Low intensity pulsed ultrasound (LIPUS) for promoting fracture healing

Evidence-based Review
Important note

- The purpose of this report is to outline and interpret the best current evidence for LIPUS as an adjunct to conservative or operative treatment of acute / fresh fractures, delayed / malunions or stress fractures to enhance fracture healing.

- It is not intended to replace clinical judgement or be used as a clinical protocol.

- A reasonable attempt has been made to find and review papers relevant to the focus of this report; however, it does not claim to be exhaustive.

- This document has been prepared by the staff of the Evidence Based Healthcare Team, ACC Research. The content does not necessarily represent the official view of ACC or represent ACC policy.

- This report is based upon information supplied up to December 2014.

Revision History

<table>
<thead>
<tr>
<th>Date</th>
<th>Version</th>
<th>Description</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/01/2015</td>
<td>V1.1</td>
<td>Second draft, LH comments added</td>
<td>Melissa Barry</td>
</tr>
<tr>
<td>7/01/2015</td>
<td>V1.1</td>
<td>Second draft, LH comments added</td>
<td>Melissa Barry</td>
</tr>
<tr>
<td>13/01/2015</td>
<td>V1.2</td>
<td>Third draft, AB comments added</td>
<td>Melissa Barry</td>
</tr>
<tr>
<td>31/03/2015</td>
<td>V1.3</td>
<td>CSD requested changes added</td>
<td>Melissa Barry</td>
</tr>
<tr>
<td>4/05/2015</td>
<td>V1.4</td>
<td>External peer review comments added</td>
<td>Melissa Barry</td>
</tr>
<tr>
<td>30/07/2015</td>
<td>V1.5</td>
<td>Post PGAG amendments made</td>
<td>Melissa Barry</td>
</tr>
</tbody>
</table>
Executive Summary

Background

Low intensity pulsed ultrasound (LIPUS) is a class of ultrasound used as an adjunct to conventional treatment for fracture healing. It has been used clinically in an attempt to enhance fracture healing by stimulating bone growth (osteogenesis) at the fracture site, leading to a decreased recovery time and faster return to full function after injury occurrence \(^1\). It has been investigated for acute fractures, malunion or delayed fractures, stress fractures, and also fractures that have been treated conservatively (immobilised in a cast) or stabilised with hardware (operatively with internal or external fixation using nails, screws and/or plates). As LIPUS is non-invasive and shown to have minimal adverse effects it is an attractive technology to use for enhancing bone healing, however the physiological mechanisms by which it works remain unknown\(^2\).

LIPUS has been marketed as easy to use by the patient and by companies that sell the product as being able to increase healing rates. In New Zealand two brands have been available: EXOGEN (Smith and Nephew, New Jersey) and Melmak (Biomedical Tissue Technologies, Everfit Healthcare, Australia). Currently EXOGEN markets these devices as highly effective and capable of accelerating healing rates by up to 38%. However these reports show a high selection bias and include evidence from animal studies and clinical studies dating from 2002, and importantly do not cite results of reviews that use high quality study designs as reported by the Cochrane Collaboration or SIGN (Scottish Intercollegiate Guidelines Network). High quality reviews report that there is potential for LIPUS to increase healing rates, but not to the extent that is reported by the companies that manufacture LIPUS devices.

It has been noted by the ACC Clinical Services Directorate that their requests for LIPUS have been increasing. The purpose of this evidence-based report is to build on previous reports prepared by the Evidence-Based Healthcare team in ACC Research to determine if the body of evidence has changed and whether the current literature-based recommendation: "LIPUS be only purchased on a case by case basis for promoting healing of fractures of the tibia and distal radius" \(^3\) needs to be amended.

Search strategy

A standard systematic search was conducted over multiple databases that included AMED, Embase, Ovid MEDLINE (1988 to December 2014), The Cochrane Library and Google Scholar. As this search was aimed at building on information for LIPUS already presented in existing reports the inclusion criteria for this report were: systematic reviews and meta-analyses from 2012 (date of last ACC Research LIPUS review) to December 2014 and randomised control trials (RCTs) from June 2014 to December 2014 that investigated LIPUS on any form of fracture from an injury in humans.

Two ACC research advisors examined all potentially relevant studies retrieved by the literature search and applied inclusion criteria to select studies to be assessed. Studies meeting the criteria for inclusion in this report were assessed by the advisors for their methodological quality using the SIGN level of evidence system.

Main results

Four systematic reviews / meta-analyses of very high to high quality study design and two RCTs of moderate quality met the inclusion criteria. The four systematic reviews included studies that investigated the effects of LIPUS on a range of different types of fractures in different locations that used mostly Exogen LIPUS devices. It is important to note that the evidence for the use of LIPUS within each of the systematic reviews largely originates from the same group of primary studies. Since the results of these studies were analysed differently, and data grouped differently between the reviews, all four reviews are included in this report. It should also be noted that although the quality of the systematic reviews was high, the quality of the design of the primary studies they analysed was consistently reported by each systematic review as poor. This was due to a large amount of heterogeneity across the primary studies detected by the review authors and small sample sizes in the primary studies. The main results of this report are outlined in Table 1 below:
Table 1. Main results for effects of LIPUS

<table>
<thead>
<tr>
<th>Results analysed</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute / Fresh fractures</td>
<td>Low quality evidence for the use of LIPUS in the upper limb or lower limb (time to third cortical bridging), high levels of heterogeneity between studies</td>
</tr>
<tr>
<td>Stress fractures</td>
<td>No evidence that LIPUS affects bone healing times</td>
</tr>
<tr>
<td>Delayed / non-union fractures</td>
<td>Little evidence to support LIPUS use due to variability within data, reviews report that primary studies had missing or incomplete data</td>
</tr>
<tr>
<td>Conservatively / operatively treated fractures</td>
<td>LIPUS decreases radiological healing times when used as an adjunct to conservative fracture management, (e.g. immobilised with cast). No evidence to favour LIPUS use with operatively treated fractures</td>
</tr>
<tr>
<td>Clinical healing</td>
<td>No significant difference in functional scores for LIPUS groups. Individual primary studies reported conflicting evidence pain scores and time to weight-bearing. Evidence for LIPUS on clinical healing outcomes is inconclusive</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>No difference in adverse effects when LIPUS was used compared to when LIPUS was not used during fracture healing</td>
</tr>
</tbody>
</table>

Conclusions

The quality and analyses of the literature by the systematic reviews was high. However, the quality of the articles that they reviewed was low and variable however this was comprehensively reported by the systematic reviews. The predominant limitation within the reviews was the high level of heterogeneity between the studies that they analysed. This heterogeneity led to non-significant meta-analyses for the majority of data, conflicting evidence and an inability to make a conclusive statement about the efficacy of LIPUS when used an adjunct for different treatments and different types of fractures.

These conclusions are in agreement with the 2012 ACC Research report that stated “the evidence for the effectiveness of LIPUS was moderate to very low and provided conflicting results. “ and that “the role of LIPUS in the management of fractures required large blinded trials”. There is evidence that is this is currently being conducted by the feasibility RCT by Busse et al (2014); however these results are preliminary and inconclusive. It is possible that more comprehensive results will arise in the future, however there has been no indication when this may be. In order for a strong recommendation to be made for LIPUS use, further high quality RCTs that focus both on radiological and clinical healing outcomes are required.

