# National Institute for Health and Care Excellence

## IP1713 Low-intensity pulsed ultrasound to promote healing of fresh fractures at high risk of non-healing

**IPAC 10/05/18:**

| Com. no. | Consultee name and organisation | Sec. no. | Comments | Response<br>Please respond to all comments |
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| 1 | Consultee 1<br>Company | **1.1** | Section 1.1: “The evidence for low-intensity pulsed ultrasound to promote healing of fresh fractures at high risk of non-healing raises no major safety concerns. The current evidence on efficacy is very limited in quantity and quality. Therefore, this procedure should only be used in the context of research.”<br>We strongly disagree with the underlined section, because the majority of studies reviewed by the Committee in the current assessment do not apply to the intended patient population with fresh fractures at high risk of non-healing.<br>• Risk factors for fracture non-healing (i.e., non-healing) have been defined and elaborated in a number of studies[i]-[ii], and include fracture location and gap, traumatic fractures, smoking status, diabetes, osteoporosis, and advanced age. These distinctions should be considered when studying, and when evaluating evidence for LIPUS efficacy in the population with fractures at high risk of non-healing.<br>• Of the six key studies selected in the Committee’s assessment (IPG10084 overview document, Table 2, pp.9-25), only two address the distinct patient population with fresh fractures at high risk of non-healing, including Zura 2015[iii], and Rutten 2016[iv]. Zura 2015 assessed LIPUS in 4190 fresh fracture patients with key risk factors | Thank you for your comments.<br>The focus of majority of the studies included in the overview was on fresh fractures with low-risk of non-healing and/or medically induced fractures (eg osteotomy, distraction osteogenesis).<br>IP team agrees that some studies included in the overview (as listed by the consultee) did not distinguish between patients with fresh fractures at high-risk of non-healing and those with fresh fractures at low-risk of non-healing. |

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| | | | elaborated above, and found LIPUS to be significantly effective at reducing the rate of fracture non-union. Rutten 2016 included a sub-analysis in patients with traumatic fractures and also found LIPUS to be significantly effective (Rutten 2016, Figure 3, page 7).<br>• The other studies reviewed as evidence, including Schandelmaier 2017[v], Lou 2017[vi], Raza 2016[vii], and Simpson 2017[viii], focus on fresh fractures with low risk of non-healing and/or purposeful, medically-induced fractures (e.g., osteotomy, distraction osteogenesis which do not apply), and did not and could not distinguish between patients with fresh fractures at high risk of non-healing versus those with fresh fractures at low risk of non-healing. Given that only approximately 5% of fractures progress to non-union[ix], which is consistent with UK NHS real-world experience in clinical practice[x], studies analyzing pooled populations of all fracture types or unspecified/ unselected fresh fractures (e.g., Schandelmaier 2017, Lou 2017) would have a very small component of the pooled population reflective of fresh fractures at high risk of non-healing. Therefore, these studies reviewed do not apply to the current NICE assessment of LIPUS in this fracture population. | IPAC acknowledged that "*whilst only two studies focused on this distinct population the other studies are likely to include a proportion of patients with fractures at high risk of non-union and were therefore included for completeness. The committee recognized the limitations of these studies and took this into account in their decision making.*"<br>IPAC amended section 2.2 about risk factors as follows:<br>*" Risk factors for non-union of fractures include systemic medical conditions (for example, diabetes, malnutrition, osteoporosis); smoking; use of non-steroidal anti-inflammatory drugs; local factors such as infection; vascular problems; magnitude of injury (for example, fracture location and gap, traumatic fractures); advanced age and other iatrogenic factors..* |
| 2 | Consultee 1<br>Company | **1.2** | Section 1.2: "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". | Thank you for your comments.<br>The committee did not agree that it is unethical and |

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| | | | While additional published studies can continue to strengthen the evidence base for fresh fractures at high risk of non-healing, Bioventus believes, that contrary to draft recommendation 1.2 (Consultation document, Draft Recommendations, Section 1.2), randomised controlled trials may not be the best approach for patients with this condition. This is why we are investing in a large observational trial, the BONES study (https://clinicaltrials.gov/ct2/show/NCT03382483). The design of the BONES study has been developed in collaboration with the FDA as part of their "big data" initiative, and will incorporate a propensity-matched comparison of the heal rate of fresh fractures at risk of non-healing in patients who have been prescribed LIPUS, versus a control group derived from a commercial database.<br>• Given it would be unethical and impractical to withhold an effective treatment (either LIPUS or surgery) in patients with fractures known to be at high risk of non-healing, randomised controlled trials (RCTs) would be inappropriate for evaluating effectiveness in this patient group. That is, it would be unethical to treat these patients with a sham LIPUS device (i.e., non-treatment) as a control. In addition, it is impractical or impossible to blind surgical intervention relative to LIPUS.<br>• In the 2013 NICE document, the Committee "recognised the difficulties in conducting comparative studies (and specifically randomised controlled trials) to collect data on healing rates" (Section 3.19, p.11)[xi].<br>• Standard evidence appraisal methodology does not require blinded RCTs to consider evidence as high quality. Specifically, the Cochrane Handbook (which is referenced within the NICE guideline manual[xii]) states: "A study may be performed to the highest possible standards yet still have an important risk of bias. For example, in many situations it is impractical or impossible to blind participants or study personnel to intervention group. It is inappropriately judgemental to describe all such studies as of 'low quality', but that does not mean they are free of bias resulting from knowledge of intervention status."[xiii] | inappropriate to conduct randomised controlled trials.<br>However, IPAC amended 1.2 as follows:<br>1.2 Further research should include details of patient selection, fracture site, and risk factors and comorbidities that delay fracture healing. |

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| 3 | Consultee 2<br>NHS professional | **General** | I've being through all three sets of the documents and tend to agree with their findings.<br>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.<br>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.<br>Consultee agrees with the recommendations for all 3 related IP topics.<br>IPAC noted that the definitions of delayed union and non-union fractures were different and authors have used a range of different definitions.<br>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'.<br>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"*.<br>NICE encourages clinicians to submit articles on the treatment of low-intensity |

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| | | | | pulsed ultrasound for consideration of publication by peer reviewed journals. |

*"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."*