National Institute for Health and Care Excellence

IP1934 Percutaneous deep venous arterialisation for chronic limb-threatening ischaemia

IPAC date: 10 August 2023

The comments have been organised into the following categories:

Comment no.	Page no.	Category
1 to 6	2 to 6	Comments on the draft recommendations, and relating to the unmet need and newly published evidence (sections 1.1 and 1.2)
7 to 10	6 to 7	Comments relating to the scope of the guidance (sections 2.1, 2.2 and 2.5)
11 to 13	7 to 8	Comments relating to the newly published evidence (section 3.1)
14 to 17	8 to 9	Comments on the key efficacy and safety outcomes (sections 3.2 and 3.3)
18 to 19	9 to 10	Comments relating to patient's feedback (section 3.4)
20 to 24	10 to 12	Comments on the committee comments (sections 3.5 to 3.7)

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response
			Comments disagreeing with the main recommendation, and highlighting the unmet need and newly published evidence	
1	Consultee 1	1	I believe this draft report has not taken key evidence into account. 1) The patient selection criteria are very clear, are included in the instructions for use, and have been reported in the PROMISE UK study protocol, as well as the American PROMISE 2 study, just published in the NEJM. The details of the procedure are very clear both in the instructions for use documents as well as the published literature (PROMISE studies). NICE has failed to identify this literature. The PROMISE UK study provided clear details of all procedural steps. The duration of anticoagulation, like any other peripheral arterial procedure, is decided by the treating clinician. This has nothing to do with the specific procedure. There is no evidence regarding duration of anticoagulation post-complex endovascular peripheral arterial procedures; this is not unique for this technology. Please refer to the recently published European guidance on antithrombotics in vascular diseases. The safety/feasibility of the procedure is clearly evidenced in the PROMISE II, PROMISE UK results. Denying patients in the NHS access to this procedure is definitely not something to be taken lightly and does not promote health/well-being in this population.	Thank you for your comment. The draft recommendation has been changed from 'research' to 'special arrangements', and the rationale behind this decision is detailed in 'why the committee made these recommendations'. The PROMISE 2 study and PROMISE UK were listed as ongoing trials in the overview. The PROMISE 2 study was published after the committee made the initial decision, and this study has been added to the overview. The committee has considered the PROMISE 2 study and the interim 6-month results of PROMISE UK (ongoing trial). The committee recognised the uncertainty around the duration of anticoagulation, so this is mentioned in 1.4 as one of the areas for research to focus on.
2	Consultee 2 NHS professional	1.1	- I would urge the committee to re-consider their draft recommendation in few of the consultations and the newly published and recently available evidence. - pDVA using the Limflow device represents the last hope for a very complex group of patients who have exhausted all available options to save their limbs. Without this procedures, these no-option patients are extremely like to end up losing their legs. - I would draw the attention of the committee members that the standardised pDVA procedure using the Limflow system, which is the only device currently used in the NHS, should not be grouped with the non-standardised, custom-made procedures which try to achieve the same outcome and have been published as case series. These non-standardised (Non-Limflow) techniques tend to use devices/materials outside their	Thank you for your comment. Please see response to comment 1. The IP programme issues guidance on procedures rather than individual devices. The committee was aware of different procedure techniques and (CE-marked and non-CE-marked) devices used, and associated limitations. Section 3.8 has been added to the final guidance.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response
			intended instructions for use which consequently negatively impact their outcomes. I would therefore urge the committee to only consider the published evidence on the use of the Limflow system to achieve the pDVA. - Based on our local institutional outcomes, which are included in the PROMISE-II interim analysis shared with the committee, we will find it ethically challenging if we have to deny patients with CLTI the pDVA procedure if they are not part of research. This will create a huge ethical dilemma/moral especially considering the fact that the published data on the natural history of these patients shows that they are extremely like to end up losing their limbs through major limb amputation. Please note that some of the patients we have treated successfully with the Limflow system had lost their other leg already and it was therefore extremely important to offer them pDVA using the Limflow system after exhausting all other options to save their limbs.	
3	Consultee 3 NHS professional	1.1	I was surprised to learn that this was the draft recommendation of the committee, particularly in the context of the surgical procedure "superficial vein arterialisation for chronic limb-threatening ischaemia" receiving the "special conditions" outcome in IPG 736. Percutaneous deep vein arterialisation is a progression and refinement of the surgical technique covered under IPG 736, and is now backed by significantly higher-quality data (see PROMISE-2 trial results which I believe you may now officially consider since its publication in NEJM) so it seems rather strange that the "early iteration" of venous arterialization has been granted "special conditions" whilst the updated, less invasive, more reproducible technique of venous arterialisation remains "research only".	Thank you for your comment. Please see response to comment 1.
