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Low Intensity Pulsed Ultrasound Fracture Healing Device

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Low-intensity pulsed ultrasound treatment **may be considered medically necessary** when used as an adjunct to conventional management (i.e., closed reduction and cast immobilization) for the treatment of fresh (<14 days), closed fractures in skeletally mature individuals who are at high risk (**see NOTE 1**) for delayed fracture healing or nonunion.

NOTE 1: Candidates for ultrasound treatment are those at high risk for delayed fracture healing or nonunion. These high-risk factors may include patient comorbidities AND/OR locations of fractures, such as:

Patient comorbidities:
- Diabetes,
- Steroid therapy,
- Osteoporosis,
- History of alcoholism,
- History of smoking.

Fracture locations:

- Jones fracture,
- Fracture of navicular bone in the wrist (also called the scaphoid),
- Fracture of metatarsal,
- Fractures associated with extensive soft tissue or vascular damage.

Low-intensity pulsed ultrasound treatment **may be considered medically necessary** as a treatment of delayed union of bones (**see NOTE 2**), excluding the skull and vertebra.

NOTE 2: Delayed union is defined as a decelerating healing process as determined by serial x-rays, 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.

Low-intensity pulsed ultrasound treatment **may be considered medically necessary** as a treatment of fracture nonunion of bones (**see NOTE 3**), excluding the skull and vertebra.

NOTE 3: A nonunion is normally defined as a fracture that shows no progressive visible signs of healing after 3 months.

Other applications of low-intensity pulsed ultrasound treatment **are considered experimental, investigational and/or unproven** including, but not limited to, treatment of congenital pseudarthroses, open fractures, fresh surgically treated closed fractures, stress fractures, arthrodesis or failed arthrodesis.

Policy Guidelines

None.

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.

Bone Fractures

An estimated 7.9 million fractures occur annually in the United States. Most bone fractures heal spontaneously over 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. (1) Factors contributing to a nonunion include which bone is

fractured, fracture site, the degree of bone loss, time since injury, the extent of soft tissue injury, and patient factors (e.g., smoking, diabetes, systemic disease). (1)

Treatment

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 (FDA) 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. FDA product code: LPQ.

Rationale

This medical policy was created in April 1996 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through February 3, 2022.

Medical policies 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.

Fresh Fractures

Clinical Context and Therapy Purpose

The purpose of low-intensity pulsed ultrasound (LIPUS) in patients who have fresh fractures (either surgically managed or non-surgically managed) is to provide an adjunctive treatment option to standard of care.

The question addressed in this medical policy is: Does the use of low-intensity pulsed ultrasound improve net health outcomes in patients with fresh fractures (either surgically managed or non-surgically managed) compared with standard care without the adjunctive use of low-intensity pulsed ultrasound?

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is patients with fresh fractures (either surgically managed or non-surgically managed). A fracture is most commonly defined as fresh for <14 days after the fracture occurs.

Interventions

The therapy being considered is low-intensity pulsed ultrasound. Low-intensity pulsed ultrasound 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 low-intensity pulsed ultrasound 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. Low-intensity pulsed ultrasound would be an adjunctive therapy following setting and immobilizing the bone. The patient takes the low-intensity pulsed ultrasound device home and self-administers the treatment. Recommended time of treatment administration is 20 minutes/day.

Comparators

The comparator is standard fresh fracture management without low-intensity pulsed ultrasound as an adjunctive therapy.

Outcomes

The general outcome of interest is time to healing, which may be measured radiologically and assessed by an orthopedic surgeon. Clinically meaningful measures for healing would involve functional outcomes such as assessment of pain, use of analgesics, the need for secondary procedures, and ability to return to activities of daily living.

