National Institute for Health and Clinical Excellence

PAD
Guideline Consultation Comments Table
9/04/12 – 24/04/12

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	British Society of Interventional Radiology	6.00	Full			The BSIR recognises the need for advice in the management of peripheral vascular disease in England and Wales and welcomes the development of these guidelines. Their publication is timely as it coincides with the reorganisation of vascular services and ongoing efforts by both the BSIR and VS to raise the profile of PAD and improve the quality of care for these patients.	Thank you for your comment. We are encouraged by the stakeholders comments.
SH	British Society of Interventional Radiology	6.01	Full			As a general concern it is noted that the evidence base on which a number of conclusions are based appears to be limited and weak with regard to the assessment of endovascular treatment used in the treatment of PAD. This presumably reflects the limited number of published randomised controlled studies on the subject available to the GDG, but nevertheless may introduce important bias by omitting data obtained from numerous other well constructed and more recent cohort studies. The practice of vascular interventional radiology continues to evolve rapidly and the guideline may fail to reflect what is already established practice. To some readers, the guideline may therefore appear outdated.	Thank you for your comment. We acknowledge that there was a lack of evidence for some of the review topics in the guideline. For most intervention evidence reviews, RCTs were included as they are the most robust type of study design that could produced an unbiased estimate of the intervention effects. However, where the GDG believed RCT data would not be appropriate, other lower levels of evidence such as cohort studies were searched for. This is detailed in the protocols in Appendix C. Cohort studies were not specified by the GDG for the endovascular treatment review. With regards to rapidly evolving techniques, the NICE Interventional procedures programme undertakes such evaluations and

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							details can be found on the NICE website.
SH	British Society of Interventional Radiology	6.02	Full			Failure of the GDG to acknowledge the use of objective measures of vessel patency following interventional procedures is questionable. Although a precise relationship between patency and symptoms may be difficult to demonstrate, return of symptoms following restenosis or reocclusion of a previously treated vessel is recognised by all of those involved in the treatment of PAD. Patency is more readily and accurately measurable and is widely cited. To ignore this data is likely to be viewed as a significant shortcoming in arriving at the conclusions drawn by the GDG.	Thank you for your comment. The GDG had considerable discussion regarding the relevance of patency as an outcome measure and reconsidered this in the light of the stakeholders comment. The GDG was primarily interested in clinical and cost effectiveness. The GDG concluded that the value of patency as a proxy outcome was only relevant where the physical effects of the treatments being compared were sufficiently similar that a measure of patency based upon degree of re-stenosis was a similar hurdle for both treatments and where there was sufficient evidence to link this proxy outcome to clinical benefits. After reconsideration the GDG decided, whilst recognising these limitations, to consider patency in the comparison of bare metal stents and drug eluting stents but not for the other comparisons. The explanation regarding patency in the methods section and the section relating to this comparison have been rewritten as a result of this decision.
SH	British Society of Interventional Radiology	6.03	Full			Recently presented randomised data strongly suggests that drug-eluting stents offer significantly improved patency in the superficial femoral artery and it is important that the GDG acknowledges the likely impact of this development in improving clinical outcomes for these patients.	Thank you for your comment. The evidence from the trials was reviewed and the recommendation was based on the clinical and cost effectiveness. After reconsideration the GDG decided, whilst recognising these limitations, to consider patency in the comparison of bare metal stents and drug eluting stents but not for the other comparisons. The explanation regarding patency in the methods section and the section relating to this comparison have been rewritten as a result of this decision.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	British Society of Interventional Radiology	6.04	Full			I have to commend the GDG for producing this piece of work to attempt to address issues relevant to UK clinical practice in PVD. They have grappled with different treatment areas and techniques for which there is some form of evidence base. However, this evidence base is often limited and poor quality as is repeatedly highlighted throughout. In terms of the endovascular techniques reviewed, such a review will always fail to reflect new and emerging techniques, especially as there is usually less evidence to support their use.	Thank you for your comment. The GDG recognise that the evidence base can be limited. In terms of the quality of studies, this is based on GRADE criteria. Studies were downgraded for a variety of reasons including risk of bias (i.e. unclear allocation concealment, blinding, unexplained heterogeneity). The GDG did prioritise clinical areas and any techniques that have not been included may be considered in future updates of this guideline.
SH	British Society of Interventional Radiology	6.05	Full			Many of the conclusions drawn are based on the weak and poor quality evidence available, particularly when looking at comparisons with endovascular techniques. As a result the levels of uncertainty are very high for many of the conclusions from the modelling processes that were performed. That said this is often acknowledged openly (e.g. p172 line 27). Because the evidence for newer techniques is likely to be even weaker than for established techniques I have concerns that some area of progressive UK practice have not been adequately addressed, such as newer and emerging techniques (e.g. drug eluting balloons, drug eluting stents, and SFA stenting generally) such that the current guidance is conservative and maintains the status quo, and will not reflect likely changes in practice occurring across the UK in the next 5 – 10 years.	Thank you for your comment. The studies included in this review question were all randomised controlled trials. As such, they represent the highest quality of clinical evidence. Based on GRADE criteria, specific outcomes from these trials were subject to a risk of bias due to factors such as unclear allocation concealment and unexplained heterogeneity. They were all downgraded for blinding, which is not possible in an intervention study of this type. In terms of newer techniques, the GDG did review the evidence on drug eluting stents. We were unfortunately unable to cover all areas and focused upon those that stakeholders and GDG members initially suggested as critical areas to address. This did not include drug eluting balloons although we acknowledge that these may be shown to be of value in the near future.
	British Society of Interventional Radiology	6.06	Full	23		I have problems with the fact that patency was not considered an appropriate means of	Thank you for your comment. The GDG had considerable discussion regarding the

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						assessing outcome. Whilst it is undoubtedly a surrogate endpoint, it is a very commonly reported endpoint in many important studies, and so ruling it out may result in important outcome data being overlooked. Also in the patient groups where intervention has been performed patency is very relevant to patient symptoms and quality of life, and so is a very valid way to assess the likely outcome of these interventions, and the need for reintervention.	relevance of patency as an outcome measure and reconsidered this in the light of the stakeholders comment. The GDG was primarily interested in clinical and cost effectiveness and concluded that the value of patency as a proxy outcome was only relevant where the physical effects of the treatments being compared were sufficiently similar that a measure of patency based upon degree of re-stenosis was a similar hurdle for both treatments and where there was sufficient evidence to link this proxy outcome to clinical benefits. After reconsideration the GDG decided, whilst recognising these limitations, to consider patency in the comparison of bare metal stents and drug eluting stents but not for the other comparisons. The explanation regarding patency in the methods section and the section relating to this comparison have been rewritten as a result of this decision.
	British Society of Interventional Radiology	6.07	Full	92 & 93		There are limitations alluded to in the document about using DUS as first line imaging investigation. Many cases will need repeat imaging (usually with MRA if that is possible) to clarify areas difficult to image with DUS- such as the aorto-iliac segments. This therefore risks the duplication of imaging that would be costly. Though DUS alone may be more cost effective (CE) compared to MRA alone, if a significant proportion of DUS examinations result in a need for MRA, then patients may be better served by an MRA first strategy, and overall this is likely to be more cost effective- see below. I agree that most units have access to MRA, and there is a statement (p93) that it is used much less frequently than DUS- I am unclear	Thank you for your comment. The GDG considered that Duplex US was a suitable first line investigation in most cases and may avoid the need for more expensive and invasive investigations in some cases.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						about the evidence for this statement. If good quality MRA is available (and can be used in an individual patient) then most clinicians would agree that in terms of a one stop option this is likely to provide the most reliable assessment of the peripheral vessels. Duplex may be used to assess equivocal lesions- e.g. disease of the common femoral artery, that may alter treatment decisions.	
SH	British Society of Interventional Radiology	6.08	Full	122		Issues around the likely uptake of exercise by reluctant patients could be considered/highlighted. Also a pragmatic approach is needed for any research questions on the actual benefits of asking patients to exercise- either supervised or not, as, though there is little doubt that if exercise is taken up by patients improvements are likely, it is the level of take up that is often the problem.	Thank you for your comment. We agree that some patients may be reluctant to exercise, but there is clear evidence of benefit from this non-invasive and cost-effective intervention and the GDG, wised to make a clear recommendation in its favour. In the research recommendation we have included that uptake of exercise programmes and level of participation in the outcomes.
SH	British Society of Interventional Radiology	6.09	Full	210		Much of the data on the use of stents is out of date and does not relate to the use of stents designed specifically for use in the SFA. Iliac stenting is less contentious and practice is reasonable mature. With SFA stents however, the data is much less mature, and older papers contain stents that are no longer either available or would not be considered appropriate for use in the SFA. The latest results focus on patency, and with improvements in stent design, and modern antiplatelet therapy the outcomes are now beginning to show improvement compared to the more outdated data.	Thank you for your comment. The evidence from the trials was reviewed and the recommendation for selective over primary stenting was based on the clinical and cost effectiveness. We agree that this is an area where there is new evidence emerging and any further publications will need to be considered in future reviews of the guidance.
SH	British Society of Interventional Radiology	6.10	Full	214		The data on the Zilver stent show some of the most promising results for drug eluting stents in the SFA, and whilst this data has been reviewed	Thank you for your comment. We have added further discussion regarding the relationship between patency and clinical benefit and the

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						issues over pricing are very relevant as the cost of these stent is a a major driver for cost-effectiveness, and it is likely that in many centres cost will be lower, or will become lower as the stent is used more widely. As patency has been underplayed by the GDG the promising results for all the SFA stents, both bare metal and drug eluting, have likely been overlooked or greatly diminished.	outcome of patency has been considered for this comparison (see sections 3.1.1, 9.6.3 and 10.4.3). Having considered all the evidence regarding patency the GDG considered that there was not robust evidence that any patency benefit resulted in a significant clinical benefit or financial savings that would justify the additional cost of the devices.
SH	British Society of Interventional Radiology	6.11	Full	215		I would also question the statement that Target lesion revascularisation was not significantly different between the stents- I think that the Zilver trial has demonstrated significantly better results in the patients receiving the drug eluting stent.	Thank you for your comment. We included target lesion revascularisation at two years within the evidence review, which was of borderline significance. The GDG discussed the results of TLR, and concluded that there was still unclear evidence of clinical benefit.
SH	British Society of Interventional Radiology	6.12	Full	23		The GDG should not shy away from accepting both the obvious benefit and usage of patency. Firstly it is counter-intuitive, and flies in the face of both common sense and clinical experience, to suggest that patency is not important in clinical practise. For those of us who sit with, and treat patients, patency is very important. We know when talking to claudicants whether their treated limb has maintained patency. If patency is not maintained, either at the treated segment or elsewhere, their claudication returns. Not only is it common clinical sense, but it is well reflected in the literature. For example Karsh [(1)]very nicely shows correlation of failed clinical outcome and patency, either at the treated site (60%), or elsewhere. And it is that failure at the treatment site that makes patency	Thank you for your comment. The GDG had considerable discussion regarding the relevance of patency as an outcome measure and reconsidered this in the light of the stakeholders comment. The GDG was primarily interested in clinical and cost effectiveness and concluded that the value of patency as a proxy outcome was only relevant where the physical effects of the treatments being compared were sufficiently similar that a measure of patency based upon degree of re-stenosis was a similar hurdle for both treatments and where there was sufficient evidence to link this proxy outcome to clinical benefits.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						such an important outcome in clinical trials. In addition patency is important in critical limb ischaemia. Dick et al[(2)] show this very elegantly, and they comment "clinical outcome can be improved by means of close follow-up and repeated target extremity revascularisation (TER)'. Indeed they comment "repetition of TER improved clinical success in diabetic patients not only significantly, but also to the same extent as non-diabetic patients". Patency is a frequent outcome measure in research for several reasons. The clinical measurement of success can be very difficult and the current outcome assessments are insufficiently granular to detect subtle but important change. However patency can easily be measured, is reproducible, can be compared between studies, and affects clinical outcome. For the GDG to ignore patency denies them and the public access to the important research in this area. 1. Karch LA, Mattos MA, Henretta JP, McLafferty RB, Ramsey DE, Hodgson KJ. Clinical failure after percutaneous transluminal angioplasty of the superficial femoral and popliteal arteries. J Vasc Surg. 2000;31:880-887. 2. Dick F, Diehm N, Galimanis A, Husmann M, Schmidli J, Baumgartner I. Surgical or endovascular revascularization in patients with critical limb ischemia: Influence of diabetes mellitus on clinical outcome. J Vasc Surg. 2007;45:751-761.	Whilst the GDG accepts that there is likely to be a correlation between patency and clinical outcome the issue is that, particularly where the treatments concerned differ in their nature, that correlation may not be strong or consistent. In fact the Karch paper to which you refer expressly states "Anatomic patency at the PTA site is irrelevant if symptomatic improvement is not achieved." and they found that "… a significant number of clinical failures occurred despite maintained anatomic patency at the PTA site". This was considered by the GDG to be of even greater concern where the physical effects of the treatment (for example angioplasty, stent or surgical treatment) may not be directly comparable. Similarly the Dick paper specifically rejected patency as a relevant outcome measure when comparing methods of revascularisation for critical ischaemia, choosing instead to use a composite clinical outcome. After reconsideration the GDG decided, whilst recognising these limitations, to consider patency in the comparison of bare metal stents and drug eluting stents but not for the other comparisons. The explanation regarding patency in the

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							methods section and the section relating to this comparison have been rewritten as a result of this decision.
SH	British Society of Interventional Radiology	6.13	Full	119		The GDG should take note of the reality of trying to engage patients in exercise programmes and make comment about the limitations of this in their guideline. The reality is that patients are not only poorly compliant but do not wish to participate in exercise programmes.	Thank you for your comment. The GDG agree that some patients may be reluctant to exercise, but there is clear evidence of benefit from this non-invasive and cost-effective intervention and the GDG wished to make a clear recommendation in its favour. In the research recommendation we have included that uptake of exercise programmes and level of participation in the outcomes.
SH	British Society of Interventional Radiology	6.14	Full	119-210		The guidelines treat too simplistically the decision to use either simple angioplasty or stent to manage SFA disease and therefore ask the wrong question. Simple angioplasty is universally used to manage short stenoses of the SFA and this is reflected in the type of disease included in the stent trials. It is only for lengthy stenoses or occlusions that a decision needs to be reached as to whether to use angioplasty or stent. If a stent is to be used then he majority of practitioners will intend that from the start, i.e. they will place the stent to restrict embolisation and then post –dilate. Some however will perform an angioplasty in complex disease and then decide to stent if the appearances are poor. Little of this differentiation unfortunately can be found in the literature. I am surprised that the GDG could not find the correct advice to guide them regarding the appropriate studies to review when looking at the use of stents to manage SFA disease in patients suffering from intermittent claudication.	Thank you for your comment. The evidence from the trials was reviewed and the recommendation for selective over primary stenting was based on the clinical and cost effectiveness. The relative risk of clinical failure (i.e. re-intervention) was based upon the Schillinger trial which was the only trial with suitable data for this parameter. The GDG membership consisted of those who treat peripheral arterial disease and applied their knowledge and experience to the interpretation of the evidence base. The GDG accepts that there will be exceptional cases in which a clinician will need to use their judgement there was no evidence identified or provided in the stakeholder responses that have made it possible to define a subgroup in whom primary stent would be a cost effective use of NHS resources.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						Were a cardiologist to place an iliac stent in the coronary arteries I doubt that a cardiology GDG would take the results seriously. Similarly, should a paper appear using aortic grafts to perform femoro-tibial bypass, I doubt that this group would have taken that data seriously. Similarly this group really needs to be critical about which SFA stent papers to review. This guideline includes several papers that review the use of the balloon expandable Palmaz stent in the SFA (e.g. Grimm et al, Vroegindewij, Cejna etc). Such practice never did make sense since they are easily crushed in this position and no one in current clinical practice would even consider using one. Similarly there are a number of papers that review the use of iliac stents placed in the SFA (e.g. Krankenberg, Greenberg) or devices that have never been used (e.g. Vascucoil Greenberg). Again no one practising currently would even consider such practice and all this means that much of the bibliography is neither credible nor clinically relevant. The SFA is known to be a hostile environment for stents and only over the last few years have sufficiently robust devices been specifically made for this clinical practise, Therefore the GDG should restrict its review to contemporary studies – Laird and Schillinger. The contemporary data clearly show that when stents that are specifically designed to be placed in the SFA are compared to simple angioplasty in patients on dual antiplatelet drugs with complex SFA disease, the patency (and therefore the clinical outcomes in claudicants – see above) is improved. This means that Recommendation 11 (p210) is incorrect – patency is very important to claudicants and	

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						metal stents improve the patency of managing complex SFA disease compared to angioplasty.	
SH	British Society of Interventional Radiology	6.15	Full	211-215		This section on SFA includes an irrelevant reference. The Rastan article looks at patients with disease below the knee, not SFA intervention. In addition they use stents that are designed for the coronary arteries and which do not have a licence for tibial intervention.	Thank you for your comment. The GDG has reconsidered this paper in the light of the comments received. Whilst symptoms due to infra-popliteal disease were not excluded from the scope we agree that invasive treatment of disease in this location for IC would be unusual in NHS practice and have therefore excluded this trial from the consideration of intermittent claudication. It has been included in the CLI section, but considered separately from the evidence on femoro-popliteal disease.
SH	British Society of Interventional Radiology	6.16	Full	214		If the GDG had approached Cook who make the Zilver stent they could have supplied a cost-effectiveness analysis undertaken in my own unit. In addition they have submitted other scientific articles on the same subject. As can be imagined, the analysis is sensitive to price. In the UK most units, including our own, are paying the same price as a bare metal stent. At that price the modelling clearly shows that since re-intervention is significantly reduced because of the reduced restenosis rate, the Zilver stent has significant long term cost savings. I would hope that either the GDG approaches Cook, or that the company willingly submit these data. This is a very valuable tool that is of great benefit to claudicants.	Thank you for your comment. We undertook a call for evidence and received a submission from Cook (referenced as Dake 2011 in the full guideline). However, the evidence which Cook submitted to us did not include cost-effectiveness and the literature searches did not yield any evidence relating to the cost-effectiveness of bare metal versus drug eluting stents. The data submitted by Cook showed borderline significance for the outcome of TLR at 2 years and provided no details of the revascularisation procedures required. They did report an unvalidated 'clinical benefit index' but this was not considered a valid measure of quality of life by the GDG. The GDG considered that there was no robust evidence that drug eluting stents lead to lower rates of revascularisation or greater quality of life compared to bare metal stents and therefore no reason to believe that they are

