

## Medical Policy



### Title: Ultrasound Accelerated Fracture Healing Device

#### Professional

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Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>With fresh fractures (surgically managed and nonsurgically managed)</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Low-intensity pulsed ultrasound as an adjunct to routine care</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Routine care without low-intensity pulsed ultrasound</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Symptoms</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Quality of life</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>With fracture nonunion or delayed union fractures</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Low-intensity pulsed ultrasound as an adjunct to routine care including surgery, if appropriate</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Routine care including surgery, if appropriate, without low-intensity pulsed ultrasound</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Symptoms</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Quality of life</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>With stress fractures, osteotomy sites, or distraction osteogenesis</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Low-intensity pulsed ultrasound as an adjunct to routine care</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Routine care without low-intensity pulsed ultrasound</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Symptoms</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Quality of life</li> </ul>

**DESCRIPTION**

Low-intensity pulsed ultrasound (LIPUS) has been investigated as a technique to accelerate healing of fresh fractures, surgically treated closed fractures, delayed unions, nonunions, stress fractures, osteotomy sites, and distraction osteogenesis. LIPUS is administered using a transducer applied to the skin surface overlying the fracture site.

**OBJECTIVE**

The objective of this policy is to evaluate whether, compared with routine care without low-intensity pulsed ultrasound, low-intensity pulsed ultrasound improves the net health outcome when used as an adjunct to routine care to treat fractures (including fresh fractures, surgically treated closed fractures, delayed unions, nonunions, stress fractures, osteotomy sites, and distraction osteogenesis).

**BACKGROUND****Bone Fractures**

An estimated 7.9 million fractures occur annually in the United States. Most bone fractures heal spontaneously over the course of several months following standard fracture care (closed reduction if necessary, followed by immobilization with casting or splinting). However, approximately 5% to 10% of all fractures have delayed healing, resulting in continued morbidity and increased utilization of health care services.<sup>1</sup> Factors contributing to a nonunion include which bone is fractured, fracture site, degree of bone loss, time since injury, extent of soft tissue injury, and patient factors (eg, smoking, diabetes, systemic disease).<sup>1</sup>

**Fracture Nonunion**

There is no standard definition of a fracture nonunion.<sup>2</sup> The Food and Drug Administration has defined nonunion as when "a minimum of 9 months has elapsed since injury and the fracture site shows no visibly progressive signs of healing for a minimum of 3 months." Other definitions cite 3 to 6 months of time from the original injury, or simply when serial radiographs fail to show any further healing. These definitions do not reflect the underlying conditions in fractures that affect healing, such as the degree of soft tissue damage, alignment of the bone fragments, vascularity, and quality of the underlying bone stock.

**Delayed Union**

Delayed union is generally considered a failure to heal between 3 and 9 months after fracture, after which the fracture site would be considered to be a nonunion. Delayed union may also be defined as a decelerating bone healing process, as identified in serial radiographs. (In contrast, nonunion serial radiographs show no evidence of healing.) It is important to include both radiographic and clinical criteria to determine the status of fracture healing. Clinical criteria include the lack of ability to bear weight, fracture pain, and tenderness on palpation.

## Treatment

Low-intensity pulsed ultrasound (LIPUS) has been proposed to accelerate healing of fractures. LIPUS is believed to alter the molecular and cellular mechanisms involved in each stage of the healing process (inflammation, soft callus formation, hard callus formation, and bone remodeling). The mechanism of action at the cellular level is not precisely known, but it is theorized that LIPUS may stimulate the production or the activities of the following compounds that contribute to the bone healing process: cyclooxygenase-2, collagenase, integrin proteins, calcium, chondroblasts, mesenchymal cells, fibroblasts, and osteoblasts.

LIPUS treatment is self-administered, once daily for 20 minutes, until the fracture has healed, usually for 5 months.

## **REGULATORY STATUS**

In 1994, the Sonic Accelerated Fracture Healing System (SAFHS®; renamed Exogen 2000® and since 2006, Exogen 4000+; Bioventus) was approved by the U.S. Food and Drug Administration through the premarket approval process for treatment of fresh, closed, posteriorly displaced distal radius (Colles) fractures, and fresh, closed, or grade I open tibial diaphysis fractures in skeletally mature individuals when these fractures are orthopedically managed by closed reduction and cast immobilization. In February 2000, the labeled indication was expanded to include the treatment of established nonunions, excluding skull and vertebra. Food and Drug Administration product code: LPQ.

## **POLICY**

- A. Low-intensity pulsed ultrasound is considered **not medically necessary** as a treatment of fresh fractures (surgically managed or nonsurgically managed).
- B. Low-intensity pulsed ultrasound is considered **not medically necessary** as a treatment of fracture nonunion and delayed union fractures.
- C. Low-intensity pulsed ultrasound is considered **not medically necessary** as a treatment of stress fractures, osteotomy, and distraction osteogenesis.

## **Policy Guidelines**

1. Fresh (Acute) Fracture
  - a. There is no standard definition for a "fresh" fracture. A fracture is most commonly defined as fresh for 7 days after the fracture occurs Heckman et al, 1994; Kristiansen et al, 1997; Emami et al, 1999), but there is variability. For example, 1 study defined fresh as less than 5 days after fracture (Lubbert et al, 2008), while another defined fresh as up to 10 days after fracture Mayr et al, 2000). Most fresh closed fractures heal without complications with the use of standard fracture care, ie, closed reduction and cast immobilization.

