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Instructional review of key factors to achieve successful outcomes when using low-intensity pulsed ultrasound in fracture repair

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- Low-intensity pulsed ultrasound (LIPUS) treatment of fractures has been available to the orthopaedic community for nearly three decades; however, it is still considered an experimental treatment by some clinicians, even though there is a wealth of clinical data.
- Based on the evaluation of clinical trial data, we have established key criteria which can lead to LIPUS success and avoid failure. These are fracture gap size and stability, accurate transducer placement and minimum treatment number.
- However, from a clinician's view, the correct attitude to treatment must be observed, and this has also been discussed.
- It is hoped, armed with this new evaluation of the clinical data, that clinicians can treat patients with LIPUS more effectively, resulting in fewer failures of treatment.

Keywords
- fracture
- LIPUS
- ultrasound

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Introduction

Fracture incidence is common, with over one million fractures occurring each year in the United Kingdom alone (1). However, failure to heal a fracture is rare, with Zura *et al.* (2) reporting a non-union rate of just 4.9% in 309,330 fractures, but when it does occur this can be disabling to the patient. Most definitions of non-union involve a time factor from the index injury of up to 9 months. During this time, the patient is placed in a state of limbo, not knowing if their fracture is healing normally, is slowly healing, is progressing to a non-union or where further intervention is necessary. The healing of a fracture requires well-orchestrated events to occur (3); however, primarily, the bone ends need to be adequately reduced and stabilized, providing the correct strain environment for bone and/or cartilage to form, depending on the method of fixation. Giannoudis and colleagues (4) highlighted these principles in the diamond concept of fracture repair, where reduction of the fracture ends is demonstrated by the concept that an osteoconductive scaffold is required for healing to progress, with the correct mechanical development. The final two factors are growth factors and osteogenic cells, which in a young healthy individual should be comfortably provided for; therefore, when correctly stabilized, the majority of fractures heal without incident. However, in some individuals, significant biological factors can impair fracture healing, and in these instances, a biological stimulation is required.

Treatment of fractures can be a demanding endeavour for clinicians. In ideal circumstances, the biology of healing will allow for the union of a majority of fractures. When fractures fail to heal, the sequelae can be challenging for clinicians and devastating for patients. The time required for the healing of fresh fractures can have a serious economic impact for the patient. In the 5% of patients who go on to non-union, that economic impact can increase exponentially. While non-union of a fracture can occur in any patient, there are known risk factors that can increase this likelihood. These risk factors include smoking (5), diabetes (6), advanced age (7) and osteoporosis (8).

Low-intensity pulsed ultrasound (LIPUS) has been used to accelerate the process of fracture repair in humans since it was first reported in 1983 by Xavier and Duarte

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(9). In 1994, it was approved in the United States for accelerated healing of certain fresh fractures. By 2000, LIPUS had also been approved in the United States for the treatment of established non-unions. The science behind LIPUS has been well studied (10, 11, 12). The ultrasonic waves produced by LIPUS devices can transmit through soft tissue to the bone and can penetrate through the bone cortex (10). LIPUS has the ability to enhance key biologic processes involved in bone repair. These include angiogenesis (13, 14), progenitor cell recruitment and differentiation (15, 16) and callus mineralization and remodelling (11, 17). This allows for the repair process steps including inflammation, soft callus formation and hard callus formation. When LIPUS is transmitted through soft tissue to the bone, the mechanical signal induces cells to create a biochemical response via integrin mechano-receptors (18, 19). This response allows the cells to increase the production of cyclooxygenase 2, which stimulates molecules to enhance the fracture repair process (12, 20). LIPUS is sensed by cell–matrix adhesions through vinculin, which in turn modulates a Rab 5-Rac1 pathway to control ultrasound-mediated endocytosis and cell motility (21). LIPUS overcomes the necessity of engagement or expression of syndecan-4 during the process of focal adhesion formation (18, 22).