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							more cost-effective.
SH	British Society of Interventional Radiology	6.17	Full	214		Is the Rastan (2011) paper appropriate in this section as this looked at infra-popliteal interventions.	Thank you for your comment. The GDG has reconsidered this paper in the light of the comments received. Whilst symptoms due to infra-popliteal disease were not excluded from the scope we agree that invasive treatment of disease in this location for IC would be unusual in NHS practice and have therefore excluded this trial from the consideration of intermittent claudication. It has been included in the CLI section, but considered separately from the evidence on femoro-popliteal disease.
SH	British Society of Interventional Radiology	6.18	Full	214		The recommendation contradicts the data available from the Zilver RCT. The Zilver stents in the RCT did show both significantly better event free survival (freedom from; death, amputation, *clinically driven* Target Lesion Revascularisation, target limb ischaemia requiring surgical re-intervention) at 12 months – i.e. the *clinically driven* safety end-point, and significantly better patency at 12 months.	Thank you for your comment. The evidence for this review question was based on the trial received from Cook Medical in response to our call for evidence (referenced as Dake 2011 in the full guideline). This trial included a double randomisation; only those patients who failed initial angioplasty were randomised to the bare metal versus drug eluting stent segment of the trial. At 12 months, all cause mortality and device related mortality were not statistically significant. The difference in patency rates was significantly in favour of drug eluting stents; this has been added to the guideline. We have added further discussion regarding the relationship between patency and clinical benefit to the linking evidence to recommendations section for this recommendation (see 3.1.1, 9.6.3 and 10.4.3.)
SH	British Society of Interventional Radiology	6.19	Full	215		The document states that "Target lesion revascularisation was also reported. The GDG	Thank you for your comment. Target lesion revascularisation was reported by Rastan

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						were less interested in this non-clinical parameter, but note that it too was not significantly different between the two types of stent". Part of lack of interest is, I presume, due to the unwillingness of the GDG to engage with the importance of patency. However, in the Zilver study re-intervention was *clinically driven* TLR. This means that the patients are undergoing less re-intervention and there are cost savings to the system.	(2011). This evidence has been removed (see comment 6.17 above). Following stakeholder consultation, we included 24 month data for target lesion revascularisation and patency. The GDG discussed this evidence and concluded that there was still insufficiently robust evidence of clinical benefit to make a recommendation of drug eluting stents over bare metal stents.
SH	British Society of Interventional Radiology	6.20	Full	215		The GDG suggest that there is 'also the potential for other side effects from the drug' If the group think that this is a credible suggestion then perhaps they should reference those papers showing toxicity from the drug in clinical trials of coronary and peripheral intervention and compare that against all the articles that have failed to show such toxicity.	Thank you for your comment. This section was not referring to any specific evidence but simply highlighting the potential risks and benefits and thus the need for appropriate clinical evidence as the use of pharmaceutical agents has the potential for harm as well as benefit. However, we accept that there is no current evidence of toxicity and this has been removed.
SH	British Society of Interventional Radiology	6.21	Full	248		The GDG includes two irrelevant articles in the SFA section. The Rastan article looks at patients with disease below the knee, not SFA intervention. In addition they use stents that are designed for the coronary arteries and which do not have a licence for tibial intervention. The DUDA papers review a drug eluting stent that never received a licence, has never been used clinically outside research, and therefore has no credibility or clinical relevance to these guidelines.	Thank you for your comment. The GDG has reconsidered this paper in the light of the comments received. Whilst symptoms due to infra-popliteal disease were not excluded from the scope we agree that invasive treatment of disease in this location for IC would be unusual in NHS practice and have therefore excluded this trial from the consideration of intermittent claudication. It has been included in the CLI section, but considered separately from the evidence on femoro-popliteal disease. Heterogeneity was actually increased when the BES trials were removed from the outcome of ABPI at 1 year (for the studies of patients with intermittent

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							claudication due to femoro-popliteal disease - person randomised data). The GDG did not agree that the DUDA trials should be excluded. It was thought that many devices undergo clinical trials before they have all the regulatory approvals etc. If we are considering that SFA stent is being treated as a class rather than looking at every device individually it would seem entirely illogical to only include published results on devices that are tested and then go on to receive regulatory approval and become a commercial success. This would simply encourage companies to carry out multiple trials on different iterations of the same device and selectively seek regulatory approval and market those that have the best results, whilst ignoring the results of those that have less favourable results.
SH	St Jude Medical UK Ltd.	7.00	Full	38	34	All options may also include non-traditional vascular procedures such as spinal cord stimulation (Ref: Augustinsson 1985; Amann 2003; Jivegard 1995; Tedesco 2004; Colini-Baldeschi 2011	Thank you for your comment and references. As Spinal cord stimulation was the subject of the NICE TA 159 and was not recommended for ischaemic pain unless in the context of a trial, we could not include this in our evidence review. Where the stakeholder feels there is new evidence for spinal cord stimulation, this should be discussed with the NICE technology appraisal team.
SH	St Jude Medical UK Ltd.	7.01	Full	41	3	The multidisciplinary team should include a pain specialist	Thank you for your comment. The GDG did not feel that they could be prescriptive in the membership of the MDT and thought that this should be agreed locally.
SH	St Jude Medical UK Ltd.	7.02	Full	41	30	The pain management service should include an interventionalists	Thank you for your comment. The GDG did not feel that they could be prescriptive in defining what a pain management service

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							should include and thought that this should be agreed locally.
SH	St Jude Medical UK Ltd.	7.03	Full	41	36	The vascular multidisciplinary team should ideally include a pain interventionalists in an attempt to avoid a decision to amputate due to severe ischaemic pain	Thank you for your comment. The GDG did not feel that they could be prescriptive in the membership of the MDT and thought that this should be agreed locally.
SH	St Jude Medical UK Ltd.	7.04	Full	54	7	The patient's problems with pain and restricted mobility emphasises the need for a pain management specialist involvement	Thank you for your comment. The section the stakeholder refers to relates to information requirements for people diagnosed with PAD. Therefore, it was not thought appropriate to include pain specialist involvement in that chapter. The role of the pain specialist is considered in chapter 11 of the full guideline.
SH	St Jude Medical UK Ltd.	7.05	Full	54	15	The patient's fear of increased pain necessitates the intervention of a pain specialist	Thank you for your comment. The role of the pain management specialist is considered in section 11 of the full guideline. The section the stakeholder refers to relates to information requirements for people diagnosed with PAD.
SH	St Jude Medical UK Ltd.	7.06	Full	222	15	It is important that all options are considered to avoid an amputation including those that may not be traditionally considered a vascular treatment e.g. spinal cord stimulation	Thank you for your comment. As spinal cord stimulation was covered in the NICE TA 159 we were unable to include this procedure in our evidence review.
SH	St Jude Medical UK Ltd.	7.07	Full	259	11	It is important that the PAD patient has access to a recognised interventional pain specialist	Thank you for your comment. The GDG agreed and have recommended referral to a pain specialist.
SH	St Jude Medical UK Ltd.	7.08	Full	259	32	St Jude Medical believes that there is adequate supportive clinical evidence of the efficacy of spinal cord stimulation on the alleviation of ischaemic pain meriting a mention in this section (not withstanding the suggestion of the need for further clinical studies to prove cost-effectiveness)	Thank you for your comment. As spinal cord stimulation was the subject of the NICE TA 159, we were unable to include this procedure in our evidence review. As such we can not comment on its use for ischaemic pain. We would encourage the stakeholder to contact the NICE technology appraisal team where they believe there is new evidence available that warrants are review of the TA.
SH	International Neuromodulation Society	8.00	Full	259	35	TAG 159 – SCS IS recommended as a treatment option for ischaemic pain IN the	Thank you for your comment. As spinal cord stimulation was the subject of the NICE TA

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						context of a clinical trial. In selected patients such as defined by the EPOS trial. (SCS Match) It is inconsistent of NICE to quote this in TAG 159 and then to barely acknowledge the role of SCS in pain relief (and in some instances tissue preservation) in this GDG.	159, we were unable to review the evidence relating to SCS. Therefore, we are unable to comment on the role of SCS in pain relief.
SH	International Neuromodulation Society	8.01	Full	264	Box on chemical sympathectomy	To invoke the placebo effect to explain the pain relief after a chemical sympathectomy and not consider the placebo effect of revascularisation procedures is incorrect. I agree that RCT does need to be done. A collaborative approach between vascular centres and pain management team experienced in managing CCLI and chemical sympathectomy is required.	Thank you for your comment. We agree that all interventions may have a placebo effect. However, the role of the RCT is to address placebo. The evidence reviews and recommendations for revascularisation were based on RCT data. Whereas, this was not the case for chemical sympathectomy. We are encouraged by the stakeholder's support of seeking RCT evidence for chemical sympathectomy. We also agree that a collaborative approach is required in the management of CLI, which prompted the GDG to make the recommendation.
SH	International Neuromodulation Society	8.02	FULL	General	chapter 11	Unreconstructable CLI exists as a clinical entity even in vascular units who believe they can be effective with extreme distal grafting. There can be no suitable conduit or vessel to graft onto. Patient may suffer from Thromboangitis obliterans or severe Raynaud's or scleroderma. Many of these patients can be managed with spinal cord stimulation. Indeed in my practice of SCS over 20 years in my personal case series of CCLI in "Buerger's disease", none of my patients have lost the target CCLI limb that responded to an initial trial period of SCS. Many of my atherosclerotic patients with CCLI and SCS survive until their eventual death with limb retained. You only appear to offer pharmacological pain relief, referral to pain management service	Thank you for your comments. As spinal cord stimulation was the subject of the NICE TA 159, we were unable to review the evidence relating to SCS. Therefore, we are unable to comment on the role of SCS in pain relief.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						(although similarly constrained in practical procedures as is this GDG) or amputation. I believe that you should state more clearly that Pain management which may include SCS should be available in refractory unreconstructable cases providing EPOS inclusion/exclusion criteria are followed with demonstrable pain relief and an appropriate rise in TcPO2 after a week of trial SCS stimulation. I agree that an RCT of SCS and usual care versus usual care alone with appropriate outcomes and cost effectiveness study needs to be done. I intend to design with my colleagues a feasibility study. It is essential that the vascular units work collaboratively with the Pain centres that are experienced with CCLI pain management and SCS treatment and follow up. This is an important question to be answered.	
SH	International Neuromodulation Society	8.03	Full	General	chapter 11	Once this multidisciplinary collaboration is established I would feel confident in designing similar clinical, cost effectiveness studies in patients with grade 3 limbs with CCLI and comparing long term outcomes after distal grafting or SCS. But for now I am content with those that are deemed unreconstructable who fulfil EPOS inclusion/exclusion criteria to be involved in a clinical trial	Thank you for your comment. We are encouraged by the stakeholders support in undertaking research for this important issue.
SH	Bard Limited	9.00	Full			Obstructive atherosclerotic disease of distal aorta and Iliac arteries is preferentially treated with Endovascular Techniques. Endovascular first strategy is recommended for all TASC A-C lesions. The European Society of Cardiologists(2011) Guidelines on the diagnosis and treatment of peripheral artery disease recommend that stenting as a primary therapy	Thank you for your comment. The GDG reviewed the evidence in these areas and concluded that primary stenting (as opposed to selective stenting) was not proven to represent the most cost effective use of resources other than for complete iliac occlusion.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						should be considered not only for common Iliac occlusions but also stenoses,stating that stenting in the Iliac arteries compares favourably to surgical revascularisation	
SH	Bard Limited	9.01	Full			Increasing number of RCT demonstrate the superiority of Superficial Femoral Artery (SFA) stenting compared to angioplasty for the treatment of intermediate length SFA lesions for lifestyle limiting claudicants.It is well documented the challenges posed to the interventionalist when treating the SFA.The improvement in clinical success has been associated with selection of a stent designed specifically for this territory and licensed for use in the superficial femoral and proximal popliteal region. Data now exists which provides long term follow up on lifestyle limiting claudicants with SFA disease. Laird et al in their study "Nitinol stent implantation vs. Balloon angioplasty for lesions in the SFA and proximal popliteal of patients with claudication:Three year follow up from the Resilient "published Journal Endovascular Therapy 2012, observed that freedom from TLR at three years was significantly better in the stent group than PTA 75.5%vs 41.8%respectively as was clinical success 63.2%for the stented group against 17.9% for angioplasty alone. Primary stent insertion in the SFA when an SFA specific stent is selected demonstrates an improvement in long term outcomes compared to angioplasty alone. The guidelines in their current format do not appear to support this strategy for patients with lifestyle limiting claudication.	Thank you for your comment and reference. We have not included the Laird study as it was published after our final cut-off date for the final literature search (January 2012).
SH	Bard Limited	9.02	Full			Increasing number of RCT demonstrate the	Duplicate comment. See comment above.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						superiority of Superficial Femoral Artery (SFA) stenting compared to angioplasty for the treatment of intermediate length SFA lesions for lifestyle limiting claudicants.It is well documented the challenges posed to the interventionalist when treating the SFA.The improvement in clinical success has been associated with selection of a stent designed specifically for this territory and licensed for use in the superficial femoral and proximal popliteal region. Data now exists which provides long term follow up on lifestyle limiting claudicants with SFA disease. Laird et al in their study "Nitinol stent implantation vs. Balloon angioplasty for lesions in the SFA and proximal popliteal of patients with claudication:Three year follow up from the Resilient "published Journal Endovascular Therapy 2012, observed that freedom from TLR at three years was significantly better in the stent group than PTA 75.5%vs 41.8%respectively as was clinical success 63.2%for the stented group against 17.9% for angioplasty alone. Primary stent insertion in the SFA when an SFA specific stent is selected demonstrates an improvement in long term outcomes compared to angioplasty alone. The guidelines in their current format do not appear to support this strategy for patients with lifestyle limiting claudication.	
SH	Bard Limited	9.03	Full			Consideration of the benefit Drug Eluting Balloons (DEB) in the treatment of peripheral arterial disease has not been included in the draft guide lines.Studies have demonstrated a significant reduction of neo-intimal proliferation compared to standard angioplasty.Primary patency for DEB is significantly better than	Thank you for your comment. We were unfortunately unable to cover all areas and focussed upon those that were suggested as critical areas to address during the scoping phase of guideline development. Therefore, the issue of drug eluting balloons was not reviewed. This could be an area for

