Washington State Health Care Authority

Varicose Veins

Draft key questions: Comment and response

December 8, 2016

Health Technology Assessment Program (HTA)
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Varicose Veins

Response to Public Comments on Topic and Draft Key Questions

December 8, 2016

Prepared by:

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Response to Public Comments, Topic and Key Questions

Selected Endovascular and Surgical Interventions for Treating Varicose Veins

Hayes, Inc. is an independent vendor contracted to produce evidence assessment reports for the Washington Health Technology Assessment (WA HTA) program. For transparency, all comments received during the comments process are included in this response document.

Draft key questions for each WA HTA report are posted online in order to gather public input and any additional evidence to be considered in the evidence review. Since key questions guide the evidence report, WA HTA seeks input on whether the questions are appropriate to address its mandate to gather evidence on safety, efficacy, and cost-effectiveness relevant to coverage determinations. Input about the following is especially helpful:

- Are appropriate populations or indications identified?
- Are appropriate comparators identified?
- Are appropriate patient-oriented outcome measures included?
- Are there special policy or clinical considerations that could affect the review?

Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only. When comments cited evidence, the vendor was encouraged to consider inclusion of this evidence in the report.

This document responds to comments from the following parties:

Topic:

- Alex C. Au-Yeung (Medtronic)

Key Questions:

- Alex C. Au-Yeung (Medtronic)
- Catherine Livingston (Oregon Health Authority Health Evidence Review Commission)

Table 1 provides a summary of comments with responses.

Table 1. Public Comments on Topic and Key Questions, *Negative Pressure Wound Therapy – Home-Use*

Comment and Source	Response
Comments on Topic	
May 19, 2016, letter and enclosures submitted electronically from Alex C. Au-Yeung (Medtronic)	
Medtronic is pleased to provide this initial response to the public request for comments issued on April 18, 2016 by the Washington State Health Care Authority (HCA) as part of a Health Technology Assessment (HTA) being conducted on "Varicose Veins". The underlying disease that causes varicose veins is often chronic venous insufficiency or venous reflux. Historically, varicose veins have been treated initially with conservative therapies such as exercise, leg elevation and compressive therapy. When the conservative measures are unsuccessful and symptoms persist, the next step has been surgical or endovascular therapies such as laser ablation as well as radiofrequency ablation. Medtronic wants to ensure that any review of varicose veins includes radiofrequency ablation as a treatment option. Enclosed for your reference, is a summary of clinical studies for radiofrequency ablation using the Medtronic ClosureFAST TM (CLF) catheter. Medtronic appreciates the opportunity to continue to support the HCA in its review of the topics and appreciates the ongoing transparency this agency has undertaken that allows for public comments.	Thank you for your comments. Radiofrequency ablation is included as an eligible intervention within the scope of the health technology assessment. The clinical studies provided with your comment will be considered for eligibility.
Comments on Draft Key Questions	
October 24, 2016, email from Catherine Livingston (Oregon Health Authority Health Evidence Review Commission)	
The PICO clearly defines the population those who have failed conservative management (oddly compression stockings not given as an example), yet I would still be interested in noting how the more invasive procedures compare to ongoing conservative therapy. One other subgroup that is included in the PICO makes this comparison especially pertinent: pregnant women. The most important outcome for other plans who do not cover these treatments for uncomplicated varicose veins would be the effectiveness of prevention of complication, such as preventing ulcers or cellulitis.	Thank you for your comments. The main focus of the HTA is to compare selected endovascular and surgical interventions with stripping and ligation; comparisons with conservative treatments is not within the proposed scope. The proposed population has been modified to be defined as adult patients being treated for varicose veins. Studies evaluating eligible interventions and comparisons among pregnant women will be considered for eligibility for the key question regarding subgroups.

Comment and Source	Response
Comments on Topic	
November 4, 2016, letter and enclosures submitted electronically from Alex C. Au-Yeung (Medtronic)	
Medtronic is pleased to provide this response to the public request for comments on the draft key questions issued on October 21, 2016 by the Washington State Health Care Authority (HCA) as part of a Health Technology Assessment (HTA) being conducted on "Varicose Veins". The underlying disease that causes varicose veins is often chronic venous insufficiency or venous reflux. Historically, varicose veins have been treated initially with conservative therapies such as exercise, leg elevation and compressive therapy. When the conservative measures are unsuccessful and symptoms persist, the next step has been surgical or endovascular therapies such as thermal ablation. The Medtronic ClosureFastTM system is an endovenous thermal ablation therapy used for the treatment of CVI. To date, ClosureFastTM is recognized and recommended by numerous clinical guidelines for treatment of various stages of CVI. ClosureFastTM minimises the associated post-procedural limitations of conventional surgery which, in turn, helps alleviate the burden of CVI on patients, health systems and wider society. Below are two examples of clinical guidelines recommending endovenous thermal ablation: **AVF/SVS 2011 Clinical Guidelines for Patients with Varicose Veins and Associated CVD:** Recommend endovenous thermal ablation (laser and radiofrequency) for the treatment of saphenous incompetence rather than high ligation and inversion stripping (Grade 1B) **ACP 2015 Clinical Guideline for Superficial Venous Disease:** Recommend endovenous thermal ablation (laser and radiofrequency) is the preferred treatment for saphenous and accessory saphenous vein incompetence (Grade 1B) The Agency for Healthcare Research and Quality (AHRQ) recently released a draft evidence review titled "Treatment Strategies for Patients with Lower Extremity Chronic Venous Disease."3 The AHRQ report was commissioned by Medicare for a July 20, 2016 meeting of the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC). At the MEDCAC meeting, the authors of the AHRQ review noted they had to narrow the scope of the evidence included given the short time they had to prepare the report for the meeting. We recognize that this report may be an input in Washington State's review of varicose veins and want to share the comments we submitted through AdvaMed and those submitted by professional societies to AHRQ highlighting a number of the report's limitations. Since the final AHRQ review is not yet available, we want to make sure you are aware of the limitations highlighted in comments to AHRQ to ensure a comprehensive evaluation of the evidence in this review. Key limitations of the draft AHRQ review include: • Excludes peer-reviewed publications prior to the year 2000. As articulated in the enclosed comment letter to AHRQ by a coalition of key professional societies, limiting the evidence review to the period after 2000 eliminated the	Thank you for your comments. There is no date limit for eligible studies in the proposed scope of work. To identify eligible evidence, following a search for good quality systematic reviews (including meta-analysis) to answer the key questions, randomized controlled trials (RCTs) of any size meeting eligibility criteria will be employed to update the selected systematic reviews. In addition, to answer key questions regarding harms, other study designs will be considered. Also to answer key question 4 on cost implications and cost effectiveness, update searches will include eligible RCTs along with eligible modelling and observational studies. The citations included in the provided list of economic studies will be considered for eligibility.