For the orthopaedic clinician, bone healing is the primary aim that is strived for. LIPUS has been demonstrated to be effective as an adjunctive non-invasive treatment for established non-unions (23, 24, 25). In addition, LIPUS has been demonstrated to accelerate the time to healing for fresh fractures in skeletally mature patients where the fractures have been managed by closed reduction and cast immobilization (26, 27). It is reassuring to know that these parameters remain true in patients with the aforementioned risk factors (25), and when internal fixation has been performed to allow for the stability of the fracture site and reduction of fracture gap (28). This indication for both established non-unions and indicated fresh fractures adds to the armamentarium of the orthopaedic trauma surgeon dealing with challenging fractures and an equally challenging patient population.

Over the years, there have been many studies investigating the potential of LIPUS to enhance fracture healing. Currently, there are eight level-1 studies (26, 27, 29, 30, 31, 32, 33, 34) showing the positive effects of LIPUS on bone repair and multiple studies on non-union demonstrating heal rates in the mid 80% (23, 24, 25). In the paper by Zura *et al.* (25), in 767 fractures greater than 12 months old, treatment with LIPUS resolved 86% of these fractures, which had an average of 3.1 previous surgical procedures prior to LIPUS treatment. However, the question remains, why did the remaining 14% not respond to this treatment? This may be addressed with some of the outcomes in this review. Similarly, as already discussed, multiple level-1 studies showed the positive effects of LIPUS on bone healing, but a level-1 study on 501 tibia fractures showed that LIPUS did not accelerate fracture repair in this patient cohort (35).

This article sets out to establish if there are aspects of treatment with LIPUS that can lead to improved outcomes.

Gap size stability and fracture fixation

Good orthopaedic practice is required to achieve fracture healing. The concepts of reduction and stabilization must be met for LIPUS to stimulate a biological response to heal the fracture. This was first identified in a continuous retrospective study on non-united fractures at 6 months or more post-surgery (36). In this study, the 6-month consolidation rate was 88%. The authors identified factors that prevented healing with LIPUS, namely that bone healing correlated significantly with the stability of the internal fixation assembly and with an inter-fragmentary gap of less than 10 mm ($P = 0.01$). It was proposed in a surgical treatment flow chart that LIPUS should only be used when these two components of fracture repair were met, and if not, a surgical revision should be made. Further to this, a group in Japan (37) evaluated a consecutive cohort of 101 delayed unions and 50 non-unions treated with LIPUS. The heal rates in this study were 68% for non-unions and 74.3% for delayed unions. Failure to heal with LIPUS was associated with instability at the fracture site and fracture gap sizes greater than 8 mm, which is in close agreement with the earlier study. It is known that the ultrasound from the LIPUS beam cannot pass through metal (38), and a study evaluating callus formation in fractures stabilized with an intramedullar nail showed that the callus immediately behind the nail did not show enhanced healing, but the anterior, medial and lateral calluses were all significantly enhanced compared to control fractures (39). Other studies, including level-1 studies, have shown that LIPUS can positively affect fracture repair with metal fixation, both plates and intramedullary nails (29). In cases where the fracture is fixed with an intramedullary nail, the health care professional needs to pay particular notice to the healing processes in the ‘shadow’ of the LIPUS beam and reposition the site of application as they see fit.

Fracture targeting

As the LIPUS intensity is 30 mW/cm^2, which is considered low when comparing other modalities, such as medium-intensity ultrasound used in physical therapy and high-intensity focused ultrasound for surgical excision, the question invariably arises: can the ultrasound from LIPUS reach deep-seated fractures such as those located in the diaphysis of the femur or humerus? This question has been addressed scientifically in that an intensity as low