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						POBA ,this was confirmed in three RCT- Fem-Pac,Thunder and Levant 1 in the SFA.The benefit of DEB has been replicated in the Impact Ampherion Deep prospective registry which observed a 61% restenosis reduction in BTK. The significant reduction of restenoses and subsequent TLR and the likely health economic benefit, warrants more attention the impact DEB will have on the treatment of PAD.	consideration in a future update of the guideline.
SH	Bard Limited	9.04	NICE	10	22 & 25	*Advice on exercise is the norm for patients with IC, however recent data from the Mimic Trial has demonstrated that patients with Aortoiliac disease and fem pop disease placed on a Supervised exercise programme and received angioplasty experienced significant improvements in average walking distances and ABPI, those improvements were maintained over 2 years (the duration of the study).The patients included in this group were those who suffered from mild to moderate Intermittent claudication.* *If the Guidelines as recommended by this document are adopted they should not mandate that all patients will need to complete an exercise programme before they are considered for Endovascular treatment due to the evidence available.*	Thank you for your comment. The MIMIC trial was included as part of the clinical evidence review and was used to inform the utility estimates included in the economic model, along with all other relevant studies which met inclusion criteria for this question. An in depth analysis of the costs, benefits and quality of life associated with exercise (supervised and unsupervised) and angioplasty (with primary and selective stent placement) as both primary and secondary treatment options, found that supervised exercise followed by angioplasty with selective stent placement is the most cost-effective strategy for the treatment of patients with intermittent claudication. Please refer to Appendix K of the full guideline for the methods and results of this study, and to better understand the way in which data from the MIMIC trial was used to inform this recommendation.
SH	Bard Limited	9.05	NICE	11	5	*The current practice in Aorto –Iliac Stenoses is to save iliac stenting for Flow limiting dissection flaps or poor results after primary angioplasty.* *In femoro-popliteal disease the majority of patients included in the clinical trials have been*	Thank you for your comment. The evidence from the trials was reviewed and the recommendation for selective over primary stenting was based on the clinical and cost effectiveness.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						patients who experience lifestyle limiting claudication Rutherford Category 3. The Resilient, Zilver PTX and Absolute trial have shown that these patients benefited from primary stent insertion compared to angioplasty. *If the Guidelines as recommended by this document are adopted, provision needs to made for those patients who should be referred for primary stent insertion of the SFA, as Level 1 evidence exists to support this.*	
SH	Bard Limited	9.06	NICE	11	8	*This is the choice most Interventional Radiologists make.*	Thank you for our comment.
SH	Bard Limited	9.07	NICE	11	10	*There is no mention of DES or Covered stents, which have sufficient supporting evidence and should therefore be included.*	Thank you for your comment. Drug eluting stents were reviewed by the GDG and were not recommended based on the evidence. Covered stents were not prioritised for this guideline. However, it may be considered in future updates of this guideline where stakeholders identify it as an issue.
SH	Bard Limited	9.08	NICE	15	9	*The proposed trial should also include the use of Drug Eluting Balloons (DEB) as initial research indicates that patency rates are superior with DEB in the infra-geniculate arteries.*	Thank you for your comment. Drug eluting balloons was not prioritised as a technology within the guideline. Therefore we could not recommend it as an area to be considered within the research recommendation.
SH	Bard Limited	9.09	NICE	17	11	*Due to the funding and resourcing for this trial, care and guidance must be issued, to ensure there is not an unintended consequence of slowing down the adoption of new technology.*	Thank you for your comment. This is outwith the remit of the guideline group to issue guidance on this.
SH	Vascular Society	10.00	Full document - NICE	10	1.5.1	**A. Supervised exercise** 1.5.1 Offer a supervised exercise programme to all people with intermittent claudication *'belief that lifestyle interventions have a positive impact on disease outcomes, and unrealistic expectations of the outcome of surgical*	Thank you for your comment. We have found this comment difficult to understand/interpret. We regret we are unable to provide a response. We would refer the stakeholder to the NICE public health behavioural change guideline. We hope the stakeholder is in support of our research recommendation.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						interventions. Much of the research has been conducted on the subpopulation of people with peripheral arterial disease who have been referred for surgical intervention, but little evidence is available on the majority of people diagnosed with peripheral arterial disease in a primary care setting. Research is required to further investigate attitudes and beliefs in relation to peripheral arterial disease, interventions that might influence these and how these may have an impact on behavioural changes in relation to risk factors for peripheral arterial disease, attitudes to intervention and clinical outcomes.' A community-based randomised controlled trial is required to compare the long-term clinical and cost effectiveness of a supervised exercise programme and unsupervised exercise. The trial should enrol people with peripheral arterial disease-related claudication, but exclude those with previous endovascular/surgical interventions.	
SH	British Pain Society	11.00	Full	General		The GDG acknowledge the importance of pain relief and its effects on QoL. Overall however we feel that the involvement of the pain specialist is delayed and the options available to the therapist are unfairly limited. It would be wise to review the timing of the involvement of the pain specialist as well as the steps recommended before that.	Thank you for your comment. We feel the recommendation was not intended to delay patients from the pain specialist. We have amended the recommendation, identifying when the patient should be referred (see recommendation number 26 in the full guideline and 1.6.9 in the NICE version). The GDG did not specifically cover the treatment options available for pain specialist and were aiming recommendations at the acute management of pain. We do not feel that we have limited the options of a pain specialist.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							The GDG were unable to recommend a specific timeframe for referral as we did not review the evidence for this. The GDG took a similar approach to other recommendations, such as referral for CLI. There are a number of reasons for this. The GDG were of the opinion that referral should be made on an individual basis depending on symptoms and patient need.
SH	British Pain Society	11.01	Full	41	29	The therapeutic options for a pain specialist are very limited after failure of strong opioids. Yet no further recommendations are made is this intentional?	Thank you for your comments. The GDG did not specifically look at the options available for the pain specialist but intended the question to cover the acute management of ischaemic pain, with a referral when appropriate. The GDG do not feel that we have restricted the options for the pain specialist. This area could be included in a future update of the guideline where stakeholders identify it as an issue.
SH	British Pain Society	11.02	Full	41	32	The limitation of the offer of a chemical sympathectomy to a trial adds a further limitation to the therapeutic options for pain relief in a difficult group of patients. While evidence is lacking for chemical sympathectomies we note it is also lacking for opioids as well as anticonvulsants and antidepressants. Those have not been banned. We urge strongly a reconsideration of the ban on chemical sympathectomies especially in view of the costs quoted for an amputation procedure. The cost of a chemical sympathectomy quoted in the tariff is a gross exaggeration of the actual procedure cost. The solution should be to revise the tariff rather than	Thank you for your comments. The GDG acknowledge that there is a lack of evidence around the options for peripheral arterial disease. We disagree that we are banning the use of chemical sympathectomy but rather are aiming to stimulate further research in this important area. The GDG came to a majority consensus about restricting chemical sympathectomy to use within a clinical trial. We have further expanded our linking evidence to recommendations section to explain the reasons for this recommendation (see section 11.2.3). The costs quoted were taken from the

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						ban the intervention based on a false cost. We would suggest chemical sympathectomy should be considered after discussion between surgeons and pain consultants on a case by case basis A trial of local anaesthetic sympathectomy is always an option first prior to neurolytic.	Hospital Episode Statistics, which we regularly use when considering costs for all treatments. The costs are average costs of procedures and treatments.
SH	British Pain Society	11.03	Full	41	35	Do not offer major amputation to people with critical limb ischaemia unless all options for revascularisation have been considered by a vascular multidisciplinary team. This assessment team should include a pain specialist particularly for patients where pain is a major issue	Thank you for your comment. The GDG did not feel that they could be prescriptive in the membership of the MDT and thought that this should be decided locally.
SH	British Pain Society	11.04	Full	182	15	While we recognise that SCS is not included in this review we would like to point out that the costs of amputation quoted here were not available at the TAG 159 for SCS and as such make SCS trial at least an attractive option to avoid the ongoing costs of an amputation	Thank you for your comment. As spinal cord stimulation was the subject of the NICE TA 159 and not recommended for ischaemic pain, we could not include the procedure within our evidence review. We will pass the stakeholders comments on to the NICE technology appraisal team.
SH	British Pain Society	11.05	Full	235	Table	The GDG state It is difficult to make a blanket recommendation for all patients with CLI. Why do they feel it is possible to make a blanket recommendation for the treatment of pain from CLI?	Thank you for your comment. We acknowledge the stakeholders comment but disagree. The GDG considers all available evidence for each clinical question and then makes as strong a recommendation as possible. This principle is identical for all questions, but as the evidence varied between the two questions the stakeholder refers to, the conclusion also varied.
SH	British Pain Society	11.06	Full	236	Table	Patient choice must be part of the decision making process. Does this imply that if a patient chooses to have a trial of chemical sympathectomy or SCS as they should be granted that choice or is patient choice only limited to the surgical options?	Thank you for your comment. We agree that patient choice is a central part of the decision making process. If the patient wishes to undergo chemical sympathectomy as part of a clinical trial then this should be offered after full discussion of all treatment options.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	British Pain Society	11.07	Full	262	Table	If no cost effectiveness data was available for any of the drug options for pain on what basis were strong opioids prioritised before cheaper options such as antidepressants. Who do the GDG propose will prescribes and manages the tolerance, opioid induced hyperalgesia, and hypogonadotrophic hypogonadism that can occur with high doses of strong opioids?	Thank you for comment. We have considered the stakeholders comment. The GDG came to a consensus recommendation on the preference for strong opioids based on their clinical experience and knowledge. The GDG did not feel it appropriate to recommend who should be responsible for the prescription and management of pain treatment. The GDG has amended the recommendation to include the clinical scenarios when a patient should be referred to a pain specialist.
SH	British Pain Society	11.08	Full	262	Table	We suggest that a pain specialist is an integral part of the assessing MDT. That pain treatment options should be discussed and individualised similar to surgical therapeutic options. As it stands the guidance runs the risk of driving patients to very high dosed of opioids before they are allowed to see a pain specialist who would then have to manage insurmountable difficulties related to tolerance and hyperlagesia.	Thank you for your comment. The GDG did not feel that they could be prescriptive in the membership of the MDT and that this should be determined locally. The GDG have considered the stakeholders comments and revised the recommendation to include criteria for when a patient should be referred to a pain specialist.
SH	British Pain Society	11.09	Full	259	36	We notice that ketamine has not been considered as a therapeutic option; we feel that there is enough evidence to justify use of Ketamine in ischaemic leg pain. Graham Hocking, Michael J. Cousins. Ketamine in Chronic Pain Management: An Evidence-Based Review. Anesth Analg 2003;97:1730 –9. The authors concluded that ketamine has a potent dose- dependant analgesic effect in clinical ischemic pain but with a narrow therapeutic window. Alison C. Mitchell, Marie T. Fallon. A single infusion of intravenous ketamine improves pain relief in patients with critical limb ischaemia:	Thank you for your comments and references. Ketamine was not considered within the evidence review as the GDG felt is should only be prescribed by a pain specialist. The aim of the recommendations was to provide guidance on the acute management of pain whilst the patient was waiting for revascularisation, amputation or referral to a pain specialist. The clinical and cost effectiveness of ketamine in the management of ischaemic pain may be an area for a future review of this guideline, where stakeholders identify it as an issue.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						results of a double blind randomised controlled trial. Pain 2002; 97 (3): 275-281	
SH	Neuromodulation Society of UK & Ireland	12.00	Full	37	33	Patients require information on their pain management as well as the items listed. Pain is the principal presenting symptom in IC.	Thank you for your comment. The GDG agreed with the stakeholder comment and have amended the recommendation on information requirements to include information on pain (see recommendation 1 in the full version of the guideline).
SH	Neuromodulation Society of UK & Ireland	12.01	Full	39	11	As above required in Full Guidelines	Thank you for your comment. The GDG agreed with the stakeholder comment and have amended the recommendation on information requirements to include information on pain (see recommendation 1 in the full guideline).
SH	Neuromodulation Society of UK & Ireland	12.02	Full	40	12	Supervised Exercise Programme is recommended in the management of IC based on low or very low quality evidence. It is also the subject of a recommendation for a trial (at 4.2). There is an inconsistency here in recommending a procedure with unknown duration of effectiveness.	Thank you for your comment. The studies included in this review question were all randomised controlled trials. As such, they represent the highest quality of clinical evidence. Based on GRADE criteria, specific outcomes from these trials were subject to a risk of bias due to factors such as unclear allocation concealment and unexplained heterogeneity. They were all downgraded for blinding, which is not possible in an intervention study of this type. However, RCTs were thought to represent a poor estimate of real-world adherence to exercise. This information could not be found in other trial designs or from registry data. Therefore, estimates of adherence to exercise were based on expert opinion. The probabilistic model used to inform this recommendation took into account uncertainty surrounding estimates of efficacy and

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							adherence. The results indicate that even with extremely wide confidence intervals, supervised exercise represents a highly cost-effective intervention. Please refer to Appendix L of the full guideline for a detailed report of the methods and results used to inform this recommendation. Given the surprising lack of knowledge into long-term adherence to each exercise programme, the GDG thought that this was an important area for future research. The results of this research could be used to inform future guidance.
SH	Neuromodulation Society of UK & Ireland	12.03	Full	41	32	Chemical Sympathectomy preceded by a diagnostic block with local anaesthetic can provide significant improvement in patients' pain symptoms. Excluding this option commits the patient with chronic pain of ischaemic origin, which is not amenable to revascularisation, to dependence on drugs with little evidence of efficacy for this condition and significant adverse side effects. The guideline will commit more patients to amputation, as no other pain management options remain available to them. Amputation has well-recognised morbidity of persistent post-amputation chronic pain.	Thank you for your comment. The issue of chemical sympathectomy was discussed at length by the GDG and we acknowledge the stakeholders comments. The majority view of the GDG was that they could not currently recommend chemical sympathectomy without RCT evidence. The GDG did not find any evidence that chemical sympathectomy reduced amputation. The linking evidence to recommendation section (section 11.2.3 of the full guideline) has been expanded to provide more rationale for the recommendation. The GDG recommended a research trial to identify the benefits and risks of chemical sympathectomy for people with critical limb ischaemia and set this as a high priority research recommendation, which we hope the stakeholder supports.
SH	Neuromodulation Society of UK & Ireland	12.04	Full	41	37	Amputation should not be considered before a trial of spinal cord stimulation has been considered by a pain management multidisciplinary team. NICE TAG 159 does recommend the use of SCS as an option for	Thank you for your comment. As spinal cord stimulation was subject of a TA we were unable to include the procedure within our evidence review. We have referred to the TA 159 recommendation within the introduction of

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						pain management in CLI within a clinical trial. This statement from TAG 159 should be included in this guideline.	the pain chapter (see section 11.2.1 of the full guideline).
SH	Neuromodulation Society of UK & Ireland	12.05	Full	124	21	Naftidrofuryl Oxalate is recommended in the absence of good quality evidence of efficacy on the basis that the GDG consider that it could be tried if other management options were ineffective.	Thank you for your comment. We disagree that there is inconsistency in the recommendations. Naftidrofuryl was considered in the context of managing intermittent claudication and was as recommended based on clinical and cost effectiveness data in the NICE TA 223. In contrast, spinal cord stimulation was only recommended for ischaemic pain as part of a clinical trial and we could not include this within our review.
SH	Neuromodulation Society of UK & Ireland	12.06	Full	125	2	Naftidrofuryl Oxalate is recommended in the absence of good quality evidence of efficacy on the basis that the GDG consider that it could be tried if other management options were ineffective. Similar criteria should be considered for other options for management including trial of lumbar sympathectomy. Some patients may not wish to proceed to amputation for their pain management without a trial of more conservative measures such as lumbar sympathectomy or trial of spinal cord stimulation. There is inconsistency in the basis of the recommendations here and an omission of patient preferences.	Duplicate. See comment above.
SH	Neuromodulation Society of UK & Ireland	12.07	Full	181	15	The costs of amputation and follow on costs are considerable. These costs should be evaluated against the costs and effectiveness of Spinal Cord Stimulation that has been shown to improve pain management and increase limb	Thank you for your comment. As spinal cord stimulation was the subject of the NICE TA 159, we were unable to include the procedure within our clinical and cost effectiveness review.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						salvage. This comparison with the long-term costs of amputation was not made in the NICE TAG 159 and has been omitted from this evaluation.	
SH	Neuromodulation Society of UK & Ireland	12.08	Full	259	22	Pain management is very important in the effective management of patients with CLI. Spinal Cord Stimulation (SCS) has been shown to relieve pain in patients with CLI and there are data suggesting that limb salvage is also improved by using SCS in selected patients. This is a different indication to the remit of the NICE TAG 159 that focused on management of neuropathic pain.	Thank you for your comment. As spinal cord stimulation was the subject of the NICE TA 159, we were unable to include SCS in our evidence review and unable to comment on its effectiveness.
SH	Neuromodulation Society of UK & Ireland	12.09	Full	261	4	The high reference costs for Chemical Sympathectomy do not reflect actual acquisition costs of the procedure to the NHS so a bias in the GDG's consensus economic evaluation has been introduced.	Thank you for your comment. In order to maintain consistency across England and Wales, the NICE reference case requires that only list prices or reference costs are used. In cases where acquisition costs are typically much different, this is taken into consideration. The reference cost for chemical sympathectomy was adjusted to account for the proportion of these procedures which are carried out as day cases; although aware that there is variability across the NHS, the GDG thought that the resulting cost estimate roughly reflected expected costs.
SH	Neuromodulation Society of UK & Ireland	12.10		263	11.2.3 (box)	The GDG make unsupported consensus statements advising on analgesia using drugs and recommend that patients should be referred to a Pain Management Specialist before considering amputation. Therapeutic options for managing these patients in a specialist unit are then limited again by a consensus statement advising against the use of a trial of lumbar sympathectomy or consideration of a trial of spinal cord stimulation. Both procedures can be	Thank you for your comment. We disagree that we have limited the options with the recommendations made. The GDG debated the issue of chemical sympathectomy at length and due to reasons captured within the linking evidence to recommendations section (see section 11.2.3) decided only to recommend in the context of a trial. The GDG believed that by recommending further research into chemical sympathectomy, a firm

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						effective, can be assessed by a trial procedure and are less costly than amputation with follow-on costs.	decision can be made as to whether to support the procedure or not. We were unable to include spinal cord stimulation in our review as there is a recommendation in TA 159.
SH	Neuromodulation Society of UK & Ireland	12.11		264	11.2.3 (box)	The GDG make various unsupported negative consensus statements on the use of lumbar sympathectomy in managing CLI. Fluoroscopic guided needle placement is not a new technique. Fluoroscopy has been the standard technique used by pain management specialists for over twenty years. Regional variations in access to this treatment do not mean that it is ineffective in managing the pain of CLI. The GDG is correct to be concerned that its recommendations will lead to patients in severe pain, refractory to standard analgesics being denied the option of a trial of effective treatment. There is inconsistency in the GDG's pragmatic approach to a trial of Naftidrofuryl Oxalate to be evaluated over a set time scale and denying patients the option of a trial of analgesia from lumbar sympathectomy. The statement made about the placebo effect applies to all therapies and is not unique to interventions for pain management.	Thank you for your comment. The evidence review looked for evidence from RCTs and observational studies comparing chemical sympathectomy to other pain options (see Appendix C for the review protocol). Unfortunately, no evidence was found to support the use of chemical sympathectomy in CLI. As such, we do not believe that an unsupported consensus statement has been made. The GDG were of the opinion that evidence should be available for this procedure before they could make a recommendation for its use (please refer to section 11.2.3 of the full guideline). This rationale was applied to other areas of the guideline, for example bypass or angioplasty. The GDG have made a high priority research recommendation, which it hopes will stimulate research in this area. With regards to Naftidrofuryl, the recommendation was based on the clinical and cost effectiveness from the TA, and relates to a different procedure for a different indication. Therefore, we do not feel that the approach is inconsistent. We agree that the placebo effect applies with all therapies and is not unique to pain management procedures. However, in the other interventions covered within the

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							guideline, the recommendations were supported by randomised controlled trials, which address the placebo effect.
SH	Neuromodulation Society of UK & Ireland	12.12	Full	272	1	Tables 102, 103, 104 highlight the very high costs of amputation and follow-on care. Some of these could be avoided by the use of spinal cord stimulation (SCS) in patients with evidence of cutaneous tissue perfusion ($TcPO_2$) in the mid range that improves after a trial of SCS.	Thank you for your comment. As spinal cord stimulation was the subject of the NICE TA 159 we were unable to include SCS within our evidence review.
SH	Neuromodulation Society of UK & Ireland	12.13	Full	275	1	The decrease in EQ5D following amputation is noted together with the high costs, suggesting that amputation is not a cost effective procedure. The intervention continues to be recommended on a pragmatic basis. Interventions that are less costly should be permitted prior to proceeding to amputation. These should include a trial of lumbar sympathectomy and a trial of spinal cord stimulation in selected patients following MDT assessment including pain specialists.	Thank you for your comment. The reasons for our recommendation on chemical sympathectomy are given in section 11.2.3 of the full guideline. We were unable to review spinal cord stimulation as it is covered in the NICE TA 159. For these reasons, we did not include the costs within the guideline.
SH	Gloucestershire Hospitals NHS Foundation Trust	13.00	NICE Version	Page 6	4	**Information requirements for people with PAD:** The guidance suggests that all people with PAD should be given information on how they can access support for dealing with depression and anxiety. I would suggest that it is made clear in the guidance that this information should be in writing, but that there is no obligation to discuss this with all patients in a consultation. It would be inappropriate to do so in many instances.	Thank you for your comment. We agree that patient information should be given in a variety of formats including as written material. We have referred to the NICE guideline on Patient Experience, which details good practice when communicating with patients.
SH	Gloucestershire Hospitals NHS Foundation Trust	13.01	NICE Version	Page 6	26	**Diagnosis:** It is suggested that people with PAD should be assessed using structured questioning. I would recommend clarification here. I hope the	Thank you for your comments. The GDG did not intend to recommend a structure template or a specific questionnaire. We have amended the wording of the recommendation