2. Delayed Union
  - a. Delayed union is defined as a decelerating healing process as determined by serial radiographs, together with a lack of clinical and radiologic evidence of union, bony continuity, or bone reaction at the fracture site for no less than 3 months from the index injury or the most recent intervention.
3. Nonunion
  - a. There is not a consensus for the definition of nonunions. One proposed definition is failure of progression of fracture-healing for at least 3 consecutive months (and at least 6 months following the fracture) accompanied by clinical symptoms of delayed/nonunion (pain, difficulty weight bearing).<sup>1</sup>
  - b. The definition of nonunion in FDA labeling suggests that nonunion is considered established when the fracture site shows no visibly progressive signs of healing, without giving any guidance regarding the timeframe of observation. However, it is suggested that a reasonable time period for lack of visible signs of healing is 3 months. The following patient selection criteria are consistent with those proposed for electrical stimulation as a treatment of nonunions:
    - i. At least 3 months have passed since the date of the fracture, AND
    - ii. serial radiographs have confirmed that no progressive signs of healing have occurred, AND
    - iii. the patient can be adequately immobilized and is of an age when he/she is likely to comply with non-weight bearing.

## **RATIONALE**

The most recent MEDLINE literature update was conducted through January 8, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

## Low-Intensity Pulsed Ultrasound

### Systematic Reviews

A systematic review by Schandelmaier et al (2017) provides the most comprehensive and rigorous overview and analysis of the existing evidence, including 26 RCTs that used low-intensity pulsed ultrasound (LIPUS) for bone healing.<sup>3</sup> Additional systematic reviews or meta-analyses are listed in Table 1. However, because there is a substantial degree of overlap in the studies included in these reports (see Table 2), we will primarily focus on the findings of Schandelmaier et al (2017), which include analyses that highlight the results of RCTs identified as of higher quality. The recently published meta-analysis by Seger et al (2017) analyzed healing index and average time to union following use of LIPUS in cases of scaphoid nonunion, but it did not report control group comparisons.<sup>4</sup> The systematic review by Lou et al (2017)<sup>5</sup> focused on fresh fractures and the review by Leighton et al (2017)<sup>6</sup> focused on nonunions. All reviewers acknowledged that the evidence for the use of LIPUS has methodologic limitations (see Table 1).

**Table 1.** Systematic Reviews Assessing Use of LIPUS to Treat Fractures

Study	No. of Studies	Study Designs	No. of Subjects	Types of Fractures	Main Conclusions on LIPUS
Schandelmaier et al (2017) <sup>3</sup>	26	RCT	1593	Multiple types	Based on moderate- to high-quality evidence in fresh fracture, LIPUS does not improve outcomes important to patients and is unlikely to affect radiographic bone healing
Seger et al (2017) <sup>4</sup>	5	<ul style="list-style-type: none"> <li>• CS</li> <li>• Registry</li> </ul>	166	Nonunion	Encouraging results for consideration as nonoperative alternative in select cases
Lou et al (2017) <sup>5</sup>	12	<ul style="list-style-type: none"> <li>• RCT</li> <li>• Quasi-RCT</li> </ul>	1099	Fresh fracture	Positive results though strength of the evidence is limited
Leighton et al (2017) <sup>6</sup>	13	<ul style="list-style-type: none"> <li>• RCT</li> <li>• CS</li> <li>• Cohort</li> <li>• Registry</li> </ul>	1441	Nonunion	Potential benefit of LIPUS; however, no evidence that LIPUS can be used instead of surgery. May be useful in patients for whom surgery is high risk.
Griffin et al (2014) <sup>7</sup>	12	<ul style="list-style-type: none"> <li>• RCT</li> <li>• Quasi-RCT</li> </ul>	648	Multiple types	Cannot rule out potential benefit but evidence insufficient
Busse et al (2009) <sup>8</sup>	13	RCT	563	Multiple types	Promising results but moderate- to low-quality evidence
TEC Assessment (1995) <sup>9</sup>	2	RCT	128	Fresh fracture	Meets TEC criteria for FDA-labeled indications in tibia and distal radius

CS: case series; FDA: Food and Drug Administration; LIPUS: low-intensity pulsed ultrasound; RCT: randomized controlled trial.

The study populations in RCTs included by Schandelmaier et al (2017) examined multiple types of fractures including fresh fractures surgically managed (n=7), fresh fractures not surgically managed (n=6), distraction osteogenesis (n=5), nonunion fractures (n=3), osteotomy (n=3), and stress fractures (n=2). The RCTs had a median population size of 30 patients (range, 8-501 patients).

The outcomes examined by this systematic review emphasized those reported by patients to be most important: functional recovery (eg, time to return to work, time to full weight bearing); pain reduction; and a number of subsequent operations. Additional outcomes included time to radiographic healing, because this may be used by physicians to influence clinical decision making and adverse events associated with LIPUS.