4	Consultee 3 NHS professional	1.2	I am not sure where the "different procedure techniques" comment has come from; whilst the committee considered both the "off-the-shelf"/"off-label" pDVA data as well as the Limflow data (the "PROMISE" series of studies), it is the Limflow system alone that has been utilised in UK patients to date, and upon which the thrust of this application is based. The whole premise of the Limflow system is to properly protocolise the procedural technique (and eventually the patient selection) to lead to predictable outcomes. I believe the PROMISE-2 data demonstrates this quite convincingly, with 105 patients across TWENTY different sites	Thank you for your comment. Please see responses to comments 1 and 2.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response
			receiving exactly the same procedural technique, yielding excellent results. Therefore I do not believe that "different procedure techniques" accurately describes any limitations of the available evidence - the PROMISE series of trials demonstrates the utility of exceptionally rigid procedural technique in optimising outcomes across a broad range of operators.	
5	Consultee 3 NHS professional	1.2	At a local level, we are now more clear as to who will benefit from the procedure, and now that the PROMISE-UK trial has completed recruitment, given the excellent outcomes, our team cannot ethically withhold the option of pDVA from patients we are convinced will benefit, simply because we have no ongoing trial to recruit them to. Therefore, we believe that the "can be perfomed under special conditions" outcome would be more appropriate for this review. We will of course continue to audit and publish our individual centre results with rolling analysis of factors predictive of success and technical refinements, and to their credit the Limflow company have remained just as involved with the small number of commercial pDVA cases we have performed since PROMISE-UK closed to recruitment as they did with the trial cases.	Thank you for your comment. Please see response to comment 1.
6	Consultee 4 LimFlow SA	1.1	We kindly ask the committee to reconsider their decision and change the final guidance for this procedure to use “under special arrangements” based on the following key points: 1. New evidence, that was not available during the initial review for the draft guidance, presenting the outcomes of the PROMISE II study with the LimFlow system, has been just published in the New England Journal of Medicine. This evidence and the fact that it was published in such a high impact journal highlight the importance of this novel procedure and the benefits it can bring to ‘no option' CLTI patients who face major amputation and have no traditional endovascular or surgical revascularization options. (details of this study are described in the comments under section 3.1) 2.The patient selection criteria in all the studies with the LimFlow system have been highly consistent and objective. Specifically, in the PROMISE I and PROMISE II studies, an independent committee of vascular surgeons confirmed that all patients undergoing the procedure had been diagnosed with CLTI, Rutherford Classification 5 or 6, and did not have other	Thank you for your comment. Please see responses to comments 1 and 2. CG147 and IPG736 were included in the 'related NICE guidance' section of the overview.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response
			endovascular or surgical revascularisation options. With the evidence available today we believe this procedure should be offered to this specific subset of CLTI patients and not the entire CLTI population. This indication of use is also explicitly described in the LimFlow devices Instructions for Use (IFU). We believe the same criteria can be applied in NHS hospitals under special arrangements requiring that every procedure is approved by the hospitals' Vascular Multi-Disciplinary Team that assesses these patients on a regular basis 3. The percutaneous deep venous arterialisation procedure (or transcatheter arterialisation of deep veins as referred to in recent studies conducted in the US) with the LimFlow system is a highly standardised procedure that has demonstrated >95% technical success in all reported studies. The procedure steps and all required dedicated devices are described in detail in the devices Instructions for Use. In addition, the LimFlow company has well-established training programmes, incorporated in their Quality Management System, and staff in place to ensure all users in the UK are appropriately trained and supported for performing the procedure in a standardised way. 4.The percutaneous deep vein arterialisation procedure with dedicated devices approved for this use by Regulatory authorities should be distinguished in the committee's final guidance decision from other physician-improvised procedures that do not use devices approved for this procedure. 5. We would like to highlight to the committee that the existing NICE guidance on "Superficial Venous Arterialisation and Selective Venous Occlusion for Critical Limb Ischemia", IPG 736, had a decision for use under special arrangements even though the evidence on that procedure is significantly less and of lower quality. This IPG notes that the NICE committee considered as justification of the guidance that "the procedure is only used for people with no other treatment options for arterial reconstruction" We believe the pDVA procedure with the LimFlow system should also be considered in the same context. 6. We would also like to highlight to the committee that the NICE Guidance on Management of Critical Limb Ischemia (CG 147_2018) includes: "1.6.11 Major Amputation Do not offer major amputation to people with critical limb ischaemia unless all options for revascularisation have been considered by a vascular	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response
			multidisciplinary team." Therefore, the pDVA procedure should be considered under special arrangements for eligible people before a major amputation is offered. Restricting the procedure to use only under research will unnecessarily deny a significant number of this frail and deprived population access to a technology that might salvage their limb.	
