MP 1.01.05
Ultrasound Accelerated Fracture Healing Device

Last Review: 7/25/2017
Effective Date: 11/01/2017
Issue: 7:2017

Related Policies:
- 7.01.07 Electrical Bone Growth Stimulation of the Appendicular Skeleton
- 7.01.85 Electrical Stimulation of the Spine as an Adjunct to Spinal Fusion Procedures
- 7.01.100 Bone Morphogenetic Protein

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POLICY
Low-intensity pulsed ultrasound may be considered not medically necessary as a treatment of fresh fractures (surgically managed or nonsurgically managed).

Low-intensity pulsed ultrasound may be considered not medically necessary as a treatment of fracture nonunion and delayed union fractures.

Low-intensity pulsed ultrasound may be considered not medically necessary as a treatment of stress fractures, osteotomy, and distraction osteogenesis.

POLICY GUIDELINES

FRESH (ACUTE) FRACTURE
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 postfracture (Mayr et al, 2000). Most fresh closed fractures heal without complications using of standard fracture care (ie, closed reduction and cast immobilization).

NONUNION
There is no consensus on the definition of nonunions. One definition is a failure of progression of fracture healing for at least 3 consecutive months (and at least 6 months postfracture) accompanied by clinical symptoms of delayed/nonunion (pain, difficulty weight bearing; Buza & Einhorn, 2016).

The definition of nonunion used in U.S. Food and Drug Administration labeling suggests that nonunion is considered established when the fracture site shows no visibly progressive signs of healing, without
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providing guidance on the timeframe of observation. The following patient selection criteria are consistent with those proposed for electrical stimulation as a treatment of nonunions (see evidence review 7.01.07):

- At least 3 months have passed since the date of the fracture, and
- serial radiographs have confirmed that no progressive signs of healing have occurred, and
- the fracture gap is 1 cm or less, and
- the patient can be adequately immobilized and, based on age, is likely to comply with nonweight bearing.

DELAYED UNION
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.

BENEFIT APPLICATION

BLUECARD/NATIONAL ACCOUNT ISSUES
State or federal mandates (e.g., Federal Employee Program) may dictate that certain U.S. Food and Drug Administration–approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only on the basis of their medical necessity.

The transducer used for ultrasound treatment is categorized as durable medical equipment.

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. 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 (e.g., smoking, diabetes, systemic disease).

Fracture Nonunion
There is no standard definition of a fracture nonunion. 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 post fracture, after which the fracture site would be considered 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 fracture healing status. 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.

**RATIONALE**

The evidence review was created in December 1995 and has been updated regularly with searches of the MEDLINE database. The most recent literature review was conducted through January 25, 2017.

**LOW-INTENSITY PULSED ULTRASOUND**

**Systematic Reviews**

A recently published systematic review by Schandelmaier et al (2017) provides the most comprehensive and rigorous overview and analysis of the existing evidence, including 26 randomized controlled trials (RCTs) that used low-intensity pulsed ultrasound (LIPUS) for bone healing. Previously published systematic reviews or meta-analyses are also listed in Table 1. However, because there is a substantial degree of overlap in the studies included in these preceding reports, we will primarily focus this review of evidence on the findings of Schandelmaier et al (2017) and highlight the results of RCTs identified to be 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.

<table>
<thead>
<tr>
<th>Systematic Reviews (Year)</th>
<th>No. of Studies⁵</th>
<th>No. of Subjects</th>
<th>Types of Fractures</th>
<th>Main Conclusions on LIPUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEC Assessment (1995)⁵</td>
<td>2</td>
<td>128</td>
<td>Fresh fracture</td>
<td>Meets TEC criteria for FDA-labeled indications in tibia and distal radius</td>
</tr>
<tr>
<td>Busse et al (2009)⁶</td>
<td>13</td>
<td>563</td>
<td>Multiple types of</td>
<td>Promising results but moderate- to low-quality evidence</td>
</tr>
</tbody>
</table>

