Supplementary Content

Exchange rates: For all non-US nations, the cost estimates have been adjusted to reflect 2019 USD values. Cost estimates were adjusted for inflation and the following exchange rates: 1 AUD = 0.69 USD, 1 Euro = 1.08 USD and 1 pound = 1.24 USD.

Suppl. Table 1a: Search Strategy and Search Terms – Search Strategy 1

<table>
<tr><th colspan="2">Disease Search Terms</th><th colspan="2">Topic Terms</th><th>Guidelines</th></tr>
<tr><th>Term</th><th>Operator separating terms</th><th>Term</th><th>Operator separating terms</th><th>Search Terms</th></tr>
<tr><td>Varicose Ulcer [Mesh]</td><td>OR</td><td>standard of care [Mesh]</td><td>OR</td><td rowspan="8">Varicose ulcer [Mesh]

Guidelines-Specific Filters: Article Types: Congress, Guideline, Practice Guideline, Technical Report</td></tr>
<tr><td>CEAP 6 [Title/Abstract]</td><td>OR</td><td>natural history [Mesh]</td><td>OR</td></tr>
<tr><td>open, active ulcer [Title/Abstract]</td><td>OR</td><td>Epidemiology [Mesh]</td><td>OR</td></tr>
<tr><td>Venous incompetence [Title/Abstract]</td><td>OR</td><td>morbidity [mesh]</td><td>OR</td></tr>
<tr><td>C-class 6 [Title/Abstract]</td><td>OR</td><td>quality of life [mesh]</td><td>OR</td></tr>
<tr><td>active venous ulceration [Title/Abstract]</td><td>OR</td><td>quality-adjusted life years [Mesh]</td><td>OR</td></tr>
<tr><td colspan="2">(Chronic venous insufficiency NOT varicose)</td><td>global burden of disease [Mesh]</td><td>OR</td></tr>
<tr><td colspan="2" rowspan="7">Disease search terms and topic search terms were joined by the operator AND; this search string was joined to guidelines terms by OR</td><td>costs and cost analysis [Mesh]</td><td>OR</td></tr>
<tr><td>technology assessment, biomedical [Mesh]</td><td>OR</td></tr>
<tr><td>expert opinion [Title/Abstract]</td><td>OR</td></tr>
<tr><td>resource utilization [Title/Abstract]</td><td>OR</td></tr>
<tr><td>incremental cost [Title/Abstract]</td><td>OR</td></tr>
<tr><td>ICER [Title/Abstract]</td><td>OR</td></tr>
<tr><td>Wound healing [Title/Abstract]</td><td></td></tr>
<tr><td colspan="5">Overall Search Filters</td></tr>
</table>

- *Publication Dates:* 10 years
- *Species:* Humans
- *Language:* English, French, German, Italian

Suppl. Table 1b: Search Strategy and Search Terms – Search Strategy 2

Disease Search Terms		Topic Terms		Specific Disease Delimiters	
Term	Operator separating terms	Term	Operator separating terms	Search Terms	Operator separating term
(Varicose Ulcer [Mesh]	OR	standard of care [Mesh]	OR	Iliac vein obstruction	OR
CEAP 6 [Title/Abstract]	OR	natural history [Mesh]	OR	May Thurner	OR
open, active ulcer [Title/Abstract]	OR	Epidemiology [Mesh]	OR	Post-thrombotic syndrome	OR
Venous incompetence [Title/Abstract]	OR	morbidity [Mesh]	OR	ilio-caval venous obstruction	OR
C-class 6 [Title/Abstract]	OR	quality of life [Mesh]	OR	Atresia	OR
active venous ulceration [Title/Abstract]	OR	quality-adjusted life years [Mesh]	OR	Ilio-femoral venous thrombosis	OR
(Chronic venous insufficiency NOT varicose)		global burden of disease [Mesh]	OR	Deep venous	OR
		costs and cost analysis [Mesh]	OR	Deep vein	
		technology assessment, biomedical [Mesh]	OR		
		expert opinion [Title/Abstract]	OR		
		resource utilization [Title/Abstract]	OR		

	incremental cost [Title/Abstract]	OR
	ICER [Title/Abstract]	OR
	Wound healing [Title/Abstract]	
Disease search terms, topic search terms, and specific disease delimiters were joined by the operator AND		
Search Filters: None		