Comment and Source	Response
Comments on Topic	
evidence base on which the more recent therapies rest. We recognize the time limits of the review necessitated narrowing the scope of the review, but it is critical that a thorough evidence review acknowledge the evidence published pre-2000. • Made the inclusion criterion for the key question on symptomatic chronic venous insufficiency too strict. Comparative observational studies were only considered if the sample size was greater than 500 subjects. There are multiple studies that the draft review excluded because of the 500 patient limit; these studies meet the rest of AHRQ's rigorous inclusion/exclusion criteria. The majority of these studies track clinical and quality of life outcomes for one year or more and would help further reinforce the durability of more invasive treatment options for CVI patients. • Did not include an evaluation of other quality of life measures, such as return to work and return to normal activities. We are also including a summary of recent health economic studies to address the cos implications and cost-effectiveness of radiofrequency ablation for treatment of varicose veins. [*See full submission attached below for list of economic studies*] Medtronic appreciates the opportunity to continue to support the HCA in its review of the topics and appreciates the ongoing transparency this agency has undertaken that allows for public comments.	

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May 19, 2016

Washington State Health Care Authority
Health Technology Assessment Program
P.O. Box 45502
Olympia, WA 98504-5502
Attn: Josh Morse, HTA Program Director

Subject: Health Technology Assessment Topic Selection - Varicose Veins

Dear Mr. Morse,

Medtronic is pleased to provide this initial response to the public request for comments issued on April 18, 2016 by the Washington State Health Care Authority (HCA) as part of a Health Technology Assessment (HTA) being conducted on "Varicose Veins".

Technology	**Safety**	**Efficacy**	**Cost**
3. Varicose Veins	Medium	High	Medium
Policy Context/Reason for Selection: A variety of treatments for varicose veins are available. Treatment goals include reducing pain or discomfort and for cosmetic reasons. The topic is identified based on uncertainties related to the safety, efficacy, and value of the certain procedures including chemical ablation, stab phlebectomy and laser ablation.			

The underlying disease that causes varicose veins is often chronic venous insufficiency or venous reflux. Historically, varicose veins have been treated initially with conservative therapies such as exercise, leg elevation and compressive therapy. When the conservative measures are unsuccessful and symptoms persist, the next step has been surgical or endovascular therapies such as laser ablation as well as radiofrequency ablation. Medtronic wants to ensure that any review of varicose veins includes radiofrequency ablation as a treatment option. Enclosed for your reference, is a summary of clinical studies for radiofrequency ablation using the Medtronic ClosureFAST ™ (CLF) catheter.

Medtronic appreciates the opportunity to continue to support the HCA in its review of the topics and appreciates the ongoing transparency this agency has undertaken that allows for public comments.

If you have any questions regarding this, please feel free to contact me at (707) 591-2246 or via email at alex.c.au-yeung@medtronic.com.

Sincerely,

[redacted]

Alex C. Au-Yeung
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Coronary/APV
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Summary of Clinical Studies for ClosureFast™

Author	Elkaffas *et al*. 2011
Title	Great saphenous vein radiofrequency ablation versus standard stripping in the management of primary varicose veins-a randomized clinical trial
Study design	Prospective, randomised, blinded, controlled trial
Country	Egypt
Duration of Follow-up	2 years
Patient Population	Patients with saphenofemoral junction and great saphenous reflux (patient n=180)
Treatment Arms	• ClosureFast™ (n=90) • Surgical management (n=90)

Key Efficacy Conclusion	• Primary occlusion rate (immediately post-operation)
	  ○ ClosureFast™: 94.5%
	  ○ Surgical management: 100%
	• Recurrence Rates (24 months)
	  ○ Kaplan- Meier analysis showed no significant differences in recurrence rates at 24 months follow-up (13.3% for ClosureFast™ versus 10.0% in surgical management)

Key Safety Conclusions	• Complication rate
	  ○ ClosureFast™: no major complications were noted. Of the 90 patients, 9 (10%) developed focal paraesthesia and 6 (6.6%) develop thrombophlebitis; 12 (13.3%) experienced severe pain requiring analgesic therapy. One patient in this group developed a haematoma. None of these patients developed DVT, pulmonary embolism, cellulitis or skin burns.
	  ○ Surgical management: higher rate of complications (p=0.02), wherein 1 patient (1.1%) developed iliofemoral DVT diagnosed in the immediate postoperative period; 3 patients (3.3%) developed severe groin infection that necessitated parenteral antibiotic therapy. Of the 90 patients, 12 (13.3%) had groin haematoma. Three patients (3.3%) had paraesthesia at the groin region; 18 (20%) of 90 had a haematoma in the saphenous fascial compartment and 12 (13.3%) of 90 patients experienced severe pain requiring analgesic therapy.
	  ○ ClosureFast™ had significantly fewer overall adverse events than surgical management (p=0.02).