Recommendation

The current available evidence is insufficient to support the use of LIPUS in the treatment of:

- Delayed / non-union fractures and,
- Acute / fresh fractures of the tibia, radius and scaphoid

And that:

- LIPUS should not be used for skull or vertebrae fractures, or if the fracture is tumour related

Although the evidence suggests there is some potential benefit of using LIPUS in acute fractures and in conservatively managed fractures of the tibia and radius (in agreement with previous ACC Research LIPUS reports) overall the evidence is conflicting and of poor quality. This means that because the quality of evidence that favours LIPUS is moderate to low, the recommendation for its use is weak.

Based on the evidence reported in the literature and guidance from the external peer-review there is little evidence that LIPUS improves fracture healing when used as an adjunct to other treatment. Based on this information purchasing recommendation for LIPUS is:

Do not purchase
Table of Contents

Executive Summary ........................................................................................................... 3
Table of Contents ............................................................................................................ 5
List of Tables .................................................................................................................. 7
Abbreviations and Definitions ......................................................................................... 7

1 Background .................................................................................................................. 8
  1.1 Description of LIPUS ............................................................................................... 8
  1.2 Previous reporting for LIPUS ................................................................................ 8
    1.2.1 ACC EBH Reports ............................................................................................ 8
    1.2.2 ACC’s current position for LIPUS .................................................................... 9
    1.2.3 NICE medical technologies guidelines report for LIPUS ................................. 9
    1.2.4 Other insurance companies’ positions ............................................................. 9
  1.3 Objective of this report ......................................................................................... 10

2 Methods ....................................................................................................................... 11
  2.1 Search Strategy .................................................................................................... 11
  2.2 Inclusion and Exclusion Criteria ......................................................................... 11
    2.2.1 Inclusion Criteria .......................................................................................... 11
    2.2.2 Exclusion Criteria ......................................................................................... 11
  2.3 Level of Evidence ................................................................................................. 12

3 Results ......................................................................................................................... 13
  3.1 Study selection .................................................................................................... 13
  3.2 Quality Assessment ............................................................................................. 13
  3.3 Effect of LIPUS on acute/fresh fractures ............................................................ 15
  3.4 Effect of LIPUS on stress fractures ..................................................................... 16
  3.5 Effect of LIPUS on delayed fractures or non-unions ........................................... 16
  3.6 Effect of LIPUS on conservative or operatively treated fractures ....................... 17
  3.7 Adverse events associated with LIPUS ............................................................... 18
  3.8 Effects of LIPUS on clinical healing ................................................................... 18
  3.9 Effect of LIPUS on scaphoid fractures ............................................................... 19

4 Discussion ................................................................................................................... 20
  4.1 Nature and quality of the evidence ...................................................................... 20
  4.2 Limitations ........................................................................................................... 20

5 Conclusion .................................................................................................................. 21
  5.1 Evidence statement .............................................................................................. 21
  5.2 Recommendations ............................................................................................... 22

6 References .................................................................................................................. 23
7 Appendices........................................................................................................................................24

7.1 Appendix 1: Evidence Tables ........................................................................................................25

7.2 Appendix 2: Cigna and Aetna guidelines for LIPUS use ...............................................................35

7.2.1 Cigna Medical Necessity Guidelines (Revised 15/8/2014) .........................................................35

7.2.2 Aetna Clinical Policy Bulletin for Bone Growth Stimulators (Revised 4/6/2014) ....................35

7.2.3 Medicare and Medicaid guidelines ............................................................................................36
List of Tables

Table 1. Main results for effects of LIPUS .................................................................4
Table 2. SIGN level of evidence .................................................................................12
Table 3. Brief outline of included systematic reviews and meta-analyses for LIPUS .................................................................13
Table 4. Brief outline of included RCTs for LIPUS ....................................................14
Table 5. Effect of LIPUS on acute/fresh fractures ......................................................15
Table 6. Effect of LIPUS on stress fractures .................................................................16
Table 7. Effect of LIPUS on delayed fractures or non-unions ....................................17
Table 8. Effect of LIPUS on conservative and operatively treated fractures .............17
Table 9. Adverse events associate with LIPUS ..........................................................18
Table 10. Effects of LIPUS on clinical outcomes .......................................................18

Abbreviations and Definitions

95% CIs 95% Confidence Intervals
DEXA scan Dual-energy X-ray absorptiometry
ESTIM Electrical stimulators
LIPUS Low intensity pulsed ultrasound
Olerud-Molander score Scoring system for ankle fractures that assesses clinical signs (pain, stiffness and swelling) and level of function on a scale of 0 (worst) to 100 (back to pre-injury levels) (Olerud and Molander, 1984)
OR Odds ratio
ORIF Open reduction, internal fixation
RCT Randomised control trial
RR Relative risk
SMD Standard mean difference
W/cm² Watts per cm²
MHz Megahertz

Definitions of outcome measures present in body of literature

Clinical healing Level of fracture healing determined through clinical examination (e.g. pain/tenderness at site, ability to weight-bear, scoring on function scales – Olerud-Molander score)

Radiological healing Measured in this body of literature as healing of three of four cortices within the bony callus, examined on an orthogonal radiograph
1 Background

1.1 Description of LIPUS

Low intensity pulsed ultrasound (LIPUS) is a class of ultrasound used as an adjunct to conventional treatment for fracture healing. It has been used clinically in an attempt to enhance fracture healing by stimulating bone growth (osteogenesis) at the fracture site, leading to a decreased recovery time and faster return to full function after injury occurrence. The efficacy of LIPUS has been investigated for acute fractures, malunion or delayed fractures and stress fractures, and also fractures that have been treated conservatively (immobilised in a cast) or stabilised with hardware (internal or external fixation using nails, screws and/or plates). The effects of LIPUS reported in the literature are mixed, due to variability between individual studies that include different fracture sites, different treatment strategies, varying outcome measures and type of patients. As LIPUS is non-invasive and shown to have minimal adverse effects, it is an attractive technology to use for enhancing bone healing; however the physiological mechanisms by which it works remain unknown.

The underlying physiological mechanisms through which LIPUS is proposed to enhance fracture healing are multifaceted and have been studied within in vitro and in vivo animal studies and human studies. When the low intensity ultrasound waves are delivered to the fracture site through a probe it is hypothesised to: promote micromotion and increase intracellular mechanisms within cells like osteoblasts, leading to increased bone formation; stimulate the formation of new blood vessels (angiogenesis) through increasing the production of growth factors; and increase fluid flow through the extracellular matrix. Mechanical stimulation through micromotion at the fracture site may also increase signaling through calcium receptors, initiating a series of intracellular cascades that result in increased mineralisation for bone formation. Another proposed mechanism is that the micromotion thought to be produced by LIPUS induces cavitation and increased fluid flow through the extracellular matrix. This changes the micro-environment by increasing nutrient delivery, increasing cellular permeability and blood flow. Although its specific mechanisms are unknown, as LIPUS is non-invasive, it can be applied at home, and is shown to have minimal adverse risk it has been marketed as a successful adjunct to conventional treatment for fractures.

LIPUS has been marketed as easy to use by the patient and by companies that sell the product as being able to increase healing rates. Application of LIPUS is typically through a probe applied to the site which has a layer of conductive gel to transmit the signal. It is applied typically for 20 minutes per day at 1.5MHz using an ultrasound head that distributes the wave at 0.03 W/cm². This wave is pulsed and used with a 20% duty cycle. The intensity of LIPUS is low as animal research showed that application of LIPUS at high intensities (over 1.0 W/cm²) could cause tissue damage. In the literature it is generally reported to be used at intensities of up to 0.03 W/cm² for acute conditions and no higher than 0.1 W/cm² for chronic conditions for fractures. It may be used at higher intensities for soft tissue healing.