			Comments relating to the scope of the guidance	
7	Consultee 4 LimFlow SA	2.1	The percutaneous arterialisation procedure with the LimFlow system has been studied only on the subset of people with CLTI that do not have further options for surgical or endovascular revascularisation. We believe the final guidance on this procedure should limit the scope of the condition to this specific population under the special arrangements proposed to NHS hospitals.	Thank you for your comment. Please see response to comment 1. The evidence included in the overview support that this procedure is used for people with 'no-option' CLTI.
8	Consultee 4 LimFlow SA	2.2	We would like to highlight to the committee that for the condition of people with CLTI with no further endovascular or surgical revascularisation options, the only treatment option is best medical management or eventually primary major amputation. The outcomes in this "no-option" population are quite dire as recently described in the meta-analysis by Ghare et al (Outcomes Among Patients With Chronic Critical Limb Ischemia With No Revascularization Option: Systematic Review and Meta-Analysis; J CRIT LIMB ISCHEM 2021;1{3):E85-E92) and major amputation should not be offered unless all other revascularisation options have been considered as clearly stated in the NICE Guidance on Management of Critical Limb Ischemia (CG 147_2018)	Thank you for your comment. Please see response to comment 7. Ghare (2021) does not meet the inclusion criteria. CG147 was described in section 2.2 and included in the 'related NICE guidance' section of the overview.
9	Consultee 4 LimFlow SA	2.2	On all the data provided from the PROMISE studies (PROMISE I, PROMISE II and PROMISE UK), we would like to clarify to the Committee that all 165 patients enrolled in these studies underwent a very standardised step-wise procedure using the LimFlow devices that have been developed, tested and certified specifically for the purposes of performing the percutaneous deep vein arterialisation(pDVA) procedure. As demonstrated in the peer reviewed publications in these high-impact and prestigious journals, there are no safety concerns associated with the pDVA procedures across several healthcare settings when the LimFlow devices have been used. Therefore, the LimFlow procedure and outcomes	Thank you for your comment. Please see response to comment 2.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response
			should not be confused or aggregated with other non-standardised/ physician-modified procedures reported in the literature (Nakama and Cangiano papers) which used other, non-LimFlow, devices outside their Instructions For Use (IFU). The standardised procedural steps with the dedicated LimFlow devices, as used in the PROMISE studies, are also described in detail in our devices' commercial Instructions for Use (IFU) that forms the basis of training on and performing the procedure in both research and non-research settings. The published work and the interim analysis of PROMISE-UK, which is specific to the NHS, demonstrates the LimFlow procedure is safe, feasible, standardised, and efficacious.	
10	Consultee 4 LimFlow SA	2.5	Regarding the devices used to perform the procedure, we would like to note that only the LimFlow system of approved devices includes (i) dedicated arterial and venous catheters to create a connection between a tibial artery and tibial vein and allow a wire to cross (ii) a conical covered stent for creating the arteriovenous fistula with appropriate transition of the blood flow from a smaller vessel into a larger vessel and (iii) a forward cutting Valvulotome to ensure that all the venous valves in the very distal segments of the veins in the foot are rendered incompetent. These devices are critical for a successful procedure and not available in the market in any other similar form. Any non-standardised physician-improvised procedures need to use other sub-optimal devices that are not indicated for this procedure and may compromise patient safety and outcomes.	Thank you for your comment. Please see response to comment 2.
			Comments relating to the newly published evidence	
11	Consultee 2 NHS professional	3.1	- Please note that the six months outcomes of PROMISE-II study (USA study which recruited >100 patients with critical limb ischaemia who had no option to save their limbs) have been recently published. This might have not been available at the time when the committee considered the published evidence - Please note that interim analysis of the PROMISE-UK has been conducted and shared with the committee for consideration	Thank you for your comment. Please see response to comment 1.
12	Consultee 3 NHS professional	3.1	Please also now review the recently-published PROMISE-2 trial data (https://www.nejm.org/doi/full/10.1056/NEJMoa2212754) which comprises over a hundred patients treated with pDVA using the Limflow system. This	Thank you for your comment. Please see response to comment 1.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response
			represents the largest series of venous arterialisation of ANY kind (superficial or deep, open or endovascular or hybrid) published to date.	