In this systematic review, 2 reviewers independently assessed the quality of selected RCTs, using GRADE, a modified Cochrane risk of bias tool. Generation of randomization sequence, concealment of allocation, and blinding of patients, caregivers, and outcome reporting were evaluated in each trial. Each outcome within each trial was assessed for blinding of outcome assessors, loss to follow-up, and additional limitations. Trial authors were contacted if there was uncertainty in the quality assessment. Of the 26 included trials, 6 were considered to have a low risk of bias, with the remaining 20 trials considered to have a high risk of bias. Reasons for high risk of bias designation included failure to report a method for allocation concealment (15 trials), high or unclear numbers of patients excluded from the analysis (13 trials), unblinded patients (10 trials), and unblinded caregivers or outcome assessors (10 trials). Of the 6 trials rated to be at low risk of bias, four were conducted in individuals with fresh fracture, three of which were operatively managed tibial fractures<sup>10-12</sup> and one of which was nonoperatively managed clavicle fractures.<sup>13</sup> The other 2 trials rated at low risk of bias included operatively managed mandibular fractures related to distraction osteogenesis.<sup>14,15</sup>

**Table 2.** Studies Included in Systematic Reviews

Studies	N	Study Design	Systematic Reviews by Fracture Type						TEC Assessment (1995), <sup>9</sup> Fresh
			Schandelmaier (2017), <sup>3</sup> Multiple	Seger (2017), <sup>4</sup> Nonunion	Lou (2017), <sup>5</sup> Fresh	Leighton (2017), <sup>6</sup> Nonunion	Griffin (2014), <sup>7</sup> Multiple	Busse (2009), <sup>8</sup> Multiple	
Busse et al (2016)	51	RCT	•		•				
Busse et al (2014)	50	RCT	•		•				
Dudda et al (2011)	36	RCT	•						
El-Mowafi et al (2005)	20	RCT	•					•	
Emami et al (1999)	32	RCT	•		•		•	•	
Exogen et al (1994)	85	RCT							•
Farkash (2015)	29	CS		•		•			
Gan et al (2014)	30	RCT	•						
Gebauer et al (2005)	66	CS		•		•			
Handolin et al (2005a)	22	RCT	•		•		•	•	
Handolin et al (2005b)	30	RCT	•		•		•	•	
Heckman et al (1994)	97	RCT	•		•		•	•	•
Hemery et al (2010)	14	CS				•			
Jingushi et al (2007)	72	CS				•			
Kamath et al (2015)	60	RCT	•						
Kristiansen et al (1997)	85	RCT	•		•		•	•	
Lerner et al (2004)	17	CS				•			
Leung et al (2004)	30	RCT	•		•		•	•	
Liu et al (2014)	81	RCT	•		•		•	•	
Lubbert et al (2008)	12	RCT	•		•		•	•	
Mayr et al (2002)	10	CS				•		•	
Mayr et al (2000)	30	RCT	•		•		•		

Studies	N	Study Design	Systematic Reviews by Fracture Type						TEC Assessment (1995), <sup>9</sup> Fresh
			Schandelmaier (2017), <sup>3</sup> Multiple	Seeger (2017), <sup>4</sup> Nonunion n	Lou (2017), <sup>5</sup> Fresh	Leighton (2017), <sup>6</sup> Nonunion n	Griffin (2014), <sup>7</sup> Multiple	Busse (2009), <sup>8</sup> Multiple	
Nolte et al (2001)	28	CS		•		•			
Patel et al (2014)	28	RCT	•						
Pigozzi et al (2004)	15	CS		•		•			
Ricardo (2006)	21	RCT	•					•	
Roussignol et al (2012)	60	CS				•			
Rubin et al (2001)	11	Review <sup>a</sup>		•					
Rue et al (2004)	40	RCT	•					•	
Rutten et al (2007)	20	RCT	•			•			
Salem et al (2014)	21	RCT	•						
Schofer et al (2010)	10	RCT	•			•			
Schortinghuis et al (2008)	9	RCT	•						
Schortinghuis et al (2005)	8	RCT	•					•	
Strauss et al (1999)	20	RCT			•		•		
Tsumaki et al (2004)	42	RCT	•					•	
Urita et al (2013)	27	RCT	•						
Wang et al (2007)	59	RCT					•		
Watanabe et al (2013)	15	Cohort				•			
Yadav et al (2008)	67	RCT					•		
Zacherl et al (2009)	52	RCT	•						
Zura et al (2015)	76	Registry				•			
	7								
<b>No. of studies</b>			26	5	12	13	12	13	2

CS: case series; RCT: randomized controlled trial.

<sup>a</sup> This review contained data from a registry analysis.

Meta-analysis results are summarized in Tables 3 and 4. None of the overall results demonstrated statistically significant differences supporting LIPUS. Variation in results was observed for days to full weight bearing, pain, or radiographic healing, and when only trials with low risk of bias were included, there was no difference between treatment and control groups (see Table 3).