In New Zealand it is reported that two brands are available: Exogen (Smith and Nephew, New Jersey) and Melmak (Biomedical Tissue Technologies, Everfit Healthcare, Australia). Currently Exogen markets these devices as highly effective and capable of accelerating healing rates by up to 38% (www.smith-nephew.com); and that the devices are portable and can be administered at home by the patient. Recently this company also requested a review of these devices from NICE (National Institute for Health and Care Excellence, UK) to inform on guidance for using these technologies (NICE, 2013). Melmak also quotes the same statistics, however their reports include selective evidence from animal studies and clinical studies dating from 2002 (http://www.biottech.com/products.html) that does not include studies that use high quality study designs as reported by the Cochrane Collaboration or SIGN. The most recent high quality systematic reviews from the Cochrane Collaboration and other authors have reported mixed results from RCTs for the success rates of LIPUS and these reviews are discussed in detail within this evidence-based report.

1.2 Previous reporting for LIPUS

1.2.1 ACC EBH Reports

There are a series of evidence-based reports and updates on LIPUS that have been produced by the Evidence-Based Healthcare (EBH) team previously. The initial report in 2002 stated in its summary of findings that the
healing time of scaphoid, distal radius and tibial fractures appeared to be decreased with LIPUS when used as an adjunct to conservative treatment. In 2012 a revised EBH report that built on the previous report and included a Cochrane Review on LIPUS concluded that there is moderate quality evidence for the effectiveness of LIPUS in accelerating healing in established non-unions as assessed by radiography, and that there was minimal evidence for improved functional outcomes from its use. From this report the recommendation for purchasing based on evidence from the literature was: “LIPUS be only purchased on a case by case basis for promoting healing of fractures of the tibia and distal radius”.

1.2.2 ACC’s current position for LIPUS

Purchasing requests for LIPUS has increased over the last year although the number of requests is small. Since 1988 there have been 22 documented claims that have been accepted to fund treatment with LIPUS. Six of these accepted claims were in 2013 and 11 in 2014. Claims were predominantly for non-union of the tibia (n = 4) or tibia and fibula (n = 6). Other accepted claims included were the femur (n = 3), clavicle (n = 2), radius and ulna (n = 2), scaphoid (n = 2), humerus (n = 1), foot (n = 1) and navicular (n = 1). The most common incidents were from mountain biking.

Within the accepted claims a mixture of operative (open reduction, internal fixation n = 6) and conservative (immobilised with cast) were used with LIPUS. Only two claimants did not return to work (2012 for non-union of the tibia; 2014 after ORIF to the femur), and two required follow-up treatment but in both of these were complex cases where other co-morbidities were involved. It was unable to be extracted from this data if healing rates or return to work rates were faster than in similar cases where LIPUS was not used.

Although the current numbers of accepted claims to fund LIPUS has been small, there has been a sudden increase in accepted claims over the last two years (2013 and 2014) indicating that the demand for these units is increasing. As it appears that the majority of accepted claimants (n = 20 out of 22) have returned to work and require no additional treatment LIPUS could be an effective adjunct to treatment. For medical advisors an aim of evidence presented in this report is to help make the decision-making process for future claims easier, especially if the numbers of requests continue to increase.

1.2.3 NICE medical technologies guidelines report for LIPUS

The NICE guidance document for LIPUS refers specifically to the EXOGEN product used in the context of the long bones only. This guidance document was the result of a submission of an evidence report by a sponsor (Smith and Nephew, manufacturer of EXOGEN) which was analysed by External Assessment Centre at Brunel University and then reviewed along with expert personal views of four Orthopaedic Surgeons from the British Orthopaedic Association as well as one patient expert.

Smith and Nephew provided a report that included 17 studies that investigated the effect of EXOGEN on long bones. Four were RCTSs, one prospective comparison and 13 case-series. No systematic reviews were included in this analysis, no analysis of bones other than long bones were included (eg, scaphoid, navicular, clavicle) and no analysis of other brands of LIPUS machines other than EXOGEN (eg, Theramed) were included.

It is also not clear how studies in this report were critiqued (eg, SIGN methodologies used in this report), and that the search strategy used for this summary was not transparent and limited as stated by the External Assessment Centre for NICE.

Recommendations from these analyses supported: use for EXOGEN to treat long bone fractures with non-union, some evidence for EXOGEN for long bone fractures with delayed healing (shown radiologically) after 3 months. One other recommendation within this guidance was that LIPUS should not be used on the skull or vertebrae however the origin of this recommendation is not stated in the guidance document.

1.2.4 Other insurance companies’ positions

Healthcare insurance companies Cigna and Aetna both fund LIPUS treatment under specific circumstances (Appendix 3). Their policies cover LIPUS used as an adjunct for acute closed fractures, non-union of fractures and stress fractures with specific criterion for each section (see Appendix 3). These policies did not provide cover for a number of conditions that included: acute fractures that required open reduction and internal fixation preoperatively
or immediately postoperatively, some fresh and stress fractures that did not meet specified criteria, and pathologies due to malignancy (See Appendix 3).

*However it should be noted that for the Aetna review, the evidence their policy for LIPUS is based on does not report the grade of the strength or quality of evidence they used within the review* ([http://www.aetna.com/cpb/medical/data/300_399/0343.html](http://www.aetna.com/cpb/medical/data/300_399/0343.html)). *It is unknown if the quality of evidence was determined for evidence contributing to the Cigna policy for LIPUS.*

The use of LIPUS has been approved by the Food and Drug Administration (FDA) in America for the enhancement of fresh fracture and nonunion healing.

Medicare also has a series of criteria (Appendix 3) for the use of ultrasonic osteogenes stimulators including:

1. nonunion of a fracture documented by a minimum of two sets of radiographs obtained prior to starting treatment with the osteogenic stimulator, separated by a minimum of 90 days alone;
2. the fracture is not of the skull or vertebrae; and
3. the fracture is not tumor related.

### 1.3 Objective of this report

The purpose of this evidence-based report is to build on previous reports prepared by the Evidence-Based Healthcare team in ACC Research to determine if the body of evidence has changed, and whether the current literature-based recommendation needs to be amended.

The report aims to:

- Determine if the current recommendation needs to be amended
- Inform on criteria for when ACC can approve entitlement of LIPUS for: fresh fractures, delayed unions and non-unions
- Inform on criteria for when ACC will not fund this treatment
- Help inform and facilitate consistent decision making by clinical advisors, case managers with regards to LIPUS use
2 Methods

2.1 Search Strategy

A standard systematic search was conducted over multiple databases using search terms as described below. This search was aimed at building on information for LIPUS already presented in existing reports. A search was conducted in October and December 2014 in the following databases:

- AMED (Allied and Complementary Medicine) <1985 to December 2014>
- Embase <1988 to December 2014>
- Ovid MEDLINE In-Process & Other Non-Indexed Citations
- Ovid MEDLINE <1946 to December 2014>,
- Google scholar
- Web of Science
- PubMed
- Cochrane Library

Search terms included: ultrasound, sonic, fracture, non-union, bone/s, heal$, stimulat$, human, randomised controlled trial

2.2 Inclusion and Exclusion Criteria

Two ACC research advisors examined all potentially relevant studies retrieved by the literature search and applied inclusion criteria (outlined below) to select studies for the review. Studies selected were any systematic reviews and meta-analyses published from January 2012, and any randomised control trials (RCTs) conducted after May 2014. From each study the pooled ORs, together with 95% CIs were extracted. Adjusted ORs were used in statistical analyses if available to minimise confounding factors. Information on participants, type of fracture, type of treatment used in adjunct to LIPUS, and outcome detail were also extracted when possible.