Author	Proebstle *et al.* 2015
Title	Five-year results from the prospective European multicentre cohort study on radiofrequency segmental thermal ablation for incompetent great saphenous veins.
Study design	Prospective, multi-centre, cohort study
Country	Germany, France
Duration of Follow-up	5 years
Patient Population	Patients with incompetent GSV (patient n=225; limb n=295)
Treatment Arms	• ClosureFast™

Key Efficacy Conclusion	• Initial vein occlusion rate of 100%
	• Kaplan-Meier analyses showed a GSV occlusion rate of 91.9% and a reflux-free rate of 94.9% at 5 years
	• Significant pain was present in the legs at baseline in 58.6% of the legs, according to the VCSS pain domain
	  ○ 3 months after treatment, this had decreased to 6.9% of legs
	  ○ 92.4% of the treated limbs were pain-free at the 5-year follow-up visit

Key Safety Conclusions	N/A
Author	Rasmussen *et al.* 2011
Title	Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins.
Study design	Randomised controlled trial
Country	Denmark
Duration of Follow-up	1 year
Patient Population	Patients with GSV reflux (patient n=500; limb n=580)
Treatment Arms	• ClosureFast™ (n=125; 148 limbs) • EVLA (n=125; 144 limbs) • UGFS (n=125; 145 limbs) • Surgical stripping (n=125; 143 limbs)
Key Efficacy Conclusion	• At 1 year, seven (5.8%), six (4.8%), 20 (16.3%) and four (4.8%) of the GSVs were patent and refluxing in the laser, radiofrequency, foam and stripping groups respectively ($p<0.001$) • The mean (SD) post-intervention pain scores (scale 0-10) were 2.58 (2.41), 1.21 (1.72), 1.60 (2.04) and 2.25 (2.23) respectively ($p<0.001$) • The median (range) time to return to normal function was 2 (0-25), 1 (0-30), 1 (0-30) and 4 (0-30) days, respectively ($p<0.001$) • The time off work, corrected for weekends, was 3.6 (0-46), 2.9 (0-14), 2.9 (0-33) and 4.3 (0-42) days, respectively ($p<0.001$)
Key Safety Conclusions	• One patient developed a pulmonary embolus after foam sclerotherapy and one a DVT after surgical stripping

Author	Proebstle *et al.* 2011
Title	Three-year European follow-up of endovenous radiofrequency-powered segmental thermal ablation of the great saphenous vein with or without treatment of calf varicosities.
Study design	Prospective, multicentre trial
Country	Germany, France
Duration of Follow-up	3 years
Patient Population	Patients with GSV reflux (patient n=255; limb n= 295)
Treatment Arms	• ClosureFast™
Key Efficacy Conclusion	• At 36 months, Kaplan-Meier survival analysis showed the probability of occlusion was 92.6%, the probability of no reflux was 95.7%, and 96.9% of legs remained free of clinically relevant axial reflux. • The average VCSS score improved from 3.9 ± 2.1 before treatment to 0.9 ± 1.5 at 3 months ($p<0.0001$) and stayed at an average of <1.0 during the complete 36 months of follow-up. • 41.1% of patients were free of pain before treatment; at 36 months, 251 (98.0%) reported no pain and 245 (95.7%) did not experience pain during the 24 months before. • At 36 months, 189 of 255 legs (74.1%) showed an improvement in CEAP class compared with the clinical assessment before treatment ($p<0.001$).
Key Safety Conclusions	• At 36 months, 1 of 256 legs showed hyperpigmentation over the course of the treated GSV, and 1 patient complained of persisting paraesthesia in an area attributable to the saphenous nerve.
Author	Roos *et al.* 2011
Title	Pain perception during and after VNUS ClosureFAST™ procedure
Study design	Prospective study
Country	Netherlands
Duration of Follow-up	1 week
Patient Population	Patients with GSV reflux (patient n=101)
Treatment Arms	• ClosureFast™
Key Efficacy Conclusion	N/A
Key Safety Conclusions	• The average VAS score during the VNUS Closure procedure was 4. • The first three days after the procedure the VAS score was 2. • After four days, the average VAS score was 1. • The average return to daily activities was on day two after the procedure.

Author	Creton *et al*. 2010
Title	Radiofrequency-powered segmental thermal obliteration carried out with the ClosureFast procedure: results at 1 year.
Study design	Prospective, multicentre trial
Country	France
Duration of Follow-up	1 year
Patient Population	Patients with GSV reflux (patient n=295)
Treatment Arms	• ClosureFast™
Key Efficacy Conclusion	• Occlusion scores were 99.7%, 99.3%, 98.6% and 96.9%, respectively, at 3 days, 3 months, 6 months and 1 year.
Key Safety Conclusions	• Pre-procedural pain that was present in 57.5% of the cases decreased to 10.8% of the cases at 3 days and 2% of the cases at 1 year ($p<0.001$, chi2 test). • During the follow-up, no painful indurations were noticed in 67.7% of the legs. • No thromboembolic complications were reported. • Paraesthesia was observed in 3.4% of the cases.