**Table 1. Systematic Reviews Assessing Use of LIPUS to Treat Fractures**
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<table>
<thead>
<tr>
<th>Systematic Reviews (Year)</th>
<th>No. of Studies(^a)</th>
<th>No. of Subjects</th>
<th>Types of Fractures</th>
<th>Main Conclusions on LIPUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffin et al (2014)(^7)</td>
<td>12(^b)</td>
<td>648</td>
<td>Multiple types of fracture</td>
<td>Cannot rule out potential benefit but evidence insufficient</td>
</tr>
<tr>
<td>Schandelmaier et al (2017)(^3)</td>
<td>26</td>
<td>1593</td>
<td>Multiple types of fracture</td>
<td>Based on moderate- to high-quality evidence in fresh fracture, does not improve outcomes important to patients and unlikely to affect radiographic bone healing</td>
</tr>
<tr>
<td>Seger et al (2017)(^4)</td>
<td>5(^c)</td>
<td>166</td>
<td>Nonunion</td>
<td>Encouraging results for consideration as nonoperative alternative in select cases</td>
</tr>
</tbody>
</table>

FDA: Food and Drug Administration; LIPUS: low-intensity pulsed ultrasound.

\(^a\) Randomized controlled trials unless noted otherwise.

\(^b\) Two quasi-randomized.

\(^c\) Inclusion criteria permitted randomized controlled trials, cohort studies, and randomized crossover studies. Limited description of study designs in the meta-analysis.

The study populations in RCTs included by Schandelmaier et al (2017) examined multiple types of fractures including patients with 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 outcomes reported by patients to be most important: functional recovery (eg, time to return to work, time to full weight bearing); pain reduction; and number of subsequent operations. Additional outcomes included time to radiographic healing, since this may be used by physicians to influence clinical decision making and adverse effects associated with LIPUS.

In this systematic review, 2 reviewers independently assessed the quality of the included 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, 4 were conducted in individuals with fresh fracture, 3 of which were operatively managed tibial fractures\(^8,9\) and one of which was nonoperatively managed clavicle fractures.\(^10\) The other 2 trials rated at low risk of bias included operatively managed mandibular fractures related to distraction osteogenesis.\(^11,12\)

Meta-analysis results are summarized in Tables 2 and 3. 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 2).
### Table 2. Summary of LIPUS Results From the Schandelmaier Meta-Analysis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>High Risk of Bias</th>
<th>Low Risk of Bias</th>
<th>Total</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n Results</td>
<td>n Results</td>
<td>n</td>
<td>95% Confidence Intervals</td>
</tr>
<tr>
<td>Percent difference in days to return to work</td>
<td>Not reported separately</td>
<td>Not reported separately</td>
<td>3</td>
<td>2.7 (-7.7 to 14.3)</td>
</tr>
<tr>
<td>Percent difference in days to full weight bearing</td>
<td>1</td>
<td>-40.0 (-48.4 to -30.3)</td>
<td>2</td>
<td>4.8 (-4.0 to 14.4)</td>
</tr>
<tr>
<td>Mean difference in pain reduction on 1-100 VAS (follow-up, 4-6 wk)</td>
<td>1</td>
<td>-28.1 (-37.1 to -19.2)</td>
<td>3</td>
<td>-0.9 (-2.5 to 0.6)</td>
</tr>
<tr>
<td>RR of subsequent operations (follow-up, 8 wk to 44 mo)</td>
<td>Not reported separately</td>
<td>Not reported separately</td>
<td>7</td>
<td>0.8 (0.6 to 1.2)</td>
</tr>
<tr>
<td>Percent difference in days to radiographic healing</td>
<td>12</td>
<td>-32.8 (-39.5 to -25.3)</td>
<td>3</td>
<td>-1.7 (-11.2 to 8.8)</td>
</tr>
<tr>
<td>Risk difference in adverse effects</td>
<td>Not reported separately</td>
<td>Not reported separately</td>
<td>9</td>
<td>0.0 (-0.0 to 0.03)</td>
</tr>
</tbody>
</table>

RR: relative risk; VAS: visual analog scale.

### Table 3. Summary of Findings for Quality of Evidence and Narrative Conclusion From the Schandelmaier Systematic Review

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

Adapted from Schandelmaier et al (2017). $^3$

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

$^a$ Because of serious imprecision.
Fresh Fractures

Surgically Managed
In 2016, Busse et al reported results from a concealed, blinded, sham-controlled, randomized trial evaluating LIPUS for the treatment of patients who underwent intramedullary nailing for fresh tibial fractures. The trial enrolled 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 [SF-36] 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% confidence interval [CI], 0.86 to 1.34; p=0.55). Moreover, there was no different in SF-36 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.