2.2.1 Inclusion Criteria

- Types of studies: systematic reviews and meta-analyses from 2012 – 2014 and randomised control trials (RCTs) post June 2014
- Types of participant: Any human participants who have had a fracture from an injury
- Types of interventions: Low intensity pulsed ultrasound
- Types of comparison: Conventional treatment
- Types of outcome measures: Radiological measurements, clinical outcome measures

2.2.2 Exclusion Criteria

- Grey literature
- Studies on distraction osteogenesis
- Animal or laboratory studies
- RCTs before June 2014, observational studies, case reports or case series
- Unable to be translated into English
2.3 Level of Evidence

Studies meeting the criteria for inclusion in this report were assessed for their methodological quality using the Scottish Intercollegiate Guideline Network (SIGN) level of evidence system as outlined in Table 2:

Table 2. SIGN level of evidence

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>High quality meta analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1-</td>
<td>Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>High quality systematic reviews of case-control or cohort studies High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal</td>
</tr>
<tr>
<td>2+</td>
<td>Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2-</td>
<td>Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies, e.g. case reports, case series</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

Scottish Intercollegiate Guidelines Network http://www.sign.ac.uk/
3 Results

3.1 Study selection

Four systematic reviews / meta-analyses and two RCTs met the inclusion criteria. The cohort of systematic reviews also included an extensive report from the Cochrane Library that was released in June 2014 and provides an in-depth analysis of all high-quality relevant literature for LIPUS. These studies and their level of evidence are outlined below in Table 2 and further detail of these studies can be found in the evidence tables located at the end of this document (Appendix 2).

It is also important to note that the evidence for the use of LIPUS within each of the systematic reviews largely originates from the same group of primary studies. The results of these studies have been analysed differently and data grouped differently by the authors of the reviews, which is why all four reviews were included in this report.

3.2 Quality Assessment

The four systematic reviews included studies that investigated the effects of LIPUS on a range of different types of fractures in different locations that used mostly Exogen LIPUS devices\(^1\),\(^7\),\(^12\),\(^13\). They commonly used imaging methods (radiographs, computed tomography) to measure the extent of bone healing. The most commonly used benchmark of bone union/fracture healing was time to cortical bridging, where indication of union was three out of four cortical bridges formed. Clinical healing included the use of visual pain scores (VAS: visual analogue scales), different pain scores and the Olerud-Molander score.

There was some overlap in the cohort of studies reported in these reviews, with some of the earlier studies\(^14\)-\(^19\) being reported in multiple reviews. However because there was variation across the reviews in which studies they did or did not include, the aspects of LIPUS healing they focused on differed, and how data was grouped within each of the reviews differed, all systematic reviews that fit the inclusion criteria from 2012 were included. The rating of these reviews ranged from \(1^{++}\) to \(1^{-}\) based on the cohort of studies they included. The most extensive review found was a Cochrane Review updated in June 2014 that was originally produced in 2012\(^1\). A brief outline of each systematic review is outlined below in Table 3, a detailed analysis and a description of the reviews is included in the evidence tables in Appendix 2 at the end of this EBH report.

<table>
<thead>
<tr>
<th>Author</th>
<th>Fracture types</th>
<th>LIPUS device</th>
<th>Fracture location</th>
<th>Outcome measures</th>
<th>SIGN rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included: 13 RCTs, double-blinded</td>
<td>Closed or grade 1 open diaphyseal fractures</td>
<td>1 study did not report type of device</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound fracture</td>
<td>Stress fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ebrahim et al, 2014</td>
<td>LIPUS delivered to fresh fractures and effects categorised across studies into</td>
<td>Sonic accelerated Fracture-healing system Exogen 2000_device</td>
<td>Tibia, radius, 5(^{th}) metatarsal, scaphoid, malleolar,</td>
<td>Radiological healing: Cortical bridging – 3 cortices = possible unions, non-union = (\leq 2) cortices</td>
<td>(1^{-})</td>
</tr>
</tbody>
</table>
effects of LIPUS after 3, 6, or 12 months after injury

TheraMed 101-B bone growth stimulator

Conventional ultrasonography

Griffin et al, 2014

Fresh fractures
Conservatively and operatively managed fractures
Not reported
Tibia, 5th metatarsal, distal radius, clavicle, scaphoid, tibia, femur, lateral malleolus

Radiological healing: time to radiographic union, evidence of callus, proportion fractures united at 6 months, multiplanar computed tomography, DEXA (dual-energy X-ray absorptiometry) scan, cortical bridging (usually 3 out of 4 cortices bridged), trabeculae bridging, loss of reduction,

Clinical outcomes: Olerud-Molander scoring, clinical examination, full painless weight bearing, pain scores, adverse events, resumption of sporting activities

1 ++

Ratings of included studies by review: generally poor to moderate

Snyder et al, 2012

Acute fractures, delayed fractures
Tibia: non-operative and operative; Radius: non-operative; Scaphoid: operative

Radiological healing: Cortical bridging (time to 3 out of 4 bridges forming) determined by radiography or computed tomography

1 –

Ratings of included studies by review: not reported

Two RCTs were included in this report that investigated the effects of LIPUS on acute and stress fractures. These RCTs (outlined in Table 4) were included because they were published after the analyses for the systematic reviews reported in Table 2 were completed, thus they represent the most up to date evidence available at the time this EBH report was written. The information included within them is limited: one RCT is a feasibility study that investigated methodology for a further large scale study 5, while the second RCT is restricted to stress fractures only in a small cohort of participants 20. As both of these studies have small sample sizes and selective restrictions within their cohorts, their risk of bias is increased leading to a lower SIGN rating (1- for both) based on their study design (Table 4). The sham and placebo devices within both of these RCTs were identical in appearance, weight and how it was used, the only difference being that it did not emit any ultrasound energy 20 5.

Table 4. Brief outline of included RCTs for LIPUS

<table>
<thead>
<tr>
<th>Author</th>
<th>Population studied</th>
<th>LIPUS device used</th>
<th>Fracture location and type</th>
<th>Outcome measures</th>
<th>SIGN rating</th>
</tr>
</thead>
</table>
| Busse et al, 2014    | N = 51 skeletally mature men and women (females made up between 21.7 – 25% of the participant groups) | EXOGEN 2000+ (Smith and Nephew), n = 23                | Open or closed tibial fracture | *Functional outcome measures and scores as labelled below:*
|                      |                                                        | Measured Against placebo device, n = 28               | Treated with intramedullary nail fixation | Physical Component Summary (PCS) score: time × treatment interaction |
|                      |                                                        |                                                      |                           | Health Utilities Index-III (HUI-III): time × treatment interaction,             | 1-          |
|                      |                                                        |                                                      |                           | Radiographic Union Scale for Tibial Fractures (RUST) score: time × treatment interaction |           |
|                      |                                                        |                                                      |                           |                                                                                   |             |

No adverse events
3.3 Effect of LIPUS on acute/fresh fractures

The effect of LIPUS on enhancing bone healing was investigated in different bones, at different time points after injury and in operatively and conservatively treated fractures. The findings across the reviews were reported using different statistics in some papers (Relative risk or RR\textsuperscript{12} and standard mean difference\textsuperscript{1}). Other differences between the reviews are how the literature is grouped, for example in Ebrahim et al (2014) the papers are reported based on time of healing after the fracture event. Another source of heterogeneity is that operatively and conservatively treated fractures are grouped together in this group. In the analysis conducted by Bashardoust Tajali et al (2012) the cohorts of two RCTS\textsuperscript{14, 21} were internally fixed tibial fractures, whereas in the other RCTs tibia fractures were conservatively managed. These differences in how studies were grouped and analysed are likely to have contributed to the significant heterogeneity reported in three of the reviews as shown in Table 5 below and make interpretation of the overall results difficult\textsuperscript{1, 7, 12, 13}.