Author	Alm *et al*. 2010
Title	VNUS Closure radiofrequency ablation of varicose veins
Study design	Prospective study
Country	N/A
Duration of Follow-up	2 years
Patient Population	Patients with great and small saphenous vein reflux (limb n=2413)
Treatment Arms	• ClosureFast™ (n=2241 veins) • ClosurePLUS™ (n=1125 veins)
Key Efficacy Conclusion	• For ClosureFast™, the primary closure rate after 7 days was 99.7%; after 6 weeks, 99.6%; after one year, 98.8%; and after two years, 100%.
Key Safety Conclusions	• For ClosureFast™, the rate of minor complications after treatment of the GSV was 5.3% and 5.9% after treatment of the small saphenous vein. • No major complications – such as DVTs or pulmonary embolisms were seen. • No skin burns were present.

Author	Calcagno *et al.* 2009
Title	Effect of saphenous vein diameter on closure rate with ClosureFAST radiofrequency catheter.
Study design	Prospective study
Country	USA
Duration of Follow-up	6 months
Patient Population	Patients with great and small saphenous vein reflux (patient n=310; limb n=338)
Treatment Arms	• ClosureFast™
Key Efficacy Conclusion	Veins were divided into ≤12 mm diameter (group A) or >12 mm diameter (group B). • Early duplex showed complete closure in 231 veins in group A (94%) and 92 veins in group B (96%; NS). • The remaining veins showed partial closure with none showing retrograde flow. Six-month duplex scans were completed in 155 veins. • Complete closure was seen in 110 veins in group A (98%) and 43 veins in group B (100%; NS). All veins partially open on early scan had closed by 6 months.
Key Safety Conclusions	N/A
Author	Subramonia *et al.* 2010
Title	Randomized clinical trial of radiofrequency ablation or conventional high ligation and stripping for great saphenous varicose veins.
Study design	Prospective randomised controlled trial
Country	UK
Duration of Follow-up	1 month
Patient Population	Patients with GSV reflux (patient n=88)
Treatment Arms	• ClosureFast™ (n=47 patients) • Surgical management (n=41 patients)
Key Efficacy Conclusion	• RFA resulted in successful obliteration of the GSV in all 47 patients. • Complete above-knee stripping was unsuccessful in seven of 41 patients receiving surgical management. • The RFA procedure took longer than conventional surgery: median interquartile range 76 (67-84) versus 48 (39-54) minutes; p<0.001. • Patients returned to their normal activities significantly earlier after RFA (median 3 (2-5) versus 12.5 (4-21) days; p<0.001). • Patient satisfaction, quality of life improvement and analgesic requirements significantly favoured RFA.
Key Safety Conclusions	• Postoperative pain was significantly less after RFA than with surgical management (median score on VAS 1.70 (0.50-4.30) versus 4.0 (2.35-6.05); p=0.001). • A significantly higher rate of cutaneous sensory abnormalities was observed after conventional surgery than with RFA (20 vs. 9 patients post-operation week 1) (p<0.001). • Groin wound problems noted after conventional surgery included mild inflammation (three patients), serous wound discharge (two), haematoma (one) and wound breakdown (one), all of which resolved spontaneously. • Clinically evident haematomas in the thigh and leg were slightly more common after conventional surgery than RFA but did not differ significantly between the groups. • Five patients developed a non-tender palpable GSV with overlying pigmentation after RFA that showed progressive resolution by the second follow-up.

Author	Hinchliffe *et al.* 2006
Title	A prospective randomised controlled trial of VNUS closure versus surgery for the treatment of recurrent long saphenous varicose veins.
Study design	Prospective randomised controlled trial
Country	UK
Duration of Follow-up	1 month
Patient Population	Patients with minimum CEAP class 3 (patient n=16; limbs n=32)
Treatment Arms	• ClosureFast™ (n=16 limbs) • Redo groin surgery (n=16 limbs)
Key Efficacy Conclusion	• Time to perform VNUS was 25.5 (20.5-31.3) minutes compared with 40 (34.5-45.5) minutes for redo groin surgery (p=0.02). • All long saphenous veins (LSVs) were sealed by VNUS at duplex follow up.
Key Safety Conclusions	• Pain score for VNUS was 1.7 (0.2-4), significantly lower than that for redo groin surgery 3.8 (0.6-6.3) (p=0.02). • Bruise score for VNUS was 1.7 (0.4-4.4) compared with 5.2 (2.6-7) for redo groin surgery (p=0.03).
Author	Lurie *et al.* 2003
Title	Prospective randomized study of endovenous radiofrequency obliteration (closure procedure) versus ligation and stripping in a selected patient population (EVOLVeS Study).
Study design	Prospective randomised multicentre trial
Country	USA and EU
Duration of Follow-up	2 years
Patient Population	Patients with GSV reflux (patient n=79)
Treatment Arms	• ClosureFast™ (n=44 limbs) • Surgical management (n=36 limbs)

Key Efficacy Conclusion	• Immediate success on the day of treatment was reported for 95% (42 of 44) of limbs in the RFA group and 100% (36 of 36) of limbs in the surgical ligation group.
	• In seven RFA limbs (16.3%) a scan obtained 72 hours after the procedure showed flow in the proximal GSV. Five of these segments had reflux in the open segment. At 1 week two of these closed, and an additional segment closed at 3 weeks.
	• In no cases did flow reappear after complete occlusion of the GSV.
	• Time to return to normal activities was significantly less in the RFA group (mean, 1.15 days; 95% confidence interval [CI], 0.05-2.34) compared with the surgical ligation group (mean, 3.89 days; CI, 2.67-5.12; p=0.02).
	  ○ In the RFA group, 80.5% of patients returned to routine activities of daily living within 1 day, compared with 46.9% of patients in the surgical group (p<0.01).
	  ○ Patients in the RFA group were able to return to work in 4.7 days (CI, 1.16-8.17), compared with 12.4 days (CI, 8.66-16.23) for the surgical group (p <0.05).