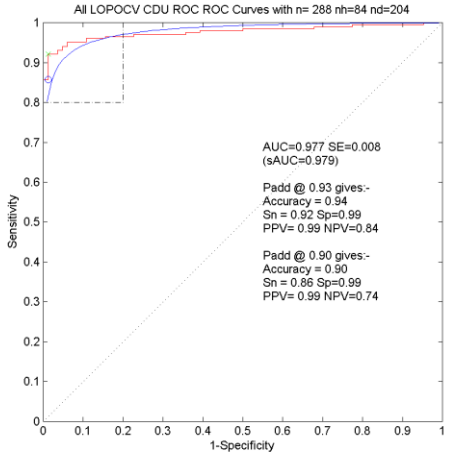
Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						guidance does not imply that there will be a mandatory structured template that hospital consultations must adhere to. It would be reasonable for relatively inexperienced doctors or nurse specialists to use a written template or follow guidance on a structured form of verbal questioning. However, I do not think we should go down the route of pinning down consultant vascular surgeons to use template structured questioning.	for greater clarification.
SH	Gloucestershire Hospitals NHS Foundation Trust	13.02	NICE Version	Page 7	17	**Imaging for revascularisation:** The statement that contrast enhanced MRA should be offered to people with PAD who need further imaging before considering an intervention is too narrow. This should be widened to the possibility of offering patients other non-invasive forms of imaging such as contrast enhanced CT angiography. This is certainly our preferred method here since we get better imaging and is the case in a very large number of other vascular units. CT angiography is mentioned further in the document, but it should not be subordinate to MRA.	Thank you for your comment. The GDG have considered this issue and reviewed the evidence regarding CTA and MRA. We concluded that MRA was preferred as it represented a more cost effective use of NHS resources. We recognise the issues relating to the availability and quality of MRA and highlighted this as a key issue for implementation. The guidance does not exclude the use of CTA where this is necessary.
SH	Gloucestershire Hospitals NHS Foundation Trust	13.03	NICE Version	Page 7	21	**Management of claudication:** It is suggested that all patients with claudication should be offered a supervised exercise programme. I think most of us would agree and would support that. At present, alongside many other units, we do not have a supervised exercise programme locally, although are striving to get one. It is a little ridiculous to offer a programme without any prospect of delivering it, so perhaps a modifier to this statement should be along the lines of "if a supervised	Thank you for your comment. The GDG are aware that there is a wide variation in the availability of supervised exercise programmes across England and Wales. For this reason, they placed a high priority on determining the clinical and cost effectiveness of supervised compared to unsupervised exercise. Based on the results of this analysis, supervised exercise was found to be the most clinically and cost-effective option for the treatment of people with intermittent

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						exercise programme is not available locally, then advice on what this programme constitutes so that the patients can follow their own self-determined programme should be discussed".	claudication. The GDG recognise that there will be a cost associated with implementing this recommendation where supervised exercise programmes are not already available. The NICE quality systems team are looking to produce shared learning examples of supervised exercise programmes, which will facilitate the implementation of the recommendation. In addition, we have added a recommendation detailing what a supervised exercise programme could consist of.
SH	Gloucestershire Hospitals NHS Foundation Trust	13.04	NICE version	Page 7	24	**Management of critical limb ischaemia:** It is recommended that all people with critical limb ischaemia are reviewed by a vascular MDT before treatment decisions are made. We would support that but occasionally time does not permit so perhaps this should read with a modifier "where time permits". The same comment could apply to major amputation for people with critical limb ischaemia. It is important that treatment is not delayed unnecessarily waiting for a MDT meeting.	Thank you for your comment. The GDG accept that some patients will need to be treated urgently. However, the GDG considered that, whilst they may require treatment prior to routine MDT meetings, there should still be mechanisms in place for them to have urgent access to all the relevant disciplines.
SH	Gloucestershire Hospitals NHS Foundation Trust	13.05	NICE Version	Page 10	24	**1.5.2 – Angioplasty and stenting:** It is recommended that angioplasty is offered for claudication when supervised exercise has not led to a satisfactory improvement in symptoms. The comments about supervised exercise classes made above apply here. However taken literally this advice suggests that patients cannot access angioplasty without having been through a supervised exercise programme and I feel that is inappropriate and too strong a message. Some patients will have done plenty of exercise in trying to overcome their claudication already and it is apparent from the	Thank you for your comment. The GDG wanted to make this a strong message as exercise is important. We acknowledge that there will be a few patients who have exercised substantially of their own volition, but the evidence indicates additional benefit from supervised compared to unsupervised exercise, and there is no evidence that this is influenced by prior exercise level.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						start that a supervised programme will add noting to that. This paragraph should therefore be modified.	
SH	Greater Manchester and Cheshire Cardiac and Stroke Network	14.00	Full	236	26	The recommendation to have an MDT before amputation has to be qualified by stating 'amputation rather than reconstruction': many patients are unsuited to any bypass or plasty by virtue of other functional limitation (stroke, bed-bound etc) or tissue loss	Thank you for your comments. This recommendation states that amputation should only be performed after all options for revascularisation have been considered. We feel that adding the words "rather than reconstruction" will not make the meaning any clearer, and indeed may serve to confuse the reader.
SH	Greater Manchester and Cheshire Cardiac and Stroke Network	14.01	Full	general		The use of MRA as first line angiography over conventional or CTA both of which are far more widespread and valuable. In our experience, the main limiting factor in MRA is the production of the 3D constructions, the plain images are virtual useless unlike the CT or DSA pictures. MRA is also well known to over-call stenosis grade.	Thank you for your comment. The GDG have considered this issue and reviewed the evidence regarding CTA and MRA. We concluded that MRA was preferred as it represented a more cost effective use of NHS resources. We recognise the issues relating to the availability and quality of MRA and highlighted this as a key issue for implementation. The guidance does not exclude the use of CTA where this is necessary.
SH	Greater Manchester and Cheshire Cardiac and Stroke Network	14.02	Full	general		Very clear hierarchy of treatment: risk factors and supervised exercise before angioplasty before bypass before amputation. The provision of supervised exercise programmes is minimal at present and would require considerable investment from primary care.	Thank you for your comment. The GDG are aware that there is a wide variation in the availability of supervised exercise programmes across England and Wales. The NICE implementation team will provide a cost impact assessment for trusts to use in planning for the delivery of these programmes.
SH	Greater Manchester and Cheshire Cardiac and Stroke Network	14.03	Full	66	10	Should further clarify the procedure for measuring ABPI. It refers to highest ankle and highest brachial - does this mean brachial on the same side or can they cross? Should both sides be measured? Also it states that when a	Thank you for your comment. The GDG have changed some of the wording of the recommendation to clarify this but did not consider that all of these points required further clarification.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						seated measurement is necessary the results should be adjusted but doesn't state how to do this. They couldn't be prescriptive on resting time prior to measurement due to lack of evidence but it is also unclear from their recommendation whether resting needs to be supine, this has a real practical implication so is worth clarifying.	
SH	Greater Manchester and Cheshire Cardiac and Stroke Network	14.04	Full	general		It would be helpful if NICE reviewed what should alert clinicians to the possibility of the diagnosis. Clearly if a patient gets pain on walking, they should be investigated. But what about an ache? What about if a patient says that for reasons they cannot explain, they just do not seem able to walk so far?	Thank you for your comment. The differential diagnosis of leg pain was outwith the scope of this guideline but an additional recommendation has been added relating to those groups of people in whom PAD should be considered, including those with unexplained leg pains.
SH	Greater Manchester and Cheshire Cardiac and Stroke Network	14.05	Full	general		The other issue should we be looking for early signs of lower limb peripheral arterial disease in those with a moderate to high risk of cardiovascular disease?	Thank you for your comment. An additional recommendation has been added relating to those groups of people in whom PAD should be considered, including those at risk of cardiovascular disease.
SH	Dialog Devices	15.00	Full	61	28-29	We wish to comment on the very thorough review of the treatment of peripheral arterial disease ("PAD"). We note that the current guideline was not intended to cover the screening of asymptomatic patients, although the definition of 'suspected PAD' in the guideline appears to include patients with risk factors for cardiovascular disease who do not have intermittent claudication or leg ulceration (page 61, lines 28-29).	Thank you for your comment. The GDG have considered the stakeholders comment and added a recommendation, which covers the assessment of asymptomatic patients.
SH	Dialog Devices	15.01	Full	67	Recommendation 4,	We also note that there appears to be an absence of published data showing any available diagnostic test adds sensitivity to a clinical history and examination (page 67,	Thank you for your comment. We agree that there was an absence of evidence in these areas and have noted this within the linking evidence to recommendations section.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
					note 1	section 7.2.3, Recommendation 4, note 1) and an absence of data on the assessment of patients with calcification in whom the arteries may not be compressible, leading to a misleading ABPI ratio (page 61, line 15).	
SH	Dialog Devices	15.02		61	15	We also note that there appears to be an absence of published data showing any available diagnostic test adds sensitivity to a clinical history and examination (page 67, section 7.2.3, Recommendation 4, note 1) and an absence of data on the assessment of patients with calcification in whom the arteries may not be compressible, leading to a misleading ABPI ratio (page 61, line 15). Dialog Devices Limited is currently developing a photoplethysmographic device which uses toe sensors and does not rely on blood pressure measurement in the arm or leg to assess the presence or otherwise of PAD (www.dialogdevices.co.uk/padd). One of the publications with a prototype device which provided proof of concept is referenced here: ME Alnaeb, A Boutin, VP Crabtree, DP Mikhailidis, AM Seifalian, G Hamilton: "Assessment Of Lower Extremity Peripheral Arterial Disease Using A Novel Automated Optical Device", Journal of Vascular and Endovascular Surgery, 2008 Jan-Feb;41(6):522-7. DOI: 10.1177/1538574407305092. The device has demonstrated sensitivity of 92% and specificity of 99%, comparing well with manual ABPI using Doppler which page 66, lines 28-30 of your draft guidance show as 70.6% and 88.5% respectively. The ROC curve for the device is shown below:	Thank you for your comment and reference. We agree that there was an absence of evidence in these areas. New studies conducted to address these issues are welcomed, and if they meet inclusion criteria they will be taken into account in any future updates of the guideline. We would also refer the stakeholder to the NICE medical technologies evaluation/diagnostic assessment programmes where new technologies are considered.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						 Whilst we understand that the current data are perhaps arriving too late to include in the guideline, we intend to perform further trials of the device in the two settings which the guideline has highlighted, namely: 1) The assessment of asymptomatic patients who have recognised risk factors for PAD in a General Practice setting, to determine the added value of a simple robust diagnostic test following a clinical history and examination. 2) The ability of the device to indicate PAD in patients with diabetes or renal disease who have a spuriously high ABPI ratio due to calcification. We would like to confirm that the Group would have an interest in the data from these studies when they are available with a view to incorporation into any future revised guideline. We would also observe that, as the method of detection is different (between the device and ABPI) there will be no obvious cause for	

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						correlation between the results other than as manifested by the disease itself. Combining the results of both tests should therefore improve both the sensitivity and specificity. Based on the above percentages, this should have particular impact on sensitivity which you have particular concerns with (page 67, section 7.2.3, Recommendation 4, note 1). Would the Group have an interest in data from studies that demonstrated this improvement with a view to incorporation into any future revised guideline?	
SH	Airedale NHS Trust	16.00	Full	General		This Guideline is consistent with our practice; we have no further comments.	Thank you for your comment.
SH	Society for Vascular Technology	17.00	Full	38	25	?Line missing - 'Offer duplex US as first line imaging' –as in full recommendations	Thank you for your comment. The section being referred to is the "Key priorities for implementation (KPI). The recommendation about duplex ultrasound was not selected as a key priority.
SH	Society for Vascular Technology	17.01	Full	61	34	?should this read manual ABPI rather than 'automatic manual ABPI'	Thank you for your comment. The guideline has been amended accordingly.
SH	Society for Vascular Technology	17.02	Full	66	39	Manual ABPI without Doppler – what technique does this refer to. I looked at the Baxter paper and could only see reference to ABPI measured with Doppler.	Thank you for your comment. In this study three techniques were compared: angiography, manual ABPI monitoring and manual ABPI with colour Doppler ultrasound.
SH	Society for Vascular Technology	17.03	Full	72		No recommendations for cuff size with ABPI measurement – Appropriate cuff size is very important for accurate ABPI measurement and this should be emphasized more strongly- the comment that cuff should fit comfortably around patient limb is misleading as it implies that is all that is required for appropriate cuff size. There are generally accepted criteria for cuff size for measuring brachial pressure (British Hypertension Society ie bladder should fit around 80-100% of arm) which would theoretically be applicable to the lower limb -is it	Thank you for your comment. The evidence review did not identify data on cuff size, however this has been covered in the NICE guidance on hypertension in relation to measuring pressure in the arm and we have cross-referred to that guidance.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						worth mentioning these?	
SH	Society for Vascular Technology	17.04	Full	General		Commonly ABPI is also measured following exercise and some studies suggest that post exercise ABPIs have improved diagnostic capabilities to resting ABPIs, particularly in less severe disease. The value of the exercise test does not appear to have been considered in producing this guideline although it is a fairly standard diagnostic test in many centres. Wondered whether it does fall within the remit of this advice.	Thank you for your comment. We were unfortunately unable to cover all areas and focussed upon those that stakeholders and GDG members initially suggested as critical areas to address. Therefore, the use of exercise testing was not included in the guideline.
SH	Society for Vascular Technology	17.05	Full	General		Poor evidence base of ABPI measurement – ABPI has been in routine use since at least the 1980s and this probably accounts for the lack of studies looking at its diagnostic accuracy compared with angiography. I think some studies have been excluded as results aren't quoted in terms of sensitivity and specificity and I wondered whether this was further limiting the evidence available. Two other early papers that appear to meet criteria (apart possibly outcome measures) are: Yao ST et al Ankle systolic pressure measurement in arterial disease affecting the lower limb BJS 09 1969 56/9 (676-9) Ouriel at al, Doppler ankle pressure: an evaluation of three methods of expression Archives of surgery 10 1982 117/10 (1297-1300)	Thank you for your comment. In order to assess the best diagnostic tool we have looked at the most meaningful outcomes that the GDG felt were appropriate to answer the question, and were most commonly reported in studies. These were sensitivity and specificity. Some of the studies did not report sensitivity and specificity, and were therefore excluded Sensitivity and specificity are usually the best measures to compare tests to the gold standard. Additionally these outcomes are able to be analysed statistically in a pooled analysis using RevMan software. The two papers that you mention did not meet our inclusion criteria because data for both studies was not presented in a suitable format to be able to calculate sensitivity and specificity. They were therefore excluded from the review.
SH	Society for Vascular Technology	17.06	Full	General		ABPI is also often considered useful as an adjunct to clinical assessment as it provides a more quantitative measure of disease severity, serial measurements can be useful in determining disease progression or	Thank you for your comment. We agree that ABPI is useful adjunct to clinical assessment and have stated this in recommendation.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						improvement following treatment and this is perhaps another reason why it should be included with the initial diagnostic assessment.	
SH	Society for Vascular Technology	17.07	NICE	7		As with comment 1 – offering duplex as first line imaging is missing and CTA as an alternative to MRA is also missing	Thank you for your comment. The section being referred to is the "Key priorities for implementation (KPI). The recommendation about duplex US was not selected as a key priority.
SH	Boston Scientific	18.00	Full	General		Boston Scientific welcomes this guideline, especially the recommendation to make amputations the absolute last resort. Boston Scientific fully supports the comments made by ABHI (Association of British Healthcare Industry)	Thank you for your comment.
SH	ArjoHuntleigh	19.00	Full Full Full	71 38 39	23 20 39	The word 'preference' effectively excludes all automated systems from being used. It is also placed inappropriately in the text. The only reference cited in this document for automated systems is the one using oscillometric technology. Oscillometric systems have been shown by the following authors to have poor correlation and agreement against Doppler: • Wohlfahrt P, Ingrischová M, Krajcoviechová A, Palous D, Dolejsová M. A novel oscillometric device for peripheral arterial disease screening in everyday practice. The Czech-post MONICA study. International Angiology, 2011: 30. 3; 256-6. • Hamel J, Foucaud D, Fanello S. Comparison of the automated oscillometric method with the gold standard Doppler ultrasound method to	Thank you for your comment and references. The evidence reviewed by the GDG led them to recommend manual over automated systems. The references identified here were mostly excluded as they relate to a healthy screened population and not those suspected of PAD (see below). The GDG considered that this evidence was not applicable to the review question. Thank you for your references. The studies referred to would be excluded as they do not meet our inclusion criteria (see Appendix C of the full guideline for protocols). Specifically. • Wohlfahrt – the population were not suspected PAD, and APBI was not compared to imaging. • Hamel - wrong population (not suspected PAD as described in protocol). • Korno - wrong population (not suspected of having PAD as described in protocol

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						access the ankle-brachial pressure index. Angiology 2010: 61. 5 : 48, 7-91. • Kornø M, Eldrup N, Sillesen H. Comparison of ankle-brachial index measured by an automated oscillometric apparatus with that by standard Doppler technique in vascular patients. European journal of vascular and endovascular surgery. 2009: 38. 5, 610-5. • Aboyans V, Lacroix P, Doucet S, Preux P-M, Criqui M H, et al. Diagnosis of peripheral arterial disease in general practice: can the ankle-brachial index be measured either by pulse palpation or an automatic blood pressure device? International journal of clinical practice 2008: 62. 7: 1001-7. • MacDougall A M, Tandon V, Wilson M P, Wilson T W. Oscillometric measurement of ankle-brachial index. The Canadian journal of cardiology 2008: 24.1:49-51. • Vinyoles E, Pujol E, Casermeiro J, de Prado C, Jabalera S, et al. Ankle-brachial index to detect peripheral arterial disease: concordance and validation study between Doppler and an oscillometric device. Medicina clínica 2007: 128. 3, 92-4. • Ramanathan A, Conaghan P J, Jenkinson A D, Bishop C R. Comparison of ankle-brachial pressure index measurements using an automated oscillometric device with the standard Doppler ultrasound technique.	• Aboyans - wrong population (not all the population were suspected of having PAD and the comparison was a healthy population). • MacDougall - wrong population - non-PAD population ("normal volunteers") • Vinyoles - wrong population (this was a hypertensive population) and does not use the gold standard imaging as its comparator. • Ramanathan - wrong population (these were 'healthy people' not those suspected of having PAD as described in protocol).