Overall the results for acute/fresh fractures show some evidence that supports the use of LIPUS in the upper limb or lower limb. It is important to note that the evidence that supports the use of LIPUS originates from the same primary studies that have been analysed slightly differently within each of the reviews. This could be due to the number of studies included in the analyses, as when all studies were combined in Griffin et al (2014) the statistical analyses favoured LIPUS. However the analyses that favoured LIPUS also reported significant heterogeneity between the papers\textsuperscript{5, 7, 13}. The analyses that support LIPUS are based solely on radiological healing measurements (time to third cortical bridging), with minimal reports on functional analyses. Preliminary functional analyses are reported in a pilot RCT and do not show significance across three different scales; however this is a preliminary study with a small sample size (n = 50) that should be followed up in the future once the full RCT has been completed\textsuperscript{5}.

Table 5. Effect of LIPUS on acute/fresh fractures

<table>
<thead>
<tr>
<th>Review</th>
<th>Notes on included studies</th>
<th>Findings: SMD/OR/RR (95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffin et al, 2014</td>
<td>Significant heterogeneity (p&lt;0.05) between studies likely due to study methodologies (loss to follow-up, patient self-reporting)</td>
<td>Time to radiographic union (as reported by study):</td>
</tr>
<tr>
<td>(Systematic Review)</td>
<td></td>
<td>Overall: SMD -0.69 (-1.31, -0.07) - Marginally favours LIPUS, but significant heterogeneity between papers (n = 8 papers; p = 0.00001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper limb: SMD -0.93 (-2.03,0.17) – Marginally no effect of LIPUS, heterogeneity (n = 3 papers; p = 0.0001),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower Limb: SMD -0.54 (-1.44, 0.35) - Marginally no effect of LIPUS, heterogeneity (n = 5 papers; p = 0.0001),</td>
</tr>
<tr>
<td>Bashardoust Tajali et al, 2012</td>
<td>Significant heterogeneity (p = 0.033), likely due to different bones measured and different types of fracture treatment across studies</td>
<td>Time to third cortical bridging:</td>
</tr>
<tr>
<td>(Systematic review)</td>
<td></td>
<td>Overall: SMD (random-effects model): 2.26 (0.18, 4.34) – Favours LIPUS</td>
</tr>
<tr>
<td>Ebrahim et al, 2014</td>
<td>Only investigated the effects of acute fractures 3 months (n = 3 studies), 6 months (n = 2) and 12 months (n = 2) after fracture</td>
<td>Rate of fracture union:</td>
</tr>
<tr>
<td>(Systematic review)</td>
<td></td>
<td>3 months: RR 1.01 (0.90, 1.13) - no effect of LIPUS</td>
</tr>
</tbody>
</table>
3.4 Effect of LIPUS on stress fractures

A small number of articles investigate the effect of LIPUS on stress fractures. The reports available do not show any difference in healing times between fractures treated with LIPUS or those treated without LIPUS in bones of the lower limb (Table 6). The effects of LIPUS on stress fractures were reported in both military personnel1,7 and a civilian population20, all of which showed no difference in radiological or functional/clinical healing parameters between those that used and those that did not use LIPUS.

### Table 6. Effect of LIPUS on stress fractures

<table>
<thead>
<tr>
<th>Review</th>
<th>Notes on included studies</th>
<th>Findings: OR (95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Griffin et al, 2014</strong></td>
<td>Two studies. One had considerable heterogeneity in pooled estimate19</td>
<td>No significant benefit of LIPUS in the treatment of tibial stress fractures:</td>
</tr>
<tr>
<td><em>(Systematic Review)</em></td>
<td>Only stress fractures in tibia reported</td>
<td>Mean difference -8.55 days, (-22.71 – 5.61) in Yadav, 2008</td>
</tr>
<tr>
<td><strong>Bashardoust Tajali et al, 2012</strong></td>
<td>Effects of Rue (2004) only reported19</td>
<td>No difference between control an LIPUS treatment groups for functional recovery (total days of symptoms an time to return to full participation of duty in midshipmen)</td>
</tr>
<tr>
<td><em>(Systematic review)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gan et al, 2014</strong></td>
<td>Grade II-IV bone stress injury diagnosed with MRI. Investigated in tibia, fibula, 2nd, 3rd, 4th metatarsal N = 23 in final analysis (Small numbers)</td>
<td>No significant difference at week 12 between LIPUS and Placebo for MRI grade (p = 0.776), and MRI edema size (p = 0.271)</td>
</tr>
<tr>
<td><em>(Prospective, double-blind, RCT)</em></td>
<td></td>
<td>No significant difference for clinical parameters (Pain and tenderness measures)</td>
</tr>
</tbody>
</table>

3.5 Effect of LIPUS on delayed fractures or non-unions

The systematic reviews showed limited reporting of the effects of LIPUS on delayed fractures or non-unions, and what was reported is variable (Table 7). This variability was due to grouping of different types of fractures together within the analyses, for example compound fractures and leg lengthening operations7 and differences in the times of follow-up assessments between studies7. The effects of LIPUS on delayed fractures were predominantly reported in the lower limb, and although delayed upper limb fractures are reported there was minimal evidence that LIPUS decreased radiological or functional healing times7.
There is little evidence that supports LIPUS use for delayed fractures or non-unions in the upper or lower limb. The data that does exist is largely low quality\(^7\), has variability within the study cohort\(^1\) and has missing data or a lack of data as outlined in Table 7 below. This means that it is very difficult to draw conclusions due to the lack of data and low quality evidence in the non-union population.

### Table 7. Effect of LIPUS on delayed fractures or non-unions

<table>
<thead>
<tr>
<th>Review</th>
<th>Notes on included studies</th>
<th>Findings: RR (95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffin et al, 2014</td>
<td>Differences in times of follow-up assessment between studies (8 weeks – 12 months). Only information for lower limb reported</td>
<td>Time to radiographic union (as reported by study): Lower Limb: RR 0.75 (0.24, 2.28) – does not favour LIPUS</td>
</tr>
<tr>
<td>(Systematic Review)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bashardoust Tajali et al, 2012</td>
<td>Variability between studies based on type of fracture (compound high energy fractures, leg lengthening operation), methods of how fracture healing was measured (time to cortical bridging) or control data was missing.</td>
<td>Due to lack of data and variability across studies meta-analysis not performed. Stated trials provided some low-quality evidence in favour of LIPUS use.</td>
</tr>
<tr>
<td>Ebrahim et al, 2014</td>
<td>Review stated a lack of available data for non-union populations</td>
<td></td>
</tr>
<tr>
<td>(Systematic review)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 3.6 Effect of LIPUS on conservative or operatively treated fractures

Two systematic reviews compared the effect of LIPUS in conservatively and operatively treated fractures. It was shown that fractures treated conservatively (immobilised in a cast) with LIPUS used as an adjunct showed significantly decreased times to radiographic union in an analysis of three studies\(^1\). These studies were conducted in the tibia, radius and scaphoid. A similar analysis in another review showed no statistically significant effect of LIPUS on conservatively treated fractures\(^13\). However these results are likely to be due to the number of studies included in the analysis as the study showing no significance included only two articles\(^13\), and the study showing significance included three\(^1\). Two of these primary studies were reported in both reviews.