Emami et al (1999) conducted a double-blind, sham-controlled trial that randomized 32 patients with a fresh tibial fracture fixed with an intramedullary rod to additional treatment with an active (n=15) or inactive (n=17) LIPUS device. 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, SD=3 for LIPUS vs 37 days, SD=3 for sham; p=0.44); time to radiographic healing assessed by radiologist (mean, 155 days, SD=days [median, 113 days] for LIPUS vs mean, 125 days, SD=11 [median, 112 days] for sham; p=0.76); and time to radiographic healing assessed by orthopedic surgeon (mean, 128 days, SD=13, for LIPUS and mean, 114 days, SD=9 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. 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 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 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 a 2017 systematic review including 13 RCTs, 4 of which rated low risk for 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 2017 meta-analysis by Seger et al included 5 studies focused on scaphoid nonunions and analyzed healing index and average time to union following LIPUS. 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 2017 systematic review published by Schandelmaier included 3 RCTs in nonunion fractures that were operatively managed; however, all studies were rated at high risk of bias. 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. 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 mm² in the LIPUS group and -0.10 mm² in the sham group (effect size, -0.47; 95% CI, -0.91 to -0.03 mm²). 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 with 20 subjects with tibial fracture nonunion that found a statistically significant reduction in time to radiographic healing (percent difference in days, -57.2%; 95% CI, -74.7% to -27.6%). However, there was a 45% loss to follow-up rate raising significant concerns about potential bias of these findings.

Ricardo et al (2006) published a blinded RCT in 21 subjects with scaphoid nonunion that also found a statistically significant reduction in time to radiographic healing (-40.4%; 95% CI, -48.7% to -30.8%).

Biglari et al (2016) conducted a prospective, single-institution, observational study on 61 nonunions in long bones of the lower extremity treated with LIPUS. 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 less 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. 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% lost to follow-up, 9% for 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 including a 2017 meta-analysis without controlled comparison results, 3 RCTs at high risk of bias (one published as a thesis) and 2 observational studies (a prospective study and a registry study). Reported outcomes do not include functional outcomes, and a wide range of healing rates were reported across the studies with a lack of comparison with routine surgical care in the observational studies, 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 issues such as pain, function, and resumption of professional and personal activities in 26 military recruits.19 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 2017 Schandelmaier meta-analysis.3

In 2013, Urita et al 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.20 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 with a high risk of bias in the 2017 meta-analysis by Schandelmaier.3

The 2017 systematic review by Schandelmaier included 6 trials of LIPUS for distraction osteogenesis following surgery and 4 of 6 studies were rated at high risk of bias.3 Four studies were in the tibia,21-24 and the other two were in the mandible.11,12 No clinically meaningful results were reported for the mandible studies in the meta-analysis.3 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)11 in the meta-analysis.3 Four of the studies21-24 were included in the meta-analysis3 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 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 low-intensity pulsed ultrasound (LIPUS), the evidence includes randomized controlled trials (RCTs) and a 2017 cumulative meta-analysis of RCTs. 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 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 effect. 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, the evidence includes only lower quality studies including a small systematic review in scaphoid nonunions, 3 low-quality RCTs, and 2 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 have 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, the evidence includes only lower quality studies including 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.

SUPPLEMENTAL INFORMATION

CLINICAL INPUT FROM 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.

2012 Input
In response to requests, input was received from 4 academic medical centers while this policy was under review in 2012. Input supported the use of low-intensity pulsed ultrasound for delayed unions and nonunions of bones excluding the skull and vertebra, and in fresh closed fractures at high risk for delayed fracture healing or nonunion. Commentators agreed that other applications of low-intensity pulsed 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.

2011 Input
In response to requests, input was received from 2 physician specialty societies and 1 academic medical center while this policy was under review in 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
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infection, Charcot neuroarthropathy, and fractures of the tibial shaft or clavicle as additional risk factors, and another supported including fractures of the talus and sesamoids as additional risk factors.

2008 Input
In response to requests, input was received from 1 physician specialty society while this policy was under review in 2008. Physician input obtained through the American Academy of Orthopaedic Surgeons supported the positions on the criteria for medical necessity and the conditions considered investigational (eg, delayed union and open/unstable grade II or III 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, 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. 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. 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. “After extensive deliberations, the panel found no compelling anatomical or physiological reasons why LIPUS would probably be beneficial in these other patient populations.”

National Institute for Health and Care Excellence
The U.K.’s National Institute for Health and Care Excellence (NICE) published guidance in 2010 on LIPUS to promote fracture healing. NICE concluded that this procedure “can reduce fracture healing” and is particularly beneficial for “delayed healing and fracture non-union.”