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						ANZ Journal of Surgery. 2003: 73. 3,105-8. So there is a danger that all technologies, other than oscillometric types, for the automatic measurement of ABPI will also be dismissed. Systolic pressure measurements using oscillometric technology have been well proven on arms. However, its performance on the ankle is questionable due to its inherent dependence upon pulses being present. The ankle presents certain challenges to the technology due to the anatomy of the lower leg and, often in the presence of PAD, the absence of detectable pulses. There are emerging technologies which are more appropriate for the challenges presented by diseased arteries in the leg. These will realistically facilitate high volume screening programs in primary care and more appropriate referrals to secondary care, leading to cost savings and more efficient patient management. (Lewis J. A comparison between a new automatic system and Doppler method for obtaining ABPI. EWMA Journal 2010, 10. 2, 47)	
SH	ArjoHuntleigh	19.01	Full Full Full	71 38 39	25 22 41	Pulse Volume Recording (PVR) waveforms taken from the ankle have a high degree of agreement (92%) with Doppler waveforms (Lewis J E A and Owens D R. The Pulse Volume Recorder as a Measure of Peripheral Vascular Status in People with Diabetes Mellitus. Diabetes Technology & Therapeutics 2010; Vol 12, 1: 75-80). Therefore PVR's could be used as an objective alternative to Doppler sounds. PVR measurements are 85% accurate	Thank you for your comment and references. The GDG were interested in the diagnosis of PAD within primary care and therefore focussed on ABPI. PVR and segmental pressures are more often used for the assessment and follow up within secondary care and were not raised in the scoping stage as a method of initial diagnosis. This area was not reviewed by the group and therefore we cannot make any recommendations. This could be an area for consideration in a future

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						compared with angiography in detecting significant occlusive lesions (Rutherford RB, Lowenstein DH, Klein MF. Combining segmental systolic pressures and plethysmography to diagnose arterial occlusive disease of the legs. Am J Surg 1979; 138(2): 211-218.) PVR waveforms are also cited in the following international guidelines as a first or second-line method to confirm the presence of PAD especially in the presence of incompressible vessels or where the ABPI>1.4: • Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg. 2007;33 Suppl 1:S1–5. • ESC Guidelines on the diagnosis and treatment of peripheral artery diseases European Heart Journal. 2011; doi:10. 1093/eurheartj/ehr 211. • Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease Circulation. 2006;113:1474 –547. It is suggested that the following is added to the bullet point "…..foot arteries or record the PVR waveform from the ankle"	update of the guideline.
SH	ArjoHuntleigh	19.02	Full Full Full	71 38 39	24 21 40	It is suggested to remove "in preference to an automated system" and add a new bullet point at the end of the table: • Alternatively, a clinically validated automated system, not based on oscillometric technology, can also be	Thank you for your comment. We cannot include the suggested bullet point because this system was not considered by the GDG (see preceding response).

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						used to measure ABPI in place of the Doppler technique.	
SH	ArjoHuntleigh	19.03	Full	61	34	Remove "automated" since 'automated manual ….' does not make sense.	Thank you for your comment. The guideline has been amended accordingly.
SH	ArjoHuntleigh	19.04	Full	72	-	Quality of Evidence section: See comments for Order Number 1 above.	Thank you for your comment. Please see answer in 19.01
SH	ArjoHuntleigh	19.05	Full	73	-	Manual Compared to Automated ABPI Measurements section: See comments for Order Number 1 above.	Thank you for your comment. Please see answer in 19.01
SH	DH	20.00				I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment.
SH	W.L. Gore & Associates	21.00	Full	General		WL Gore welcomes this guideline, which will improve the quality of care for patients with PAD.	Thank you for your comment.
SH	W.L. Gore & Associates	21.01	Full	157	7	References 100, 101 and 102 (Kedora 2007, McQuade 2010 and McQuade 2009) all report on the same study of a primary stent placement vs prosthetic bypass. However, this study (McQuade 2010) was included in section 9.47, which addresses angioplasty vs bypass. Since a stent was intended to be placed in all patients randomized to that arm, we feel this study is mistakenly included in this section.	Thank you for your comment. The evidence review included all endovascular techniques. We have amended the heading to reflect this.
SH	W.L. Gore & Associates	21.02	Full	195	19	References 116 and 132 (Cejna 2001 and Grimm 2001) are included in the analysis. Although these studies do match the selection criteria, we feel that they are inappropriate given the currently available technology and best practices. These studies address the use of the Palmaz balloon-expandable stainless steel stent in the femoropopliteal artery. Balloon expandable stainless steel stents have high radial strength but very limited flexibility when compared to self-expanding nitinol stents. Since the femoropopliteal artery has a large	Thank you for your comment. We have since looked at the data in terms of separating SES studies from the BES studies for outcomes where these were pooled together. When data from the two types of stents was separated out, there were no changes to the existing level of statistical significance for any of the outcomes (ie. those that showed a non-significant difference remained non-significant and those that showed a significant difference remained significant). Heterogeneity was actually increased when the BES trials were

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						amount of motion, flexibility is considered a key attribute of a stent which would be placed here. The current clinical usage of balloon expandable stents in this vessel segment has been virtually eliminated due to known poor outcomes. We feel it is appropriate to only include nitinol self-expanding stents in this analysis for the femoropopliteal segment.	removed from the outcome of ABPI at 1 year (for the studies of patients with intermittent claudication due to femoro-popliteal disease - person randomised data). Additionally, it is worth noting that data for all of the outcomes that showed a statistically significant difference favouring primary stenting were based on SES trials alone. We therefore feel that separating the two types of stents in the analysis is unnecessary and would not lead to any change in our conclusion or recommendations. We have added a statement to this effect in section 9.5.3 of the full guideline.
SH	NHS Direct	22.00	Full			NHS Direct welcome the guideline and have no comments on its content other than below typos.	Thank you for your comment.
SH	NHS Direct	22.01		1.3.1	14	should be "in terms of"	Thank you for your comment. The guideline has been amended accordingly.
SH	NHS Direct	22.02		1.4	23	Needs a space between "aspirin" and "statins"	Thank you for your comment. The guideline has been amended accordingly.
SH	Foot in Diabetes UK	23.00	Full	general		General consensus of the group is that this is an excellent document and will promote management and improvement for this group of patients. A few minor comments:	Thank you for your comment.
SH	Foot in Diabetes UK	23.01	Full	general		Didn't see any agreed criteria for critical limb ischaemia (acknowledge that acute ischaemia is not part of the guideline). This may be on purpose?	Thank you for your comment. This is stated in section 1.3 table 1 of the full guideline.
SH	Foot in Diabetes UK	23.02	Full	general		Criteria for referral to the vascular multidisciplinary team and who makes up that team?	Thank you for your comment. The GDG did not feel that they could be prescriptive in the membership of the MDT.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Foot in Diabetes UK	23.03	Full	general		The development of a PAD register in primary care- was this considered? This would aid any link to any new QOF requirement.	Thank you for your comment. This is outwith the scope of the guideline development group. We agree that this suggestion is a good idea and will pass these suggestions to the quality systems team at NICE.
SH	Foot in Diabetes UK	23.04	Full	general		The description of how to undertake an ABPI will hopefully standardise practise, a recommendation/ statement on competency /training for people undertaking the test would have been useful	Thank you for your comment. Competency and training was not prioritised as a clinical issue for this guideline. This could be considered in a future update of the guideline where stakeholders identify this as an important clinical issue.
SH	Association of British Healthcare Industries	24.00	Full	General		The ABHI welcomes this guideline, which makes a number of positive recommendations that will improve the quality and consistency of care of patients with PAD.	Thank you for your comment.
SH	Association of British Healthcare Industries	24.01	Full	23	2	The GDG expressed concerns that patency as an outcome measure has little relevance to patients. Patency is an important morphologic outcome in PAD, particularly in the devices world. It is measurable and comparable, and it reflects the success of an intervention as it applies to the revascularised or bypassed segment only. There is a link between patency and TLR (patency can be used as a proxy for TLR when TLR rates are not reported), and between TLR/patency and symptoms (recurrence of symptoms as a result of loss of patency leads to the need for reinterventions). In this context, patency provides a measure of whether the intervention has achieved its objective. We would request that the GDG consider patency, particularly where it may inform guideline questions for which other evidence is lacking.	Thank you for your comment. The GDG had considerable discussion regarding the relevance of patency as an outcome measure and reconsidered this in the light of the stakeholder's comments. The GDG was primarily interested in clinical and cost effectiveness and concluded that the value of patency as a proxy outcome was only relevant where the physical effects of the treatments being compared were sufficiently similar that a measure of patency based upon degree of re-stenosis was a similar hurdle for both treatments and where there was sufficient evidence to link this proxy outcome to clinical benefits. After reconsideration the GDG decided, whilst recognising these limitations, to consider patency in the comparison of bare metal stents and drug eluting stents but not for the other comparisons. The explanation regarding patency in the methods section and the section relating to this comparison have

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							been rewritten as a result of this decision.
SH	Association of British Healthcare Industries	24.02	Full	General		The evidence on stents includes multiple studies on devices that do not have a CE-mark and are not available to treat patients (not even off-label), as well as devices which may not necessarily have a specific CE mark for aorto-iliac, femoro-popliteal or infra-geniculate indications. Evidence on devices without a CE mark should not be included. Also, evidence of devices being used in an off-label fashion should not be included unless there are indications that the device(s) are deemed to be commonly used in this off-label fashion. The guideline should include a note that clinicians should be mindful of the approved indications when making their selection of stent.	Thank you for your comment. The GDG did not consider that CE-mark or current commercial availability were necessary criteria for inclusion of relevant trials. It is common for trials considered by NICE to include evidence gained before a treatment has full regulatory approval or to consider evidence relating to treatments that are not currently marketed in the UK.
SH	Association of British Healthcare Industries	24.03	NICE	15	9	The proposed trial should also include the use of Drug Eluting Balloons (DEB) as initial research indicates that patency rates are superior with DEB in the infra-geniculate arteries.	Thank you for your comment. Drug eluting balloons was not prioritised as an area for inclusion in the guideline. This was due to the limitation in resources in preparing the guideline decisions had to be taken regarding the technologies that would be identified as requiring full review. Therefore, we were unable to include DEB within our research recommendation. This may be considered in a future update of the guideline where it is highlighted as a priority by stakeholders.
SH	Association of British Healthcare Industries	24.04	Full	27	20	Type of studies included for intervention evidence reviews should not be limited to RCTs but also include good quality observational studies, in the same fashion as for the diagnostic evidence reviews. This may be helpful, particularly where RCT evidence is limited. Also, in some situations, procedures in patients whose disease is such that they may not be candidates for multiple therapies (such	Thank you for your comment. We acknowledge that there was a lack of evidence for some of the review topics in the guideline. For most intervention evidence reviews, RCTs were included as they are the most robust type of study design that could produced an unbiased estimate of the intervention effects.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						as bypass and/or endovascular),randomised trials to assess the effectiveness of the intervention may not be appropriate or possible, in which case observational studies may help inform the guideline questions.	However, where the GDG believed RCT data would not be appropriate, other lower levels of evidence such as cohort studies were searched for. This is detailed in the protocols in Appendix C. Cohort studies were not specified by the GDG for the endovascular treatment review.
SH	Association of British Healthcare Industries	24.05	Full	39	27	As one of the new QOF indicators asks GP to keep a register of patients with PAD, NICE may wish to create linkage between this guideline and QOF by recommending that the diagnosis criteria set out on this section should form the basis of admission of patients onto these registers.	Thank you for your comment. The GDG thought this was an implementation issue. We have forwarded this to the NICE quality systems team for this guideline.
SH	Association of British Healthcare Industries	24.06	Full	39	29	The GDG may wish to consider making a specific recommendation on the use of questionnaires (such as the Edinburgh Claudication Questionnaire), in order to promote uniformity of approach across the whole NHS.	Thank you for your comment. We have now removed the reference to structured questioning as the GDG did not review the evidence on specific questionnaires to identify PAD.
SH	Association of British Healthcare Industries	24.07	Full	41	35	This is a very important recommendation. There would be real benefit in creating linkage between this section of the guideline and the 'In-patient management of diabetic foot problems' guideline, which stopped short of making such an overt recommendation.	Thank you for your comment. The NICE guideline mentioned is referred to in section 2.6 of the guideline
SH	Cook Medical  Cook Medical_ISPOR 2010_1Nov10 FINAL.  CRT2011_Ansel_2yr ZPTX_Randomized_fir	25.00	Full	196	1	The table includes data from reference 136 (Zilver PTX RCT) and therefore the clinical outcomes reported for the angioplasty group effectively reflect the following mix: 50% of patients with acutely successful PTA (no acute stent placement), 25% with acute PTA failure and placement of bare metal stent (BMS) and 25% with acute PTA failure and placement of drug-eluting stent (DES). Furthermore, we would like to note that all	Thank you for your comment. The GDG were aware that the trials identified in the comparison of primary stenting and selective stenting include a variety of stent types and had differing rates of stent use. All relevant evidence was included and, where relevant, consideration was given to heterogeneity. The recommendation was based on the data reviewed by the GDG.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
	Zilver_PTX_Randomized_Dake_LINC_17Jar					patients in the primary stenting group had DES placed and although this group has been classified as "angioplasty with primary stent placement", angioplasty was usually performed but was not required.	
SH	Cook Medical	25.01	Appendices	299	1	Clinical evidence table The description of "Intervention" should clarify that 50% of these patients had successful PTA and the other 50% had acute PTA failure, which required one repeat balloon inflation for 2-3 minutes prior to being considered an acute PTA failure with provisional stent placement (of these patients requiring provisional stenting, 50% received BMS and 50% DES). The description of "Comparison" states that it is "Angioplasty with primary self expanding nitinol stent". This is not entirely correct and should be replaced with "self-expanding drug-eluting nitinol stent", which was the type of stent used for all primary stent placements.	Thank you for your comment. We have amended the evidence table in response to the stakeholders comment.
SH	Cook Medical	25.02	Appendices	300		Allocation concealment: randomization in this study was based on the most rigorous current statistical methodology. The study was block randomized by site with multiple block sizes that were randomly assigned to each site and the site was unaware of block size. Those enrolling patients were not aware to which group the next enrolled patient would be randomized. Blinding: not blinded. Drop outs: Angioplasty group: this information is wrong and	Thank you for your comments. When undertaking quality assessment of papers, the guideline developers follow the NICE Guideline Manual. Whilst we acknowledge the stakeholders comments, we have not amended the randomisation and blinding as insufficient detail had been given in the paper. This is standard practice when we assess the quality of all papers. We can only report or make a judgement on what is written within in the paper. We have amended the drop-out data in response to the stakeholders comment.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						should be replaced with: 13 dropped out (11 withdrew and 2 lost to follow up – 5 and 1 in the optimal PTA group, 4 and 1 in provisional BMS group, 2 and 0 in provisional DES group)	
SH	Cook Medical	25.03	Appendices	301		Although not yet published in the peer-reviewed literature, 2-year follow-up results have been reported for this study, for example: Dake M. The Zilver PTX randomized trial of paclitaxel-eluting stents for femoropopliteal disease: 24-month update. Presented at: LINC 2011; January 17, 2011; Leipzig, Germany. (enclosed) Table with patient characteristics is incomplete (see table 1 in reference 136 of the draft guideline).	Thank you for your comment and reference. We have since contacted Cook Medical regarding the data referred submitted during a call for evidence. We did not include this data at the time as the Cook had requested we keep this confidential. We have now been given permission to use this data and have included it within our analysis. With regards the table of patient characteristics, we did not make the amendment as this table was not intended to be a replication of the paper. It is standard practice to discuss which characteristics are of clinical importance or interest to the GDG to inform their discussion of the evidence.
SH	Cook Medical	25.04	Full	211	18	One study identified by NICE (reference 138) is a RCT comparing the use of a polymer free sirolimus-eluting stent with a placebo- coated BMS in the treatment of infra-popliteal lesions. The other randomized study (reference 136), for which clinical data was submitted by Cook Medical during the call for evidence, compares a paclitaxel-eluting stent with its bare metal version in the treatment of femoro-popliteal lesions. Results for the two studies should not be pooled together as presented in table 82 "BMS compared to DES for people with intermittent claudication due to femoro-popliteal disease	Thank you for your comment. The GDG has reconsidered the paper to which you refer (reference 138) in the light of the comments received. Whilst symptoms due to infra-popliteal disease were not excluded from the scope we agree that invasive treatment of disease in this location for IC would be unusual in NHS practice and have therefore excluded this trial from the consideration of intermittent claudication. It has been included in the CLI section, but considered separately from the evidence on femoro-popliteal disease. The DURABILITY study (Bosiers) is a non-

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						after angioplasty failure". In fact, we question why the results of a stenting study of infra-popliteal disease are included in this section of the guidance, which discusses treatments for SFA disease. Femoro-popliteal stenting and infra-popliteal stenting are very distinct procedures, requiring different types of stents, and treating distinct vascular beds. Therefore stenting of these regions should be analyzed separately. Very importantly, a balloon-expandable coronary stent such as the Yukon stent could not possibly be used to stent in the femoro-popliteal segment. The Zilver PTX stent has fulfilled all the requirements to obtain regulatory approval and effectively obtained CE-mark in July 2009. It is the only DES approved for use in the UK for treatment of femoro-popliteal lesions in PAD patients. In the absence of any other randomized studies relevant for the review question being addressed, and in light of the number of patients who had acute PTA failure followed by stent placement in the Zilver PTX trial (n=61 in the DES arm and n=59 in the BMS arm), we strongly encourage NICE to also use the data from the prospective, single-arm, multicenter Zilver PTX clinical study which between April 2006 and June 2008 enrolled 787 patients at 30 international sites: Dake MD, Scheinert D, Tepe G, et al. (2011) Nitinol stents with polymer-free paclitaxel coating for lesions in the superficial femoral and popliteal arteries above the knee: twelve-month	randomised study was therefore excluded as per the review protocol (see Appendix C in the full guideline).