Operatively treated fractures (internally fixated with screws and/or plates) showed no decreased healing times when LIPUS was used as an adjunct to treatment. There was variability between studies where one RCT favoured LIPUS\(^15\) but the other RCTs did not. It is important to note that randomisation bias was detected for the paper that favoured LIPUS\(^13\).

These reviews show that there is weak evidence that LIPUS decreases radiological healing times when used as an adjunct to conservative fracture treatment. Although there were trends supporting time to radiographic union, there was significant heterogeneity see in both reviews. This was seen in studies on the tibia, radius and scaphoid, however no clinical healing times were included in this analysis. Little evidence shows LIPUS affects radiological healing times in operatively treated fractures (Table 8).

### Table 8. Effect of LIPUS on conservative and operatively treated fractures

<table>
<thead>
<tr>
<th>Review</th>
<th>Notes on included studies</th>
<th>Findings: OR (95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffin et al, 2014</td>
<td>Significant heterogeneity (p&lt;0.05) between studies likely due to study methodologies (loss to follow-up, patient self-reporting). Subgroups showed significant heterogeneity for operatively treated group (p&lt;0.00001)</td>
<td>Time to radiographic union (as reported by study): Overall: SMD -0.62 (-1.29, 0.05) - Marginally no effect of LIPUS, but heterogeneity (n = 7 papers; p = 0.00001). Operatively treated: SMD -0.21 (-1.42, 1.00) – No effect of LIPUS.</td>
</tr>
<tr>
<td>(Systematic Review)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
but not the conservatively treated group (p = 0.44).

Non-operative studies: Tibia fractures 22, Radius 23, scaphoid 17
Operative studies: Tibia 14, 15, Lateral malleolus 24

LiPUS, heterogeneity (n = 4 papers; p = 0.00001), Conservatively treated: SMD -1.09 (-1.38, -0.80) - Favours LiPUS, no heterogeneity (n = 3 papers; p = 0.44),

Synder et al, 2012 (Meta-analysis)
Non-operative studies: Tibia fractures 22, and Radius 23
Operative studies: Tibia 14, 15, Scaphoid 18

Time to third cortical bridging (radiography or CT):
Non-operative: Mean difference (days) -57 (-118, 4) – No effect of LiPUS
Operative: Mean difference (days) -22 (-70, 25) – No effect of LiPUS

3.7 Adverse events associated with LiPUS
Two systematic reviews and the pilot RCT show that adverse events were reported within the study groups. However there is little evidence that this was associated with use of LiPUS as seen in Table 9 below.

Table 9. Adverse events associated with LiPUS

<table>
<thead>
<tr>
<th>Review</th>
<th>Reported adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffin et al, 2014</td>
<td>No difference between LiPUS and placebo groups for occurrences of: Deep vein thrombosis; compartment syndrome, deep infection, pulmonary embolus, some skin irritation/erythema/swelling.</td>
</tr>
<tr>
<td>Synder et al, 2012</td>
<td></td>
</tr>
<tr>
<td>(Systematic Review)</td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>Delayed union</td>
</tr>
<tr>
<td>LiPUS (n=104 fractures)</td>
<td>8</td>
</tr>
<tr>
<td>Control (n=104 fractures)</td>
<td>12</td>
</tr>
<tr>
<td>Busse et al, 2014</td>
<td>Adverse events reported, however investigators stated that they did not believe these were associated with the study treatment</td>
</tr>
<tr>
<td>(Pilot RCT)</td>
<td></td>
</tr>
</tbody>
</table>

3.8 Effects of LiPUS on clinical healing
The effects on clinical healing were difficult to pool together due to differences in methodology across studies included in the reviews (Table 10). Within the reviews the results differed, one review reported no difference in the Olerud-Molander score, whereas another review showed that some studies reported decreased pain within a reduced timeframe and decreased time to weight bearing. However within this same review other studies reported no effect of LiPUS on pain or weight-bearing status.

The pilot RCT investigated the effect of LiPUS on functional scores and quality of life scores but showed no difference between participants that used LiPUS and those that did not in addition to their conventional fracture treatment.

Overall the evidence of LiPUS on clinical healing is variable and minimal. There is currently little evidence to show that LiPUS improves function and it is stated in the literature that more research is required to understand how LiPUS affects function.

Table 10. Effects of LiPUS on clinical outcomes

<table>
<thead>
<tr>
<th>Review</th>
<th>Reported clinical outcomes</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffin et al, 2014</td>
<td>Clinical outcomes: Olerud-Molander scoring, clinical examination, full painless weight bearing, pain scores, no significant difference between treatment and return to work times</td>
<td>16</td>
</tr>
</tbody>
</table>
3.9 Effect of LIPUS on scaphoid fractures

It is noted that through the systematic reviews included in this report that there are only two primary non-English studies that investigate the effect of LIPUS on scaphoid fractures\(^{17,18}\). Both of these studies show a positive effect of LIPUS on scaphoid fractures and although they have low sample sizes they met the inclusion criteria of the systematic reviews included in this report\(^{13,7,1,12}\). Between these studies there is differences between fracture treatment; one study is in operatively treated scaphoid fracture\(^{18}\) whereas the other appears to be in conservatively treated scaphoid fracture\(^{17}\). The scarcity of studies (compared to long bones) and limitations on their quality of evidence should be taking into account when considering using LIPUS as an adjunct to conventional scaphoid treatment. However, as with the long bones there are no adverse effects reported against using LIPUS for scaphoid fracture.

No guidelines were found that recommended against the use LIPUS for scaphoid fractures even though there is little evidence to support its use. It is noted that American College of Occupational and Environmental Medicine (ACOEM) guidelines specifically state that “there is insufficient evidence to support a recommendation for or against the use of osteogenic ultrasound for non-union of the scaphoid bone” (http://apgi.acoem.org/TreatmentPlanRecommendations/List.aspx). Also although it is not readily available how the quality of evidence was critiqued for the Aetna and Cigna (Appendix 3) LIPUS related guidelines, both approve funding for LIPUS for scaphoid fracture.
4 Discussion

4.1 Nature and quality of the evidence

The studies included in this report were systematic reviews of RCTs and two additional recently published RCTs. The reviews were graded as providing a very high to high quality analysis of the evidence with a low risk of bias using the SIGN criteria (Table 1). The RCTs provided a good quality of analysis but both exhibited a high risk of bias due to small sample size and selective populations included in the studies. However it is important to remember that the high quality systematic reviews included in this report are secondary analyses of primary articles from the literature.

