

Impact case study (REF3)

Institution: University of Hull		
Unit of Assessment: 03 – Allied Health Professions, Dentistry, Nursing and Pharmacy		
Title of case study: Minimally Invasive treatment for varicose veins in the legs gives patients a significantly improved quality of life		
Period when the underpinning research was undertaken: 2006 to date		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Mr Dan Carradice	Senior Lecturer NIHR Lecturer	2017 – present 2012-2017
Prof Ian Chetter Mr George Smith	Professor Senior Lecturer NIHR Lecturer	1999 - present 2017 – present 2012-2017
Mr Tom Wallace	Senior Lecturer NIHR Lecturer	2017 – present 2012-2017
Miss Emma Clarke Miss Tracey Roe	Trials Nurse Trials Nurse	2010 - 2018 2015 - present
Period when the claimed impact occurred: 2014 – ongoing		
Is this case study continued from a case study submitted in 2014? No		
1. Summary of the impact		
<p>University of Hull's research has underpinned new National Institute for Health and Care Excellence (NICE), European and Royal Society of Medicine guidelines on how to treat varicose veins and venous leg ulcers (VLUs). NHS data have shown that the application of these evidence-based guidelines has significantly improved quality of life in over 80% of patients for whom the pain levels are equivalent to a heart attack. The research has led to the first improvements in healing of VLUs utilising minimally-invasive surgery since compression bandaging was introduced in ancient times. Importantly the technique is also cost-effective as early intervention reduces the need in many for more invasive treatments in the future.</p>		
2. Underpinning research		
<p>Varicose vein (VV) and varicose leg ulcer (VLU) treatment aims to reduce hypertension in the veins of the leg. Surgical ligation and stripping was introduced around 1,000AD and, with little refinement, has remained the mainstay of treatment into modern times. This involves making a wound, tying off the diseased vein and stripping it out of the leg, usually during general anaesthetic (unconscious). Ultrasound guided endothermal ablation (ETA) was first introduced in 2000. The aim of this, minimally-invasive treatment, is to access the vein with a needle, and using either laser or radiofrequency energy to produce heat, occluding the vein; all performed under a local anaesthetic (awake).</p> <p>Prof Chetter and Dr Carradice have led a research team of surgeons and nurses at the University of Hull (UoH) since 2006. The team has worked both independently and collaboratively to drive forward understanding of the disease and improve treatment. Key collaborators include: Prof J.Brittenden (University of Aberdeen), Prof B.Campbell (NICE), Prof A.Davies and Dr M.Gohel (Imperial College). The key research topics are:</p>		
Technique Refinement		
<p>Based upon preliminary data from our unit and others, laser ETA appeared to have the most promising results, but a number of important factors remained undefined. The UoH team optimised the quantity and mode of energy delivery; determined how close the treatment could be used to the deep vein to improve efficacy whilst maintaining safety; and how to manage the side tributaries to the main vein. A series of randomised controlled trials (RCTs) were undertaken, e.g. an RCT of immediate versus delayed treatment of tributaries, which proved that immediate treatment is associated with increased quality of life (QoL) and was highly cost-effective [1]. An RCT of buffered versus unbuffered tumescent demonstrated that the former is associated with significantly less pain and improved QoL [2]. Tumescent anaesthesia is when a very dilute local anaesthetic solution is put into the leg, and Hull's work demonstrated that balancing the pH significantly reduces discomfort.</p>		

RCTs to identify the optimal treatment

UoH performed the largest two arm RCTs (HELP1 and HELP2 n=380) comparing surgical ligation with ETA. These proved that both treatments were safe and effective, but that ETA was associated with less pain, lower morbidity, improved early QoL, reduced recovery time and decreased disease recurrence up to 5 years [3]. UoH then worked with a multicentre team to perform the largest three arm RCT (top recruiter NIHR CLASS n=798) [4]. The aim was to compare the three basic modalities of treatment Surgery, ETA and foam sclerotherapy (FS). This study showed that the efficacy of FS was significantly lower than ETA or surgery.