Follow-up should extend for months, the duration of time required for fracture healing.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews with Mixed Populations of Fresh Closed Fractures, Open Fractures and Surgically Treated Closed Fractures

A 2002 meta-analysis conducted by Busse et al. supported the use of low-intensity pulsed ultrasound (LIPUS) as a technique for fractures treated nonoperatively. (2) This review was updated in 2009 and included RCTs of LIPUS for any type of fracture. (3) Thirteen trials were included; in 5 of them, patients were managed conservatively, and in 8 studies, patients received ultrasound (US) therapy after operative management (distraction osteogenesis in 3 studies, bone graft for nonunion in 1, operative treatment of fresh fractures in 4. US therapy significantly accelerated radiographic healing of fractures in all 3 RCTs of conservatively managed fresh fractures that assessed this outcome.

The trials of operatively managed (open) fresh fractures outcomes were inconsistent; 4 trials provided low-quality evidence for acceleration of healing by US therapy. Pooled results of 2 trials showed a nonsignificant mean reduction in radiographic healing time of 16.6%.

A 2014 update of a Cochrane review on US and shockwave therapy included 12 studies on US; 8 of the studies were RCTs with placebo controls, 2 were RCTs without placebo controls, and 2 were quasi-randomized. (4) Selected studies were limited in methodologic quality, with all having some evidence of bias. There was very limited evidence on functional outcomes. Pooling results from 8 studies (446 fractures) showed no significant reduction in time to union of complete fractures. This systematic review included studies of conservatively managed fractures along with surgically treated fractures and stress fractures. Subgroup analysis comparing conservatively, and operatively treated fractures raised the possibility that pulsed US may be effective in reducing healing time in conservatively managed fractures, but a test for subgroup differences did not confirm a significant difference between the subgroups. The review concluded that while a potential benefit of US for acute fractures could not be ruled out, the currently available evidence was insufficient to support its routine use.

Fresh Closed Fractures

In a 1997 multicenter RCT by Kristiansen et al., 60 patients with dorsally angulated fractures of the distal radius treated with manipulation and cast were randomly assigned to 10 weeks of daily treatment with a pulsed US device or an inactive device. (5) All patients started US within 7 days of fracture. Blinded radiographic and clinical examinations showed faster healing in the US group (61 days) than in the control group (98 days; $p<0.001$). Each radiographic stage of healing also was significantly accelerated in the treatment group.

Heckman et al. (1994) performed a double-blind RCT comparing US treatment (n=33) with a placebo control device (n=34) in closed or grade-I (clean, <1 cm puncture) open fractures of the tibial shaft. (6) Treatment began within 7 days post fracture and consisted of one 20-minute daily session. Time-to-healing was 86 days in the treatment group and 114 days in the control group ($p=0.01$); time to overall (clinical and radiographic) healing was 96 days in the treatment group compared with 154 days in the control group ($p<0.001$).

Scaphoid fractures were treated with US in a 2000 study done in Germany. (7) Fifteen patients with fresh scaphoid fractures (≤10 days) were randomly assigned to treatment and 15 to a placebo device. Healing was assessed by computed tomography (CT) scans every 2 weeks. Fractures treated with US healed faster (43.2 days) than with placebo (62 days; $p<0.01$). Pooled data from these studies demonstrated a mean reduction in radiographic healing time of 36.9% (95% confidence interval [CI], 25.6% to 46.0%).

The benefit of LIPUS may depend on the location and type of bone. Lubbert et al. performed a multicenter double-blind RCT of US treatment of fresh (<5 days) clavicle shaft fractures. (8) Patients were taught to use US devices for 20 minutes daily for 28 days and to record daily their subjective feeling as to whether the fracture healed (the primary outcome measure), pain on visual analog scale (VAS), level of daily activities expressed as hours of activity (work, household work, sport), and analgesic use. A total of 120 patients (61 active, 59 placebo) started treatment. The day that the fracture clinically healed according to patient perception was determined in 92 patients (47 active, 45 placebo); mean duration of time to clinical healing was 26.77 days in the active group versus 27.09 days in the placebo group. Between-group differences in terms of analgesic use and mean VAS were not significant. The time to healing with these fractures is substantially lower than in other studies.