as 2 mW/cm^2 can elicit a biological effect (40) and that the LIPUS beam can theoretically pass through ~10 inches (254 mm) of tissue (41). Clinically, when comparing data on deep-seated bones, LIPUS demonstrated a heal rate of 95.6% in femurs ($n = 431$) and 95.7% in the tibia ($n = 981$) (42), therefore suggesting that the depth of penetration is not a major concern in treating fractured bones with this technology. However, although intensity may not be an issue, accurate targeting of the fracture gap with the ultrasound transducer might present some concerns. This was demonstrated in a study of 69 consecutive delayed unions of the humerus ($n = 19$) or femur ($n = 50$), for which LIPUS was applied. Fractures of participants were detected by x-ray, but a portion of patients received extra targeting of the fracture with visualization ultrasound or sonography (43). Forty-three bones (15 humerus and 28 femurs) were targeted by x-ray alone, and 26 bones (4 humerus and 22 femurs) were targeted by x-ray and sonography. The bone union rate for fractures located with x-ray was 58% (60% for humerus and 57% for femurs) and with x-ray plus sonography was 77% (75% for humerus and 77% for femurs). Bone union rate was significantly higher when the two visualization methods were used to target the fracture ($P < 0.05$).

Patient compliant use

Another major concern when providing a patient with a 'self-use' device is the reliance of the treating physician that the patient will use the device appropriately. In a large placebo-controlled trial to evaluate LIPUS in accelerating fracture repair, it was discovered that the percentage of subjects who used the device greater than or equal to 18 min per day over 80% of the days in their treatment period was 44.6% for the LIPUS-treated group and 42.3% for the placebo (44). To address this issue, some manufacturers have developed a usage monitor to assess the compliance of treatments. In one study, 12,984 data files were analysed from patients prescribed either a device that did not capture LIPUS use or one with a compliance calendar. The incorporation of the calendar feature resulted in compliance never decreasing below 76% over the analysis period, whereas compliance with the product without treatment monitoring fell to 51% (45).

The addition of LIPUS devices that can capture treatment usage has led to studies being conducted that measure treatment to outcome success. One study evaluated patients monthly after discharge from the hospital, to assess fracture healing (46). Bone healing was defined as evidence of callus bridging or disappearance of fracture line in three of four cortices, as assessed on anteroposterior and lateral plain radiographs. The percentage of days that LIPUS was used divided by the number of possible days of usage was used as the LIPUS usage rate. The number of days and the usage rate of LIPUS were analysed for 229 bones with a heal rate of 96.5%. Receiver operating characteristic analysis was performed to determine the effect of LIPUS usage rate on bone healing. The cut-off value for LIPUS usage rate was 57.1%, separating cases with and without bone union (sensitivity 79.2%, specificity 75% and area under the curve = 0.779). The results of this indicate that LIPUS must be applied at least 60% of the time to impact bone healing. In a previous study, LIPUS was used by 26 patients who had failing to heal of lower limb fractures, separating the LIPUS treatment compliance to either high at ≥80% or low compliance as <80%. The outcome of the high compliance resulted in a heal rate of 86%, whereas the outcome of low compliance resulted in a heal rate of 58% (47).

Length of treatment

The question of how long to maintain LIPUS treatment often arises. Primarily when LIPUS was used to accelerate acute fracture repair, the answer was simply to use the device once a day until the fracture healed. In the case of level-1 evidence, this was for 20 weeks for the tibia to achieve a 38% acceleration in healing (26, 27). However, LIPUS is also indicated for non-union fractures where it achieves high levels of success. In two prospective cohort studies (level-II), non-union heal rates were demonstrated to be 85% and 86% (23, 24). While these data are undoubtedly impressive for a device that affects the biology of bones within the body, without breaking the skin, it remains that 14–15% of people in these studies did not heal, and therefore the clinician needs to understand if their individual patient is not responding to LIPUS and plan a revision surgery. A study where data from a previous prospective multicenter study on LIPUS treatment for postoperative delayed union and non-union of long bone fractures were reanalysed demonstrated that the final outcome could be predicted with radiological progression of healing at certain time points (48). The patient's fractures were regularly radiographed, and an assessment was made as to whether there was radiological progression. If the fracture was treated within 6 months of the last surgical intervention and then after 5 months of LIPUS treatment if it was considered that fracture healing had progressed since the first x-ray, then with continued treatment 96% of these fractures would eventually heal. However, at this same time point, if no difference was seen over the history of treatment, then 100% of these would fail to heal, even with continued LIPUS treatment. If LIPUS treatment was started after 6 or more months after the last operation then the chance of healing after 5 months of treatment was 82% if the changes had been observed radiographically, but at this time if radio-progression was not seen there was still a 33% chance that the fracture would still heal.

