National Institute for Health and Care Excellence

IP1714 Low intensity pulsed ultrasound to promote healing of delayed-union and non-union fractures

IPAC 10/05/18:

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 NHS professional	**General**	In my single surgeon series of 13 patients with clinical and radiological established non unions, I found the use of LIPUS satisfactory. All patients with established non unions were referred to me by my Consultant Colleagues (8 Consultants, 13 patients in total). Minimum time to referral after original fracture was 9 months (range 9-14 months). Over a period of 6-9 months with LIPUS, 12 out of 13 showed clinical and radiological union. I am an advocate of the use of LIPUS, to avoid further surgery and expensive implants and use of biologics such as BNP.	Thank you for your comments.
2	Consultee 2 NHS professional	**1.1 & General**	I work in the foot and ankle orthopaedic department at [redacted] – Specialist Orthopaedic Centre – as an advanced practitioner. We have been using LIPUS fairly regularly over the last 3 years for a variety of cases of delayed / non union following fracture, ORIF as well as elective foot / hind foot fusion surgery. We have been auditing our results as well as gathering patient reported outcome measures and have seen excellent results. We are yet to formally publish the results but hopefully this will happen in the next 6-12 months. The raw results :- 57 patients treated over 3 years	Thank you for your comment and sharing information about your experience. Efficacy data that have not been published or accepted for publication by peer reviewed journals are not normally selected for presentation to the committee. NICE would encourage clinicians to submit articles on the treatment of low-intensity pulsed ultrasound for consideration of publication by peer reviewed journals. IPAC may review the guidance upon publication of substantive new body of evidence in peer-reviewed journals. Costs of

			39 patients improved to the point of needing no further intervention – these were patients who would have otherwise been listed for revision / ORIF surgery. 1 patient improving and still on review 6 patients – no effect – went on to revision surgery or primary ORIF 4 patients – no effect – now not wanting to proceed with surgery / managing symptoms – on follow up 2 patients – not compliant with treatment 5 patients still on treatment We have seen: A mean reduction in MOXFQ score from 43 to 21 (max 64 – higher score = more pain / dysfunction) A mean reduction in VAS pain score from 7.3 to 2.6 A mean improvement in EQ5D5L index score from 0.46 to 0.73 (max 1 – no effect on quality of life) A mean improvement in Overall Health score 64 to 76 (max 100 = perfect health) These results have not yet been scrutinised / statistically analysed – only mean scores collated. Many patients had significant co-morbidities (Diabetes, heart disease, smokers etc). As a tertiary referral centre we receive a number of referrals asking for 2nd / 3rd opinions, complex cases of non-union. Having the ability to offer these patients, many of who have significant co-morbidities, a non-surgical and risk free way of solving their problem is invaluable. The only other options for treatment in these cases would be complex revision surgery or primary ORIF. These options come with significant risk to the patient. Economically, the cost of the treatment (which comes with a money back guarantee if ineffective when appropriately used and followed up), is far less than the costs associated with surgery	treatment is also outside the remit of this guidance. The IP Programme issues guidance on procedures after having reviewed the best existing evidence on its safety and efficacy. The Committee has considered that there is limited evidence on the efficacy of this procedure and has recommended 'special arrangements'. NICE guidance is advisory and it is a commissioner decision as to whether a service is commissioned. However, IPAC have indicated that providers using this procedure should do so with "special arrangements" for clinical governance, consent and audit or research. This recommendation is intended to address the practical steps that clinicians should take to carry out the procedure in relation to the hospital's clinical governance arrangements, the patient consent process and the collection of data. The committee recommended data collection by audit because the quantity of the evidence is currently inadequate and there are significant inconsistencies in the evidence on the efficacy of the procedure.