Analysis of an FDA-required postmarketing registry was published by Zura et al. in 2015. (9) This study included 4190 patients, representing 73% of patients in the registry with fresh fractures. The healing rate was 96% for patients who were compliant; 11% of patients were noncompliant or withdrew from the study. Factors found to reduce healing rate were open fracture, current smoking, diabetes, vascular insufficiency, osteoporosis, cancer, rheumatoid arthritis, and prescription nonsteroidal anti-inflammatory drugs. Older age (≥60 years) did not reduce the healing rate.

Subsection Summary: Fresh Closed Fractures
A number of RCTs and systematic reviews have evaluated LIPUS to improve healing in fresh fractures. A 2009 systematic review found that LIPUS significantly accelerated radiographic

healing of fractures in all 3 RCTs of conservatively managed fresh fractures that assessed this outcome. More recently, in a 2014 Cochrane review that included 12 trials but did not distinguish between closed and open fractures; subgroup analysis found that pulsed US may be effective in reducing healing time in conservatively managed fractures. The efficacy of LIPUS to accelerate fracture healing may depend on the location and type of bone along with risk factors for healing.

Open Fractures and Surgically Treated Closed Fractures

For the treatment of open fractures, data are conflicting regarding the efficacy of LIPUS, specifically for patients treated surgically with placement of an intramedullary nail. For example, 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. (10) 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).

In 2011, Dijkman et al. reported a substudy of 51 patients from a larger RCT that enrolled patients with open or closed tibial shaft fractures that were treated surgically with an intramedullary nail. (11) A 2014 publication from Busse et al. reported a sham-controlled pilot of the industry-sponsored TRUST trial to determine feasibility for the larger trial. (12) According to www.ClinicalTrials.gov (NCT00667849), 501 patients were enrolled, but the trial was "terminated due to futility" at study midpoint. Results posted on the website show no benefit for the primary outcomes measures of 36-Item Short-Form Health Survey Physical Component Summary score or days to radiographically confirmed healing.

Lou et al. (2017) conducted a meta-analysis focusing on fresh fractures. (13) Studies included patients that had been surgically managed and conservatively managed. Time to fracture union was significantly lower in patients receiving LIPUS than inpatients not receiving LIPUS (standard mean difference, -0.65; 95% 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.

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. (14) 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).

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. (15) There were no significant differences between groups (11% in patients receiving LIPUS vs 10% in patients receiving sham) in need for secondary procedures (e.g., 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.

Subsection Summary: Open Fractures and Surgically Treated Closed Fractures
Findings are not consistent for studies of fresh open fractures. The inconsistent results from randomized trials and the negative findings of the meta-analyses do not support use of LIPUS for treating open fractures. In addition, a large and well-designed sham-controlled trial of LIPUS for surgically treated fresh tibial fractures was terminated due to futility after half of the patients completed the study.

Fracture Nonunion or Delayed Union Fracture
Clinical Context and Therapy Purpose
The purpose of low-intensity pulsed ultrasound in patients who have fracture nonunion or delayed union fracture is to provide an adjunctive treatment option to standard of care.

The question addressed in this medical policy is: Does the use of low-intensity pulsed ultrasound improve net health outcomes in patients with fracture nonunion or delayed union fracture compared with standard care without the adjunctive use of low-intensity pulsed ultrasound?

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is patients with fracture nonunion or delayed union fracture.

Interventions

The therapy being considered is low-intensity pulsed ultrasound. Low-intensity pulsed ultrasound 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 low-intensity pulsed ultrasound 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. Low-intensity pulsed ultrasound would be an adjunctive therapy following setting and immobilizing the bone. The patient takes the low-intensity pulsed ultrasound device home and self-administers the treatment. Recommended time of treatment administration is 20 minutes/day.

Comparators
The comparator is standard nonunion or delayed union fracture management without low-intensity pulsed ultrasound as an adjunctive therapy.