VLU management

The UoH team proceeded to evaluate whether the new techniques could improve outcomes in VLU. They completed a Cochrane review in 2013 which led to a multicentre RCT project (NIHR EVRA n=450) [5]. This trial demonstrated that early minimally-invasive treatment was associated with a significant improvement in healing when compared with delayed treatment, and that early treatment is cost-saving to the NHS. The UoH team then repeated the Cochrane analysis providing the first level 1a evidence to support improved VLU healing following this treatment (due early 2021, delayed due to Covid).

Policy evaluation

The UoH team demonstrated, using hospital-episode statistics, that despite high-quality, evidence-based national guidelines, patients were not receiving the recommended treatments. Following the hypothesis that this was related to the commissioning of care, UoH examined the funding decisions by NHS Clinical Commissioning Groups in England [6]. This study demonstrated widespread non-compliance with the guidelines and identified rationing mechanisms being employed to limit access; this caused significant geographical variation in the quality and access of care.

3. References to the research

1. Carradice D, Mekako AI, Hatfield J, Chetter IC. Randomized clinical trial of concomitant or sequential phlebectomy after endovenous laser therapy for varicose veins. *Br J Surg.* (2009) 96: 369-75
2. Nandhra S, Wallace T, El-Sheikha J, Leung C, Carradice D, Chetter I. A Randomised Clinical Trial of Buffered Tumescence Local Anaesthesia During Endothermal Ablation for Superficial Venous Incompetence. *Eur J Vasc Endovasc Surg.* (2018) 56(5):699-708.
3. Samuel N, Carradice D, Wallace T, Mekako A, Hatfield J, Chetter I. Randomized clinical trial of endovenous laser ablation versus conventional surgery for small saphenous varicose veins. *Ann Surg.* (2013)257(3):419-26.
4. Brittenden J, Cotton SC, Elders A, Ramsay CR, Norrie J, Burr J, Campbell B, Bachoo P, Chetter I, Gough M, Earnshaw J, Lees T, Scott J, Baker SA, Francis J, Tassie E, Scotland G, Wileman S, Campbell MK. A randomized trial comparing treatments for varicose veins. *N Engl J Med.* (2014) 371: 1218-27.
5. Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N, Epstein DM, Nyamekye I, Poskitt KR, Renton S, Warwick J, Davies AH; EVRA Trial Investigators. A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. *N Engl J Med.* (2018) 378(22):2105-2114.
6. Carradice D, Forsyth J, Mohammed A, Leung C, Hitchman L, Harwood AE, Wallace T, Smith GE, Campbell B, Chetter I. Compliance with NICE guidelines when commissioning varicose vein procedures. *British Journal of Surgery Open.* 2018 2(6):419-425.

Grants

The AVSU has been awarded almost £8 million in national and international peer reviewed funding for research into treating varicose veins, claudication, exercise and peripheral arterial disease, including the following major awards:

- NIHR HTA Bypass v Angioplasty in Severe Ischaemia of the Leg (BASIL-2) trial – co-applicant with Prof A Bradbury (Birmingham); 2014 – 2023; £2,024,094
- NIHR HTA Balloon vs Stenting in Severe Ischaemia of the Leg (BASIL-3) trial; co-applicant with Prof A Bradbury (Birmingham); 2015-2021; £1,938,633

- NIHR EME Does Neuromuscular Electrical Stimulation Improve the Absolute Walking Distance in Patients with Intermittent Claudication (NESIC) compared to best available treatment? A Multicentre Randomised Controlled Study; co-applicant with Prof A Davies (London); 2017-2021; £1,073,008

Prizes & awards to members of ASVU

Since 2014, members of the AVSU have won 10 conference prizes including the British Journal of Surgery Research Prize Presentation twice, the Vascular Society of Great Britain and Ireland's Sol Cohen Prize on 2 occasions and the Richard Wood Prize.