			and the aftercare required, particularly in the case of complications. Our results do not confirm radiological union in all cases where the treatment has improved / abolished symptoms as in many cases the only way to assess this would be with a CT scan – in the pain free patient this is not deemed to be ethical and a good reason for the development of a robust RCT in this area. I am aware that LIPUS has come under scrutiny in the past year, however the negative conclusions were drawn from studies where it was used on fresh fractures. This is not something we would advise and indeed have never attempted to use it on fresh fractures here. It would limit our treatment options if the ability to use LIPUS in the case of delayed / non-union was not supported by NICE, leaving risky revision surgery as the only option for this cohort of patients. I agree, as with ESWT, that we should: • Inform the clinical governance leads • Ensure that patients understand the uncertainty about the procedure's efficacy and provide them with clear written information to support shared decision-making. • Audit and review clinical outcomes of all patients having low-intensity pulsed ultrasound to promote healing of delayed-union and non-union fractures. As this will help grow the evidence base. For information, I have no affiliation to any company providing LIPUS, the machine we use in practice here is 'Exogen' supplied by [redacted]	

			In summation, we have had excellent results in terms of symptomatic relief, avoidance of revision surgery and radiographic union with 'simple' and 'complex' cases of non union utilising LIPUS. This has led to life changing improvements in pain and quality of life without the need for risky and costly surgical intervention. As you know, many CCGs will base their funding decisions around NICE guidelines and I hope, once this guideline is published, it will support its continued use in our specialist centre.	
3	Consultee 3 NHS professional	**1.1 & General**	I am writing to you to give my support in the use of LIPUS bone stimulation for delayed unions. I have used the Exogen bone stimulator for 3-4 patients this year who have failed to unite after 3-4 months of conservative management. If the bone stimulator does not work the other option is operative intervention with fixation which has cost implications and carries risks of infection, refracture around fixation and ongoing non-union. These patients are currently ongoing treatment and as such I cannot comment on my personal success rate with bone stimulation as of yet but the literature supports this form of management with a recent paper published in the foot showing 90% success rates and a cost saving of over £7000 a year when compared to operative fixation. **https://www.sciencedirect.com/science/article/pii/S0958259217301438** The aim of this study is to investigate the use of LIPUS treatment for delayed union of fifth metatarsal fractures. **Methods:** Retrospective review of patients who were treated with LIPUS following a delayed union of fifth metatarsal fracture was conducted over a three-year period. **Results:** There were thirty patients (9 males, 21 females) in our cohort. The average age was 39.3 years. Type 2 fractures made up 43% of our cohort. Twenty-seven (90%) patients went on to progress to union clinically and radiologically following LIPUS	Thank you for your comment and sharing your experiences. IP team added the recent publication listed by the consultee to appendix as larger studies with efficacy data are included in table 2 and economic costs are outside the remit of IP programme. Teoh KH, Whitham R et al (2018). The use of low-intensity pulsed ultrasound in treating delayed union of fifth metatarsal fractures. The Foot (in-press, accepted manuscript, available online January 2018).