Number of compliant days of use vs fracture age

Fractures do appear to remain responsive for a considerable period. In a study, it was reported that for 767 fractures of greater than 12 months in duration, the heal rate of LIPUS was 86.2%. There was no statistical drop off with heal rate from 1 year to 10 years post-fracture. Only after 10 years, was there a statistical drop off in the heal rate to 63.2% ($n = 19$) (25). To the authors of this article, the longest time that a fracture has successfully responded to LIPUS is 30 years (Mr M Morris, personal communication, Chesterfield UK).

To understand the average number of LIPUS treatments needed to resolve non-unions of different ages, data from three non-union sources were reanalysed. Data from Gebauer's study in 2005 (24) and Nolte's study in 2001 (23) were used to propensity score data from a large FDA database (25) to increase the pool of non-unions. Zura *et al.* (25) restricted fractures to those older than 365 days at treatment start. However, the youngest fracture in the level-2 studies analysed was 178 days at treatment start. Therefore, the Zura registry data source (25) was opened to fracture ages ≥178 days to 365 days. This added 1132 records eligible to be pooled with the Zura data, which had 767 records. The combined data will be referred to as Zura (2015)+or Zura+ for short (Table 1).

Propensity score

In the experimental context, a propensity score is the probability to be treated, given the reasons to be treated. In the current analysis, the subjects from all three data sources had been treated with LIPUS so, what is the treatment? For this analysis, Gebauer/Nolte serves as the treated group and Zura+ as the untreated group. A propensity score estimated this way will be used to identify Zura+ subjects who most resemble the Gebauer/Nolte subjects. This will enlarge the set of Gebauer/Nolte like non-union subjects for further analyses. The propensity score was estimated using logistic regression. The dependent variable was Gebauer/Nolte (assigned 1) and Zura+ (assigned 0).

If any of these characteristics is imbalanced between Gebauer/Nolte and Zura+, then there is greater potential for bias when interpreting their pooled outcomes. Therefore, the goal of the propensity score methods is to demonstrate balance in these characteristics before proceeding with a pooled analysis. Note that separate bone covariates were not used due to the variety of bones and sample sizes. Instead, bones were classified, and the classifications became surrogates for bone covariates.

After the propensity scores are estimated with logistic regression, the Gebauer/Nolte propensity scores are compared to the Zura+ propensity scores. Finding close matches from Zura+ subjects for all the Gebauer/Nolte subjects was the goal. There can be more than one close match, and up to five were allowed. Unfortunately, seven Gebauer subjects did not find at least one qualifying match in Zura+ and were, therefore, not included in the analyses. The standardized mean differences between Gebauer/Nolte and Zura+ before and after propensity score selection are displayed in Fig. 1. Differences within the shaded area are negligible.

Before propensity score adjustment, all differences except current smoking and fracture age were negligible. After propensity score selection, all differences were negligible. This demonstrates balance on all covariates.

On analysis of the data, we have found that there is a correlation between the age of the fracture non-union and the number of LIPUS treatments needed to achieve healing. The average number of LIPUS treatments needed to treat fractures which are 6 months old was 139.8; this increased to 179.5 treatments for fractures greater than 6 months to 24 months, and for fractures greater than 24 months old the average number of treatments needed to heal these fractures was 237.68 (Table 2). These data are particularly useful in helping clinicians decide when to abandon LIPUS treatment and plan a surgical intervention, as can be observed from the Kaplan–Meier

Table 1 Records which were not included in analysis.