Outcomes
The general outcome of interest is time to healing, which may be measured radiologically and assessed by an orthopedic surgeon. Clinically meaningful measures for healing would involve functional outcomes such as assessment of pain, use of analgesics, the need for secondary procedures, and ability to return to activities of daily living.

Follow-up should extend for months, the duration of time required for fracture healing.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- Studies with duplicative or overlapping populations were excluded.

Fracture Nonunion
The evidence on nonunion of fractures is based on data presented to the FDA as part of the approval process for the Sonic Accelerated Fracture Healing System (SAFHS®). The following data were reported and are included in the device package insert. (16)

- Data were collected on 74 cases of established nonunion with a mean fracture age of nearly 3 years. The principal outcome measure was the percentage of patients with healed nonunions, as determined clinically and by radiographic analysis. Each case served as its own control, based on the definition of nonunion that suggests that nonunions have a 0% probability of achieving a healed state without an intervention.
- A total of 64 (86%) of 74 cases healed with use of low-intensity US. Time-to-healing was 173 days. The healing rate of scaphoid bones was lower, at 33% (2 of 6 cases), which was

partially responsible for a significant difference between the healing rates of long bones (92%) versus other bones (67%).
- Fracture age also affected healing rates, with fractures over 5 years old having a healing rate of 50% compared with a healing rate of 95% in those present for no more than 1 year.

Ricardo (2006) published a blinded RCT evaluating 21 subjects with scaphoid nonunion who were treated with low-intensity pulsed ultrasound or a sham device following a pedicled vascularized bone graft. (17) Time to healing was defined as the number of days from the operation to healing both clinically (solid and not causing tenderness or pain) and radiographically (bridging cortices). Additional outcomes included pain, wrist range of motion, radiographic evidence of union, carpal height index, and scapholunate-capitolunate angles. The authors reported a statistically significant reduction in time to radiographic healing (-40.4%; 95% CI, -48.7% to -30.8%) with low-intensity pulsed ultrasound.

A 2007 study used prospectively defined criteria to analyze all Dutch patients (96 participating clinics) who had been treated with US for established nonunion of the tibia (characterized by a total stop of all fracture repair processes). (18) Included in the analysis were 71 patients at least 3 months from the last surgical intervention who did not show any healing improvements in the 3 months before US treatment (average fracture age, 257 days; range, 180-781 days). All patients completed follow-up (average, 2.7 years) by questionnaire, or by phone, if needed. The overall healing rate was 73%, at an average 184 days to healing (range, 52-739 days). No differences in healing rates for open and closed fractures were observed.

In 2015, Zura et al. analyzed data from a FDA-required postmarketing registry that included 767 patients with chronic fracture nonunion. (19) Patients with chronic (>1 year) nonunion were selected if they had the following information recorded: date of fracture, start of US treatment, end of US treatment, and healed/failed status using both clinical and radiographic outcomes. Patients had undergone an average of 3.1 prior surgical procedures without success. The reported healing rate was compared with the expected healing rate for chronic nonunion, which is negligible without intervention. With an average of 179.5 days of US treatment, the overall healing rate was 86.2%. For patients with a nonunion of at least 5 years in duration (n=98), the healing rate was 82.7%; for patients with a nonunion of greater than 10 years (n=12), the healing rate was 63.2%. Age was the only factor affecting healing rate.

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 low-intensity pulsed ultrasound. (20) Among 166 cases in the analysis, 78.6% (range, 33%-100%) were reported to show healing following low-intensity pulsed ultrasound, with an average time to union of 4.2 months (range, 2.3-5.6 months).

Subsection Summary: Fracture Nonunion
Due to the low likelihood of healing without intervention, cohort studies demonstrating high rates of healing are considered adequate evidence to demonstrate improved outcomes for this indication. The largest study analyzed data from a registry and focused on patients with chronic

nonunion. Many of these patients had failed to heal despite surgical treatment but had a high rate of healing with ultrasound.