			treatment. Smoking (p = 0.014) was predictive of non-union. Assuming that we had 10 delayed unions a year and 6 went on to non-union as previously suggested by a systematic review, the cost savings of using LIPUS (90% success rate; 10 LIPUS machine and surgery for 1 non-union) vs operative intervention (surgery for 6 non-union) equates to a cost saving of £7765 a year. **Conclusion:** There is a role for the use of LIPUS in delayed union of fifth metatarsal fractures and can serve as an adjunct prior to consideration of surgery. The findings of this study also suggest the use of LIPUS to be a cost effective treatment modality compared to surgical management. **Level of evidence: Level 4.**	
4	Consultee 4 NHS professional	**1.1 General**	I would like to share my experience of using Exogen on my patients with delayed and non union of Fractures in Foot and Ankle. Although it's is anecdotal evidence but I find current equipment for Exogen delivery more patient compliant with built in feature to help sure that it has been used consistently everyday. The device is now portable than form its early days. I have found that so far in all of my patients this has lead to bony Union in Fractures. I am currently using this on a delayed union of a firearm fracture as well. I would strongly support that this technology gets NICE approvals as it is way cheaper than undergoing revision surgery for delayed or nonunion and is non invasive. From health economics pint of view it makes sense that all Delayed non unions should have this stimulation tried and exhausted before embarking on repeat or initial surgery like 5th Metatarsal Fractures. I trust that this would receive a strong support from NICE on basis of its cost effectiveness and no / low harm. I would be more than happy to provide scientific evidence if required but I think you may already have all the latest info.	Thank you for your comment and sharing information about your experiences. Efficacy data that have not been published or accepted for publication by peer reviewed journals are not normally selected for presentation to the committee. NICE would encourage clinicians to submit articles on the treatment of low-intensity pulsed ultrasound for consideration of publication by peer reviewed journals. IPAC may review the guidance upon publication of substantive new body of evidence in peer-reviewed journals. Costs of treatment is also outside the remit of this guidance. The IP Programme issues guidance on procedures after having reviewed the best existing evidence on its safety and efficacy. The Committee has considered that there is limited evidence on the efficacy of this procedure and has recommended 'special arrangements'.

				NICE guidance is advisory and it is a commissioner decision as to whether a service is commissioned. However, IPAC have indicated that providers using this procedure should do so with “special arrangements” for clinical governance, consent and audit or research. This recommendation is intended to address the practical steps that clinicians should take to carry out the procedure in relation to the hospital’s clinical governance arrangements, the patient consent process and the collection of data.
5	Consultee 5 NHS professional	**General**	I am a Consultant Trauma and Orthopaedic Surgeon with over twenty years of experience in my field. My work is based at the [redacted]. I am the local clinical lead for this type of treatment. I have been using Exogen (one of the fracture healing products) for six years. Initially I stumbled by accident into the use with a patient who had a non-union of her plated forearm fracture in 2011. She did not want to have revision surgery. Within six weeks of using Exogen her fracture had healed. I have since learned about the science behind this treatment and have been involved in a prospective outcome audit of all patients being treated with Exogen in our Trust. We have submitted our findings to the next European Orthopaedic Congress. Our submission is of almost 100 patients with a union rate of 78%. This includes patients with and without surgery prior the their non-union at multiple sites. Also those who had nerve injuries during the primary surgery and would have been at significant risk of further complications with revision surgery. From our experience we learned to ensure we only treat patients with stable fractures that are not united. The gap must be under 1cm. Compliance is linked to successful outcome. The same as one cannot expect to cure an infection if one does not take the	Thank you for your comment and sharing information about your experiences. Efficacy data that have not been published or accepted for publication by peer reviewed journals are not normally selected for presentation to the committee. NICE would encourage clinicians to submit articles on the treatment of low-intensity pulsed ultrasound for consideration of publication by peer reviewed journals. IPAC may review the guidance upon publication of substantive new body of evidence in peer-reviewed journals. Costs of treatment is also outside the remit of this guidance. The current guidance is under review because significant new evidence has been published.

			antibiotics one cannot expect fracture healing if one does not apply the unit on a daily basis. We have saved our Trust well over £50000 since using Exogen. I believe there are flaws in some of the recent publications which may be the reason for the revision of the original NICE guidance on the use of Exogen.	NICE guidance is advisory and IPAC have indicated that providers using this procedure should do so with “special arrangements” for clinical governance, consent and audit or research. This recommendation is intended to address the practical steps that clinicians should take to carry out the procedure in relation to the hospital’s clinical governance arrangements, the patient consent process and the collection of data.
6	Consultee 6 NHS professional	**1.1 General**	I’ve being through all three sets of the documents and tend to agree with their findings. The only comment I would make is that the time to delayed union is not defined and the commissioners tend to use 9 months therefore we could potentially use LIPUS sooner than this, however in the longer document 9 months is stated. My data has never been published and is therefore anecdotal but approximately 60% of delayed/non-unions heal with LIPUS.	Thank you for your comments. Consultee agrees with the recommendations for all 3 related IP topics. IPAC noted that the definitions of delayed union and non-union fractures were different and authors have used a range of different definitions. In the systematic review by Rutten 2016 study 6 in table 2) *‘delayed union was defined as no union for 3 months and non-union was defined as no union for a period of 9 months or no progression of healing at 6 months following the fracture’.* IPAC considered your comment and added to section 2.2 a definition of non-union as follows: *“There is no agreed precise definition of a fracture non-union but, typically, it is considered to be when there is failure of bony union 6 to 9 months after the fracture”* NICE encourages clinicians to submit articles on the treatment of low-intensity