**Table 3.** Summary of LIPUS Results from the Schandelmaier Meta-Analysis

Outcomes	No. of Trials and Results (95% Confidence Intervals)					Heterogeneity		
	High Risk of Bias		Low Risk of Bias		Total	p	I <sup>2</sup>	
	n	Results	n	Results	n	Results		
Percent difference in days to return to work	Not reported separately		Not reported separately		3	2.7 (-7.7 to 14.3)	0.76	0%
Percent difference in days to full weight bearing	1	-40.0 (-48.4 to -30.3)	2	4.8 (-4.0 to 14.4)	3	-16.6 (-44.9 to 26.1)	<0.001	95%
Mean difference in pain reduction on 1-100 VAS (follow-up, 4-6 wk)	1	-28.1 (-37.1 to -19.2)	3	-0.9 (-2.5 to 0.6)	4	-6.9 (-15.4 to 1.6)	<0.001	91%

Outcomes	No. of Trials and Results (95% Confidence Intervals)				Heterogeneity			
RR of subsequent operations (follow-up, 8 wk to 44 mo)	Not reported separately		Not reported separately		7	0.8 (0.6 to 1.2)	0.67	0%
Percent difference in days to radiographic healing	1	-32.8 (-39.5 to -25.3)	3	-1.7 (-11.2 to 8.8)	1	-27.3 (-34.7 to -19.0)	<0.001	85%
Risk difference in adverse events	Not reported separately		Not reported separately		9	0.0 (-0.0 to 0.03)	0.40	4%

Adapted from Schandelmaier et al (2017).<sup>3</sup>

RR: relative risk; VAS: visual analog scale.

**Table 4.** Summary of Findings for Quality of Evidence and Narrative Conclusion

Outcomes	QOE	Narrative Conclusion for LIPUS Effect on Outcome
Percent difference in days to return to work	Moderate <sup>a</sup>	Probably little or no impact
Percent difference in days to full weight bearing	High	No impact
Mean difference in pain reduction on 1-100 VAS (follow-up, 4-6 wk)	High	No impact
Relative risk of subsequent operations (follow-up, 8 wk to 44 mo)	Moderate <sup>a</sup>	Probably little or no impact
Percent difference in days to radiographic healing	Moderate <sup>a</sup>	Probably little or no impact
Risk difference in adverse events	High	No impact

Adapted from Schandelmaier et al (2017).<sup>3</sup>

LIPUS: low-intensity pulsed ultrasound; QOE: quality of evidence; VAS: visual analog scale.

<sup>a</sup> Due to serious imprecision.

### Fresh Fractures

Lou et al (2017) conducted a meta-analysis focusing on fresh fractures.<sup>5</sup> The literature search, conducted through November 2016, included 12 studies, all of which were included in the Schandelmaier et al (2017) meta-analysis, except for a small study (N=20) by Strauss et al (1999), which only appeared in a conference abstract.<sup>16</sup> Studies included patients that had been surgically managed and conservatively managed. Time to fracture union was significantly lower in patients receiving LIPUS than in patients not receiving LIPUS (standard mean difference, -0.65; 95% confidence interval [CI], -1.13 to -0.17). Subgroup analysis showed that this significant reduction in healing time with LIPUS was seen only among patients conservatively managed, while there was no difference in healing time among patients surgically managed. Reviewers concluded that patients with fresh fractures might benefit from the use of LIPUS but warned that there were methodologic limitations in the trials. Separate analyses using only low risk of bias trials was not conducted.

### Surgically Managed

Busse et al (2016) reported on results from a concealed, blinded, sham-controlled, randomized trial (TRUST) evaluating LIPUS for the treatment of patients who underwent intramedullary nailing for fresh tibial fractures.<sup>10</sup> This is the largest RCT to date, enrolling 501 patients; 250 received a LIPUS device, and 251 received a sham device. Treatment was self-administered for 20 minutes a day until there was radiographic evidence of healing. Coprimary end points were radiographic healing and return to function (as measured by the 36-Item Short-Form Health Survey Physical Component Summary score). Both radiographic and functional assessments had to show a clinically important effect for the results to be considered positive. All patients, clinicians, investigators, data analysts, and the industry sponsor were blinded to allocation until data analysis was complete. Patient compliance was considered moderate, with 73% of patients administering over half of all recommended treatments. There was no difference in time to radiographic healing between the treatment groups (hazard ratio, 1.07; 95% CI, 0.86 to 1.34;

p=0.55). Additionally, there was no difference in the 36-Item Short-Form Health Survey Physical Component Summary scores (mean difference, 0.55; 95% CI, -0.75 to 1.84; p=0.41). A previously conducted pilot double-blind RCT by Busse et al (2014), including 51 subjects not assessed in the 2016 study, also did not find any statistically significant differences in pain reduction, subsequent operations, or radiographic healing time.<sup>12</sup>

Tarride et al (2017) provided additional analyses using data from the TRUST trial, comparing health care resource use among patients using LIPUS with patients using the sham device.<sup>17</sup> There were no significant differences between groups (11% in patients receiving LIPUS vs 10% in patients receiving sham) in need for secondary procedures (eg, removal of lock screw, implant exchange or removal). There were also no statistically significant differences in use of physical therapy (44% vs 46%), use of anticoagulants (42% vs 36%), or use of nonsteroidal anti-inflammatory drugs (28% vs 35%) among patients receiving LIPUS compared with patients receiving sham, respectively.

Emami et al (1999) conducted a double-blind, sham-controlled trial that randomized 32 patients who had a fresh tibial fracture fixed with an intramedullary rod to additional treatment with an active (n=15) or inactive (n=17) LIPUS device.<sup>11</sup> LIPUS treatment began within 3 days of surgery (1 patient began treatment within 7 days of injury) and was self-administered for 20 minutes a day for 75 days. Radiographs were taken every third week until healing. Results showed that LIPUS did not shorten healing time based on any of the following measures: time to first visible callus (mean, 40 days for LIPUS vs 37 days for sham; p=0.44); time to radiographic healing assessed by radiologist (mean, 155 days [median, 113 days] for LIPUS vs mean, 125 days [median, 112 days] for sham; p=0.76); and time to radiographic healing assessed by orthopedic surgeon (mean, 128 days, for LIPUS vs mean, 114 days for sham; p=0.40).