4. Details of the impact

The research impacts are multifaceted, manifesting in the development of improved national and International guidelines (4.1), significant improvements in patient treatment and the provision of these services (4.2), whilst delivering economic benefits to medical device companies providing minimally-invasive interventions for varicose veins (VV) and vascular leg ulcers (VLU) (4.3).

4.1 Supporting National & International treatment guidelines

UoH research has been used to underpin national and international treatment guidelines both promoting an increase in the number of patients offered treatment and shaping the recommendations of what that treatment should be. Four UoH studies were cited (including References 1 and 4) as significant sources of evidence for the NICE guidelines updated in 2016 on diagnosis and management of varicose veins (CG168) (**Evidence 1i, ii**). Prior to this, there was inconsistency about which patients were referred for treatment and about which treatments were most appropriate. The 2001 guidance provided the basis for referral only when VV resulted in complications, and at that point open surgery was the standard intervention. The new guidelines, based on UoH work, introduced two key changes: Endothermal ablation (ETA) is now the preferred first line intervention for VV; and that the QoL and cost effectiveness benefits, mean that **the recommendation is for all symptomatic patients to be referred for vascular treatment, irrespective of complications.**

In 2015 the European Society for Vascular Surgery released its own practice guidelines for Europe. The UoH studies were again used to support the preferential use of endothermal techniques over all other treatment options (**Evidence 2**). In 2018 The Royal Society of Medicine released guidelines on the management of VLUs, and using evidence from the EVRA trial (Reference 7), for the first time these guidelines incorporated a recommendation that all patients amenable for endovenous treatment should receive this, and that it should be delivered expeditiously (**Evidence 3**).

4.2 Impact on clinical care and policy implementation

In the UK in 2000 open surgery for VV or VLU accounted for 97% of the surgical procedures undertaken in the UK NHS. By 2019/20 this had dropped to 23%, and ETA had risen to 50% (**Evidence 4**). The revised guidelines, based on UoH work, also served to increase the total number of procedures performed. These had fallen from 55,609 in 1998 to 24,300 in 2012, but rose again to 33,439 by 2016. The global trend has mirrored these findings, but with a significantly higher rate of growth overall than seen in the UK NHS (**Evidence 5**).

The NHS introduced the mandatory collection of Patient Reported Outcome Measures (PROMs) for a number of treatments in 2009, this included for the treatment of VV. This real-world data demonstrated that following the NICE-approved, minimally-invasive, venous treatment discussed above in section 4.1, over 80% (5,260 of 6,575) patients reported significant improvements in QoL in 2018. This compares very favourably against other healthcare interventions and was not only reflected in disease-specific measures, but also the generic health questionnaire, EQ5D, which demonstrated a significant gain in Quality Adjusted Life Years (**Evidence 6i, ii**). These outcomes clearly demonstrate the impact of UoH research on patients, through the adoption into guidelines and thus clinical practice.

UoH policy research has highlighted the barriers in access to care that are present across the UK. This work was included in a recent publication by the All Party Parliamentary Group on Vascular and Venous Disease (**Evidence 7**) and the evidence was quoted during a debate on the floor of the House of Commons on 23rd July 2019 by Ann Clwyd MP. These events and the evidence

based guidelines from the Royal Society of Medicine, co-authored by Dr Carradice, resulted in efforts by NHS England to incentivise the care of these patients through the establishment of an NHS CQUIN (Commissioning for Quality and Innovation) scheme. This will support further improvements in the care of patients with VLU nationally (**Evidence 8**).

