to ignore it completely for the content is highly relevant to the clinical argument.
8	**4.1**	**Page 10 3rd paragraph 12th line** **The report states** "The EAC noted that the study (Jawad (coagulation;2012) did not compare the results in the contralateral (unstimulated) leg during either session and stated that it was therefore difficult to ascertain the clinical significance of these values" **The Sponsor would like to highlight to the MTAC that:** The paper does compare with contralateral leg to demonstrate local effect, and with control session to demonstrate systemic effect. As such the EAC would appear to be incorrect.
9	**4.1**	**Page 11 2nd Paragraph** **The report states** "The EAC noted that both IPC devices demonstrated an average percentage change in comparison to baseline for venous blood flow of −4%. In relation to this finding, the EAC noted the fact that the Sponsor's evidence centres on the assertion that IPC devices work by increasing venous blood flow" **The Sponsor would like to highlight to the MTAC that:** This increases the Sponsor's concern about the the EAC's fundamental lack of understanding in respect to the proposed clinical hypothesis for adoption. The proposed mechanism for the efficacy of IPC (and any mechanical compression device including the geko™ device) is not an increase in aggregate venous volume flow, but a reduction in stasis: i.e. periodic, intermittent, or pulsatile augmentation of instantaneous venous velocity. Intermittently increased flow, causing opening and closing of the venous valves, has been shown to be preferable to augmented continuous flow from a prophylactic perspective (2) . Pulsatile flow (regularly increased flow at approximately 1Hz) is known to be better still (2, 11). This study shows that the geko™ device was superior to IPC in respect to this primary outcome of blood flow velocity and as such the Sponsor believes it is of significant relevance to the clinical hypothesis.

10	**4.1**	**Page 12, 1st paragraph line 5** **The overview states in respect to Tucker et al 2010** "The EAC rejected this study because it considered the use of baseline measures and voluntary muscle action as comparators did not fit with the scope" **The Sponsor would like to highlight to the MTAC that:** It is well understood that voluntary dorsiflexions of the foot provide maximal activation of the venous leg pumps. The haemodynamic parameters measured when using the geko™ device were therefore compared to voluntary foot dorsiflexions as a gold standard, and resting as a baseline, to establish where the augmentative effect of technology figured in this range. The Sponsor can see no basis for excluding this study, and fail to see how it falls outside the scope
11	**4.1**	**Page 12, 2nd Paragraph, line 5.** **The overview states in respect to Jawad (Cardiac) 2012) "**After electrical stimulation, femoral arterial volume flow and velocity increased by more than 50% and 24% respectively. Micro-vascular velocity increased by 1186% following pulse width 400 microseconds and 1552% following pulse width 600 microseconds". **The Sponsor would like to highlight to the MTAC that:** The Jawad study measured several parameters which are very pertinent here: femoral arterial volume flow, femoral arterial velocity, and lower limb micro-vascular flow. How is this considered outside the scope?
12	**4.1**	**Page 12, 3rd Paragraph line 4.** **The overview states in respect to Warwick et al 2013 "**The EAC rejected this study because it considered the use of a plaster cast as a comparator did not fit within the scope". **The Sponsor would like to highlight to the MTAC that:** The plaster cast is not a comparator in this study and as such this rejection is incorrect. The study examines the efficacy (to enhance lower limb blood flow velocity) of geko™ device when used with a plaster cast. Such patients are within the MTEP scope and as such this study is highly relevant to the clinical and technology adoption debate
13	**4.1**	**Page 13 1st paragraph last sentence** **The EAC states in respect to Warwick et al 2013** "The EAC noted that no time period was given for the application of the device or for the duration of different subject positions". **The Sponsor would like to highlight to the MTAC that:** It is clearly stated in the method that a biostabilisation period of 30 minutes is given in each position prior to measurement

14	**4.2**	**The overview states:** The EAC noted that Nicolaides et al (1983) found that the use of IPC with compression stockings was just as effective as receiving low-dose subcutaneous heparin in reducing the incidence of DVT, whereas electrical calf stimulation was not as effective (4%, 9% and 18% respectively **The Sponsor would like to highlight to the MTAC that:** This was not the finding. No statistically significant difference was found between NMES and IPC in this study.
15	**4.3**	**Page 17, final paragraph and page 18.** **Professor Stansby makes the following observation:** **Question posed by the EAC:** There has been duplex in the popliteal vein, photoplethysmography at the dorsal foot vein and strain gauge plethysmography at the mid-calf. These too would suggest an increase in blood flow. Although I feel the comparator in that situation (the patient performing 10 dorsiflexions) may not be described fully enough. It's really a question of whether any of this would be ever be sufficient to show a mechanism by which this device could work. And there is still a lack of clinical trial evidence of course. **Response received by Professor Stansby (ARO report Appendix 7, pp59):** "I think it is reasonable to consider that a device that increased venous flow and prevented venous stasis would reduce VTE – and if the increases in flow were similar or better than those with intermittent compression devices it would be reassuring - but obviously a clinical trial would be required to prove it conclusively As well as flow I think venous volume is important – in distended veins you are more likely to get stasis behind valves etc." This statement adds further credibility to the clinical hypothesis of the Sponsor that the current blood flow data is indicative of risk reduction for patients within scope and who cannot have other forms of VTE prophylaxis.