Delayed Fracture Union

In 2010, Schofer et al. reported an industry-sponsored, multicenter, randomized, double-blinded, sham-controlled trial of LIPUS in 101 patients with delayed union of the tibia. (21) Delayed union was defined as 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. Fifty-one patients were randomized to daily treatment with US and 50 were randomized to an inactive sham device (20 minutes daily for 16 weeks). The primary outcome measure was change in bone mineral density (BMD) over the 16 weeks, assessed by CT attenuation coefficients (or Hounsfield units). Gap area at the fracture site was a secondary end point. The primary analysis was intention-to-treat with imputation of missing values. Mean improvement in BMD was 34% (90% CI, 14% to 57%) greater for US-treated subjects than for sham-treated subjects. Analysis of "completers" showed a medium effect size (0.53) of the treatment. A mean reduction in bone gap area (as measured on a log scale) also favored US treatment, with a mean change in log gap area of -0.13 mm^2 for active treatment and -0.10 mm^2 for sham (effect size, -0.47; 95% CI, -0.91 to -0.03 mm^2). Untransformed data showed a difference between groups of -0.457 mm^2 (90% CI, -0.864 to -0.049), which was statistically significant. The clinical significance of this difference is unclear. There was a trend (p=0.07) for more subjects receiving LIPUS to be judged as healed by participating physicians at the end of the 16-week study period (65% [33/51] of US vs 46% [23/50] of sham).

Subsection Summary: Delayed Fracture Union

The best evidence for US treatment for delayed fracture union is from a moderately sized (n=101), double-blinded, sham-controlled trial. Analysis of patients who completed the study showed a moderate effect size for increased bone mineral density and a trend for increased rate of clinical healing. While there was not a statistically significant improvement in the rate of healing, improvements in intermediate outcomes and corroborating evidence from trials of patients with similar indications (e.g., fracture nonunion) make it very likely that this treatment is efficacious for delayed union.

Stress Fractures, Osteotomy Sites or Distraction Osteogenesis

Clinical Context and Therapy Purpose

The purpose of low-intensity pulsed ultrasound in patients who have stress fractures, osteotomy sites or distraction osteogenesis is to provide an adjunctive treatment option to standard of care.

The question addressed in this medical policy is: Does the use of low-intensity pulsed ultrasound improve net health outcomes in patients with stress fractures, osteotomy sites or distraction osteogenesis compared with standard care without the adjunctive use of low-intensity pulsed ultrasound?

The following PICO was used to select literature to inform this policy.

Populations
The population of interest consists of patients with stress fractures, osteotomy sites or distraction osteogenesis.

Interventions
The therapy being considered is low-intensity pulsed ultrasound. Low-intensity pulsed ultrasound 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 Low-intensity pulsed ultrasound 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. Low-intensity pulsed ultrasound would be an adjunctive therapy following setting and immobilizing the bone. The patient takes the low-intensity pulsed ultrasound device home and self-administers the treatment. Recommended time of treatment administration is 20 minutes/day.

Comparators
The comparator is standard stress fracture or osteotomy site management without low-intensity pulsed ultrasound as an adjunctive therapy.

Outcomes
The general outcome of interest is time to healing, which may be measured radiologically and assessed by an orthopedic surgeon. Clinically meaningful measures for healing would involve functional outcomes such as assessment of pain, use of analgesics, the need for secondary procedures, and ability to return to activities of daily living.

Follow-up should extend for months, the duration of time required for fracture healing.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- Studies with duplicative or overlapping populations were excluded.

Stress Fractures
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. (22) 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 et al. (2017) meta-analysis. (23)

Osteotomy Sites

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. (24) 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 trial was rated with a high-risk of bias in the Schandelmaier et al. (2017) meta-analysis. (24)

Distraction Osteogenesis

The 2009 systematic review by Busse et al. found 3 trials of distraction osteogenesis that used a variety of surrogate outcome measures with inconsistent results and provided very low-quality evidence of accelerated functional improvement. (3) In 2011, a small (n=36) nonblinded RCT of LIPUS found no significant differences between active and control groups in efficacy measures, although the treatment period (fixator gestation period) was decreased by more than 1 month. (25) A 2014 study randomized 21 patients undergoing callus distraction for posttraumatic tibial defects to LIPUS or no treatment (controls). (26) In this nonblinded study, US shortened healing by 12 d/cm and the total fixator time by 95 days.