				pulsed ultrasound for consideration of publication by peer reviewed journals.
7	Consultee 7 NHS professional	**General**	The LIPUS treatment has been in use at our institution at [redacted] since Aug 2016. The clinics has been set up and been running successfully since then. Our main patient cohort has diagnosed delayed and non union fractures treated operatively and non operatively. We successfully enrolled 40 + patients so far and achieved satisfactory outcomes. However, We have not used LIPUS treatment in fresh fractures or high risk fractures.Please do not hesitate to contact if you need any further information.	Thank you for your comment and sharing information about your experiences.
8	Consultee 8 Company	**1.1**	Section 1.1: "The evidence for low-intensity pulsed ultrasound to promote healing of delayed-union and non-union fractures raises no major safety concerns. The current evidence on efficacy is inadequate in quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research." We strongly disagree with the underlined section, because when one considers the NICE requirements as defined by the Committee nothing has changed since the previous (IPG374) NICE 2010 and (MTG12) 2013 [1,2] reviews. The IPAC even concludes correctly that the 2018 NICE Rapid review confirms the 2010 and 2013 guidance: "Evidence shows that LIPUS treatment may be beneficial for delayed unions and non-unions and has the potential to accelerate healing."[3] •Under the Validity and generalizability of the studies section (p.20), the 2018 Overview document states under that "The majority of evidence was from randomised controlled trials"; however, both the Leighton 2017[4] and Seger 2017[5]	Thank you for your comments. IPAC considered your comment but decided not to change the guidance. The Committee has considered that there is limited evidence on the efficacy of this procedure and has recommended 'special arrangements'. NICE guidance is advisory and IPAC have indicated that providers using this procedure should do so with "special arrangements" for clinical governance, consent and audit or research. This recommendation is intended to address the practical steps that clinicians should take to carry out the procedure in relation to the hospital's clinical governance arrangements, the patient consent process and the collection of data. IP team acknowledges the error on page 20 that was inadvertently carried over from the original overview 810/2 and thank the consultee for pointing out the error. The team agrees with the consultee that a number of observational studies have been included in the systematic reviews and