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment

safety and effectiveness results from the Zilver PTX single-arm clinical study. J Endovasc Ther, 18(5):613-623

This publication also provides a comparison of 12-month TLR and restenosis rates from published studies of contemporary bare metal stents matched to like patient cohorts from the Zilver PTX single-arm study.

Published Studies	12-Month Rates From the Study	Matched Subset Fro Zilver PTX Single Arm Study
FAST(1)	Lesion length 45±28 mm 15% TLR (n=123) 32% restenosis (n=100)	Lesion leng 48±26 mm 5% TLR (n=260) 13% resten (n=258)
Durability I (2)	Lesion length 96±27 mm 21% TLR (n=134) 28% restenosis (n=133)	Lesion leng 95±21 mm 4% TLR (n=154) 13% resten (n=152)
RESILIENT (3)	Lesion length 99±50 mm	Lesion leng 71±44 mm

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						<table><tr><td></td><td>13% TLR (n=134) 19% restenosis (n=134)</td><td>4% TLR (n=434) 13% restenosis (n=420)</td></tr></table> (1) Krankenberg H, Schluter M, Steinkamp HJ, et al. (2007) Nitinol stent implantation versus percutaneous transluminal angioplasty in superficial femoral artery lesions up to 10 cm in length: the femoral artery stenting trial (FAST). Circulation, 116(3):285-292 (2) Bosiers M, Torsello G, Gissler HM, et al. (2009) Nitinol stent implantation in long superficial femoral artery lesions: 12-month results of the DURABILITY I study. J Endovasc Ther, 16(3):261-269 (3) Laird JR, Katzen BT, Scheinert D, et al. (2010) Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery: twelve-month results from the RESILIENT randomized trial. Circ Cardiovasc Interv, 3(3):267-276	
SH	Cook Medical	25.05	Full	214	17	Cook Medical provided NICE with the 24-month update on the primary safety endpoint (event free survival) and the primary effectiveness endpoint (patency). Moreover, data submitted to NICE during the call for evidence shows that the 12-month and 24-month TLR rates for Zilver PTX are lower than for BMS. The TLR rates for both arms are statistically significant at 12- and 24-months.	Thank you for your comment. Following discussion with Cook Medical regarding the data referred to we have now included this evidence within our review. We had not considered the evidence at the time, as Cook Medical had requested the data remain confidential. We have now included the data within our analysis. The 24 month TLR data showed a borderline significance. The GDG discussed

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						From what we can tell, the above was not taken into account in the analysis performed by NICE. The TLR rates that we have submitted do not appear to have been used at all, since the statement in the full guideline document is simply that statistically significant differences were not observed. Despite the fact that those TLR rates were submitted in-confidence, this could have been mentioned in the guideline, as well as a note on how the analysis took that data into account (or if not, why).	this evidence further and concluded that there remained insufficient evidence of clinical benefit of drug eluting stents.
SH	Cook Medical	25.06	Full	214	17	The absence of statistically significant differences between BMS and DES for a number of clinical outcomes is neither expected nor surprising: 1) Peri-procedural complications and in-hospital mortality as well as mortality during follow-up; The procedure of stenting is exactly the same – whether it is DES or BMS. Therefore, a difference in these outcomes would have been unexpected. Mortality during follow-up is normally a result of other causes. 2) Clinical improvement as measured by ABPI, Rutherford class improvement, walking scores Patients where a worsening of symptoms occurs (and is confirmed) as a result of unsustained success in the treatment of the target lesion have a TLR event and need another revascularization procedure. The clinical outcomes reported during follow-up will	Thank you for your comments. We have now included the data within our analysis. The 24 month TLR data showed a borderline significance. The GDG discussed this evidence further and concluded that there remained insufficient evidence of clinical benefit of drug eluting stents. We have added further discussion regarding the relationship between patency and clinical benefit and the outcome of patency has been considered for this comparison.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						reflect the success of repeat revascularizations and since the revascularization procedures will provide improvement of symptoms, the end result is an improvement in the ABI, Rutherford scores, and walking scores after TLR events. It is not expected that differences in those outcomes are observed or if observed are statistically significant for the two groups. 3) Reinterventions and TVR rates Reinterventions on the same patient but which are not related to the target lesion treated with the stent, although they may be in the same limb or vessel where the target lesion was located, are not a relevant outcome for comparing the performance of BMS and DES. These reinterventions reflect progression of atherosclerosis beyond the target lesion treated, i.e. problems arising outside the lesion initially treated. To compare DES with BMS in the treatment of femoro-popliteal lesions, TLR is the key outcome, as it is one of the few outcomes that actually reflect a difference in the effect of the stent itself. Patency would also reflect that.	
SH	Cook Medical	25.07	Full	214	29	The question regarding cost-effectiveness of DES versus BMS is a question of cost-consequence, in light of no difference observed in key clinical outcomes addressing mortality and morbidity directly related to the stenting procedure itself. However, the difference in TLR rates is crucial to obtain a realistic estimate of cost of treatment of PAD patients. TLR procedures range between angioplasty and	Thank you for your comment. Although we are grateful to Cook for providing us with this budget impact analysis, the evidence included in the analysis was not considered of sufficient quality for inclusion within the guideline. The primary reason for this is that the estimates of efficacy used to inform the budget impact model are based on unpublished registry data (which does not

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						bypass surgery, and some patients require multiple reinterventions (for example two angioplasties in the 24-month period following the procedure). Furthermore, patients who have recurring symptoms would require additional doctor visits and diagnostic imaging, which also have a cost to the NHS. A simplistic analysis based on the price of stents as being the only cost difference between BMS and DES is not at all accurate as it does not reflect the cost-consequence of the type of stent chosen. A budget impact model was developed to compare the pathway costs of treating patients with paclitaxel-eluting versus BMS in France, and the results of the model were presented at the ISPOR European Conference in November 2010 in Prague (enclosed): PCV32 BUDGET IMPACT ANALYSIS OF PACLITAXEL DRUG ELUTING STENT (DES) FOR THE TREATMENT OF LOWER LIMB PERIPHERAL ARTERIAL DISEASE (PAD) IN FRANCE The model results show that adoption of the DES at a higher cost than BMS will have a cost saving impact in the healthcare system because savings in reintervention costs are higher than the cost difference between BMS and DES. The model was initially developed to support reimbursement of the Zilver PTX stent in France, which was obtained in September 2011. The model has been updated since, to reflect the reimbursement indications and costs. A manuscript has been prepared for publication	appear to be comparative) and expert opinion. This level of clinical evidence is not compatible with that included in the clinical review as it is highly likely to result in a biased estimate of estimate of difference between treatments.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						and is currently in the final review process before submission to a peer-reviewed journal. The economic assessment currently performed in the NICE draft guideline is solely based on price and fails to take into account the true costs of treatment of PAD patients. There is a group of PAD patients where the use of paclitaxel-eluting stent will be associated with lower cost than use of BMS, by avoiding reinterventions compared to BMS. At the price difference NICE presents in the draft guideline document (£900 for DES and £550 for BMS), it may well be cost saving for the NHS to use a DES. The current cost of reinterventions to the NHS is the Payment by Results tariff for the procedure and any diagnostic work that needs to be done. A simple cost calculation based on the Zilver PTX RCT TLR rates for provisional BMS versus provisional DES shows the following: - At 24 months post procedure with the DES, a lower number of TLR events will be observed compared to BMS. The absolute difference in TLR rates* from the Zilver PTX RCT is 12.3%. Therefore, in a cohort of 100 patients, 12 of those will not need a reintervention due to the superior performance of DES, compared to BMS. - The cost of a reintervention can vary between angioplasty and bypass surgery. Additionally, patients who need reinterventions are first submitted to	

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						diagnostic imaging and may require follow-up outpatient visit(s) before the actual reintervention. A calculation based on the observed distribution of reinterventions for the Zilver PTX RCT provisional stenting population, using the 2012-13 NHS Payment by Results tariffs, estimates an average cost of £3,216 per reintervention, including diagnostic work. - By using DES in 100 patients, the NHS would spend an extra £35,000 on the DES compared to BMS. - By using DES in 100 patients the NHS would not have to spend at least an additional £38,592 in reinterventions during the 2 years post procedure, compared to BMS (calculations assume that TLR events require one single procedure, and some patients may have multiple procedures). - The cost of reinterventions is higher than the extra cost of the DES. - In the larger NHS scale, this potential for cost savings cannot be ignored. *Reference: Ansel G. Zilver PTX randomized trial of paclitaxel-eluting stents for femoropopliteal disease: 24-month update. Presented at: CRT 2011; March 7, 2011. Washington DC, USA.	
SH	Cook Medical	25.08	Full	214	30	This recommendation needs to be revised based on the arguments presented above. There is evidence on over 1,000 patients who have received paclitaxel-eluting SFA stents. Being that this is the only drug-eluting stent	Thank you for your comment. We have considered the stakeholder comments and responded as above. The GDG were satisfied that all the relevant evidence was reviewed and the recommendation was based on the

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						which has obtained regulatory approval (CE mark) for use in the SFA – it is not acceptable that the evidence gets mixed up with infra-popliteal stenting and with devices that have not obtained regulatory approval for femoro-popliteal stenting. It is also misleading that NICE advises against using DES for economic reasons, solely based on a comparison of prices obtained by GDG members, ignoring the potential for cost-savings through avoided repeat procedures.	clinical and cost effectiveness. The trial relating to infra-popliteal disease has now been excluded from this comparison. . The GDG did not consider that there was robust evidence of clinical benefit that would result in lower re-intervention rates to offset the increased cost of the DES. We would hope that if such evidence emerges then this could be incorporated into economic modelling for future revision of the guidance.
SH	Cook Medical	25.09	Appendices	320	1	Descriptions for "Intervention" and "Comparison" appear to be switched. Outcomes should include statement that 12-month and 24-month freedom from TLR were reported, as per data submitted to NICE in January 2011.	Thank you for your comment. This has been amended in the relevant evidence table. We have now included TLR data after receiving permission from the stakeholder.
SH	Cook Medical	25.10	Appendices	321		The secondary randomization to BMS or DES was alternating assignment of patients across the entire study. Since the randomization was not limited to a single site, but rather included all investigative sites, it was not possible for those enrolling patients to know which group the next patient would be assigned. Although follow-up duration is reported in the table as 2 years, which effectively corresponds to the data submitted to NICE by Cook Medical, only 12-month results seem to have been included in the analysis. TLR results have now been presented. At 12	Thank you for your comment. We follow a standard quality assessment process and base our assessment on the details within the paper. As there was insufficient detail on blinding and allocation concealment (to meet our standard criteria) we were unable to amend this. Following discussion with Cook Medical, we have now been given permission to use the 24 month follow up data. We did not include this originally as the stakeholder had requested that this information remain confidential. We have now included the data within our analysis. The 24 month TLR data

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						months there were 10 TLR in the BMS group and 3 in the DES group; Kaplan-Meier estimates for TLR = 17.6% for BMS and 5.3% for DES (p-value=0.02). At 24 months there were 13 in the BMS group and 6 in DES group; KM estimates = 23.1% and 10.8% (p-value=0.05). Reference: Ansel G. Zilver PTX randomized trial of paclitaxel-eluting stents for femoropopliteal disease: 24-month update. Presented at: CRT 2011; March 7, 2011. Washington DC, USA. (enclosed)	showed a borderline significance. The GDG discussed this evidence further and concluded that there remained insufficient evidence of clinical benefit of drug eluting stents.
SH	Cook Medical	25.11	Full	247	10	The two trials identified (references 138 and 149-151) are not an appropriate evidence base to answer the review question "what is the clinical and cost effectiveness of BMS compared to DES for the treatment of CLI in adults with PAD?" for the following reasons: - The Yukon stent (reference 138) is a coronary balloon expandable-stent. Furthermore the study reports the results of a trial of sirolimus-eluting versus placebo-coated BMS in patients with infra-popliteal (below the knee) disease and therefore it is not a trial of BMS compared to DES for CLI due to femoro-popliteal disease. Being that it is not a self-expandable stent it cannot be used in the SFA at all. - The sirolimus-eluting stent from the SIROCCO trial (references 149-151) is not a treatment option. This DES was used in the clinical study but never obtained CE-mark, and therefore has	Thank you for your comment. The GDG has reconsidered the papers to which you refer (reference 138) in the light of the comments received. The evidence in the CLI section, has been split into femoro-popliteal and infra-geniculate.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						never been available for use in the NHS. Therefore, neither of the two trials above should be used to compare BMS and DES in treatment of patients with CLI due to femoropopliteal-disease. Furthermore, there is only one DES that has obtained regulatory approval and is available to treat this patient population, which is the paclitaxel-eluting stent Zilver PTX. The RCT where Zilver PTX was directly compared to its bare metal version only included about 8.5% patients with CLI.	
SH	Cook Medical	25.12	Full	253	Table	Again, and besides the underlying data being inappropriate to answer the research question, price is not the only economic consideration to be taken into account. TLR procedures have a cost to the NHS. Therefore, economic considerations need to compare the overall budget impact of BMS versus DES. Previous comments provide further information on existing budget impact analysis of DES versus BMS in the treatment of femoro-popliteal disease.	Thank you for your comment. We were unable to consider the budget impact mentioned by the stakeholders for the reasons given in previous responses. Where the outcomes associated with two interventions are the same, then the decision becomes one of cost minimisation and the least costly option ought to be recommended. The GDG concluded on the basis of the clinical review not to change the recommendation.
SH	Cook Medical	25.13	General			By ignoring patency as a relevant clinical outcome, NICE is ignoring a lot of data on medical devices which would allow for a comparison of the efficacy of the device in treating the target lesion. Although NICE uses TLR rates for this purpose, not all trials report TLR rates, but most trials do report patency rates. TLR rates and patency are closely related, as the need for a reintervention in the target lesion is the result of a loss of patency.	Thank you for your comment. The GDG had considerable discussion regarding the relevance of patency as an outcome measure and reconsidered this in the light of the stakeholders comment. The GDG was primarily interested in clinical and cost effectiveness and concluded that the value of patency as a proxy outcome was only relevant where the physical effects of the treatments being compared were sufficiently similar that a

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						Using patency would allow for including more device data in the evidence base considered by NICE, and we strongly encourage NICE to reconsider its decision not to include this outcome.	measure of patency based upon degree of re-stenosis was a similar hurdle for both treatments and where there was sufficient evidence to link this proxy outcome to clinical benefits. After reconsideration the GDG decided, whilst recognising these limitations, to consider patency in the comparison of bare metal stents and drug eluting stents but not for the other comparisons. The explanation regarding patency in the methods section and the section relating to this comparison have been rewritten as a result of this decision.
SH	Pfizer UK Ltd	26.00	Full	39	21	Pfizer welcomes the inclusion of advice on smoking cessation within this guideline. The evidence clearly demonstrates that smoking is a known risk factor for the development of peripheral artery disease, and smoking cessation has shown to be effective in preventing the morbidity associated with this disease.	Thank you for your comment.
SH	Pfizer UK Ltd	26.01		58	30-32	It is misleading to only refer to the quit rates that are associated with the use of nicotine replacement therapy, as the related NICE guidelines on smoking cessation that are referred to in this guideline make recommendations for the use of varenicline in addition to recommendations for NRT. To that end, the Guideline Development Group wish to consider the inclusion of a similar statement about the 12-week and 52-week quit rates seen in the literature regarding the use of varenicline. Gonzales et al (2006) and Jorenby et al (2006) provide quit rates for varenicline at both 12 and 52 weeks. It is important to note, however, that these quit rates are in "healthy"	Thank you for your comments and references. This section was intended to be an introduction as to the importance of smoking cessation and not a full evidence review. Smoking cessation was not considered in detail by the GDG and we refer to other NICE guidance on smoking cessation, including TA123 on varenicline. However, we have included the words "for example" to clarify that this is not intended to a full review of the subject.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						smokers and not specifically in those with PAD. It is also important to note that since the publication of NICE TA123 for varenicline, there has been a randomised controlled trial of varenicline conducted in the cardiovascular (CVD) patient population. The CVD trial (Rigotti et al, 2010) shows that in patients with cardiovascular disease, varenicline has an acceptable safety profile and is an effective treatment for smoking cessation regardless of gender, age, race or presence of cardiac disease. Rigotti et al (2010) was a randomised double-blind placebo-controlled multicentre trial compared the efficacy and safety of varenicline for smoking cessation with placebo in smokers (>10 cigarettes/day) aged 35–75 years, who had stable cardiovascular, cerebrovascular, or peripheral vascular disease for at least 2 months. Subjects received weekly counselling plus either varenicline (1mg BID) or placebo for 12 weeks and were followed for 52 weeks. The carbon monoxide (CO)-confirmed continuous abstinence rate (CAR) for the last 4 weeks of treatment (Weeks 9–12) was the primary outcome. Secondary endpoints were CAR for Weeks 9–52, adverse events (AE), CV events and mortality. 714 subjects (mean age=57; 79% male; 81% white) were randomised to varenicline (355) or placebo (359). CO-confirmed continuous abstinence rate was higher for varenicline than placebo at the end of treatment (Weeks 9-12: 47.0% vs. 13.9%; OR: 6.11; 95% CI: 4.18-8.93,	

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						p<0.0001) and through 52 weeks (Weeks 9-52: 19.2 % vs. 7.2%, OR 3.14, 95% CI 1.93-5.11, p<0.0001). In this study, a quarter of the study population had peripheral arterial disease as a baseline characteristic (n=82 in varenicline and n=97 in placebo). The superiority of varenicline over placebo in continuous abstinence was statistically significant in post-hoc analyses of subgroups defined by age, Fagerström score, daily cigarette consumption, and presence of coronary heart disease. Significant effects of varenicline were seen in subgroups of male and white participants. Female and non-white participant samples were too small to permit significance testing, but abstinence rates were consistent with those of the overall analysis. The varenicline and placebo groups did not differ significantly in CV events (7.1% vs. 5.7%; difference 1.4%, 95%CI -2.3, 5.0), serious AEs (6.5% vs. 6.0%; difference 0.5%, 95% CI -3.1, 4.1), CV mortality (0.3% vs. 0.6%; difference -0.3%, 95% CI -1.3, 0.7), all-cause mortality (0.6% vs. 1.4%; difference -0.8%, 95% CI -2.3, 0.6), AEs due to depressed mood disorders (3.1% vs. 2.3%; difference 0.8%, 95% CI -1.6, 3.2), or suicidal behaviour (0 subjects). As described in the SPC for varenicline, deaths and serious cardiovascular events in Rigotti et al (2010) were adjudicated by a blinded, committee. The following adjudicated events occurred with a frequency ≥1% in either treatment group during treatment (or in the 30-day period after treatment): nonfatal myocardial infarction (1.1% vs. 0.3% for CHAMPIX and	

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						placebo, respectively), and hospitalisation for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, the adjudicated events included need for coronary revascularisation (2.0% vs. 0.6%), hospitalisation for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularisation underwent the procedure as part of management of nonfatal MI and hospitalisation for angina. Cardiovascular death occurred in 0.3% of patients in the CHAMPIX arm and 0.6% of patients in the placebo arm over the course of the 52-week study. These and other studies are included in the recently published update to the Cochrane review of nicotine receptor partial agonists for smoking cessation (Cahill et al, 2012), which the GDG may wish to consider. Refs: Gonzales, D. et al. Varenicline, an α4β2 Nicotinic Acetylcholine Receptor Partial Agonist, vs Sustained-Release Bupropion and Placebo for Smoking Cessation: A Randomized Controlled Trial. JAMA. 2006;296(1):47-55. Jorenby, D. et al. Efficacy of Varenicline, an α4β2 Nicotinic Acetylcholine Receptor Partial Agonist, vs Placebo or Sustained-Release Bupropion for Smoking Cessation: A Randomized Controlled Trial. JAMA. 2006;296(1):56-63.	