Suppl. Table 2: Key Guidelines by Countries of Interest

Specialty Organization	Title	Year	Country/Region
Germany Society for Phlebology	[Medical Compression Therapy of the Extremities with Medical Compression Stocking (MCS), Compression Bandage and Adaptive Compression Systems][*]	2018	Germany
NICE	Varicose veins: diagnosis and management Clinical guideline [CG168][†]	2017	UK
Wound Ostomy Continence Nursing Society (WOCN)	Compression for Primary Prevention, Treatment, and Prevention of Recurrence of Venous Leg Ulcers: An Evidence-and Consensus-Based Algorithm for Care Across the Continuum[‡]	2016	US
Wound Healing Society	Wound Healing Society 2015 update on guidelines for venous ulcers[§]	2016	US
European Dermatology Forum	S3-Guideline on Venous Leg Ulcer Developed by the Guideline Subcommittee 'Diagnostics and Treatment of Venous Leg Ulcers' of the European Dermatology Forum[**]	2016	Europe
Germany Society of Dermatology	[Consensus statement on the symptom-based treatment of chronic venous diseases][††]	2016	Germany
Italian Society of Vascular and Endovascular Surgery and the Italian Society of Phlebology	[Guideline of the Italian Society of Vascular and Endovascular Surgery and the Italian Society of Phlebology][‡‡]	2016	Italy
European Society for Vascular Surgery	Management of Chronic Venous Disease	2015	Europe

[*] *Rabe E, Földi E, Gerlach H, Jünger M, Lulay G, Miller A et al. Deutsche Gesellschaft für Phlebology. Medizinische Kompressionstherapie der Extremitäten mit Medizinischem Kompressionsstrumpf (MKS), Phlebologischem Kompressionsverband (PKV) und Medizinischen adaptiven Kompressionssystemen (MAK). AWMF-Registernummer: 037/005. 31.12.2018. https://www.awmf.org/uploads/tx_szleitlinien/037-005l_S3k_Medizinische-Kompressionstherapie-MKS-PKV_2019-05.pdf*

[†] *NICE. 2013. Varicose veins: diagnosis and management: Clinical guideline [CG168]. Retrieved from https://www.nice.org.uk/guidance/cg168*

[‡] *Ratliff C., Yates S, McNichol L, Gray M. Compression for Primary Prevention, Treatment, and Prevention of Recurrence of Venous Leg Ulcers: An Evidence-and Consensus-Based Algorithm for Care Across the Continuum. Journal of Wound Ostomy Continence Nursing, 2016. 43(4). doi: 10.1097/WON.0000000000000242*

[§] *Marston W, Tang J, Kirsner RS, Ennis W. Wound Healing Society 2015 update on guidelines for venous ulcers. Wound Repair Regen. 2016;24(1):136-144. doi:10.1111/wrr.12394*

[**] *Evidence-based (S3) guidelines for diagnostics and treatment of venous leg ulcers. J Eur Acad Dermatol Venereol. 2016;30(11):1843-1875. doi:10.1111/jdv.13848*

[††] *Stücker M, Debus ES, Hoffmann J, Jünger M, Kröger K, Mumme A., Konsensuspapier zur symptomorientierten Therapie der chronischen Venenerkrankungen Consensus statement on the symptom-based treatment of chronic venous diseases. JDDG Journal der Deutschen Dermatologischen Gesellschaft 2016;14; 575-584. https://onlinelibrary.wiley.com/doi/epdf/10.1111/ddg.13006_g*

[‡‡] *Italian Society of Vascular and Endovascular Surgery and the Italian Society of Phlebology: Guideline SICVE-SIF 2016. Retrieved from http://www.sicve.it/wp-content/uploads/2016/10/R46Y2016S02A0001.pdf*

	Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS)[*]		
International Union of Phlebology	Society for Vascular Surgery and American Venous Forum Guidelines on the management of venous leg ulcers: the point of view of the International Union of Phlebology[†]	2015	International
Association for the Advancement of Wound Care (AAWC) Guideline Task Force	The Association for the Advancement of Wound Care (AAWC) venous and pressure ulcer guidelines[‡]	2014	North America
American Heart Association	Chronic venous insufficiency[§]	2014	US
Society for Vascular Surgery® and the American Venous Forum	Management of venous leg ulcers: Clinical practice guidelines of the Society for Vascular Surgery® and the American Venous Forum[**]	2014	US
Italian College of Phlebology	[Guideline of the Italian College of Phlebology Revised 2013][††]	2013	Italy
German Wound Healing Society	[Local treatment of chronic wounds in patients with risks of PAD, diabetes mellitus, chronic venous insufficiency][‡‡]	2012	Germany
Australian Wound Management Association, New Zealand Wound Care Society	Australian and New Zealand Clinical Practice Guideline for Prevention and Management of Venous Leg Ulcers[§§]	2011	Australia and New Zealand