Reason	Reason for exclusion	Gebauer *et al.* (24)	Nolte *et al.* (23)	Zura *et al.* (25)	Total
	Sample size before exclusions	67	29	1899	1995
Replicate records	Zura+ ≥178 days to 356 days had replicate fracture bone/ types*	0	0	13	13
Surgery	Gebauer and Nolte allowed qualified past surgeries. Zura+ excluded all surgeries.	0	0	685	685
Joints	Knee, ankle, shoulder, wrist, hip	4	1	115	120
Disqualified	Foot, other, phalanx, vertebra	0	0	11	11
Missing	Smoking status missing	0	0	153	153
Missing	Age missing	0	0	1	1
Total excluded		4	1	978	983
Total included		63	28	921	1012

*Nine records in the registry had the exact same subject, fracture bone and days to heal/fail. Four records had the exact same subject and fracture bone but different days to heal/fail. The longest days to heal/fail were used.

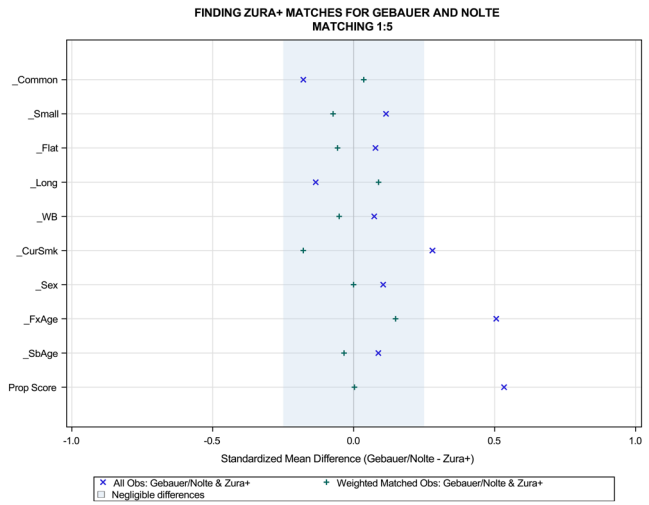

Figure 1
Standardized mean differences between Gebauer/Nolte and Zura+ before and after propensity score selection.

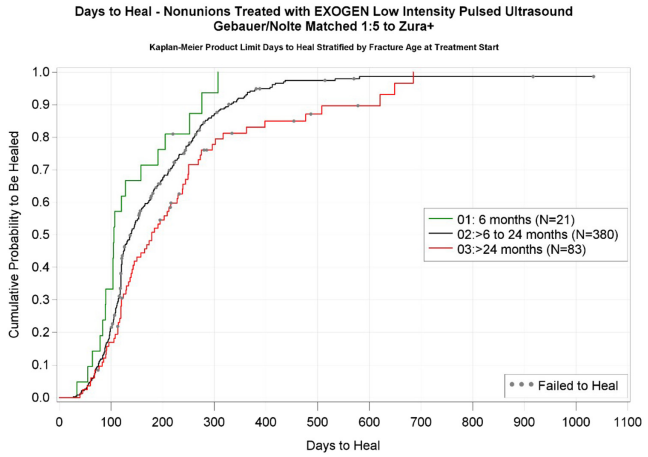

Figure 2
Kaplan–Meier curve illustrating days to heal of non-unions that were 6 months old, between 6 months and 24 months old and, >24 months old when LIPUS treatment began. Gebauer and Nolte matched 1:5 with Zura+.

curve in Fig. 2. Some fractures that were considered to be unresponsive to LIPUS might have healed if treatment had continued, whereas others could have ceased treatment early. An example of this would be the four failures in the >6- to 24-month group with greater than 500 treatments. It would seem reasonable that these fractures would not be responsive to LIPUS, and the treatment pathway could have been changed earlier.