Key Safety Conclusions	• Analysis of the QoL surveys showed statistically significant differences in favour of the RFA group for global score and pain score during follow-up.

Author	Nordon *et al*. 2011
Title	A prospective double-blind randomized controlled trial of radiofrequency versus laser treatment of the great saphenous vein in patients with varicose veins.
Study design	Prospective randomised controlled trial
Country	UK
Duration of Follow-up	3 months
Patient Population	Patients with GSV reflux (patient n=159)
Treatment Arms	• ClosureFast™ (n=79 patients) • EVLA (n=80 patients)
Key Efficacy Conclusion	• Duplex scanning confirmed 100% vein occlusion at 1 week in both groups. • At 3 months, occlusion was 97% for RFA and 96% for EVLA p=0.67. • Changes in the AVVQ (p=0.12) and EQ-5D (p=0.66) at 3 months were similar in both groups.
Key Safety Conclusions	• Median (interquartile range) percentage above-knee bruise area was greater after EVLT 3.85% (6.1) than after RFA 0.6% (2); p=0.0001. • Postoperative pain assessed at each of the first 7 postoperative days was less after RFA (p=0.001).

Author	Shepherd *et al*. 2010
Title	Randomized clinical trial of VNUS ClosureFAST radiofrequency ablation versus laser for varicose veins.
Study design	Prospective randomised controlled trial
Country	UK
Duration of Follow-up	6 weeks
Patient Population	Patients with GSV reflux (patient n=131)
Treatment Arms	• ClosureFast™ (n=67 patients) • EVLA (n=64 patients)
Key Efficacy Conclusion	N/A

Key Safety Conclusions	• Mean (SD) pain scores by VAS over 3 days were 26.4 (22.1) for RFA and 36.8 (22.5) for EVLA (p=0.010).
	• Over 10 days, mean (SD) pain scores were 22.0 (19.8) mm versus 34.3 (21.1) mm for RFA and EVLA respectively (p=0.001).
	• Changes in AVVQ, SF-12 and VCSS scores at 6 weeks were similar in the two groups: AVVQ (p=0.887), VCSS (p=0.993), SF-12 physical component score (p=0.276) and mental component score (p=0.449).
	• During the study, two major complications were observed. One patient randomised to RFA suffered a pulmonary embolus 2 weeks after intervention (the patient was treated with warfarin, although no evidence of DVT or clot extension in the leg veins was found on duplex imaging). One patient in the EVLA group developed a lymphatic leak from the cannulation site, and lymphoscintigraphy confirmed increased lymphatic collateral flow consistent with trauma at the site.
	• Minor complications included wound infection (4 patients RFA versus 2 patients EVLA), haematoma (0 patients RFA versus 2 patients EVLA), thrombophlebitis (5 patients RFA versus 3 patients EVLA), saphenous nerve paraesthesia (8 patients RFA versus 5 patients EVLA) and skin pigmentation (6 patients RFA versus 2 patients EVLA).
	• Despite the intention to perform procedures as a day case, 4 patients required overnight admission after the procedure:
	  o Due to nausea (RFA, 1; EVLA, 1)
	  o Hypotension secondary to general anaesthesia (RFA, 1)
	  o Pain requiring opioid analgesia (RFA, 1)

Author	Almeida *et al*. 2009
Title	Radiofrequency endovenous ClosureFAST versus laser ablation for the treatment of great saphenous reflux: a multicenter, single-blinded, randomized study (RECOVERY study).
Study design	Prospective randomised multicentre trial
Country	USA and EU
Duration of Follow-up	4 weeks
Patient Population	Patients with GSV reflux (patient n=69; limbs=87)
Treatment Arms	• ClosureFast™ (n=46 limbs) • EVLA (n=41 limbs)
Key Efficacy Conclusion	• VCSS evaluations were recorded on all patients at the initial evaluation, and subsequently at all visits - there were no significant differences in VCSSs between RFA and EVLA at screening (4.7 vs 4.9; p=0.6907). o However, at the 48-hour (4.7 vs 6.2; p=0.0009), 1-week (4.2 vs 5.9; p=0.0002), and 2-week visits (4.0 vs 5.3; p=0.0035), subjects in the RFA group had significantly reduced scores compared with the EVLA group.
Key Safety Conclusions	• The ClosureFast™ group reported significantly lower pain levels than the EVLA group during visits at 48 hours (0.7 vs 1.9), 1 week (0.2 vs 1.8), and 2 weeks (0.1 vs 1.2; all p<0.0001). • RFA group reported significantly lower tenderness than the EVLA group during visits at 48 hours (0.9 vs 2.0; p=0.0048), 1 week (0.5 vs 1.6; p=0.0036), and 2 weeks (0.3 vs 1.2; p=0.0005). • 67% of limbs in the ClosureFast™ group had no bruising at the 48-hour visit versus only 20% in the EVLA group. • One limb in the ClosureFast™ group (2.2%) showed ecchymosis covering more than 25% of the treated area across all visits compared with 21 of the EVL-treated limbs (51.3%). • Complications were statistically more prevalent in the EVLA group than the RFA group (22.0% vs 4.4% p=0.21): o At 48 hours: EVLA: 12.2% experienced phlebitis, 2.4% experienced paraesthesia, 7.3% experienced erythema, and 2.4% experienced a thromboembolism. o At 1 month, one patient (2.2%) in the RFA group experienced hyperpigmentation of the skin.