#### *Nonsurgically Managed*

Lubbert et al (2008) performed a multicenter, double-blind RCT (N=101) of LIPUS treatment of fresh (<5 days) clavicle shaft fractures.<sup>13</sup> Patients used the LIPUS devices for 20 minutes once daily for 28 days and recorded their subjective feeling as to whether the fracture healed (the primary outcome measure), pain on a visual analog scale, level of daily activities (hours of work, household work, sport), and analgesic use. Patient perception of the day the fracture healed was determined in 92 patients (47 active, 45 placebo); mean time to healing was 26.77 days in the active group and 27.09 days in the placebo group (p=0.91). Between-group differences regarding analgesic use and mean visual analog scale scores for pain also did not differ significantly.

#### *Section Summary: Fresh Fractures*

Evidence for the use of LIPUS following fresh fracture, either surgically or nonsurgically managed, consists of 2 systematic reviews (2017) which included nearly identical studies. One systematic review, which included 13 RCTs, only conducted a separate analysis using the 4 trials with a low risk of bias. The overall results of the systematic review and meta-analysis and particularly the results including only RCTs with a low risk of bias did not demonstrate statistically significant improvements for LIPUS on functional outcomes, pain, or radiographic healing time.

#### Fracture Nonunion or Delayed Union Fracture

The meta-analysis by Seger et al (2017) included 5 studies focused on scaphoid nonunions and analyzed healing index and average time to union following LIPUS.<sup>4</sup> Among 166 cases in the

analysis, 78.6% (range, 33%-100%) were reported to show healing following LIPUS, with an average time to union of 4.2 months (range, 2.3-5.6 months). Comparative results were not the focus of the analysis.

The meta-analysis by Leighton et al (2017) included 13 studies, one of which was an RCT.<sup>6</sup> The date of the literature search was not provided. Quality of the studies was assessed using the Methodological Index for Non-Randomized Studies. Quality scores ranged from 5 to 12 (an "ideal" is 16 for nonrandomized trials). While the pooled estimate of effect size for the healing rate was 82% (95% CI, 77% to 87%), significant heterogeneity was detected ( $I^2=62$ ). A separate analysis, excluding studies with quality scores of 6 or lower, resulted in a comparable heal rate of 80% (95% CI, 74% to 85%). Because some patients in the analysis were treated conservatively and some underwent surgical interventions, the authors could not recommend LIPUS as a replacement for surgery or as an adjunct to surgery. Reviewers contended that LIPUS might be useful in patients for whom surgery is high risk.

The systematic review by Schandelmaier et al (2017) included 3 RCTs in nonunion fractures operatively managed; however, all studies were rated at high risk of bias.<sup>3</sup> One of the trials, by Schofer et al (2010), reported on a multicenter, randomized, double-blinded, sham-controlled trial of LIPUS in 101 patients with delayed union of the tibia.<sup>18</sup> Delayed union was defined as a lack of clinical and radiologic evidence of union, bony continuity, or bone reaction at the fracture site for no less than 16 weeks from the index injury or the most recent intervention. Roughly one-third of patients had an open fracture. Patients were randomized to LIPUS (n=51) or to an inactive sham device (n=50), to be administered 20 minutes a day for 16 weeks. The primary outcome was change in bone mineral density assessed by computed tomography attenuation coefficients. Gap area was a secondary outcome. Intention-to-treat analysis showed that LIPUS improved mean bone mineral density by 34% (90% CI, 14% to 57%) compared with sham treatment. The mean reduction in bone gap area was -0.13 mm<sup>2</sup> in the LIPUS group and -0.10 mm<sup>2</sup> in the sham group (effect size, -0.47; 95% CI, -0.91 to -0.03 mm<sup>2</sup>). At the end of 16 weeks, physicians judged 65% of patients in the LIPUS group healed and 46% of the patients in the sham group healed (p=0.07). This trial did not report functional outcomes or pain assessment, limiting the utility of results.

Rutten et al (2012), published only as a thesis, reported on a blinded RCT evaluating 20 subjects with tibial fracture nonunion and found a statistically significant reduction in time to radiographic healing (percent difference in days, -57.2%; 95% CI, -74.7% to -27.6%) with LIPUS.<sup>19</sup> However, the 45% loss to follow-up rate raises significant concerns about potential bias of these findings. Ricardo (2006) published a blinded RCT evaluating 21 subjects with scaphoid nonunion and found a statistically significant reduction in time to radiographic healing (-40.4%; 95% CI, -48.7% to -30.8%) with LIPUS.<sup>20</sup>

Biglari et al (2016) conducted a prospective, single-institution, observational study on 61 nonunions in long bones of the lower extremity treated with LIPUS.<sup>21</sup> To be included in the study, patients could not have had an intervention at least 90 days before beginning LIPUS treatment. Successful therapy was defined as a radiographically confirmed consolidation and no further surgical revision needed for the next year. All patients were available for all follow-up visits. The average age of the patients was 45 years (range, 18-63 years). Twenty (32.8%) cases met the successful therapy definition. An analysis comparing successful and unsuccessful outcomes found

that LIPUS was more beneficial in patients with a fracture gap size less than 1 cm, a fracture age of fewer than 6 months, and a low Non-Union Scoring System score.