13	Consultee 4 LimFlow SA	3.1	We would like to bring to the committee's attention the paper on the PROMISE II pivotal study outcomes of 105 patients at 6 months that was just published on March 30th in the New England Journal of Medicine. The PROMISE II study is a prospective, single-arm, multi-centre study to evaluate the effect of transcatheter arterialization of the deep veins in patients with nonhealing ulcers and no surgical or endovascular revascularization treatment options. The composite primary endpoint was amputation-free survival (defined as freedom from above-ankle amputation or death from any cause) at 6 months, as compared with an objective performance goal of 54%. "Transcatheter Arterialization of Deep Veins in Chronic Limb-Threatening Ischemia" by Mehdi H. Shishehbor et al. ; N Engl J Med 2023;388:1171-80 https://www.nejm.org/doi/full/10.1056/NEJMoa2212754?query=featured_home#author_affiliations&uccLastUpdatedDate=2022-11-21%2013%3A40%3A28.666%20%2B0000&uccLastUpdatedDate=2022-11-21%2013%3A40%3A28.666%20%2B0000 (please note the percutaneous deep vein arterialisation procedure is also referred to as "transcatheter arterialisation of deep veins" in the US based studies) In addition, we kindly ask the committee to consider the report we have provided in confidence on the interim outcomes of the PROMISE UK study with the LimFlow system. The PROMISE UK is a prospective, single-arm, multi-centre study that enrolled patients in 6 NHS hospitals to collect "real-life" clinical data among a population of NHS patients treated with the commercially available LimFlow System to evaluate the ongoing safety and effectiveness of the LimFlow System for performing the percutaneous deep vein arterialization procedure. All 28 patients enrolled in this study had been diagnosed with CLTI Rutherford Class 5 or 6 and did not have any further options for surgical or endovascular revascularisation. Each patient's eligibility was decided by the local NHS vascular multi-disciplinary team and further confirmed by an independent committee in all cases.	Thank you for your comment. Please see response to comment 1.
			Comments on the key efficacy and safety outcomes	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response
14	Consultee 2 NHS professional	3.2	It is important to know that limb salvage procedures, including pDVA, aim to avoid MAJOR (above the ankle) amputations. This is particularly important in patients with no-revascularisation option, in whom pDVA is currently the only available revascularisation option. This should not be mixed with minor/foot amputations which are a common feature of CLTI. - By avoiding major limb amputations, patients maintain their independence which has a positive impact on their quality of life.	Thank you for your comment. 'Reduction in amputation' has been changed to 'reduction in major amputation' in section 3.2
15	Consultee 3 NHS professional	3.2	We aim a little more specifically than simply "improvement in limb perfusion" with pDVA - the key efficacy outcomes would being with speed and completeness of wound healing, as I mentioned in my PEQ.	Thank you for your comment. 'Wound healing' has been added to section 3.2.
16	Consultee 2 NHS professional	3.3	The safety outcomes considered by the committee are the same for any lower limb revascularisation/ limb salvage procedure which aims to save the leg. In our practice we now have effective strategies implemented at various stages starting from patient selection, intraoperatively and finally postoperatively to address these issues.	Thank you for your comment. The committee is pleased to know that the effective strategies have been implemented locally to address the safety issues caused by lower limb revascularisation or salvage procedure.
17	Consultee 3 NHS professional	3.3	Reduced distal tissue perfusion due to steal syndrome leading to worsening gangrene is a linked safety outcome, all as one point. Suffering major adverse cardiovascular events is unfortunately the lot of "no-option CLTI" patients given that the arterial disease in the lower limbs is replicated in their brain and heart; this should not be considered a key safety outcome related to the procedure itself. Indeed, a successful pDVA procedure, by healing a wound (thus eliminating the chronic inflammatory state that is linked with increased risk of coronary events) and preserving a limb (which maintains a patient's ambulatory functions) may well actually REDUCE their risk of suffering a major adverse cardiovascular event.	Thank you for your comment. ‘Major adverse cardiovascular events’ has been removed from section 3.3 of the draft guidance.
			Comments relating to patient’s feedback (section 3.4)	
18	Consultee 2 NHS professional	3.4	We will be happy to facilitate contacts between NICE and some of the patients from the cohort we treated so far if the committee see this helpful	Thank you for your comment. NICE contacted this consultee and found that the patients this consultee refers to took part in research. NICE gains commentaries from people who have had the procedure

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response
				but not those who were part of research (as their experience would be included in the research paper).