Type of non-union: hypertrophic vs atrophic non-union responsiveness

There is a discussion that LIPUS should not be used for atrophic pseudarthrosis/non-union (49). From a meta-analysis of non-union data, it can be shown that hypertrophic non-unions benefitted more than biologically inactive atrophic non-unions with LIPUS. However, this does not mean that atrophic non-unions do not respond to LIPUS. In the same analysis, it was shown that hypertrophic healed at 84.7% (139/164) and atrophic/oligotrophic at 76.9% (291/378) (50). In specific studies, Mayr *et al.* (51) also showed that both forms of non-union can respond to LIPUS in their paper demonstrating that atrophic non-union healed at 83.3%, whereas hypertrophic healed at 100%. In addition, a study performed in the UK which only recruited atrophic non-unions demonstrated a union rate of 93% (52). Finally, in a study performed in France of 59 non-united fractures, 58 of these were defined as atrophic. The heal rate of these atrophic non-unions was 88% (36). These data indicate that atrophic non-unions can respond to LIPUS to achieve consolidation.

Table 2 Average number of LIPUS treatments needed to treat non-unions of various duration.

Fracture time frame	Mean (S.E.M.) treatments	50% quartile	Lower limit	Upper limit
6 months	139.8 (17.56)	106	89	158
>6 to 24 months	179.5 (5.95)	138	124	154
>24 months	237.7 (20.81)	179	141	228

The impact of the surgeon/physician on the efficacy of LIPUS

Over the 25 years that the LIPUS has been in widespread clinical use, a large volume of evidence has been collected to support its efficacy and its success. This evidence is from basic science research (12, 18, 13) as well as from clinical trials (26, 24, 29), and large volumes of real-world data reported both scientifically and anecdotally (52, 53, 54). However, at the same time, there has also been significant evidence suggesting that LIPUS is not successful in the stimulation of bone healing (55, 56, 57). Numerous personal anecdotes are damaging to its reputation. It is important, however, to be aware that individual trial design might not be applicable to all aspects of LIPUS use, such as studies on the acceleration of fresh fracture healing that are not useful in determining if LIPUS is useful in non-union treatment.

As clinicians and scientists, this is both fascinating and frustrating. A close inspection of this negative evidence or anecdote demonstrates that user error is a common cause of the discrepancy. After a decade of clinical experience with LIPUS in a regional trauma centre and close observation of its use, it is clear that several common mistakes are made which can be shown to significantly reduce the efficacy of LIPUS in achieving the desired outcome. Broadly speaking, these fall into errors of patient (or fracture) selection, poor

understanding of the desired effect, poor support of good compliance and practical errors. These are clinical errors in the use of what is, after all, a medical device.

As discussed earlier in this article and elsewhere, it has been shown that accurate patient/fracture selection, marking of the fracture site and the transducer position and compliance all have a significant impact on the efficacy. What has not yet been formally investigated is why some patients may have low compliance and why some surgeons continue to make the same technical errors, even in the face of poor outcomes in their patient groups.

There can be a failure amongst surgeons to fully understand the technical aspects of the use of LIPUS, but the clinician's attitude can be just as important and impactful. We, as clinicians, routinely take responsibility for monitoring the effect of and evaluating the success or failure of any intervention that we prescribe or carry out. Perhaps, because of its non-invasive and patient-directed nature, as well as its excellent safety record, surgeons may feel less of a sense of responsibility towards the ongoing management and review of LIPUS treatment. However, we do retain responsibility for the clinical decision to use LIPUS, its cost as well as the ongoing monitoring and management of the patients with their injury or non-union.

Clinicians need the willingness to engage in both up-to-date education about the appropriate indications for the use of LIPUS and an improved understanding of how to achieve the best efficacy from its use.

Patient and injury selection

Both clinicians and researchers need to understand what exactly they are trying to achieve when using or investigating LIPUS. They need to compare the results to the efficacy of other common interventions. Surgery for non-union is not 100% effective either. Not all acute fractures unite, even when appropriately managed. For example, the use of LIPUS in healthy patients with acute fractures that are well reduced and stabilized (35, 55) is unlikely to reveal significant differences in accelerating fracture repair compared to placebo, given that a very high proportion of these would be expected to unite uneventfully in a reasonable time frame.