Zura et al (2015) published an industry-sponsored analysis of the effect of LIPUS on patients with nonunion, defined as a failure to heal for more than 12 months using clinical and radiographic criteria.<sup>22</sup> Patients were a subset in a U.S. Food and Drug Administration–required postmarket registry of consecutive patients who have used the Exogen LIPUS device. The registry had 1286 patients with nonunion. The analysis was performed on 767 (60%) records. Reasons for being excluded from the analysis included: 18% loss to follow-up, 9% noncompliance, 8% withdrawals, and 5% other factors. The reported healing rate was 86.2%, with the average time for healing 6.0 months.

#### *Section Summary: Fracture Nonunion or Delayed Union Fracture*

The evidence for LIPUS treatment of fracture nonunion consists only of lower quality and mostly uncontrolled studies. There are 2 meta-analyses (2017) without controlled comparative results. A third meta-analysis, which included all types of fractures, identified 3 RCTs of patients with nonunion; however, all 3 trials were considered at high risk of bias (one published as a thesis). Reported outcomes do not include functional outcomes, and a wide range of healing rates was reported across the studies with a lack of comparison with routine surgical care, limiting meaningful interpretation of these results.

#### Stress Fractures, Osteotomy Sites, or Distraction Osteogenesis

Rue et al (2004) reported on a double-blind RCT that examined the effects of 20 minutes of daily LIPUS on tibial stress fracture healing outcomes such as pain, function, and resumption of professional and personal activities in 26 military recruits.<sup>23</sup> The delay from onset of symptoms to diagnosis was 32 days in the LIPUS group and 28 days in the placebo group. This trial found no significant difference in healing times between LIPUS treatment and sham, with a mean time of return to duty of 56 days for both groups. The trial was rated with a high risk of bias in the Schandelmaier (2017) meta-analysis.<sup>3</sup>

Urita et al (2013) published a small (N=27) quasi-randomized study (alternating assignment) of LIPUS after ulnar-shortening osteotomy for ulnar impaction syndrome or radial-shortening osteotomy for Kienböck disease.<sup>24</sup> Patients in the LIPUS group received a daily 20-minute treatment for at least 12 weeks postoperatively. Blinded evaluation of radiographic healing showed that LIPUS reduced the mean time to the cortical union by 27% (57 days vs 76 days) and endosteal union by 18% (121 days vs 148 days) compared with sham treatment. At the time of endosteal healing, the osteotomy plus LIPUS group and the osteotomy-only group had similar results, as measured using the Modified Mayo Wrist Score and no pain at the osteotomy site. The study was rated at high risk of bias in the meta-analysis by Schandelmaier.<sup>3</sup>

The Schandelmaier systematic review also included 6 trials of LIPUS for distraction osteogenesis following surgery and 4 of 6 studies were rated at high risk of bias.<sup>3</sup> Four studies were in the tibia,<sup>25-28</sup> and the other two were in the mandible.<sup>14,15</sup> No clinically meaningful results were reported for the mandible studies in the meta-analysis.<sup>3</sup> The remaining studies in the tibia were all unblinded. No statistically significant difference was noted in subsequent operations (relative risk, 0.63; 95% CI 0.13 to 2.99) as reported by Dudda et al (2011)<sup>25</sup> in the meta-analysis.<sup>3</sup> Four of the studies<sup>25-28</sup> were included in the meta-analysis<sup>3</sup> for time to radiographic healing with mixed results, three not reporting statistically significant results.

*Section Summary: Stress Fractures, Osteotomy Sites, or Distraction Osteogenesis*

The evidence for LIPUS treatment of stress fractures, osteotomy sites, or distraction osteogenesis consists only of lower quality RCTs and were all rated to have a high risk of bias. Results do not generally include functional outcomes and results across various outcomes, primarily including time to radiographic healing, are inconsistent.

**SUMMARY OF EVIDENCE**

For individuals who have fresh fractures (surgically or nonsurgically managed) who receive LIPUS as an adjunct to routine care, the evidence includes RCTs and several meta-analyses. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence base has recently evolved with the publication of a large RCT and meta-analysis significantly shifting the weight of the evidence. Conclusions based on several earlier and small RCTs, rated at high risk of bias, showed a potential benefit of LIPUS; however, the large RCT published in 2016, rated at low risk of bias, showed no benefit. A 2017 meta-analysis including only trials with low risk of bias found no difference in days to full weight bearing, pain reduction, or days to radiographic healing. Similarly, the overall results of the meta-analysis found no significant difference in return to work, subsequent operations, or adverse events. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have fracture nonunion or delayed union fracture who receive LIPUS as an adjunct to routine care including surgery, if appropriate, the evidence includes only lower quality studies consisting of a small systematic review in scaphoid nonunions, a meta-analysis of nonunion in various locations, 3 low-quality RCTs, and observational studies. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Reported outcomes in this subgroup of fractures do not include functional outcomes. A wide range of healing rates has been reported across the observational studies with a lack of comparison with routine surgical care, limiting any meaningful interpretation of these results. Additionally, the evidence base on the use of LIPUS in the management of fresh fractures has evolved as described above, and there is no demonstrated physiologic mechanism suggesting differential results of LIPUS in fracture nonunion or delayed union. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have stress fractures, osteotomy sites, or distraction osteogenesis who receive LIPUS as an adjunct to routine care, the evidence includes only lower quality studies consisting of small RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Results do not generally include functional outcomes and results across various outcomes, primarily time to radiographic healing, are inconsistent. Additionally, the evidence base on the use of LIPUS in the management of fresh fractures has evolved as described above and there is no demonstrated physiologic mechanism suggesting differential results of LIPUS in stress fractures, osteotomy sites, or distraction osteogenesis. The evidence is insufficient to determine the effects of the technology on health outcomes.