4.3 Benefits to the healthcare technologies sector

The evidence from UoH has helped unlock brand new markets for minimally-invasive technology in the management of VV and VLU, especially through working with Medtronic, the world's leading medical technology company. The Senior Director of Global Medical Science | Endovenous states "*Minimally-invasive endovenous treatments of varicose veins for chronic venous disease have revolutionized the treatment of patients globally. The University of Hull's research helped to outline these benefits and drive changes in national guidelines culminating in a change of practice. This technology has subsequently improved the quality of life and outcomes of a large population of patients. As a market leader in catheter based endovenous technologies for treating chronic venous disease, we are focused on innovation and research to expand minimally invasive innovation to improve the quality of life for all patients with venous disease.....Our market estimates that the global opportunity for Chronic Venous Insufficiency (CVI) is over 7 million patients per year, of which nearly 4 million are within the US and Europe.*" (**Evidence 9**) Medical device Industries have continued to refine existing products, Medtronic offer ClosureFast™ and the VenaSeal™, and there has been a proliferation of new companies and technologies all aiming to improve the outcomes and applicability of this treatment paradigm. Thus, there has been a tremendous growth in the global market for these new technologies from a negligible base at the commencement of UoH's research programme in 2006; the revenue from a single modality of treatment (EVLA) in 2016 was US\$ 273.6 million and market analysis predicts that this will grow to an estimated US\$ 550 million by 2026 (**Evidence 10**).

5. Sources to corroborate the impact

Evidence 1i. Varicose veins: diagnosis and management. NICE Clinical Guideline CG168, published 24 July 2013. <https://www.nice.org.uk/guidance/cg168/resources/varicose-veins-diagnosis-and-management-35109698485957>. Updated 2016

Evidence 1ii. NICE news article: Offer less invasive treatments before surgery for varicose veins <https://www.nice.org.uk/guidance/cg168/resources/surveillance-report-2016-varicose-veins-in-the-legs-2013-nice-guideline-cg168-2307804013/chapter/Surveillance-decision>

Evidence 2. Management of Chronic Venous Disease Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS) Eur J Vasc Endovasc Surg (2015) 49, 678-737

Evidence 3. Royal Society of Medicine: Venous Forum. Management of Patients with Leg Ulcers. <https://www.rsm.ac.uk/media/5472579/management-of-patients-with-leg-ulcers.pdf>

Evidence 4. NHS Digital Hospital Episode Statistics database. <https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics>

Evidence 5. Varicose Vein Treatment Market: Endovenous Laser Therapy Market: Global Industry Analysis and Opportunity Assessment, 2016-2026. Future Market Insights. Published April 2017 <https://www.futuremarketinsights.com/reports/varicose-veins-treatment-devices-market>

Evidence 6i. Special topic: A study on varicose vein treatments, Patient Reported Outcome Measures (PROMs) in England, April 2009 to March 2015. Health and Social Care Information Centre, published 11 February 2016. <https://files.digital.nhs.uk/publicationimport/pub19xxx/pub19984/proms-spec-topi-vari-vein-trtm-2009-15.pdf>

Evidence 6ii. Finalised Patient Reported Outcome Measures (PROMs) in England – For Groin Hernia and Varicose Vein Procedure. NHS Digital. Published 14 June 2018. https://files.digital.nhs.uk/A6/CE8A7A/PROMs_GH_VV_Apr17_Sep17%20V2.pdf

Evidence 7. All-Party Parliamentary Group on Vascular and Venous Disease. Venous Leg Ulcers: A Silent Crisis

<https://static1.squarespace.com/static/5981cfcfe4fcb50783c82c8b/t/5da742db4b4d0146eb8b8b9e/1571242723193/Venous+leg+ulceration+2019+web> . (accessed May 2020)

Evidence 8. NHS England 2020/21 CQUIN programme. <https://www.england.nhs.uk/wp-content/uploads/2020/01/FINAL-CQUIN-20-21-Core-Guidance-190220.pdf>

Evidence 9. Testimonial letter. Medtronic
Sr Director Global Medical Science | Endovenous. Plymouth MN, USA

Evidence 10. Varicose Veins Treatment Devices Market to 2025 - Global Analysis and Forecasts by Product, Treatment, End User, and Geography. Research and Markets. Published January 2019. <https://www.researchandmarkets.com/reports/4747989/varicose-veins-treatment-devices-market-to-2025>.