16	**4.3**	The above summary appears to be **all of the expert feedback to the relevant clinical questions** posed by the EAC to nominated experts in respect to the likely impact of increased venous flow and velocity and how this would impact VTE risk. On the basis of this analysis, expert opinion would appear to be on the side of the Sponsor. This is in conflict to the EAC's general conclusions in respect to expert opinion. An example of this is page 75, issue 14 (of ARO report Appendix E) "Given these weakness in the major clinical parameter (aka surrogate endpoints) 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" Further in column 4 of the same issue: "**The EAC believes the (clinical) hypothesis that drives the economic model is not valid** as it lacks suitable clinical justification. The EAC believes it has reflected fairly the opinions of the nominated experts (who are not EAC experts, but independent expert advisers to NICE).**The EAC's conclusions agree with the majority of replies**". And also page 76, issue 16, column 1 "**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**". Further in column 4 of the same issue: "**The EAC believes it has reflected the opinions of the nominated experts fairly**. Any inconsistencies reflect the responses given by experts to the various questions posed. **The EAC's conclusions agree with the majority of replies**, and the EAC has indicated when opinion was not unanimous".

17	**4.3**	In conflict to what the EAC is suggesting here and as defined within this section, the majority of expert opinion **does appear to support** the Sponsor in respect to the pertinent and decision critical clinical question at the centre of the Sponsor's hypothesis The Sponsor strongly believes that the above EAC statements which suggest that the "majority" of the experts agreed with the EAC's view of the critical clinical issues falls significantly short of reflecting the reality of the expert opinion. This is central to the outcome of this technology review, for expert opinion is everything in respect to this process as they are clearly in place to advise a MTAC, which understandably, is made up of a variety of clinical disciplines. Further the EAC has not provided a reasonable and balanced representation of critical references (e.g. those used to cite fibrinolytic effect of IPC). Again this could have wrongly influenced the MTAC **The Sponsor concludes that the above data is supportive of MTAC issuing guidance as per the current MTEP scope and if it were to do so the MTAC would appear to have the backing of expert and peer reviewed opinion.**
18	**6**	**Page 28, 4th paragraph** **The overview states:** "The Sponsor's case for the clinical effectiveness of the geko™ device, in the absence of directly-observed VTE outcomes in patients, is that an increase in blood flow is a credible surrogate for reduction in risk of VTE. Taking into account a review by Ciani et al (2013) that demonstrated, when compared with equivalent trials, surrogates give over-optimistic results, the EAC has concluded that this is a flawed assumption". **The Sponsor would like to highlight to the MTAC that:** See Appendix 2 Section 6. The Sponsor concludes that the EAC finding in respect to Ciani et al may be misrepresented.

19		**Page 28, 5th paragraph** **The overview states:** "The EAC's opinion was based on the belief that venous thrombosis has 3 major risk factors, known as Virchow's Triad. It stated that although it agreed that venous stasis is a risk factor, it does not believe the literature shows it is essential for venous thrombosis (Morris & Woodcock [2004]). The EAC also noted results from a study by Proctor et al. [2001]), which highlighted the difficulties in assuming that an increase in venous blood flow leads to a reduction in the risk of VTE (see the assessment report page 90 for further details)". **The Sponsor would like to highlight to the MTAC that:** See Appendix 2 Section 6. The Sponsor concludes that the EAC finding in respect to the above references may have been misrepresented. To clarify and educate on this issue, the Sponsor commissioned Dr. Rhys Morris (Medical Physicist at Cardiff University hospital and author of Morris and Woodcock 2004) to complete a review for the Sponsor and this is cited in Appendix 1 section 4 of the consultation feedback document.
20		**Page 50 Appendix 3** **The overview** reports the minutes as taken by the EAC of a visit made by the Sponsor to KITEC. **The Sponsor would like to highlight to the MTAC that:** 1) Whilst MTAC process states that the EAC will publish relevant findings from any interaction with the Sponsor, it is the Sponsor's belief that these minutes should be summarised at the end of any meeting so that an accurate representation of fact will always be made public. This did not happen and unfortunately inaccuracies have entered the public domain. 2) The Sponsor agrees that relevant facts about the technology such as mode of action etc. should be sought and published. However the EAC have gone further (page 51) – The wrongly assigned Professor Nicolaides name (and significant reputation) with a video showing a vein valve being opening by the blood flow associated with the geko™ device. This is unfortunate because the video was created by the Sponsor in house. – Videos of the deep vein clearance were shown but in any event this was not to be assigned to any individual - It is not correct to suggest that the "son of the CEO" devised the product brand. This is an inappropriate comment and factually incorrect. Many qualified people had input into the branding exercise under professional direction and the comment from the EAC undermines this process.