			Systematic Literature Reviews (SLR) which were very specific to delayed- and non-union fractures included a number of observational studies that had also been previously included in NICE guidance from 2010 and 2013 as evidence supporting use of LIPUS (e.g., Nolte 2001[6], Lerner 2004[7], Gebauer 2005[8], Jingushi 2007[9]) •Further, the Validity and generalizability of the studies section (p.20) goes on to say that the RCT "quality was generally poor due to limitations such as high loss to follow-up, lack of blinding and allocation concealment; use of surrogate measures and potential publication bias" and that "All systematic reviews have suggested that trials are at high risk of bias". These statements are not consistent with findings of the Leighton 2017, Seger 2017, and Rutten 2016[10] SLRs, which were specific to or which had sub-analyses on non-union patients, all found the majority of studies in delayed-and non-union fracture patients to be of high-to-moderate quality, and LIPUS to be effective in fracture healing. The findings of these SLRs regarding safety and effectiveness of LIPUS also align with the previous critical appraisals by NICE from 2010 and 2013. •The Schandelmaier 2017 meta-analysis noted as a key evidence source did not include even a single delayed-union or non-union fracture in any efficacy outcome presented in the summary of findings (Table 3 therein) upon which the conclusions were based. Extrapolating results from a largely fresh fracture population (and one that did not specifically parse out high-risk patients) to other fracture types is scientifically inappropriate. Other conclusions in the NICE Rapid review concern other types of fractures and thus fall out of scope of the GID-IPG10085 review. Furthermore [redacted] kindly requests the Committee to also consider for their decision making, a very recent (2018), and highly relevant publication describing UK-based evidence which	amended the statements on pg 20 in the overview as follows: Four systematic reviews have assessed the effectiveness of LIPUS on delayed union and non-union fractures and found the treatment may be beneficial. Reviews had different inclusion criteria, evaluation techniques, and focused on different outcomes and indications. Studies included were mainly observational and LIPUS was used as an adjunct in some studies. A range of different definitions of fracture non-union were used by authors of primary studies. The systematic review by Schandelmaier 2017 included 3 RCTs on operatively managed non-unions (Schofer 2010, Ricardio 2006, Rutten 2012) and 2 RCTs on non-operatively managed stress fractures (Gan 2014, Rue 2004). However, pooled efficacy data presented in table 2 (from 15 studies of different types of fractures) included only 2 studies (Rutten 2012, Ricardio 2006) on non-unions. Therefore, the team agrees that this pooled evidence presented in table 2 is not highly relevant to this IP and deleted it.

			confirms the validity and appropriateness of the 2010 and 2013 NICE recommendations for delayed unions and non-unions, and demonstrating significant effectiveness, clinical utility and cost-saving impact of the EXOGEN LIPUS technology [11]. Given the aforementioned points and the fact that the NICE scope and assessment criteria have not changed, we would argue and propose that section 1.1. remains unchanged from the original 2010 and 2013 recommendations reflecting: “Current evidence on the efficacy of low-intensity pulsed ultrasound to promote fracture healing is adequate to show that this procedure can reduce fracture healing time and gives clinical benefit, particularly in circumstances of delayed healing and fracture non-union. There are no major safety concerns. Therefore this procedure may be used with normal arrangements for clinical governance, consent and audit”[1,2] **References:** 1.National Institute for Health and Care Excellence (NICE). Page 1, Section 1. Interventional Procedures Guidance (IPG374): Low-intensity pulsed ultrasound to promote fracture healing. 2010; https://www.nice.org.uk/guidance/ipg374/evidence/overview-pdf-495678493. 2.National Institute for Health and Care Excellence (NICE). Page 4, Section 1. Medical Technologies Guidance (MTG12): EXOGEN ultrasound bone healing system for long bone fractures with non-union or delayed healing. 2013; https://www.nice.org.uk/guidance/mtg12. 3. National Institute for Health and Care Excellence (NICE). Page 20, Validity and generalizability of studies. Interventional Procedures Guidance (GID-IPG10085): Low intensity pulsed ultrasound to promote healing of delayed-union and non-union fractures. 2018; https://www.nice.org.uk/guidance/indevelopment/gid-ipg10085.	IP team added the recent publication listed by the consultee to appendix as larger studies with efficacy data are included in table 2 and economic costs are outside the remit of IP programme. *Teoh KH, Whitham R et al (2018). The use of low-intensity pulsed ultrasound in treating delayed union of fifth metatarsal fractures. The Foot (in-press, accepted manuscript, available online January 2018).* NICE guidance is advisory and IPAC have indicated that providers using this procedure should do so with “special arrangements” for clinical governance, consent and audit or research. This recommendation is intended to address the practical steps that clinicians should take to carry out the procedure in relation to the hospital’s clinical governance arrangements, the patient consent process and the collection of data.