19	Consultee 5 NHS professional	3.4	I am emailing on behalf of one of my patient's here at St. Thomas Hospital, London in regards to percutaneous deep venous arterialisation for chronic limb-threatening ischaemia. I include his feedback below, as he was enrolled in the PROMISE-UK trial, sponsored by LimFlow. He doesn't have access to a computer so has requested to feedback through me. He has consented for me to give his name which is [redacted]. I include a direct quote below. 'I'm glad I've had it done, or I would have had no other choice but to lose my leg and I don't know what I would have done if that had happened. I don't know how I would have coped with wheelchairs etc as I like getting out and about. I wouldn't be me. 'Life is back to normal and I feel a lot better than went I went into hospital before the procedure, I am very grateful to the nurses and surgeons at the hospital' If you need any more information please do not hesitate to ask.	Thank you for your comment and for sharing the person's positive experience of having this procedure as part of research.
			Comments on the committee comments (sections 3.5 to 3.7)	
20	Consultee 2 NHS professional	3.5	- Many of the extreme lower limb revascularisation procedures are performed as staged procedures. This is because of the extensive and multi-level nature of advanced peripheral arterial disease in patients with CLTI. This should not be considered as a drawback, on the contrary should be seen as an adequate strategy to maximise the outcomes of these procedures while minimising the impact on patients who are too frail to have everything done in one setting. - Patients who undergo lower limb revascularisation should be enrolled in close surveillance programmes to identify those who have threatened limb vascularity. They should then undergo all possible salvage procedures to restore adequate circulation to the limb/ foot, which is by definition the purpose of the surveillance programmes. This is not unique to pDVA, it is the same for patients with open bypass surgery, as well as those who underwent lower limb endovascular treatment in our institution.	Thank you for your comment. Section 3.5 has been changed.
21	Consultee 3	3.5	The requirement for reinterventions must be considered in the context of both the natural progression of the underlying disease, and the	Thank you for your comment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response
	NHS professional		invasiveness of the reintervention. DVAs develop at different speeds in different patients, and most reinterventions to maintain patency of the circuit and increase the speed of DVA maturation can be considered in a similar vein to routine oil and filter changes in a car - minimal hassle, and a necessary step to keep the car on the road. Aside from in the most multimorbid and frail patients we have performed pDVA for, the majority of reinterventions have been done under local anaesthesia on a daycase basis.	Section 3.5 has been changed. The procedure is usually (but not only) done using general anaesthesia, as stated in section 2.5.
22	Consultee 2 NHS professional	3.6	- Again, as per my comments on 3.5, these points are not unique to pDVA alone. Patient selection is of paramount importance in any open or endovascular limb salvage procedure to ensure patients receive the treatment which is optimal to them considering their individual circumstances/clinical condition/ anatomy etc.. - As per my response to 3.5, patients with CLTI who undergo a revascularisation procedure, either open or endovascular, should be followed until their wounds have healed. Afterwards they received infrequent follow up appointments and also have a direct access to foot clinics if they feel their foot condition started to worsen. This is not unique to pDVA and should be seen as optimal patient care, not a drawback or limitation.	Thank you for your comment. Section 3.6 is specifically relevant to this procedure, but it does not mean that this comment has to be unique to this procedure.
23	Consultee 3 NHS professional	3.6	I believe this comment was made in the context of a combined UK experience of less than thirty patients - of course at this stage we are following patients up for life, but this is: 1) to allow us to learn the long term implications of the pDVA procedure, and 2) because patients with chronic limb threatening ischaemia require continuous follow-up anyway - even after a healed wound - to ensure that no further areas of skin are at risk of breakdown, no osteomyelitis is present etc.	Thank you for your comment.
24	Consultee 2 NHS professional	3.7	- Similar to many other vascular procedures, either open or endovascular, there is a learning curve with pDVA. From our local experience, the first case took 4-5 hours to perform. This decreased quickly until we routinely now perform it in an average of 2.5 hrs, which is what a routine below-knee endovascular treatment takes especially for multi-level disease.	Thank you for your comment. Section 3.7 specifically relates to this procedure, but it does not mean that this comment has to be unique to this procedure.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response
			- pDVA could be performed by clinicians who have adequate endovascular skills/ training. This is usually a team made of both endovascular surgeons and vascular interventional radiologists. This is a set up similar to most of the other endovascular procedures such as aortic stent-grafts, hybrid lower limb revascularisation, carotid stenting etc. This is therefore not unique to pDVA and should not be seen as a limitation.	

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."