Lou et al. (2018) conducted a systematic review and meta-analysis on the use of low-intensity pulsed ultrasound for the treatment of patients with distraction osteogenesis. (27) The literature search, conducted in May 2018, identified 7 RCTs (172 patients) for inclusion. The Cochrane risk of bias tool was used to assess trial quality. Three of the trials were considered low risk of bias and 4 were considered to have high-risk of bias. Main limitations in the trials were related to the lack of treatment allocation details and outcome assessors' knowledge of treatment. Pooled results did not find statistically significant differences in treatment time, radiological gap fill area, histological gap fill length, or bone density.

Subsection Summary: Distraction Osteogenesis

The literature on LIPUS for distraction osteogenesis consists of small trials with inconsistent results. Double-blind trials with larger numbers of subjects are needed to evaluate the health benefits of this procedure.

Summary of Evidence

For individuals who have fresh closed fractures who receive low-intensity pulsed ultrasound (LIPUS) as an adjunct to conventional management, the evidence includes randomized controlled trials (RCTs) and systematic reviews of RCTs. Relevant outcomes are symptoms,

morbid events, functional outcomes, and quality of life. This evidence indicates that LIPUS improves clinical and radiographic healing for these types of fractures, although the magnitude of benefit may differ depending on the location of the bone and risk factors for healing. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have open fractures or surgically treated closed fractures who receive LIPUS, the evidence includes RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Results from RCTs of LIPUS for this patient population are mixed, and do not consistently demonstrate improved outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have fracture nonunion who receive LIPUS, the evidence includes prospective case series. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The case series are considered adequate evidence for nonunions, due to the negligible chance of healing without intervention and the lack of other noninvasive alternatives. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have delayed fracture union who receive LIPUS, the evidence includes a single RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Evidence for ultrasound (US) treatment for delayed fracture union (a moderately sized double-blinded sham-controlled trial) showed a moderate effect size for increased bone mineral density and a trend toward increased rate of clinical healing with US treatment. In addition, improvements in intermediate outcomes (e.g., radiographic appearance), combined with the efficacy of US for fresh closed fractures and fracture nonunion, make it very likely that this treatment is also efficacious for delayed union. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have tibial stress fractures, osteotomy sites, or distraction osteogenesis who receive LIPUS, the evidence includes small RCTs and nonrandomized comparative trials. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. One small RCT was identified on US for the treatment of tibial stress fractures. LIPUS did not significantly reduce healing time for these fractures in this double-blind study. One small quasi-randomized study was identified on use of US for osteotomy sites. Clinical outcomes appear to have been assessed only at the time of radiographic healing and did not show any differences between groups at that time point. The literature on pulsed US for distraction osteogenesis (small trials) has shown inconsistent results. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements
National Institute for Health and Care Excellence

In 2018, the National Institute for Health and Care Excellence (NICE) published guidance on the use of low-intensity pulsed ultrasound to promote healing of fresh fractures at low-risk of non-healing. (28) The guidance states that the "current evidence does not show efficacy. Therefore, this procedure should not be used for this indication."

In 2018, the NICE published guidance on the use of low-intensity pulsed ultrasound to promote healing of fresh fractures at high-risk of non-healing. (29) The guidance states that the "current evidence on efficacy is very limited in quantity and quality. Therefore, this procedure should only be used in the context of research.

In 2018, the NICE published guidance on the use of low-intensity pulsed ultrasound to promote healing of delayed and nonunion fractures. (30) The guidance states that the "current evidence on efficacy is inadequate in quality. Therefore, this procedure should only be used with special arrangements for clinical governances, consent and audit or research."