When using LIPUS in elderly, high-risk, comorbid and complex fracture patients, or in long-standing non-unions, we have to accept that whatever our treatment of choice there will be a failure rate. LIPUS is no different. It is the surgeon's responsibility to select the right management for the right patient and the right injury and to monitor that treatment appropriately.

Compliance

It is unclear why certain individuals, or cohorts of patients, exhibit such low compliance with a painless, side-effect-free and relatively uncomplicated treatment regime. Our hypothesis, when reviewing results, in a unit with a long experience of high-volume use, is that this appears to relate to two factors: surgeons' attitudes and patients 'buy in'. This first came to our attention when investigating the disparity in outcomes and efficacy between upper and lower limb cases. A qualitative review of the surgeons' indications and attitudes to LIPUS, communication with the patient, follow-up protocols as well as the impact of the non-union itself on the patients' activities of daily living all pointed to a cohort who were 'set up to fail'.

The attitude of the prescribing surgeon towards the use of LIPUS is important. This attitude is often highlighted by the choice of language used by prescribers. Those with insight into its mode of action and its place in the management of acute fractures or in non-unions refer to it as an 'adjunct' or a 'non-operative treatment option'. They use terms such as 'encourage' or 'stimulate' the bone to heal. They explain to the patient the time frame required for a beneficial effect and continue to actively follow-up with the patient at regular intervals looking for signs of progress to union as well as issues with the LIPUS treatment itself.

Others often use terms such as 'trial of ultrasound', 'nothing to lose' or 'give it a go'. Some have been seen to have LIPUS prescribed to use whilst on the waiting list for revision surgery which gives an unclear message to the patient about their faith in the treatment. Their patients are given the device with little or no education and go for long periods without clinical review or further imaging. Patients respond to the input of the surgeon and to being held accountable. Patients who are asked to bring their machines to their clinic appointments to allow for compliance checks by their surgeon are likely to be more motivated.

Holistic patient selection is just as important as it is with our surgical decision-making. Patients with complex psycho-social issues or addictions may struggle with compliance. Surgeons need careful discussion with patients, as well as their families or carers, about likely compliance before prescribing the use of LIPUS.

Another hypothesis to explain the different compliance rates is the impact of the injury or non-union itself on the patient's daily activities and ongoing fracture management. This is highlighted in the differing efficacy in complex lower limb injuries as compared to scaphoid non-unions.

Lower limb injuries affect weight-bearing status, mobility and most daily activities. Many are in casts, splits or external fixators such as Ilizarov frames. Failure of treatment in this group has an immediate impact. Many scaphoid non-union patients, especially with non-dominant side injuries, are able to carry out many daily activities, often with the support of just a splint. Many

are relatively asymptomatic from the non-union, and the desire to achieve solid union is to prevent future complications in the wrist which can be difficult for patients to comprehend. The impact of the non-union may be less or less immediate.

Unlike the craft of surgery and fracture fixation, the technical aspects of the use of LIPUS are not complicated nor difficult to assimilate. But the impact of poor application of the device, poor patient or injury selection as well as poor surgeon engagement is no less detrimental to its efficacy than the same errors made in surgical practice. To achieve results in the clinical setting that can be demonstrated in research trials, it is imperative that we learn these lessons and review our practice.

Discussion

The LIPUS technology has been used in the orthopaedic field for a considerable time, with the device known as Exogen being approved by the FDA for accelerating fracture repair as early as 1994 (26). However, the efficacy of LIPUS and its precise mode of action was demonstrated at a much later stage than the actual commercialization of the original system. This has in many ways produced the views held by many practitioners that it is a device of 'last resort', which has led to it being used inappropriately in situations that clearly required surgical intervention. Although the scientific and clinical results have gathered pace and reached critical mass in some indications, the device has failed to shake off this reputation. Busy surgeons predominantly learn by a mentorship approach and often cannot or will not find the time to delve into the nuances of the literature and science behind every device they use. This is one of the reasons that changing surgical practice is so difficult and practice altering research even when backed by the holy grail of level-1 evidence struggles to pervade into clinical practice for many years, if at all.