Author	Rautio *et al*. 2002
Title	Endovenous obliteration versus conventional stripping operation in the treatment of primary varicose veins: a randomized controlled trial with comparison of the costs.
Study design	Prospective randomised controlled trial
Country	Finland
Duration of Follow-up	1 month
Patient Population	Patients with GSV reflux (patient n=28)
Treatment Arms	• ClosureFast™ (n=15 patients) • Surgical management (n=13 patients)
Key Efficacy Conclusion	• All operations were successful, and the complication rates were similar in the two groups. • The sick leaves were significantly shorter in the endovenous obliteration group (6.5 (SD: 3.3) days versus 15.6 (SD: 6.0) days; 95% CI, 5.4 to 12.9; p<0.001, with t test). • The estimated annual investment costs of ClosureFast™ were US $3360. The other direct medical costs of the ClosureFast™ were about $850, and those of the conventional treatment were $360. • With inclusion of the value of the lost working days, ClosureFast™ was cost-saving for society, and when 40% of the patients are retired (or 60% of the productivity loss was included), ClosureFast™ became cost-saving at a level of 43 operations per year.
Key Safety Conclusions	• Postoperative average pain was significantly less severe in the ClosureFast™ group as compared with the stripping group (at rest: 0.7, SD 0.5, versus 1.7, SD 1.3, p=0.017; on standing: 1.3, SD 0.7, versus 2.6, SD 1.9, p=0.026; on walking: 1.8, SD 0.8, versus 3.0, SD 1.8, p=0.036; with t test).

Author	Harlander-Locke *et al*. 2012
Title	Combined treatment with compression therapy and ablation of incompetent superficial and perforating veins reduces ulcer recurrence in patients with CEAP 5 venous disease.
Study design	Prospective trial
Country	USA
Duration of Follow-up	18 months
Patient Population	Patients with CEAP Class 5 (patient n=20; limb n=28)
Treatment Arms	• ClosureFast™
Key Efficacy Conclusion	• Technical success rates for the ablation procedures were 100% for superficial veins and 89% for perforators (96.4% overall). • All patients underwent closure of at least one incompetent vein. • Ulcer recurrence rates were 0% at 6 months and 4.8% at 12 and 18 months.
Key Safety Conclusions	N/A

Author	Harlander-Locke *et al*. 2012
Title	The impact of ablation of incompetent superficial and perforator veins on ulcer healing rates.
Study design	Prospective trial
Country	USA
Duration of Follow-up	18 months
Patient Population	Patients with CEAP Class 6 (limb n=140)
Treatment Arms	• ClosureFast™
Key Efficacy Conclusion	• Following successful ablation, the healing rate for healed ulcers improved from + 1.0 ± .1 cm^2/month to -4.4 ± .1 cm^2/month ($p>0.05$). • Ulcer healing rate for healed ulcers, based on the last vein ablated, was GSV = 6.4 cm^2/month, SSV = 4.8 cm^2/month, and PTPV = 2.9 cm^2/month. • After a minimum observation period of 6 months (mean follow up, 12 ± 1.25 months), 76.3% of patients healed in 142 ± 14 days. • Twelve patients with 26 ulcers did not heal: two patients died from unrelated illnesses, six patients were still actively healing, and four patients were lost to follow up. • Of the healed ulcers, four patients with six ulcers (7.1%) recurred; two re-healed.
Key Safety Conclusions	N/A

Author	Shaĭdakov *et al*. 2013
Title	[Radiofrequency obliteration of veins in surgical treatment of varicose disease].
Study design	Prospective trial
Country	Russia
Duration of Follow-up	2 years
Patient Population	Patients with CVI (patient n=110, limb n=135)
Treatment Arms	• ClosureFast™
Key Efficacy Conclusion	• RFA was successfully used in patients in all venous basins, irrespective of the diameter and anatomical course of the venous structures. • In 98% of cases occlusion was achieved with the removal of the reflux within the terms of up to one year. • Regress of clinical symptoms and improvement of quality of life were reflected in the VCSS. • 100% of patients returned to the daily activity on the day of operation.
Key Safety Conclusions	N/A

Author	Tolva *et al*. 2013
Title	Radiofrequency ablation of the great saphenous vein with the ClosureFAST™ procedure: mid-term experience on 400 patients from a single centre.
Study design	Prospective trial
Country	Italy
Duration of Follow-up	2 weeks
Patient Population	Patients with GSV reflux (limb n=407)
Treatment Arms	• ClosureFast™
Key Efficacy Conclusion	• Occlusion of the GSV was seen on 98% of completion scans and in all patients within 1 week of the procedure. • Persistent occlusion was documented in all cases.
Key Safety Conclusions	• One patient had paraesthesia and one had skin pigmentation. • Three patients had transient superficial thrombophlebitis in a treated segment of a superficial collateral of the GSV. • One patient was found to have extension of an asymptomatic, nonocclusive thrombus into the common femoral vein 1 week after the procedure.

Author	García-Madrid *et al*. 2011
Title	[New advances in the treatment of varicose veins: endovenous radiofrequency VNUS Closure®].
Study design	Prospective trial
Country	Spain
Duration of Follow-up	5 years
Patient Population	Patients with GSV reflux (limb n=153)
Treatment Arms	• ClosureFast™
Key Efficacy Conclusion	• Occlusion rate of the treated vein was 97%, and there was a reflux rate of 6.6%. Inguinal neovascularisation was present in 0.7%.
Key Safety Conclusions	• There was no neuritis, skin burns or DVT.