In 2013, NICE published guidance on Exogen for the treatment of long bone fractures with nonunion and delayed fracture healing. 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 at which bone healing progresses without adjunctive 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 to begin in April 2017.

American Academy of Orthopaedic Surgeons
The American Academy of Orthopaedic Surgeons published 2009 guidelines on the treatment of distal radius fractures. The Academy issued a limited recommendation for the use of LIPUS for adjuvant treatment of distal radius fractures. While evidence from 1 study demonstrated an increased rate of healing (measured by the absence of pain and radiographic union), the additional cost of LIPUS, resulted in a “limited” recommendation.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.
MEDICARE NATIONAL COVERAGE
Effective January 2001, ultrasonic osteogenic stimulators were covered as medically reasonable and necessary for the treatment of nonunion fractures. Nonunion fractures of the skull, vertebrae, and those that are tumor-related are excluded from coverage. Ultrasonic osteogenic stimulators may not be used concurrently with other noninvasive osteogenic devices. Ultrasonic osteogenic stimulators for fresh fractures and delayed unions are not covered.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
One currently unpublished trial that might influence this review is listed in Table 4.

Table 4. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>A Randomized Controlled Trial Comparing Low-Intensity, Pulsed Ultrasound to Placebo in the Treatment of Operatively Managed Scaphoid Non-unions</td>
<td>154</td>
<td>Dec 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

REFERENCES
MP 1.01.05
Ultrasound Accelerated Fracture Healing Device

details.aspx?NCDId=65&ncdver=2&DocID=150.2&ncd_id=150.2&ncd_version=2&basket=ncd*3a%24150.2*3a%242*3a%24Osteogenic+Stimulators&bc=gAAAAAgAAAAA%3d%3d&. Accessed January 30, 2017.

CODES

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>20979</td>
<td>Low-intensity ultrasound stimulation to aid bone healing, non-invasive (nonoperative)</td>
</tr>
<tr>
<td>HCPCS</td>
<td>E0760</td>
<td>Osteogenesis stimulator, low-intensity ultrasound, non-invasive</td>
</tr>
<tr>
<td>ICD-10-CM</td>
<td></td>
<td>Investigational for all relevant diagnoses</td>
</tr>
<tr>
<td>ICD-10-PCS</td>
<td></td>
<td>Fracture codes – 7th digit “A,” as shown in the list, is initial encounter for closed fracture. The same codes with 7th digit “K” is subsequent encounter for nonunion (in forearm, femur, lower leg &amp; ankle fractures 7th digits “M” and “N” are also nonunion for certain types of open fractures – in fractures of the shoulder, humerus, wrist, hand and foot there isn’t separation of open vs closed nonunions). 7th digit “G” represents subsequent encounter for fracture with delayed healing. This list does not include any skull or vertebral fracture codes. There are also other codes for pathological and stress fractures (M80-M84) which are not listed here.</td>
</tr>
<tr>
<td>ICD-10-PCS</td>
<td></td>
<td>ICD-10-PCS codes are only used for inpatient services.</td>
</tr>
<tr>
<td>Type of service</td>
<td>DME</td>
<td></td>
</tr>
<tr>
<td>Place of service</td>
<td>Outpatient, Home</td>
<td></td>
</tr>
</tbody>
</table>

POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/01/95</td>
<td>Add to Durable Medical section</td>
<td>New policy</td>
</tr>
<tr>
<td>07/16/99</td>
<td>Replace policy</td>
<td>Updated; new indications</td>
</tr>
<tr>
<td>11/01/99</td>
<td>Replace policy</td>
<td>New CPT code; policy unchanged</td>
</tr>
<tr>
<td>08/18/00</td>
<td>Replace policy</td>
<td>New indication for treatment of fracture nonunions</td>
</tr>
<tr>
<td>12/15/00</td>
<td>Replace policy</td>
<td>Editorial revisions; policy statement unchanged</td>
</tr>
<tr>
<td>12/18/02</td>
<td>Replace policy</td>
<td>Policy updated; new references added; policy statement unchanged</td>
</tr>
<tr>
<td>02/25/04</td>
<td>Replace policy</td>
<td>Policy updated with literature review; policy statement unchanged</td>
</tr>
<tr>
<td>04/01/05</td>
<td>Replace policy</td>
<td>Policy updated with literature review; policy statement revised</td>
</tr>
</tbody>
</table>