			4. Leighton R, Watson JT, Giannoudis P, Papakostidis C, Harrison A, Steen RG.Healing of fracture nonunions treated with low-intensity pulsed ultrasound (LIPUS): A systematic review and meta-analysis. Injury. 2017 Jul;48(7):1339-1347. 5.Seger EW, Jauregui JJ, Horton SA, Davalos G, Kuehn E, Stracher MA. Low-Intensity Pulsed Ultrasound for Nonoperative Treatment of Scaphoid Nonunions: A Meta-Analysis. Hand (N Y). 2017 Apr 1:1558944717702470. 6. Nolte PA, van der Krans A, Patka P, Janssen IM, Ryaby JP, Albers GH.Low-intensity pulsed ultrasound in the treatment of nonunions.J Trauma. 2001 Oct;51(4):693-702; discussion 702-3. 7. Lerner A, Stein H, Soudry M. Compound high-energy limb fractures with delayed union: our experience with adjuvant ultrasound stimulation (exogen). Ultrasonics. 2004 Apr;42(1-9):915-7. 8. Gebauer D, Mayr E, Orthner E, Ryaby JP. Low-intensity pulsed ultrasound: effects on nonunions. Ultrasound Med Biol. 2005 Oct;31(10):1391-402. 9. Jingushi S1, Mizuno K, Matsushita T, Itoman M. Low-intensity pulsed ultrasound treatment for postoperative delayed union or nonunion of long bone fractures. J Orthop Sci. 2007 Jan;12(1):35-41. 10. Rutten S, van den Bekerom MP, Sierevelt IN, Nolte PA. Enhancement of Bone-Healing by Low-Intensity Pulsed Ultrasound: A Systematic Review. JBJS Rev. 2016 Mar 29;4(3).	
9	Consultee 8 Company	**1.4**	Section 1.4: “Further research, preferably in the form of randomised controlled trials, should include details of patient selection, fracture site, and risk factors and comorbidities that delay fracture healing.” We disagree with this section. Since the NICE scope and assessment criteria have not changed, and as determined in the NICE 2013 guidance the Committee “recognised the difficulties in	Thank you for your comments. IPAC considered the comment and amended 1.4 as follows: 1.4 Further research should include details of patient selection, fracture site, and risk factors and comorbidities that delay fracture healing.

			conducting comparative studies (and specifically randomised controlled trials) to collect data on healing rates" [12]. While additional published studies can continue to strengthen the evidence base for delayed- and non-union fractures, [redacted] feels that sufficient evidence currently exists to support the use of LIPUS in these patients. Further, we feel that randomised controlled trials (RCTs) may not be the best approach for patients with this condition. Thus, from a clinical perspective, it would be unethical to withhold an effective treatment (either LIPUS or surgery) in patients with fractures known to be at high risk of non-healing. In addition, it is impractical or impossible to blind surgical intervention relative to LIPUS. We hope that our input will move the Committee to uphold the current guidance on LIPUS in delayed-union and non-union fractures as it falls in line with the current requirements confirmed by local real-world data in the UK, including that generated within the NHS [11,13]. References: 11.Teoh KH, Whitham R, Wong JF, and Kariharan K. 2018. The use of low-intensity pulsed ultrasound in treating delayed union of fifth metatarsal fractures. The Foot, in press. https://doi.org/10.1016/j.foot.2018.01.004. 12. National Institute for Health and Care Excellence (NICE). Page 11, Section 3.19. Medical Technologies Guidance (MTG12): EXOGEN ultrasound bone healing system for long bone fractures with non-union or delayed healing. 2013; https://www.nice.org.uk/guidance/mtg12. 13. Maidstone and Tunbridge Wells NHS Trust. Use of the EXOGEN ultrasound bone healing system for delayed and non-unions. 2014; https://www.nice.org.uk/sharedlearning/use-of-the-exogen-ultrasound-bone-healing-system-for-delayed-and-non-unions.	

10	Consultee 10 NHS professional		I have had a very positive experience using Exogen in complex fractures and non-unions and have encouraged my colleagues to do so. Patients have been happy with the results of this non-invasive treatment modality.	Thank you for your comment and sharing information about your experiences.

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