The data for non-unions using the Exogen device were reviewed originally by National Institute for Health and Care Excellence (NICE) in 2013; it was shown it could provide both a clinical and financial benefit to the NHS when compared to surgical alternatives (MTG12) (58). The evidence was reviewed again in 2019, and NICE did not change the guidance on efficacy but increased the cost savings from £1164 to £2407 per patient saving for non-union when compared with current/standard management, through avoiding surgery (59). However, there are other aspects of the original guidance (2013) that has yet to be fulfilled which include the correct audit of the use of these devices at a national level. This would allow monitoring of outcomes and inform clinicians and managers of variation in practice that could influence outcomes. It should also narrow variance and improve the consistency of a gold standard for use.

LIPUS has been demonstrated to perform consistently well when used correctly. The precise method of use alongside clinician and patient engagement is key to positive outcomes. One of the recommendations from the LIPUS expert user group in the UK was to have LIPUS champions to enhance compliance and avoid mixed messaging to patients. The use of the device requires engagement, and this is usually harnessed by education and positive messaging alongside readily available support. This can be difficult to achieve in busy outpatient services predominantly staffed by clinicians that are 'rotating' through the hospital. Limb reconstruction services have a proven model of improved outcomes by the engagement of dedicated nurses and physiotherapists who support patients undergoing prolonged external fixator regimes. We would recommend a similar service to improve access, efficacy and the need for surgery for that small group of patients per year that would benefit from the use of LIPUS.

In this review, we have demonstrated that key components need to be satisfied to achieve consistently positive results when using LIPUS to treat fractures that are either slow to heal or where the healing response has ceased completely. These key criteria are:

- Fracture gap size (<10 mm)
- Stability of the fracture site
- Accurate placement of the transducer
- Appropriate treatment times and high daily use compliance

The concept of adequate reduction and stabilization of the fracture is part of the basic orthopaedic process and was highlighted in the diamond concept of fracture repair. It must be remembered that the LIPUS signal initiates a biological stimulus, and this should not be substituted for good orthopaedic practice. The activity of LIPUS can only enhance the body's response to repair and not grossly manipulate the bone ends of a fracture. Until recently, very little was known about the efficacy on accurately targeting the fracture site with the LIPUS. However, from clinical data emerging from Japan, this would appear to be a very important factor. We would not necessarily suggest that ultrasound fracture location should replace radiographic methods; however, the complementary use of radiographs with ultrasound location, especially in the position that the patient plans to use the device, may be beneficial to the final outcome.

As already outlined, the number of treatments needed to treat fractures has not been established. In the first LIPUS level-1 fracture, study patients were instructed to treat their fracture for 20 weeks (140 treatments) or until healed (26). The LIPUS group healed on average at 96 days; however, this was an acute fracture study and from

the reanalysis of studies in this review, we have shown that the length of duration that the non-union has persisted contributes to the number of treatments needed to resolve a non-union. On average, 140 treatments will be sufficient to treat a fracture with a 6-month duration, but an extra 100 treatments will be needed to resolve a fracture that has persisted for greater than 24 months.

The LIPUS technology has now been available for clinicians for over 25 years, but critical parameters for success have only recently been determined. It is hoped, that armed with this new data, clinicians can treat patients more effectively with fewer failures.

ICMJE Conflict of Interest Statement
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Author contribution statement
AH: Performed majority of writing and paper concept; MR: Wrote the majority of 'Introduction' section ; MT: Wrote 'The impact of the surgeon/physician on the efficacy of LIPUS' section; AM: Wrote the majority of the 'Discussion' section; JJ: Performed statistical input and wrote analysis; AY: Contributed to the fracture gap size, fracture stability and fracture targeting; YW: Contributed to the fracture gap size, fracture stability and fracture targeting.

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