Original Policy Date: December 1995
<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/27/05</td>
<td>Replace policy</td>
<td>Policy updated with literature review for November 2004 through May 2005 and new Medicare coverage decision; policy statement unchanged</td>
</tr>
<tr>
<td>10/10/06</td>
<td>Replace policy</td>
<td>Policy updated with literature search from May 2005 through July 2006. Policy statements unchanged.</td>
</tr>
<tr>
<td>02/14/08</td>
<td>Replace policy</td>
<td>Policy updated with literature review and clinical vetting; references added; policy statements unchanged</td>
</tr>
<tr>
<td>09/10/09</td>
<td>Replace policy</td>
<td>Policy updated with literature search through July 2009, Rationale extensively edited, references added. One reference removed. No change to existing policy statements; use in stress fractures added as investigational.</td>
</tr>
<tr>
<td>01/13/11</td>
<td>Replace policy</td>
<td>Policy updated with literature search, clinical input reviewed, references reordered, policy statements modified by moving information from policy guidelines to policy statements about risk factors for nonunion</td>
</tr>
<tr>
<td>09/01/11</td>
<td>Replace policy</td>
<td>Policy updated with literature search through July 2011; references 12-13 added; treatment of delayed unions considered medically necessary. Fresh fracture defined.</td>
</tr>
<tr>
<td>09/13/12</td>
<td>Replace policy</td>
<td>Policy updated with literature search through July 2012; references 1, 5, and 15 added; arthrodesis added to investigational statement; definition of delayed unions revised to 3 months for consistency with definition of nonunion.</td>
</tr>
<tr>
<td>12/13/12</td>
<td>Replace policy</td>
<td>Clinical input reviewed; reference 17 added; policy statements unchanged</td>
</tr>
<tr>
<td>01/09/14</td>
<td>Replace policy</td>
<td>Policy updated with literature review through November 18, 2013, references 12, 16, and 18 added; clarification of delayed union and nonunion of previously surgically treated fractures; fresh surgically treated closed fractures added to investigational statement</td>
</tr>
<tr>
<td>02/12/15</td>
<td>Replace policy</td>
<td>Policy updated with literature review through November 25, 2014; references 11 and 20 added; reference 5 corrected; policy statements unchanged</td>
</tr>
<tr>
<td>08/11/16</td>
<td>Replace policy</td>
<td>Policy updated with literature review through July 1, 2016; references 14 and 16 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>03/21/17</td>
<td>Replace policy</td>
<td>Reviewed by consensus with plans for future literature review.</td>
</tr>
<tr>
<td>07/25/17</td>
<td>Replace policy</td>
<td>Policy updated with literature review through January 25, 2017; references 3-4, 7, 17, and 25-26 were added. The following indications were changed from medically necessary to not medically necessary: fresh fractures (surgically and nonsurgically managed) and nonunion/delayed union fractures.</td>
</tr>
</tbody>
</table>

**MP 1.01.05**

**Ultrasound Accelerated Fracture Healing Device**

to explicitly state that ultrasound treatment of open fracture is investigational. Information on Medicare policy added. References 5-6 added.

**Original Policy Date:** December 1995

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APPENDIX

SEARCH STRATEGY
The MEDLINE database was searched (via PubMed) using the following search strategy:

((ultrasound OR ultrasonography OR ultrasonic) AND ("fracture healing" OR "non union" OR "non-union" OR "delayed union") AND (device OR aid OR split OR splints))

The search was performed through January 25, 2017, limited to English-language articles on human subjects. The search was supplemented by manual bibliography review of selected references, review of data or literature reported on manufacturer websites (particularly for analytic validity) and ClinicalTrials.gov. Biodesix also provided a list of potential publications without date restrictions for consideration.

STUDY SELECTION
We included studies that combined all types of fractures in their analysis, as well as studies that focused on only 1 type of fracture (eg, surgically managed fresh fractures or stress fractures). If systematic reviews and meta-analyses were available, they were included. We also included randomized controlled trials. If no randomized controlled trials were available for a specific type of fracture, we included nonrandomized designs.

DATA ABSTRACTION AND BIAS/QUALITY ASSESSMENT
Data were abstracted by a single reviewer. The quality of randomized controlled trials not included in systematic reviews was assessed using the Cochrane risk of bias tool.

MEDICAL ADVISORY PANEL REVIEW
This Evidence Opinion was reviewed by the Blue Cross Blue Shield Association Medical Advisory Panel on June 7, 2017.