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. Circulation. 2010 Jan 19;121(2):221-9 Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No.: CD006103. DOI: 10.1002/14651858.CD006103.pub6.	
SH	Perimed AB	27.00	Full	General		Several recently published *(Practical guidelines on the management and prevention of the diabetic foot IWGDF, 2012,* and *Guidelines for Critical Limb Ischaemia and Diabetic Foot, ESVS CLI Guideline Committee 2011)*, as well as older consensus documents *(Inter-Society consensus for the Management of Peripheral Arterial Disease, TASCII,2007, Practical guidelines on the management and prevention of the diabetic foot, IWGDF, 2007,* and *Transcutaneous Oximetry in Clinical Practice: Consensus statements from an expert panel based on evidence, Fife et al. 2009)*, emphasize the importance of supporting the measured ABPI value with additional objective vascular test for correct diagnosis of PAD in patients with diabetes, CLI and end-stage renal disease. It is well known that the number of diabetics is increasing worldwide and, with an ageing population, so will the number of CLI patients. Many of these patients have calcified arteries showing falsely high ABPI values. In addition, ABPI only reflects the macrovascular status, but the microvascular status also plays an important	Thank you for your comments and references. We agree about the risk of elevated pressures in diabetes mellitus. We have acknowledged this in the guideline (see section 7.3.3 in the full guideline). The recommendations relating to ABPI relate to the diagnosis of PAD. This usually takes place in primary care and we would agree with you that in this circumstance ABPI is usually sufficient. There are separate guidelines on the management of diabetic foot problems to which the guideline refers. The predictive value of tcp02 and toe pressures were not identified as priority for the guideline and no evidence in this area was reviewed by the GDG and therefore we cannot make any recommendations. This could be an area for consideration in a future update of the guideline.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						role in patients with CLI and diabetic foot ulcers. Furthermore, neuropathy, present in many diabetics, may "mask" the classical clinical signs of PAD such as walking- and rest pain. The feet may even appear warm and red, clinical signs atypical for an ischemic foot. Toe pressure or/and tcpO2 are hence recommended as accurate, additional, objective test in these patients. Moreover, toe pressures and tcpO2 are considered to provide better predictive value for assessing severity of PAD as well as wound healing potential whenever an ulcer is present. It is even questioned whether an ABPI>0.6 has any predictive value at all in these patient groups. Besides, time is an important factor in the salvation of limbs and a correct diagnosis early, is necessary to make the appropriate clinical decisions. With respect to this, we therefore believe that it is important to stress this risk for underestimation of PAD in these particular patient groups in order to increase the awareness and attention amongst those diagnosing these patients. We also think it is important to mention the alternative methods available. Furthermore, there is not a clear distinction between diagnosing PAD in the primary care and the much more demanding diagnosis in secondary care. For primary care the ABPI normally sufficient, even if the guideline lacks information on when to refer to secondary care and what pitfalls to look out for, but, for secondary care, specialized staff and more advanced diagnostic methods such as the mentioned toe pressure and tcpO2, are needed. This is stressed in the consensus documents	

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						mentioned earlier. As an example: Three recommendations from the European Society for Vascular Surgery, CLI Guideline Committee *(European Journal of Vascular and Endovascular Surgery (2011) 42(S2), S4–S12):* • Ankle systolic pressure (absolute value or ABI) is not a reliable parameter for CLI diagnosis. (Level 2b;Grade B) • Toe pressure measurement is more accurate and is recommended in all patients with suspected CLI. (Level 2b; Grade B) • Assessment of distal tissue perfusion pressure by forefoot TcPO2 measurement should be recommended for diagnostic validation and prognostic stratification, at least in the setting of clinical trials. (Level 2b; Grade B)	
SH	Perimed AB	27.01	Full	General		REFERENCES 1. International Working Group on the Diabetic Foot (IWGDF) Practical guidelines on the management and prevention of the diabetic foot 2012, 2. European Society for Vascular Surgery, CLI Guideline Committee (ESVS) Guidelines for Critical Limb Ischaemia and Diabetic Foot, 2011 3. TASC II The Trans- Atlantic Inter-Society consensus for the Management of Peripheral Arterial Disease, 2007	Thank you for your references.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						4. International Working Group on the Diabetic Foot (IWGDF) Practical guidelines on the management and prevention of the diabetic foot 2007 5. Fife, Smart, Sheffield, Hopf, Hawkins, Clarke Transcutaneous Oximetry in Clinical Practice: Consensus statements from an expert panel based on evidence, 2009	
SH	Perimed AB	27.02	Full	14	11	No referral to alternative techniques. Several recent consensus documents strongly recommend determination of toe pressure and/or toe brachial pressure index (TBPI) in addition to the ABPI. Ankle pressures can be falsely elevated due to media sclerosis in patients with diabetes and renal insufficiency. This unreliability in ankle pressure measurements supports assessment of toe pressure and/or TBPI and measurement of tcpO2 for more accurate diagnosis of PAD. IWGDF uses threshold values of TBPI < 0.7 for PAD, and toe pressure < 50 mmHg or tcpO2 < 30 mmHg for CLI.	Thank you for your comment. We were unfortunately unable to cover all areas and focussed upon those that were suggested as critical areas to address during the scoping phase of guideline development. Therefore, the issue of toe pressure was not reviewed. This could be an area for consideration in a future update of the guideline.
SH	Perimed AB	27.03	Full	38	14	ABPI can be complemented with toe pressure assessment and/or TBPI and measurement of tcpO2 to avoid the risk of underestimation of PAD. ABPI values may be falsely elevated in patients with diabetes, end-stage renal disease or CLI due to calcification of the arteries.	Thank you for your comment. We were unfortunately unable to cover all areas and focussed upon those that were suggested as critical areas to address during the scoping phase of guideline development. Therefore, the issue of toe pressure was not reviewed. This could be an area for consideration in a

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							future update of the guideline.
SH	Perimed AB	27.04	Full	39	33	ABPI can be complemented with toe pressure assessment and/or TBPI and measurement of tcpO2 to avoid the risk of underestimation of PAD. ABPI values may be falsely elevated in patients with diabetes, end-stage renal disease or CLI due to calcification of the arteries.	Thank you for your comment and references. We were unfortunately unable to cover all areas and focussed upon those that were suggested as critical areas to address during the scoping phase of guideline development. Therefore, the issue of toe pressure was not reviewed. This could be an area for consideration in a future update of the guideline.
SH	Perimed AB	27.05	Full	61	16	Several consensus documents (References 1-5) strongly recommended determining TBPI and/or toe systolic pressure and tcpO2 for more accurate assessment of PAD in patients with long-standing diabetes, CLI, end-stage renal disease and advanced age- as ABPI may be falsely elevated in these patients and thereby conceal the presence of disease. Furthermore, toe pressure and tcpO2 have proven to provide better predictive value to establish severity of PAD and assess wound healing potential.	Thank you for your comment and references. We were unfortunately unable to cover all areas and focussed upon those that were suggested as critical areas to address during the scoping phase of guideline development. Therefore, the issue of toe pressure was not reviewed. This could be an area for consideration in a future update of the guideline.
SH	Perimed AB	27.06	Full	61	27	Why has no literature search been performed regarding diagnostic studies comparing ABPI with toe pressure or tcpO2?	Thank you for your comment. Toe pressure or tcpO2 was not considered as a comparison and therefore no literature search was conducted.
SH	Perimed AB	27.07	Full	67	16	In the section ”Trade off between clinical benefits and harms”: In particular in diabetics, CLI and end stage renal disease patients whom may have falsely elevated ABPI values due to calcification of the arteries.	Thank you for your comment. This potential problem with ABPI has been acknowledged in the relevant linking evidence to recommendations in section 7.3.3. of the full guideline.
SH	Perimed AB	27.08	Full	69	4	An additional review question ought to be: “In people with suspected PAD or CLI, do ABPI, TBPI and TcpO2 result in different diagnostic	Thank you for your comment. We are unable to include further review questions at this stage. This could be an area for consideration

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						accuracy?"	in a future update of the guideline.
SH	Perimed AB	27.09	Full	73	17	"Other considerations" In these cases a toe pressure or tcpO2 is of better diagnostic value. Hence TBPI and tcpO2 measurements should be added into the text.	Thank you for your comment. We did not review the evidence on toe pressure and can not make reference to this in the recommendations or linking evidence to recommendations table.
SH	Perimed AB	27.10	Full	222	6	Important to note is that it is not enough to diagnose the severity of the disease relying only ABPI measurement. Patients can be missed due to falsely elevated ABPI values or regarded as less severe. In CLI, both macrocirculation and microcirculation is involved and many consensus documents strongly recommend the use of toe pressure and tcpO2in these patients.	Thank you for your comment. We agree and the GDG have recommended that diagnosis is based on clinical assessment, history taking and ABPI. We did not consider toe pressures and tcpO2 in our evidence review. Please also refer to the above comments.
SH	Perimed AB	27.11	Full	234	11	Determinations of tcpO2 and toe pressures in patients with CLI should be included in "Recommendations".	Thank you for your comment. This area was not reviewed by the GDG and therefore we cannot make any recommendations on tcpO2 or toe pressures.
SH	Perimed AB	27.12	Full	266	1	In this section, nothing is mentioned about objective methods such as tcpO2 that has been proven useful to determine the correct level for amputation.	Thank you for your comment. We were unfortunately unable to cover all areas and focussed on those that the GDG suggested as key areas to address.
SH	North of England Cardiovascular Network	28.00	General			The NECVN welcomes the production of this NICE Guidance and hope that it will enable patients with Peripheral Arterial Disease to receive better treatment in the NHS. In particular the NECVN LSAG welcomes the emphasis on secondary prevention of cardiovascular risk factors and the need to encourage patients with PAD, and their health professionals, to act and intervene appropriately.	Thank you for your comment. We are encouraged by the stakeholder's support particularly in relation to the secondary prevention of cardiovascular risk factors.
SH	North of England Cardiovascular Network	28.01	Full	37	30	Hyperlipidaemia or if preferred, dyslipidaemia, should be mentioned specifically, so instead of "the key modifiable risk factors, such as smoking, managing diabetes, diet, weight and	Thank you for your comment. We have amended the wording of the recommendation to include hyperlipidaemia.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						exercise" we recommend "the key modifiable risk factors, such as smoking, improving diabetes glycaemic control, **hyperlipidaemia** and lifestyle factors including diet, weight and exercise"	
SH	North of England Cardiovascular Network	28.02	Full	38	3	Instead of "lipid modification and statin therapy" we recommend "lipid modification" ,since other non-statin treatments may be required.	Thank you for your comment. After reconsideration we have not altered the wording of the guidance as the GDG wished to specifically mention statins, which they consider to be relevant to most of those with PAD. However the guidance does cross-refer to the lipid modification guidance including statins.
SH	North of England Cardiovascular Network	28.03	Full	39	23	Instead of "lipid modification and statin therapy" we recommend "lipid modification" , since other non-statin treatments may be required.	Thank you for your comment. After reconsideration we have not altered the wording of the guidance as the GDG wished to specifically mention statins, which they consider to be relevant to most of those with PAD. However the guidance does cross-refer to the lipid modification guidance including statins.
SH	North of England Cardiovascular Network	28.04	Full	59	Section 6.1.3 ; line 8.	After line 8 we recommend addition of a further sentence; "Dependent on response after optimisation of statin treatment, or where side effects limit such use, other lipid modifying agents may need to be considered, as in detailed in CG67, CG71 and or TA132."	Thank you for your comment. The related NICE guidance is referred to in section 2.6.
SH	North of England Cardiovascular Network	28.05		6	Key priorities	In addition the to "prevention, diagnosis and management of diabetes" and "the prevention, diagnosis and management of high blood pressure" the guidance should recommend "the diagnosis and management of hyperlipidaemia" (or dyslipidaemias if the latter term is preferred (see below)	Thank you for your comment. We have amended the wording of the recommendation to include hyperlipidaemia.
SH	North of England Cardiovascular Network	28.06		9	1.3	The guidance fails to recognise that specific lipid disorders are associate with lipid abnormalities in PAD and may require	Thank you for your comment. We have amended the wording of the recommendation

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						additional investigations to confirm the diagnosis with referral to appropriate specialists if required (e.g. Familial Dysbetalipiproteinaemia, Familial Hypercholesterolaemia, Familial combined Hyperlipdiaemia and Hyperlipiporotein(a)). Therefore in addition the to "prevention, diagnosis and management of diabetes" and "the prevention, diagnosis and management of high blood pressure" the guidance should recommend "the diagnosis and management of hyperlipidaemia" (or dyslipidaemias if the latter term is preferred	to include hyperlipidaemia.
SH	North of England Cardiovascular Network	28.07				Duplex ultrasound as first line investigation for PAD may not be appropriate, particularly in aorto-iliac disease, although good investigation for fem/pop disease.	Thank you for your comment. The GDG considered that Duplex US was a suitable first line investigation in most cases and may avoid the need for more expensive and invasive investigations.
SH	North of England Cardiovascular Network	28.08				Some confusion in the guidance in that Duplex in one section is stated as preferred investigation, then MRA is preferred in advance of any intervention: seems costly and inefficient to scan any patient unless intervention is planned and if MRA is required by NICE prior to intervention, why put in an extra investigation? Perhaps distinction needs to be made around suspected level of disease? For example, we often go straight to angioplasty for SFA stenosis if Duplex suggest no significant inflow disease and suitable lesion for angioplasty. However if Duplex and/or clinical history and examination suggests aorto-iliac disease, we would usually get MRA (or CTA if MR not possible due to patient factors) before proceeding.	Thank you for your comment. We do not consider that the recommendations would be at odds with your current practice or lead to duplication of investigations as MRA is only recommended in those "who need further imaging", which would not preclude proceeding to treatment without MRA in those in whom the Duplex provided sufficient information.
SH	North of England Cardiovascular Network	28.09				The statement on Not stenting aorto-iliac stenosis is based only on short term outcome data. There is some evidence of improved long term patency after stenting for severe iliac	Thank you for your comment. We have reviewed all the evidence that met our criteria and found no evidence of long term benefit that would justify the cost of routine stenting.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						stenosis compared to angioplasty so this should be taken into account.	
SH	North of England Cardiovascular Network	28.10				25 Offer contrast-enhanced magnetic resonance angiography to people with peripheral arterial 26 disease who need further imaging before considering an intervention. Add :CT angiography can be used instead since it offers superior imaging is the vessel diameter needs measuring and the vessels wall assessing for calcifications or aneurysmal disease.	Thank you for your comment. NICE recommendations are phrased according to the standards set out in the NICE technical manual.
SH	North of England Cardiovascular Network	28.11				25 13. Use bare metal stents where stenting is indicated for the treatment of intermittent claudication. There is level I RCT evidence that covered stent grafting is offering a better patency for TASC C AND D A comparison of covered vs bare expandable stents for the treatment of aortoiliac occlusive disease. Vasc Surg. 2011 Dec;54(6):1561-70. Epub 2011 Sep 9.	Thank you for your comment and reference. The GDG were of the opinion that covered stent grafts are really a different category of device that would require separate consideration with different comparators and patient populations. The GDG did not prioritise this device. This could be an area for consideration in a future update of the guideline.
SH	North of England Cardiovascular Network	28.12				16. Consider naftidrofuryl oxalate for the treatment of intermittent claudication – THE "EVIDENCE" IS VERY DOUBTFULL BASED ON ONE REVIEW IT IS AROUND SINCE 50 YEARS AND HAS NEVER DONE ANYTHING	Thank you for your comment. Naftidrofuryl was recommended based on the evidence reviewed for the NICE TA 223.
SH	North of England Cardiovascular Network	28.13	General			We welcome the production of this NICE Guidance and hope that it will enable patients with Peripheral Arterial Disease to receive better treatment in the NHS.	Thank you for your comment.
SH	North of England Cardiovascular Network	28.14				Under Section 1.4.1, we are concerned that duplex ultrasound may not be the best first line	Thank you for your comment. The GDG considered that Duplex US was a suitable first