NICE published guidance (2013) on Exogen for the treatment of long-bone fractures with nonunion and delayed fracture healing. (31) 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. In 2019, the Exogen guidance was updated with a review of studies published after June 2012. The review decision stated, "Overall the additional clinical evidence identified since the guidance was published in 2013 supports the current recommendations."

American Academy of Orthopaedic Surgeons

In 2020, the American Academy of Orthopaedic Surgeons published updated guidelines on the treatment of distal radius fractures. (32) Although the Academy issued a limited recommendation for the use of low-intensity pulsed ultrasound for adjuvant treatment of distal radius fractures in its prior 2009 guidelines, low-intensity pulsed ultrasound was not mentioned in the updated guidelines.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02383160[a]	A Randomized Controlled Trial Comparing Low-Intensity, Pulsed	154	Dec 2023

	Ultrasound to Placebo in the Treatment of Operatively Managed Scaphoid Non-unions		
NCT03382483[a]	A Prospective, Patient-centric, Observational, Consecutive Enrollment, Non-interventional Study of Patients At Risk for Fracture Non-union Treated With EXOGEN Compared to a National Healthcare Claims Database Control	12,387	May 2022

NCT: national clinical trial.
[a] denotes an industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	20979
HCPCS Codes	E0760

*Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) **does** have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been **changed** since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
08/15/2023	Reviewed. No changes.
05/15/2022	Document updated with literature review. Coverage unchanged. Reference 28 added and 32 updated; others removed.
05/15/2021	Reviewed. No changes.
11/15/2020	Document updated with literature review. Coverage unchanged. Added references 18, 21, 24, 28-30. Title changed from: Ultrasound Accelerated Fracture Healing Device.
07/01/2019	Reviewed. No changes.
08/15/2018	Document updated with literature review. Coverage unchanged. Added references 1-2, 11, 15-18, 20, 27. Document title changed from: Low Intensity Ultrasound Accelerated Fracture Healing Device.
12/01/2017	Reviewed. No changes.
11/01/2016	Document updated with literature review. The following criteria: "who are at high risk (see NOTE #1) for delayed fracture healing or nonunion" was added to the following coverage statement: "Low-intensity ultrasound treatment may be considered medically necessary when used as an adjunct to conventional management (i.e., closed reduction and cast immobilization) for the treatment of fresh (<14 days) , closed fractures in skeletally mature individuals." In addition Note #1 was added to the coverage section noting the following: "Candidates for ultrasound treatment are those at high risk for delayed fracture healing or nonunion. These high risk factors may include either patient comorbidities or locations of fractures and include the following: diabetes, steroid therapy, osteoporosis, history of alcoholism, history of smoking, jones fracture, fracture of navicular bone in the wrist (also called the scaphoid), fracture of metatarsal, and factures associated with extensive soft tissue or vascular damage." The condition of "fresh surgically treated closed fractures" was added to the listing of the experimental, investigational and/or unproven coverage statement.
01/01/2015	Reviewed; no changes
03/15/2013	Document updated with literature review. The following was added: 1) Low-intensity ultrasound treatment may be considered medically necessary as a treatment of delayed union of bones, excluding the skull and vertebra. NOTE: Delayed union is defined as a decelerating healing process as determined by serial x-rays, 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. 2) Arthrodesis or failed arthrodesis added as examples of experimental, investigational and unproven indications.
07/01/2011	Document updated with literature review. No change in coverage. Stress fracture added as example of experimental, investigational and unproven

	indications. Rationale completely revised. Title changed to Low Intensity Ultrasound Accelerated Fracture Healing Device.
06/01/2009	Coverage revised
04/15/2008	Revised/updated entire document
11/01/2000	Revised/updated entire document
03/01/2000	Revised/updated entire document
04/01/1999	Revised/updated entire document
02/01/1997	Revised/updated entire document
04/01/1996	New medical document