[*] *Wittens C, Davies NB, Bækgaard N., Broholm A., Cavezzi A., Chastanet S., et al. Management of Chronic Venous Disease: Clinical Practice Guidelines of the European Society for Vascular Surgery. Eur J Vasc Endovasc Surg (2015) 49, 678e737*

[†] *Mosti G, De Maeseneer M, Cavezzi A, Parsi K., Morrison N., Nelzen O., et al. Society for Vascular Surgery and American Venous Forum Guidelines on the management of venous leg ulcers: the point of view of the International Union of Phlebology. Int Angiol. 2015;34(3):202-218.*

[‡] *Bolton L, Girolami S, Corbett L, Rijswijk L.V. The Association for the Advancement of Wound Care (AAWC) venous and pressure ulcer guidelines. Ostomy Wound Manage. 2014 Nov;60(11):24-66.*

[§] *Eberhardt RT, Raffetto JD. Chronic venous insufficiency. Circulation. 2014;130(4):333-346. doi:10.1161/CIRCULATIONAHA.113.006898*

[**] *O'Donnell TF, Passman MA, Marston W, Ennis W, Dalsing M, Kistner R, Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery ® and the American Venous Forum. J Vasc Surg. 2014 Aug;60(2 Suppl):3S-59S. doi: 10.1016/j.jvs.2014.04.049. Epub 2014 Jun 25.*

[††] *Italian College of Phlebology. Guidelines, Revision of 2013. Retrieved from www.aiuc.it/clients/www.aiuc.it/public/files/LineeGuidaCIF2013.pdf*

[‡‡] *Deutsche Gesellschaft für Wundheilung und Wundbehandlung: Lokaltherapie chronischer Wunden bei Patienten mit den Risiken periphere arterielle Verschlusskrankheit, Diabetes mellitus, chronische venöse Insuffizienz.AWMF-Registriernummer 091 – 001. https://www.awmf.org/uploads/tx_szleitlinien/091-001l_S3_Lokaltherapie_chronischer_Wunden_2012-ungueltig.pdf*

[§§] *Australian Wound Management Association and the New Zealand Wound Care Society. 2017. Australian and New Zealand Clinical Practice Guideline for Prevention and Management of Venous Leg Ulcers. Retrieved from https://www.nzwcs.org.nz/images/luag/2011_awma_vlug.pdf*

Healthcare Improvement Scotland (SIGN)	Management of chronic venous leg ulcers: A national clinical guideline [*]	2010	Scotland
NICE	Lower limb deep vein valve reconstruction for chronic deep venous incompetence Interventional procedures guidance [IPG219][†]	2007	UK
Haute Autorité de Santé	[Management of predominantly venous leg ulcer without bandaging. Professional recommendations and economic and public health evaluations from June 2006][‡]	2006	France

Suppl. Table 3: Key Assumptions Supporting the Analysis

DRV accounts for 40% of VLU	• Ilio caval obstruction (ICO) of > 50% noted in 37% of patients with open or healed VLU[§] • 50% ICO obstruction noted in 57.1% of patients with advanced venous disease (of which, 30% had VLUs)[**] • ICO Accounted to 37-52% of all VLU.[††] • 73% of VLU patients noted to have ICO.[‡‡] *Although the mean of the two studies cited would suggest a rate of DRV underlying VLU of 47%, the authors elected to use a slightly conservative assumption of 40%; for patients in whom superficial venous disease is co-existent with deep venous disease, treatment solely of the superficial disease is unlikely to lead to optimal healing of the wound.*
60% of DRV remain unhealed at 6 months with conservative therapy	• 30% and 47% of VLUs, with ICO, healed at 12 months with conservative therapy stenting respectively[§§] • 80% DRV healed at six months, after IVCO stenting[***].