geko MTCD consultation comments table Appendix 7 (EAC review of Barnes et al. 2014 abstract)

Abstract presented at the Society of Academic and Research Surgery Annual Meeting, Cambridge, January 2014.

Parallel Oral Presentation 1A Vascular Surgery

Abstract no. 021

HAEMODYNAMIC EFFICACY OF THE GEKOTM ELECTRICAL EUROMUSCULAR STIMULATION DEVICE IN CLAUDICANTS

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Introduction

Claudication results from arterial insufficiency. Increasing arterial flow to the lower limbs may alleviate symptoms and improve function. Spinal cord stimulation has been shown to be efficacious in improving flow in claudicants but has a high rate of complications. This study aimed to establish the efficacy of the gekoTM, transcutaneous electrical neuromuscular stimulation device on arterial, venous and microcirculatory flow.

Methods

A prospective observational series. All claudicants attending the departmental exercise programme were approached for inclusion. Following a 30minute acclimatisation period, baseline measurements of arterial, venous and microcirculatory flow (Laser Doppler) were taken bilaterally. The gekoTM device was applied for 40 minutes, unilaterally, and flow measurements repeated. The difference in flow from baseline was calculated for each measurement and statistical analysis performed utilising SPSS.

Results

16 patients, 11 male, 5 female, with a mean age of 67 years (SD 7.7) were recruited. The mean resting ABPI of the active limbs was 0.68(SD 0.23). The mean change in arterial volume flow in the active limb was 0.65 L/min compared to control limb 0.003L/min($p=0.026$). Venous volume flow increased by 0.041L/min in the active limb versus control 0.0005L/min($p=0.023$). Microcirculatory flow, measured by laser Doppler increased by a mean of 21.16 flux units in the active compared to a decrease of 6.21 in the control group($p<0.01$).

Conclusion

Transcutaneous electrical neuromuscular stimulation with the gekoTM device augments arterial, venous and microcirculatory flow in patients with claudication and may prove a useful treatment adjunct in this cohort of patients. The effects appear to be local and not systemic.

Take-home message **Transcutaneous electrical neuromuscular stimulation, with the gekoTM device, may prove a useful treatment adjunct in patients with claudication.**

EAC comments on Haemodynamic Efficacy of the GEKO™ Electrical Euromuscular[1] Stimulation Device in Claudicants. Barnes R, Shahin Y, Tucker AT, Chetter IC.

Main points

- The patient population used in this study is not that specified in the scope. It would not be appropriate to generalize the results of this study in patients with claudication to those at risk of VTE.
- There is insufficient evidence provided in the abstract to assess the quality and validity of the study, for example, sample size, design and choice of statistical analysis.
- If further evidence was provided and assessed as valid in terms of the scope, the study could only provide evidence as to whether venous blood flow has changed. However, previous evidence provided has already shown that flow is increased when using geko™, therefore, this is not adding to the knowledge about the device.
- The study does not investigate outcomes specified in the draft recommendation of MTAC.
- The activation period of geko™ of 40 minutes is not equivalent to the typical intervention period for VTE.
- This study cannot answer the questions on the effects of the device on activation of substances from the endothelial lining or the consequences for prevention of VTE.
- The study refers to claudication and does not assess VTE.
- The arterial and microcirculatory measures are not relevant in terms of the scope.

Final comment

The EAC has reviewed this additional conference abstract, and given the main points listed above, concludes that it does not add anything of significance to the evidence base previously assessed. Therefore, the EAC suggests that this abstract is not included as a tabled document at the forthcoming MTAC meeting on the 23rd January 2014.

[1] The EAC notes the typo in the title: ‘Euromuscular’ presumably should be ‘Neuromuscular’.