Author	Sufian *et al*. 2011
Title	Superficial vein ablation for the treatment of primary chronic venous ulcers.
Study design	Retrospective study
Country	USA
Duration of Follow-up	12 months
Patient Population	Patients with CEAP Class 6 (limb n=25)
Treatment Arms	• ClosureFast™
Key Efficacy Conclusion	• During a follow-up period of 6-12 months, one patient failed ulcer healing despite sequential ablations of refluxing veins. • There was one case that developed recurrence of a small ulcer after six months and was successfully treated with a perforator ablation.
Key Safety Conclusions	N/A

Author	Bisang *et al*. 2012
Title	Results of endovenous ClosureFast treatment for varicose veins in an outpatient setting.
Study design	Retrospective study
Country	Switzerland
Duration of Follow-up	12 months
Patient Population	Patients with GSV reflux (patient n=155)
Treatment Arms	• ClosureFast™
Key Efficacy Conclusion	• After a mean follow-up of 12.2 months (range 1-29 months), duplex ultrasound showed six (5.9%) open GSV and an occlusion of all treated SSV. • Mean patient satisfaction was 8.7 (10 = very satisfied) • Absence of work was 0.9 day (range 0-14 days).
Key Safety Conclusions	• One pulmonary embolism occurred. • Pain after one week was 2.0 (no pain = 0, maximal = 10).

Author	Kliment *et al*. 2009
Title	[Procedure on low extremities varicose veins using the VNUS-Closure radiofrequency ablation method].
Study design	Prospective study
Country	Czech Republic
Duration of Follow-up	12 months
Patient Population	Patients with lower extremity varicose veins (patient n=334)
Treatment Arms	• ClosureFast™
Key Efficacy Conclusion	• The mean duration of the procedure on a single lower extremity was 29 minutes. • The mean duration of hospitalisation was 1 day. • Relapses at 12 months were recorded in 3 patients in the operated area (0.9%); however, in all three subjects the relapse affected a side venous branch, never the main branch.
Key Safety Conclusions	N/A

Author	Subramonia *et al*. 2010
Title	Randomized clinical trial of radiofrequency ablation or conventional high ligation and stripping for great saphenous varicose veins.
Study design	Prospective randomised controlled trial
Country	UK
Duration of Follow-up	2 weeks
Patient Population	Patients with GSV reflux (patient n=88)
Treatment Arms	• ClosureFast™ (n=47 patients) • Surgical management (n=41 patients)
Key Efficacy Conclusion	• RFA resulted in successful obliteration of the GSV in all 47 patients. • Complete above-knee stripping was unsuccessful in seven of 41 patients receiving surgical management. • RFA took longer than conventional surgery: median interquartile range 76 (67-84) versus 48 (39-54) minutes; p<0.001. • Patients returned to their normal activities significantly earlier after RFA than surgical management (median 3 (2-5) versus 12.5 (4-21) days; p<0.001).
Key Safety Conclusions	• Postoperative pain at week 1 was significantly less after RFA than surgical management (median score on VAS 1.70 (0.50-4.30) versus 4.0 (2.35-6.05); p=0.001). • A significantly higher rate of cutaneous sensory abnormalities was observed after conventional surgery: 20 patients versus 9 patients in the RFA group. • Clinically evident haematomas in the thigh and leg were slightly more common after conventional surgery but did not differ significantly between the groups. Five patients developed a non-tender palpable GSV with overlying pigmentation after RFA that showed progressive resolution by the second follow-up.

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November 4, 2016

Washington State Health Care Authority
Health Technology Assessment Program
P.O. Box 45502
Olympia, WA 98504-5502
Attn: Josh Morse, HTA Program Director

Subject: Health Technology Assessment Topic Selection - Varicose Veins

Dear Mr. Morse,

Medtronic is pleased to provide this response to the public request for comments on the draft key questions issued on October 21, 2016 by the Washington State Health Care Authority (HCA) as part of a Health Technology Assessment (HTA) being conducted on "Varicose Veins".

The underlying disease that causes varicose veins is often chronic venous insufficiency or venous reflux. Historically, varicose veins have been treated initially with conservative therapies such as exercise, leg elevation and compressive therapy. When the conservative measures are unsuccessful and symptoms persist, the next step has been surgical or endovascular therapies such as thermal ablation.

The Medtronic ClosureFast™ system is an endovenous thermal ablation therapy used for the treatment of CVI. To date, ClosureFast™ is recognized and recommended by numerous clinical guidelines for treatment of various stages of CVI. ClosureFast™ minimises the associated post-procedural limitations of conventional surgery which, in turn, helps alleviate the burden of CVI on patients, health systems and wider society. Below are two examples of clinical guidelines recommending endovenous thermal ablation:

> **AVF/SVS 2011 Clinical Guidelines for Patients with Varicose Veins and Associated CVD:** Recommend endovenous thermal ablation (laser and radiofrequency) for the treatment of saphenous incompetence rather than high ligation and inversion stripping (Grade 1B)[1]
> **ACP 2015 Clinical Guideline for Superficial Venous Disease:** Recommend endovenous thermal ablation (laser and radiofrequency) is the preferred treatment for saphenous and accessory saphenous vein incompetence (Grade 1B) [2]

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[1] Gloviczki P, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg. 2011 May;53(5 Suppl):2S-48S.

[2] American College of Phlebology's Clinical Practice Guidelines: Superficial Venous Disease. 2015. Available at http://www.phlebology.org/wp-content/uploads/2015/03/VaricoseVeinGuidelines3.9.15.pdf

The Agency for Healthcare Research and Quality (AHRQ) recently released a draft evidence review titled "Treatment Strategies for Patients with Lower Extremity Chronic Venous Disease."[3] The AHRQ report was commissioned by Medicare for a July 20, 2016 meeting of the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC). At the MEDCAC meeting, the authors of the AHRQ review noted they had to narrow the scope of the evidence included given the short time they had to prepare the report for the meeting. We recognize that this report may be an input in Washington State's review of varicose veins and want to share the comments we submitted through AdvaMed and those submitted by professional societies to AHRQ highlighting a number of the report's limitations. Since the final AHRQ review is not yet available, we want to make sure you are aware of the limitations highlighted in comments to AHRQ to ensure a comprehensive evaluation of the evidence in this review.