The quality of the studies analysed by the reviews was reported by the review authors to be of moderate to low quality\(^1,7,12,13\). The authors reported a high risk of bias within these studies due to insufficient randomisation of the study populations, selection bias, missing data and small sample sizes. Other issues within the studies were variability in the definitions of fracture healing used (radiograph measurements compared to clinical measurements) and in the timing of when these measurements were performed. None of the included articles analysed in Griffin et al (2014) used independent radiographers to assess radiological union, which was one of the predominant outcome measures between the studies. Meta-analyses were unable to be performed for most of the clinical healing outcomes because of variability of data. Due to the variability of data and bias across articles it is difficult for these reviews to draw conclusions from the current body of evidence that exists for the effect of LIPUS on fracture healing.

This is especially evident for scaphoid fracture as only two primary studies were reviewed across the systematic reviews. The populations analysed were variable with small sample sizes, meaning the evidence is insufficient for recommending for or against LIPUS use in scaphoid fracture.

The NICE review stated that LIPUS should not be used for skull or vertebrae fractures\(^10\). It is unclear where this recommendation arose from as the skull and vertebrae were not mentioned in the reviews that were examined in this report. However it should be noted that Medicare also recommends LIPUS not be used for skull or vertebrae or fractures that are tumour related.

4.2 Limitations

The predominant limitation within the reviews was the high level of heterogeneity between the studies that they analysed. This heterogeneity led to non-significant meta-analyses for the majority of data and made it difficult to make a conclusive statement about the efficacy of LIPUS when used an adjunct for different fracture treatments and different types of fractures.

The structure of the systematic reviews also reflected the heterogeneous nature of the data. The reviews grouped the data from the studies together into fresh/acute fractures, delayed union, conservatively/operatively treated as is structured in this report. This meant that the studies included in the fresh/acute fracture category included fractures that were treated conservatively and operatively and may have been from the upper limb and lower limb. However, attempts to subgroup within these categories did not increase statistical significance within the group: this was probably due to small sample sizes and small number of articles that fit these categories. These systematic reviews do statistically emphasise the heterogenic nature of the available data, and that further high quality RCTs need to be performed to understand better the effects of LIPUS on functional outcomes when used in fracture healing. It is reported that an extension of the Busse et al, 2014 pilot RCT is being conducted, however no information has been made publicly available on when the outcome of this study may be made available. If this or other studies become available, this can be critiqued against data in this report and if needed, the recommendation for LIPUS could be reassessed.

One final limitation of this report is that some literature may have been missed. For example inclusion criteria limited the included articles to systematic reviews since 2012 and RCTs published between June 2014 and December 2014. However it is unlikely as very high quality and comprehensive systematic reviews were summarised in this report\(^1\).
5 Conclusion

This report shows there is marginal evidence supporting use of LIPUS as an adjunct for fracture healing. A relatively large body of research exists of studies that have investigated its efficacy, however the evidence produced is heterogenic and of low quality. The same group of studies have been analysed by different high quality systematic reviews, however due to the heterogenic nature of the evidence it is hard to make conclusions about whether LIPUS does facilitate healing in different types of fractures.

Overall the studies used the following brands of LIPUS units with the following settings:

*Type of machine used:* Sonic Accelerated Fracture-Healing System (SAFHS 2A) / Exogen 2000+ (Smith and Nephew, New Jersey)
TheraMed 101-B System (Instituto Nacional de Investigaciones en Metrología (Havana, Cuba)
Melmak (by Surgical Synergies Pty Ltd)

*Settings of the machine:* Typically applied for 20 minutes, once a day
200 µs burst width of 1.5MHz sine waves with a spatial intensity of 30mW/cm²

These conclusions similar to those from the 2012 ACC Research report³ that stated “the evidence for the effectiveness of LIPUS was moderate to very low and provided conflicting results. “ and that “the role of LIPUS in the management of fractures required large blinded trials”. There is evidence that such a trial is currently being conducted in the feasibility RCT by Busse et al (2014)⁵; however these results are preliminary and inconclusive. In order for a strong recommendation to be made for LIPUS use⁴, more high quality RCTs that focus both on radiological and clinical healing outcomes are required.

5.1 Evidence statement

The systematic reviews included within this report were of very high to high quality and the two included RCTs were deemed to be of good quality. The systematic reviews provided a high quality analysis of the current available literature on the use of LIPUS in fracture healing with a low to moderate risk of bias present based on the inclusion criteria for available studies. The quality of the evidence the reviews analysed was stated to be of moderate to low quality based on high risk of bias due to small sample sizes and the methodology used in the included primary studies.

The evidence that supports LIPUS is solely based on radiological healing times (e.g. time to third cortical bridging) as pooled analyses were generally not performed for clinical outcomes due to high levels of heterogeneity across the studies (e.g. decreased pain or decreased time to weight-bearing). However this evidence is inconclusive and not significant.

There is minimal evidence that supports the use of LIPUS for stress fractures and inconclusive evidence for its use in delayed / non-union fractures, operatively treated fractures, and scaphoid fractures.

There is minimal evidence to show that LIPUS has any additional adverse effects when used as an adjunct to fracture healing.

5.2 External peer-review comments for use of LIPUS

External peer-review for this report was conducted by an Associate Professor who is a practicing orthopaedic surgeon with a research interest in clinical orthopaedic surgery. His concluding comments facilitate the understanding of evidence present in this report:

“The evidence is inconclusive and difficult to interpret. Most upper limb fractures heal reliably without the need for adjunct therapy whether treated operative or non-operatively. Any statistically significant decrease in time to union may have little clinical relevance. In the lower limbs times to union are longer and there may be an important difference. Within the acute/fresh fracture group it should be considered whether the fracture is open or closed and whether treated operatively or non-operatively. The long bone fractures (tibia and femur) are the most relevant
for this report. The other problem area is the delayed/ non unions and the evidence presented does not support the use in this situation.”

“Evidence for the use in stress fractures is lacking and for scaphoid fractures it is inadequate to make a recommendation.”

- “Overall here is really very little evidence that LIPUS works and it is difficult to make strong recommendations.”

### 5.3 Recommendations

The current available evidence is **insufficient to support** the use of LIPUS in the treatment of:

- Delayed / non-union fractures and,
- Acute / fresh fractures of the tibia, radius and scaphoid

And that:

- LIPUS should not be used for skull or vertebrae fractures, or if the fracture is tumour related

Although the evidence suggests there is some potential benefit of using LIPUS in acute fractures and in conservatively managed fractures of the tibia and radius (in agreement with previous ACC Research LIPUS reports) overall the evidence is conflicting and of poor quality. This means that because the quality of evidence that favours LIPUS is moderate to low, the recommendation for its use is weak⁴.