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						imaging for patients with absent femoral pulses as iliac disease is not well identified. If intervention is being considered then such patients are better having MR or CT angiography as a first line investigation. We are in agreement that supervised exercise programmes should be available for people with intermittent claudication, however not all patients would be suitable for these and the exact type of exercise needs to be specified as well as its duration. Equally in Section 1.5.2, the statement that supervised exercise has not led to a satisfactory improvement in symptoms needs to be qualified by the duration of the programme. We would recommend a 6 month period as minimum be stated. In Section 1.5.2 we think the use of the word reinforced in relation to advice is confusing especially as it refers back to Section 1.2.1 in which not just advice but also the drug treatment with statins and antiplatelet agents is specified. We would prefer a statement that is more definite about what is required here. In effect advice, support and drug treatment should have been tried for a period of time, probably 6 months at minimum. We agree that there is little evidence supporting chemical sympathectomy; however we feel that there may still be a place for this in patients where other modalities of treatment have failed and the patient does not wish to proceed to amputation. An exception would be diabetic patients with significant neuropathy. Anecdotally we feel it may work I some patients. We are not aware of any trial that the patient could currently be enrolled in, at present.	line investigation in most cases and may avoid the need for more expensive and invasive investigations in some cases. Thank you for your comment. We have added a recommendation on features that could be considered for a supervised exercise programme, including reference duration of the programme. The GDG did not feel they could recommend more than a 3 month period due to the lack of evidence around the long-term effects of supervised exercise. Thank you for your comment. We hope the stakeholder is supportive of the research recommendation for chemical sympathectomy. Thank you for your comment. The GDG did not feel they could comment on the specific questionnaires as we did not review the evidence. This may be an area for a future update of the guideline.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						Although suggested that details of diagnostic questionnaires are out of the scope of the guidelines - arguably this is a fairly important aspect for primary care so some more coverage may be needed here. No evidence was reported comparing clinical assessment to ABPI Also needed is advice on the use of toe rather than ankle level pressure measurements in patients with rigid / calcified arteries (which can be found in diabetes, renal disease, connective tissue disease as example diseases). There is uncertainty on which methodology is best to use in measurement and reporting (acclimatization time ?10 minutes, obtain pressure measurements from ?2 or 3 ankle arteries, body position ?supine, and ABPI calculated using ?highest or lowest ankle pressure reading). This may put some people attempting this assessment. Also what is the cost?	Thank you for your comment. Thank you for your comment. The GDG did not review the evidence on toe pressures. However, this may be an area for inclusion within a future update of this guideline. Thank you for your comment. We agree that there is uncertainty on the best measurements. The GDG came to a consensus recommendation in an effort to standardise the measurement. The costs are given in section 7.2.1.2.
SH	RCGP	29.00	General			The guidelines do appear relevant to primary care. Not clear though on the regional variation in the offer and provision of structured exercise programmes.	Thank you for your comment. The GDG are aware that there is a wide variation in the availability of supervised exercise programmes across England and Wales. For this reason, they placed a high priority on determining the clinical and cost effectiveness of supervised compared to unsupervised exercise. Based on the results of this analysis, supervised exercise was found to be the most clinically and cost-effective option for the treatment of people with intermittent claudication. The GDG recognise that there

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							will be a cost associated with implementing this recommendation where supervised exercise programmes are not already available. The NICE implementation team will provide a cost impact assessment for trusts to use in planning for the delivery of these programmes.
SH	HEART UK	30.00	Full General			HEART UK welcome the emphasis on secondary prevention of cardiovascular risk factors and the need to encourage patients with PAD, and their health professionals, to act and intervene appropriately.	Thank you for your comment.
SH	HEART UK	30.01	Full	37	30	Rather than: "the key modifiable risk factors, such as smoking, managing diabetes, diet, weight and exercise" we recommend "the key modifiable risk factors, such as smoking, managing diabetes and hyperlipidaemia, diet, weight and exercise"	Thank you for your comment. We have amended the wording of the recommendation to include hyperlipidaemia.
SH	HEART UK	30.02	Full	37	30	Rather than: "the key modifiable risk factors, such as smoking, managing diabetes, diet, weight and exercise" we recommend "the key modifiable risk factors, such as smoking, managing diabetes and hyperlipidaemia, diet, weight and exercise"	Duplicate. Please see comment above.
SH	HEART UK	30.03	Full	38	3	Rather than: "lipid modification and statin therapy" we recommend "lipid modification" ,since other non-statin treatments may be required.	Thank you for your comment. After reconsideration we have not altered the wording of the guidance as the GDG wished to specifically mention statins, which they consider to be relevant to most of those with PAD. However the guidance does cross-refer to the lipid modification guidance.
SH	HEART UK	30.04	Full	39	23	Rather than: "lipid modification and statin therapy" we recommend "lipid modification" , since other	Thank you for your comment. After reconsideration we have not altered the wording of the guidance as the GDG wished

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						non-statin treatments may be required.	to specifically mention statins, which they consider to be relevant to most of those with PAD. However the guidance does cross-refer to the lipid modification guidance.
SH	HEART UK	30.05	Full	59	Section 6.1.3 ; line 8.	After line 8 we recommend addition of a further sentence; "Dependent on response after optimisation of statin use, or where side effects limit such use, other lipid modifying agents may need to be considered, as in CG67 and or TA132."	Thank you for your comment. We were unable to locate the section the stakeholder referred to, as there is no section 6.1.3. The related NICE guidance is referred to in section 2.6.
SH	Faculty of pain Medicine at Royal College of Anaesthesia	31.00	Full	23	Chapter 11	Most of the previous questions compared a standard treatment to another standard treatment; whereas chemical sympathectomy (CS) has been compared with pharmacological therapy that has no evidence in direct use on PAD? Why was this particular question selected?	Thank you for your comment. The review question was developed by the GDG, which included a pain specialist. The GDG discussed the various options available and decided on those options based on clinical experience and knowledge.
SH	Faculty of pain Medicine at Royal College of Anaesthesia	31.01	Full	260	2,3	There will not be any comparisons as none of these drugs are used as a gold standard for treating critical limb ischemia (CLI). There are many observational studies available to show that CS improves pain management and prevents amputation.	Thank you for your comment. The review included the most commonly used pain management options for CLI based on the GDG clinical experience and knowledge. The GDG discussed the possibility of observational studies for chemical sympathectomy and included these in our literature search (see appendix C for the review protocol). Whilst the GDG recognise that there are observational studies, no evidence was found comparing chemical sympathectomy to the GDG were interested in.
SH	Faculty of pain Medicine at Royal College of Anaesthesia	31.02	Full	261	4	It is interesting to see that one third of the sympathectomies were done on in-patients. We would assume that most of the in-patient sympathectomies are to try and control pain in patients, who can otherwise not be discharged from vascular inpatient beds. Do we have the data on this? Or where they in-patients for other	Thank you for your comment. These data are based on HES data. This does not provide additional details of the indications for sympathectomy and, whilst we accept the potential shortcomings of such data, these were considered to be the best estimates available to the GDG.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						reasons. Any economic data derived from this data cannot be used without sufficient details.	
SH	Faculty of pain Medicine at Royal College of Anaesthesia	31.03	Full	261	10	Wrong question asked.	Thank you for your comment. We disagree that that the wrong question was asked. The review question was developed by the guideline development group, which included a pain specialist and was based on their clinical experience and knowledge.
SH	Faculty of pain Medicine at Royal College of Anaesthesia	31.04	Full	262	Recommendation 23	We are concerned about the guideline encouraging the use of strong opioids without strong evidence. Also on the recommendations (other considerations paragraph 5), that dosing increase with no ceiling can have implications. We as pain physicians are currently dealing with a large number of inappropriately high dose users of strong opioids in the community. This suggestion also contradicts the NICE guidelines on the management of Neuropathic pain.	Thank you for your comment. We disagree that the guideline is recommending the use of strong opioids. We have discussed the comments further and have added in to the recommendations that patients requiring ongoing opioid management should be referred to a pain specialist. We hope that this new recommendation will avoid the situations suggested by the stakeholder. We disagree that the recommendations contradict the neuropathic pain guideline. The evidence review in the current guideline was in relation to managing ischaemic pain.
SH	Faculty of pain Medicine at Royal College of Anaesthesia	31.05	Full	265	CS heading-Paragraph 2 line 14	"Placebo effect was also noted to be common in Pain management". We disagree to this statement, as placebo effect is present in every intervention that a medical profession offers to a patient and cannot be generalised to pain management. Do we have evidence to prove that outcome of a bypass surgery is not placebo related?	Thank you for your comment. We agree that the placebo effect is present in every intervention. However, the use of RCT evidence can control for the placebo effect. In the case of bypass surgery, there was RCT evidence to support its use. In contrast, we did not find any RCT evidence for the pain management options the GDG were interested in. Therefore, the GDG felt comfortable in making this statement.
SH	Faculty of pain Medicine at Royal College of Anaesthesia	31.06	Full	275	7	We agree that all other options should be used before embarking on amputation. There is enough observational study evidence that CS can be useful. Why is this not considered by the GDG?	Thank you for your comment. The GDG recognised that observational evidence may be available and for this reason we looked for this evidence (see the review protocol see appendix C of the full guideline)Unfortunately

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						Ref: Aliu Sanni*, Arief Hamid, Joel Dunning Is sympathectomy of benefit in critical leg ischaemia not amenable to revascularisation?, Interactive CardioVascular and Thoracic Surgery 4 (2005) 478–483	no evidence was found comparing chemical sympathectomy to the other treatment options as stated in the protocol. Thank you for your reference. We have looked at the paper. This paper does not meet our inclusion criteria as stated in the review protocol (see Appendix C in the full guideline). The cohort studies in the review paper use either surgical sympathectomy (which was not the intervention of interest),or did not include the comparisons the GDG were interested in or did not include a comparison intervention group.
SH	RCN	32.00	General			The Royal College of Nursing welcomes this guideline. It seems fairly comprehensive.	Thank you for your comment.
SH	Baxter Healthcare Ltd	33.00	Full	41	7	We suggest that, although the list of options is quite comprehensive, a more detailed explanation of the options would make it clearer. For example, in relation to the co-morbidities, it may be worthwhile giving a few examples of co-morbidities like diabetes, coronary disease, etc, and for the pattern of the disease, it may be worthwhile clarifying whether it means acute or chronic.	Thank you for your comment. The GDG did not feel that the recommendation required this level of detail.
SH	Baxter Healthcare Ltd	33.01	Full	41		The scope of surgical intervention as a management option for critical limb ischemia has been well covered in this document along with the non surgical interventions. Whilst discussing the surgical option (vascular reconstruction) and especially for purposes of patient education, we feel that it would be beneficial to include the role of certain adjuncts to operative surgery e.g. synthetic sealants. The use of synthetic sealants in vascular reconstructive procedures is an evidence based	Thank you for your comments. We are unfortunately unable to cover all areas and focussed upon those that were suggested by stakeholders and GDG members as the most important areas to address. Detailed aspects of operative techniques were not in the scope of this guideline.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						intervention which we feel is worthy of mention in the guidance document. Moreover, the role of synthetic sealant in itself forms an important variable in the intra-operative environment and the post operative environment in terms of patient recovery and post operative complications. We feel that expanding the guidance to include intra-operative management would help in optimizing the surgical plan whether prior to, or during the surgery. This would further help to elucidate the role of surgical adjuncts like synthetic sealants, methods for haemostasis, reconstructive materials, etc.	
SH	Baxter Healthcare Ltd	33.02	Full General			We feel that the inclusion of guidance related to post operative management of patients undergoing angioplasty and bypass surgery would be important. While the guidance document provides an excellent protocol of the proposed diagnostic protocol with relation to the pre op and intra operative management, we did not find any guidance related to post operative management. Surgical management forms an important route for a selected cohort of patients and the post operative guidance along with a detailed intra-operative guidance would be of benefit. In particular, this would guide the clinician to tailor the post operative management keeping the same variables into consideration that were taken into account while considering the surgical option in the first place e.g. – co-morbidities, pattern of disease, etc, along with an optimized follow up protocol (clinic appointment, investigations etc).	Thank you for your comment. The post operative management was outwith the scope of this guideline.

These organisations were approached but did not respond:

3M Health Care UK
Abbott Vascular Devices
Abertawe Bro Morgannwg University NHS Trust
Action on Smoking and Health
Airedale NHS Trust
AMORE health Ltd
AMORE Studies Group
Anglian Community Enterprise
AntiCoagulation Europe
Association of Anaesthetists of Great Britain and Ireland
Association of British Insurers
Association of Clinical Pathologists
Atrium Medical Corporation
Avon, Gloucestershire and Wiltshire Strategic Health Authority
Basildon and Thurrock University Hospitals NHS Foundation Trust
Bayer HealthCare
Bayer Schering
Bradford District Care Trust
Bristol-Myers Squibb Pharmaceuticals Ltd
Bristol-Myers Squibb Pharmaceuticals Ltd
British Association for Cardiovascular Prevention & Rehabilitation
British Association for Nursing in Cardiovascular Care
British Association of Prosthetists & Orthotists
British Cardiovascular Society
British Infection Association
British Medical Association
British Medical Journal
British National Formulary
British Society for Antimicrobial Chemotherapy
British Society of Interventional Radiology
British Society of Interventional Radiology
BUPA Foundation
C. R. Bard, Inc.
C. R. Bard, Inc.
Cambridge University Hospitals NHS Foundation Trust
Camden Link
Capsulation PPS
Cardiac and Stroke Networks in Lancashire & Cumbria

Cardiff and Vale University Health Board
Care Quality Commission (CQC)
Chartered Society of Physiotherapy
Commission for Social Care Inspection
Covidien Ltd.
Cumberland Infirmary
Cumbria and Lancashire Cardiac and Stroke Network
Department for Communities and Local Government
Department of Health
Department of Health, Social Services and Public Safety - Northern Ireland
Dorset Primary Care Trust
East and North Hertfordshire NHS Trust
East Lancashire Hospitals NHS Trust
Faculty of Occupational Medicine
Frimley Park NHS Foundation Trust
George Eliot Hospital NHS Trust
GlaxoSmithKline
Gloucestershire LINk
Great Western Hospitals NHS Foundation Trust
Health Protection Agency
Health Quality Improvement Partnership
Healthcare Improvement Scotland
Hindu Council UK
Independent Healthcare Advisory Services
Institute Metabolic Science
Institute of Biomedical Science
iQudos
Johnson & Johnson
KCARE
Kidney Research UK
Lambeth Community Health
Lancashire Care NHS Foundation Trust
Lancashire Teaching Hospitals NHS Trust
Leeds Primary Care Trust (aka NHS Leeds)
Leg Ulcer Forum
Liverpool Community Health
Lothian University Hospitals Trust
Luton and Dunstable Hospital NHS Trust
McCallan Group, The
Medicines and Healthcare products Regulatory Agency

Medrad UK Ltd
Medtronic
Mental Heath and Vascular Wellbeing Service
Merck Sharp & Dohme UK Ltd
Ministry of Defence
National Institute for Health Research Health Technology Assessment Programme
National Institute for Health Research Health Technology Assessment Programme
National Patient Safety Agency
National Public Health Service for Wales
National Treatment Agency for Substance Misuse
NHS Bournemouth and Poole
NHS Bournemouth and Poole
NHS Clinical Knowledge Summaries
NHS Connecting for Health
NHS Islington
NHS Plus
NHS Sheffield
NHS Warwickshire Primary Care Trust
Norfolk and Norwich University Hospital
Norfolk Community Health and Care NHS Trust
Northumberland Hills Hospital, Ontario
Nottingham City Hospital
OPED UK Ltd
Otsuka Pharmaceuticals
Oxfordshire Primary Care Trust
Oxleas NHS Foundation Trust
P.M.S
Peninsula Community Health Services
PERIGON Healthcare Ltd
Pharmametrics GmbH
Primary Care Cardiovascular Society
Public Health Agency
Public Health Wales NHS Trust
ReNeuron Limited
Royal Berkshire NHS Foundation Trust
Royal Brompton Hospital & Harefield NHS Trust
Royal Brompton Hospital & Harefield NHS Trust
Royal College of Anaesthetists
Royal College of General Practitioners in Wales
Royal College of Midwives

Royal College of Obstetricians and Gynaecologists
Royal College of Paediatrics and Child Health
Royal College of Paediatrics and Child Health , Gastroenetrology, Hepatology and Nutrition
Royal College of Pathologists
Royal College of Physicians
Royal College of Psychiatrists
Royal College of Radiologists
Royal College of Surgeons of England
Royal National Institute of Blind People
Royal Pharmaceutical Society
Royal Pharmaceutical Society
Royal Society of Medicine
Sacyl
Sanofi
Scanmed Medical
Scarborough and North Yorkshire Healthcare NHS Trust
Scottish Clinical Biochemistry Managed Diagnostic Network
Scottish Intercollegiate Guidelines Network
Sheffield Teaching Hospitals NHS Foundation Trust
SNDRi
Social Care Institute for Excellence
Society of Chiropodists & Podiatrists
Society Of Vascular Nurses
South Asian Health Foundation
South Tees Hospitals NHS Trust
Southport and Ormskirk Hospital NHS Trust
Stockport Primary Care Trust
Target PAD
The British In Vitro Diagnostics Association
The Rotherham NHS Foundation Trust
Trafford NHS Provider Services
Trafford NHS Provider Services
UK Clinical Pharmacy Association
UK Ophthalmic Pharmacy Group
Urgo Medical Ltd
Welsh Government
Welsh Scientific Advisory Committee
West Midlands Ambulance Service NHS Trust
Western Cheshire Primary Care Trust
Western Health and Social Care Trust

Westminster Local Involvement Network
York Hospitals NHS Foundation Trust