**CLINICAL INPUT RECEIVED THROUGH PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

### 2008 Input

In response to requests for input from physician specialty societies and academic medical centers for the 2008 policy update, input was received from 1 physician specialty society while this policy was under review. Physician input obtained through the American Academy of Orthopaedic Surgeons agreed with the positions regarding the criteria for medical necessity and the conditions that are considered investigational (eg, delayed union and open/unstable grade II or III fractures).

### 2011 Input

In response to requests, input was received through 2 physician specialty societies and 1 academic medical center for the policy review in January 2011. Input supported the use of ultrasound for nonunion and for fresh closed fractures at high risk for delayed fracture healing or nonunion as described in the policy. One reviewer supported including chemotherapy, immunosuppressive agents, history of infection, Charcot neuroarthropathy, and fractures of the tibial shaft or clavicle as additional risk factors, and a different reviewer supported including fractures of the talus and sesamoids as additional risk factors.

### 2012 Input

In response to requests, input was received through 4 academic medical centers for the policy review in December 2012. Input supported the use of low-intensity ultrasound in delayed union and nonunion of bones excluding the skull and vertebra, and in fresh closed fractures at high risk for delayed fracture healing or nonunion. Input agreed that other applications of low-intensity ultrasound treatment are investigational, including, but not limited to, treatment of congenital pseudoarthroses, open fractures, stress fractures, arthrodesis or failed arthrodesis. Additional risk factors were noted, including: use of anticoagulants, immunosuppressive drugs or chemotherapy; infection at the fracture site; severe anemia; obesity; and fracture locations more prone to nonunion such as tibial and distal radial fractures.

## **PRACTICE GUIDELINES AND POSITION STATEMENTS**

### British Medical Journal Rapid Recommendation

The *British Medical Journal* (BMJ) Rapid Recommendations are a series of articles, produced by BMJ in collaboration with the MAGIC group,<sup>28</sup> to provide clinicians with practice guidelines. In 2017, BMJ Rapid Recommendations published guidelines on the use of low-intensity pulsed ultrasound (LIPUS) for bone healing.<sup>29</sup> The guidelines were based on a 2017 systematic review, which included 26 randomized controlled trials evaluating patients with fresh fractures not surgically managed, fresh fractures surgically managed, nonunion fractures, osteotomy, and distraction osteogenesis.<sup>3</sup> The committee concluded that there is “moderate to high certainty evidence to support a strong recommendation against the use of LIPUS for bone healing.” Furthermore, the guideline expert panel discussed whether the results of higher quality studies in patients with fresh fractures reported in Schandelmaier et al (2017) would apply to other types of fractures including nonunions and osteotomies.<sup>3</sup> “After extensive deliberations, the panel found no compelling anatomical or physiological reasons why LIPUS would probably be beneficial in these other patient populations.”<sup>29</sup>

### National Institute for Health and Clinical Excellence

The U.K.’s National Institute for Health and Clinical Excellence (NICE) published guidance in 2010 on LIPUS to promote fracture healing.<sup>30</sup> NICE concluded that this procedure can reduce fracture healing and is particularly beneficial for delayed healing and fracture nonunion.

NICE published a medical technology guidance on Exogen for the treatment of nonunion and delayed fracture healing in 2013.<sup>31</sup> NICE concluded that use of the Exogen bone healing system to treat long-bone fractures with nonunion is supported by clinical evidence and cost savings through avoiding surgery. For long-bone fractures with delayed healing, defined as no radiologic evidence of healing after 3 months, there was some radiologic evidence of improved healing. However, due to substantial uncertainties about the rate of bone healing without treatment between 3 and 9 months after fracture and need for surgery, cost consequences were uncertain. The next review by NICE of the Exogen system is scheduled for publication in 2018.

American Academy of Orthopaedic Surgeons

The American Academy of Orthopaedic Surgeons (AAOS) published 2009 guidelines on the treatment of distal radius fractures.<sup>32</sup> AAOS provided a weak recommendation for use of ultrasound for adjuvant treatment of distal radius fractures. This recommendation was based results from 2 studies that used nonvalidated patient outcome measures.

**U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS**

Not applicable.

**ONGOING AND UNPUBLISHED CLINICAL TRIALS**

One currently unpublished trial that might influence this review is listed in Table 5.