Key limitations of the draft AHRQ review include:

- **Excludes peer-reviewed publications prior to the year 2000.** As articulated in the enclosed comment letter to AHRQ by a coalition of key professional societies, limiting the evidence review to the period after 2000 eliminated the evidence base on which the more recent therapies rest. We recognize the time limits of the review necessitated narrowing the scope of the review, but it is critical that a thorough evidence review acknowledge the evidence published pre-2000.
- **Made the inclusion criterion for the key question on symptomatic chronic venous insufficiency too strict**. Comparative observational studies were only considered if the sample size was greater than 500 subjects. There are multiple studies that the draft review excluded because of the 500 patient limit; these studies meet the rest of AHRQ's rigorous inclusion/exclusion criteria. The majority of these studies track clinical and quality of life outcomes for one year or more and would help further reinforce the durability of more invasive treatment options for CVI patients.
- **Did not include an evaluation of other quality of life measures, such as return to work and return to normal activities**.

We are also including a summary of recent health economic studies to address the cos implications and cost-effectiveness of radiofrequency ablation for treatment of varicose veins.

Author	**Gohel *et al.* 2010**
Title	Cost-effectiveness of traditional and endovenous treatments for varicose veins
Economic Model Type	Markov Model
Country	UK
Time Horizon	5 years
Perspective	UK National Health System

[3] AHRQ draft review available at: http://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/drafts-for-review/lecvd_draft.pdf

[2]Gloviczki P, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg. 2011 May;53(5 Suppl):2S-48S.

Patient Population	Patients with primary unilateral great saphenous vein (GSV) reflux requiring treatment
Discounting	3.5% for costs and outcomes
Treatment Modality	• Radiofrequency ablation • Surgery • Endovenous laser ablation (EVLA)
Key Conclusions	• Radiofrequency ablation performed as an outpatient procedure is likely to be a cost-effective strategy for patients compared to day-case surgery o ICER: £19,000 per QALY (UK ICER threshold per QALY: £20,000) • Radiofrequency ablation performed as an outpatient procedure is likely to be cost-effective compared to local anaesthetic EVLA o ICER: £17,350 per QALY
Sensitivity Analysis	• Univariate sensitivity analyses of uncertainty around parameters including costs and effectiveness

Author	**Kuhlmann *et al.* 2013**
Title	Impact of radiofrequency ablation for patients with varicose veins on the budget of the German statutory health system
Economic Model Type	Markov Model
Country	Germany
Time Horizon	5 years
Perspective	German Statutory Health System
Patient Population	Patients with varicose veins
Discounting	No discounting was considered
Treatment Modality	• World without ClosureFast™ o Surgery o Ultra-sound guided foam sclerotherapy (UGFS) • World with ClosureFast™ o ClosureFast™ o Surgery o Ultra-sound guided foam sclerotherapy (UGFS)
Key Conclusions	• The introduction of ClosureFast™ for the treatment of varicose veins saves costs of about € 19.1 million over a time horizon of five years in Germany. ClosureFast™ • General reimbursement of ClosureFast™ has the potential to be cost-saving
Sensitivity Analysis	• One-way, scenario probabilistic sensitivity analyses to address the uncertainty around input parameters

Author	**Eidson *et al.* 2011**
Title	Economic and outcomes-based analysis of the care of symptomatic varicose veins
Economic Model Type	Non-economic model (Analysis of actual direct costs), retrospective single center, cohort study
Country	US
Time Horizon	6-months follow-up
Perspective	n/a

Patient Population	Patients with symptomatic varicose veins
Discounting	n/a
Treatment Modality	• Radiofrequency ablation o N=100 patients • Surgery o N=100 patients
Key Conclusions	• Seventy-nine percent of the radiofrequency ablation therapies were performed in an outpatient clinic treatment room vs. 100% of surgery being performed in the operating room (OR) setting with 68% of patients requiring at least one night of hospital stay. • Estimated direct cost of performing radiofrequency ablation in the treatment room was $906 compared to total direct cost of $4,241 for open surgery followed by in-hospital stay. • Cost of outpatient surgery was higher compared to outpatient radiofrequency ablation in OR setting ($2,622 vs. $2,533).
Sensitivity Analysis	• n/a

Medtronic appreciates the opportunity to continue to support the HCA in its review of the topics and appreciates the ongoing transparency this agency has undertaken that allows for public comments.

If you have any questions regarding this, please feel free to contact me at (707) 591-2246 or via email at alex.c.au-yeung@medtronic.com.

Sincerely,

[redacted]

Alex Au-Yeung
Sr. Director, Medtronic Health Economics, Policy & Payment
Coronary/APV
Email: alex.c.au-yeung@medtronic.com

From: LIVINGSTON Catherine
To: HCA ST Health Tech Assessment Prog
Subject: Public Comment on Varicose Veins
Date: Monday, October 24, 2016 9:41:09 AM

The PICO clearly defines the population those who have failed conservative management (oddly compression stockings not given as an example), yet I would still be interested in noting how the more invasive procedures compare to ongoing conservative therapy. One other subgroup that is included in the PICO makes this comparison especially pertinent: pregnant women.

The most important outcome for other plans who do not cover these treatments for uncomplicated varicose veins would be the effectiveness of prevention of complication, such as preventing ulcers or cellulitis.

Cat Livingston, MD, MPH
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Health Evidence Review Commission
Oregon Health Authority
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[redacted]