[*] *Health Improvement Scotland (2010)..Management of chronic venous leg ulcers: A national clinical guideline. Retrieved from https://www.sign.ac.uk/assets/sign120.pdf*

[†] *NICE. Lower limb deep vein valve reconstruction for chronic deep venous incompetence: Interventional procedures guidance [IPG219], 2007 Retrieved from https://www.nice.org.uk/guidance/IPG219*

[‡] *Haute Autorite de Sante. Recommendations for Clinical Practice: Management of leg ulcers predominantly venous, excluding dressing. 2006. Retrieved from https://www.has-sante.fr/upload/docs/application/pdf/recommandations_finales_pdf.pdf*

[§] *Marston W, Fish D., Unger J., Keagy B., Incidence of and risk factors for iliocaval venous obstruction in patients with active or healed venous leg ulcers. Journal of Vascular Surgery. 2011. 53(3). doi: 10.1016/j.jvs.2010.10.120*

[**] *Rossi FH, Gama C, Fonseca I, Barros K, Rodrigues T, Francisco I et al. Computed Tomograpy Venography diagnosis of iliocaval venous obstruction in advanced chronic venous insufficiency. Jornal Vascular Brasileiro, 2004, 13(4), 306-311. https://dx.doi.org/10.1590/1677-5449.0067*

[††] *Labovitz J, Gagne P, Penera K, Wainwright S. Nonhealing Venous Ulcers and Chronic Venous Outflow Obstruction A Case Report. J Am Podiatr Med Assoc. 2015;105(6):541-549. doi:10.7547/14-075.1*

[‡‡] *Alhalbouni S, Hingorani A, Shiferson A, Gopal K., Jung D., Novak D., et al. Iliac-femoral venous stenting for lower extremity venous stasis symptoms. Ann Vasc Surg. 2012;26(2):185-189. doi:10.1016/j.avsg.2011.05.033*

[§§] *Lawrence PF, Hager ES, Harlander-Locke MP, Pace N., Jayaraj A., Yohann A., et al. . Treatment of superficial and perforator reflux and deep venous stenosis improves healing of chronic venous leg ulcers [published online ahead of print, 2020 Feb 20]. J Vasc Surg Venous Lymphat Disord. 2020;S2213-333X(19)30534-7. doi:10.1016/j.jvsv.2019.09.016*

[***] *Raju S, Neglen P. High prevalence of nonthrombotic iliac vein lesions in chronic venous disease: a permissive role in pathogenicity. J Vasc Surg. 2006;44(1):136-43.*

	• 61% DRV healed at 6 months after IVCO[*] • Of 26 patients with VLUs, 19 limbs had ICO, 11 of VLUs (58%) healed at 1 week to 8 months (avg – 5 months)[†] • 59% of 36 VLUs healed at 6 weeks and 51% healed at 15 months after ICO stenting[‡] • 2016 Meta-analysis – At 6 months stenting resulted in healing of 70.3% of PTS related DRVs and 86.9% of NIVL related DRVs[§] • In patients with VLUs, endovenous treatment, including superficial venous treatment in 61% of patients and venous stenting in 33% of patients compared to the conservative arm showed healing of 21% in the conservative care arm and 80% in the intervention arm, at 12-months • In patients with VLU, 60% of patients (50 of 84) healed at a mean of 122 days and the remaining patients either never healed (17 of 34, 20%) or healed and then recurred (17 of 34, 20%)[**] *Based on these studies, this analysis conservatively presumes that at an average follow up time of 6 months, 60% of conservatively managed DRV remained unhealed, while 40% were healed.*
DRV recur at a higher rate (36% annually) than VLU without deep venous involvement	• VLU recurrence at 12 months of 36% of patients with deep venous disease compared to only 11% of patients with superficial venous disease[††]
Unhealed VLU is 4.5 times higher than the cost of managing a patient with a healed wound	• Retrospective cohort analysis of 505 patients in The Health Improvement Network (THIN) Database demonstrated that the cost of managing a patient with unhealed VLU is 4.5 times higher than of managing a patient with a healed wound[‡‡]
The useful life of compression therapy systems is 3 months	• Current guidelines recommend long term use of compression therapy even after the ulcer has healed. Manufacturer recommendations for the useful life of compression therapy devices range from 2 to 6 months

[*] *Neglén, P., Hollis, K. C., Olivier, J., Raju, S., Stenting of the venous outflow in chronic venous disease: Long-term stent-related outcome, clinical, and hemodynamic result. Journal of Vascular Surgery, 2007, 46(5). doi:10.1016/j.jvs.2007.06.046*

[‡] *R. George, H. Verma, B. Ram, R. Tripathi The Effect of Deep Venous Stenting on Healing of Lower Limb Venous Ulcers Journal of Vascular Surgery. 2014.*

[§] *Wen-da W, Yu Z, Yue-Xin C. Stenting for chronic obstructive venous disease: A current comprehensive meta-analysis and systematic review. Phlebology. 2016;31(6):376-389. doi:10.1177/0268355515596474*