**Table 5.** Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT02383160	A Randomized Controlled Trial Comparing Low-Intensity, Pulsed Ultrasound to Placebo in the Treatment of Operatively Managed Scaphoid Non-unions	154	Dec 2018
NCT03382483 <sup>a</sup>	Observational, Non-Interventional Use of LIPUS to Mitigate Fracture Non-Union in Patients at Risk (BONES)	3000	Dec 2019

NCT: national clinical trial.

<sup>a</sup> denotes an industry-sponsored trial

**CODING**

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

CPT/HCPCS

- 20979 Low intensity ultrasound stimulation to aid bone healing, noninvasive (nonoperative)
- E0760 Osteogenesis stimulator, low intensity ultrasound, noninvasive

ICD-10 Diagnoses

Not Medically Necessary for all diagnoses related to this medical policy.

**REVISIONS**

11-12-2014	Policy added to the bcbsks.com web site on 11-12-2014. Update effective for Professional on 11-12-2014. Effective for Institutional on 12-11-2014.
02-16-2015	In Coding section: <ul style="list-style-type: none"> <li>▪ Added ICD-10 diagnosis codes, effective October 1, 2015.</li> </ul>
04-28-2015	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> <li>▪ In Policy Guidelines, Item 1 A, added "There is no standard definition for a "fresh" fracture." and ",(1-3) but there is variability. For example, 1 study defined fresh as less than 5 days after fracture,(4) while another defined fresh as up to 10 days after fracture.(5)"</li> </ul>
	Updated Rationale section.
	Updated References section.
10-12-2016	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> <li>▪ In Item A, added "pulsed" to read "Low-intensity pulsed ultrasound treatment may be considered medically necessary when used as an adjunct to conventional management (ie, closed reduction and cast immobilization) for the treatment of fresh, closed fractures in skeletally mature individuals. Candidates for ultrasound treatment are those at high risk for delayed fracture healing or nonunion. These risk factors may include either locations of fractures or patient comorbidities and include the following:"</li> <li>▪ In Item A 2, added "e) Tibial diaphysis fracture that is closed or grade I open (skin opening is ≤1 cm with minimal muscle contusion)"</li> <li>▪ In Item B, added "pulsed" to read "Low-intensity pulsed ultrasound treatment may be considered medically necessary as a treatment of delayed union of bones, including delayed union of previously surgically-treated fractures, and excluding the skull and vertebra. (See Policy Guidelines for definition of delayed union.)"</li> <li>▪ In Item C, added "pulsed" to read "Low-intensity pulsed ultrasound treatment may be considered medically necessary as a treatment of fracture nonunions of bones, including nonunion of previously surgically-treated fractures, and excluding the skull and vertebra. (See Policy Guidelines for definition of nonunion.)"</li> <li>▪ In Item D, added "pulsed" and "and" to read "Other applications of low-intensity pulsed ultrasound treatment are experimental / investigational, including, but not limited to, treatment of congenital pseudarthroses, open fractures, fresh surgically-treated closed fractures, stress fractures, and arthrodesis or failed arthrodesis."</li> <li>▪ In Policy Guidelines Item 3 B, removed "3) the fracture gap is 1 cm or less, AND"</li> </ul>
	Updated Rationale section.
	Updated References section.
03-01-2018	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> <li>▪ Removed previous policy language, "A. Low-intensity pulsed ultrasound treatment may be considered medically necessary when used as an adjunct to conventional management (ie, closed reduction and cast immobilization) for the treatment of fresh, closed fractures in skeletally mature individuals. Candidates for ultrasound treatment are those at high risk for delayed fracture healing or nonunion. These risk factors may include either locations of fractures or patient comorbidities and include the following: 1. Patient comorbidities: a) Diabetes b) Steroid therapy c) Osteoporosis d) History of alcoholism e) History of smoking 2. Fracture locations: a) Jones fracture b) Fracture of navicular bone in the wrist (also called the scaphoid) c) Fracture of metatarsal d) Fractures associated with extensive soft tissue or vascular damage e) Tibial diaphysis fracture that is closed or grade I open (skin opening is ≤1 cm with minimal muscle</li> </ul>

	<p>contusion) B. Low-intensity pulsed ultrasound treatment may be considered medically necessary as a treatment of delayed union of bones, including delayed union of previously surgically-treated fractures, and excluding the skull and vertebra. (See Policy Guidelines for definition of delayed union.) C. Low-intensity pulsed ultrasound treatment may be considered medically necessary as a treatment of fracture nonunions of bones, including nonunion of previously surgically-treated fractures, and excluding the skull and vertebra. (See Policy Guidelines for definition of nonunion.) D. Other applications of low-intensity pulsed ultrasound treatment are experimental / investigational, including, but not limited to, treatment of congenital pseudarthroses, open fractures, fresh surgically-treated closed fractures, stress fractures, and arthrodesis or failed arthrodesis." and added, "A. Low-intensity pulsed ultrasound is considered not medically necessary as a treatment of fresh fractures (surgically managed or nonsurgically managed). B. Low-intensity pulsed ultrasound is considered not medically necessary as a treatment of fracture nonunion and delayed union fractures. C. Low-intensity pulsed ultrasound is considered not medically necessary as a treatment of stress fractures, osteotomy, and distraction osteogenesis."</p>
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> <li>▪ Removed diagnosis codes.</li> </ul>
	Updated References section.
	Added Appendix section.
04-11-2018	Updated Description section.
	Updated Rationale section.
	Updated References section.
	Removed Appendix section.

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