[**] *Ma H, O'Donnell TF Jr, Rosen NA, Iafrati MD. The real cost of treating venous ulcers in a contemporary vascular practice. J Vasc Surg Venous Lymphat Disord. 2014 Oct;2(4):355-61. doi: 10.1016/j.jvsv.2014.04.006. Epub 2014 Jun 24. PMID: 26993537.*

[††] *McDaniel HB, Marston WA, Farber MA, Mendes R., Owens L., Young ML. et al. Recurrence of chronic venous ulcers on the basis of clinical, etiologic, anatomic, and pathophysiologic criteria and air plethysmography. J Vasc Surg. 2002;35(4):723-8.*

[‡‡] Guest JF, Fuller GW, Vowden P. Venous leg ulcer management in clinical practice in the UK: costs and outcomes. Int Wound J. 2018;15(1):29-37. doi:10.1111/iwj.12814

Assumptions related to cost of medication, skin-substitutes, and diagnostics	• Costs of pain control, topical medications, and systemic therapies are estimated to incur every three weeks, based on authors report of standard practice. • Cost of cellular and tissue-derived products are included only for the US analysis since cost-effectiveness analysis is available only for this cohort. For rest of the countries, it is assumed that autologous skin grafting costs are accounted within inpatient hospitalization costs. • It is assumed that the cost of pathology, radiology, or other specialist medical tests are accounted under physician and clinic visit costs. • Costs of open or endovascular options for the underlying superficial or deep disease were not included in this analysis since health economic literature reviewed focuses on costs associated with conservative management, that is the focus of this analysis

Suppl. Table 4: Costs in 2019 USD

	Australia		*France*		*Germany*		*Italy*		*Spain*		*UK*		*US*	
Cost items per patient	Model Inputs (USD)	Reference	Model Inputs (USD)	Reference	Model Inputs (USD)	Reference	Model Inputs (USD)	Reference	Model Inputs (USD)	Reference	Model Inputs (USD)	Reference	Model Inputs (USD)	Reference
General Practitioner	$52.71	*Cheng Q., 2018*	n/a Unit cost not available		$274.82	*Annual, Purwin, 2010*	n/a		$69.65	*2014, Castilla La Mancha*	$2.92	*J. F. Guest, 2017*	CPT 99203, 99213, 11042, 99212, 97597, C2F2S1, Carter M. J, 2014	
Nurse Practitioner	$43.04	*Cheng Q., 2018*			$1333.98		$14.70	*Lombardia Outpatient tariff l 201ist8*	$31.53		$30.92			
Specialist	$62.89	*Cheng Q., 2018*			n/a		n/a		n/a		n/a			
Community nurse hourly wage rate	$22.71	*Cheng Q., 2018*			n/a		n/a		n/a		$169.42	*J. F. Guest, 2017*		
Clinic visits / Diagnostics	n/a				$707.08	*Cheng Q., 2018*	$19.63	*Lombardia Outpatient tariff list 2018*	$56.52	*2014, Castilla La Mancha*	$105.21			
Total Practitioner cost	n/a		$756.46	Lévy E, 2001	n/a		n/a		n/a		n/a		n/a	
Hospitalization cost (annual)	$13,476.04	Cheng Q, 2018	$242.69	Lévy E, 2001	$ 4,538.58	Purwins, 2010	$ 2,964.00	Allegra C, 2003	683.13	2014, Castilla La Mancha	$ 2,195.31	J. F. Guest, 2017	$ 10,543.00	CPT 603, Carter M. J, 2014
Annual Compression therapy costs	$ 329.17	*Cheng Q., 2018*	n/a		$ 259.06	Annual, M, Gutknecht., 2015	$ 328.86	*M Giovanni, 2019*	$ 108.00	*Vitoria-Gasteiz, 2015*	$ 295.18	*J. F. Guest, 2017*	$ 360.00	*Carter M. J, 2014*
Dressings, bandages	$64.73	*Barnsbee. L. 2018*	n/a		$ 1,547.69	*Annual, Purwins, 2010*	n/a		$ 586.44	*Annual, Calculated, Rubio Terrés C, Domínguez-Gil Hurle A.*	$ 543.69	*J. F. Guest, 2017*	n/a	
Drug, prescriptions			$ 515.67	*Annual, Lévy E, 2001*	$ 1,059.50		$ 129.98	*Allegra C, 2003*	$ 733.32		$ 146.48		$ 146.48	*Carter M. J, 2014*
Skin grafts	n/a		n/s		n/a		n/a		n/a		n/a		$ 1729.57	*CPT code*

For ease of comparison all model inputs are adjusted for inflation and converted to 2019 USD dollars