**Based on the evidence reported in the literature and external peer-review there is little evidence that LIPUS improves fracture healing when used as an adjunct to treatment. Based on this information purchasing recommendation for LIPUS is:**

_Do not purchase_
6 References

10. NICE. EXOGEN ultrasound bone healing system for long bone fractures with non-union or delayed healing. In: Excellence NIf HaC, ed. NICE medical technology guidance 12; 2013:3 - 29.
7 Appendices
### Evidence Table 1. Systematic Reviews

<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Outcomes &amp; results</th>
<th>Quality assessment</th>
<th>Reviewer comments &amp; evidence level</th>
</tr>
</thead>
</table>
| Snyder et al. (2012) | **Number of studies:** N=5 | **Outcomes assessed:**  
- Primary outcome: time to fracture healing  
- Secondary Outcomes: Rates of delayed union; adverse events | Clearly defined research question  
Two people selected studies and extract data  
Comprehensive literature search carried out  
Authors clearly state how limited review by publication type  
Included and excluded studies listed  
Characteristics of included studies are provided  
Scientific quality of included studies assessed and documented  
Scientific quality of included studies assessed | SIGN evidence level 1+ | Y |
| Am J Orthop. 2012;41(2):E12-E19. | **Total number of patients:** n=209 (266 fractures) | **Results:**  
**Time to fracture healing:**  
- Overall: Mean effect size = -36 days (95% CI = -60, -13)  
- Non-operative subgroup = -57 days (95% CI = -118, 4 days)  
- Operative subgroup = -22 days (95% CI = -70, 25 days)  
**Adverse Outcomes: LIPU group vs. Placebo group:**  
- Delayed union: 7.7% vs. 11.2  
- Swelling: 3.8% vs. 0.9 | | |
| **Comprehensive Literature search:**  
- Electronic search: MEDLINE, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), and Cochrane Central Register of Controlled Trials (CENTRAL), Nursing and Allied Health Literature (CINAHL), National Library of Medicine (NLM) Gateway, ProQuest Dissertations & Theses, and Physiotherapy Evidence Database.  
- Manual Search | **Author Conclusions:**  
Polled results showed a mean reduction in fracture healing time of 36 days. However the results should interpreted with caution due to the significant heterogeneity. | | |
| **Assessment of methodological quality:**  
Ten-question criteria adapted from a list published by the Cochrane Collaboration Back Review Group | **Reviewer comments:**  
The review addressed a clear question, supported by appropriate inclusion criteria. The review process was clearly reported, and this included steps to minimise error and bias. Appropriate quality assessment criteria were applied to the included trials. Characteristics of included study were presented, and this indicated a high level of variability. A random-effects meta-analysis was undertaken and statistical heterogeneity was assessed. Significant statistical heterogeneity was indicated in the overall pooled results and | Y | |
| **Data extraction:**  
- Using a standardized electronic data collection form.  
- Exclusion of studies with missing data | | | |

#### Study design:
Meta-Analysis

#### Research Question:
To estimate the effect of low-intensity pulsed ultrasound (LIPUS) versus placebo on the acceleration of fracture healing in skeletally mature persons and to determine if any serious adverse events are associated with LIPU when used to accelerate
Funding: N/R

### Inclusion criteria:
- Randomized, double-blinded, placebo-controlled trial
- Skeletally mature study participants with at least 1 fracture, traumatic or surgically induced
- LIPU intervention with control arm receiving sham (placebo)ultrasound
- Time to fracture healing determined by radiography

### Heterogeneity:
- Statistical heterogeneity was tested using the chi-square test ($I^2$ statistic).
- Clinical heterogeneity was considered.

<table>
<thead>
<tr>
<th>Griffin et al. (2014)</th>
<th>Number of studies: N=12</th>
<th>Outcomes assessed:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total number of patients: n=622 (648 fractures)</td>
<td>Primary outcome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall quantitative functional improvement of the participant using recognised patient-reported outcome measures and the return to normal activities, including work</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time to fracture union</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secondary Outcomes:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clear definition of research question</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Two people selected studies and extract data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comprehensive literature search carried out</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Authors clearly state how limited review by</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SIGN evidence level 1++</td>
</tr>
</tbody>
</table>

Reviewer comments:
This was a well-conducted Cochrane review with clear inclusion criteria in terms of the study design, participants, intervention and outcome. There was a comprehensive literature search carried out. The subgroup analysis did not explain the source of the heterogeneity. The authors identified some potential limitations including: potential for selective bias, significant heterogeneity, high potential for publication bias. The authors’ cautious conclusions, alongside their recommendations for future practice and research are likely to be reliable.
To assess the effects of low-intensity ultrasound (LIPUS), high-intensity focused ultrasound (HIFUS) and extracorporeal shockwave therapies (ECSW) as part of the treatment of acute fractures in adults.

**Funding:**
No funding

**Assessment of methodological quality:**
- The Cochrane Collaboration’s ‘Risk of bias’ tool
- Randomisation (sequence generation and allocation concealment)
- Blinding (trial participants and personnel, and outcome assessors)
- Completeness of outcome data
- Selection of outcomes reported and other sources of bias.

**Data extraction:**
*Form:* Cochrane Bone, Joint and Muscle Trauma Group’s data extraction form.
*Software:* Review Manager software

**Fixed or random effects:**
Both fixed and random effects models

**Inclusion criteria:**
- Types of studies: randomised and quasi-randomised controlled clinical studies evaluating any type of ultrasound treatment in the management
- Participants: any skeletally mature adults, over the age of 18 years, with acute traumatic fractures.
- Intervention: Trials of all three types of ultrasound, low-intensity pulsed ultrasound (LIPUS), high-intensity focused ultrasound (HIFUS) and extracorporeal shock wave therapy (ECSW), were eligible provided the treatment was compared with either no additional treatment or a placebo (sham failure of fixation or for delayed or non-union
- Adverse effects
- Pain using validated pain scores
- Costs
- Patient adherence

**Results:**

**Functional outcome: Ultrasound group vs. Control group**
- Complete fractures - time to return to work: Mean difference = 1.95 days (95% CI = -2.18, 6.08), favouring control
- Stress fractures – time to return to training or duty in soldiers or midshipmen: Mean difference = -8.55 days (95% CI = 22.71, 5.61), no significant benefit of LIPUS

**Time to union:**

<table>
<thead>
<tr>
<th>Fracture</th>
<th>Standardised mean difference (SMD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper limb</td>
<td>-0.66 (95% CI = -1.93, 0.60), NOT significant</td>
</tr>
<tr>
<td>Lower limb</td>
<td>-0.35 (95% CI = -1.27, 0.56), NOT significant</td>
</tr>
<tr>
<td>Total</td>
<td>-0.47 (95% CI = -1.14, 0.20), NOT significant</td>
</tr>
</tbody>
</table>

**Delayed union and non-union: LIPUS group vs. Placebo group**
- 10/168 vs. 13/165; RR = 0.75 (95% CI = 0.24, 2.28), NOT significant

**Adverse event: treatment group vs. Placebo group**

<table>
<thead>
<tr>
<th>Publication type</th>
<th>Included and excluded studies listed</th>
<th>Characteristics of included studies are provided</th>
<th>Scientific quality of included studies assessed and documented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

*search to identify published and unpublished data. The publication bias was not formally assessed but the author explained the reason. There was very substantial statistical heterogeneity both in the pooled estimate of effect from all the studies and in the subgroup analyses. Trials differed widely and there was also insufficient high-quality evidence to reach definite conclusions. Thus, despite the potential biases, the conclusion appears to be reliable and is able to direct the way for further clinical trials in this area.*
Exclusion criteria:
- Trials evaluating treatment for delayed union, non-union or post-corticotomy (e.g. distraction osteogenesis).

Heterogeneity:
- Statistical heterogeneity was tested using the chi-square test ($I^2$ statistic).
- Clinical heterogeneity was considered.

Placebo group:
- Compartment syndrome: n=1 vs. n=2, NOT significant
- Deep infection: n=0 vs. n=2
- Requiring the removal of locking screws: n=2 vs. n=1
- Others: deep vein thrombosis, pulmonary embolus, skin irritation, erythema and swelling

Author Conclusions:
While a potential benefit of ultrasound for the treatment of acute fractures in adults cannot be ruled out, the currently available evidence from a set of clinically heterogeneous trials is insufficient to support the routine use of this intervention in clinical practice. Future trials should record functional outcomes and follow-up all trial participants.

---

**Tajali et al. (2012)**

**Study design:** Systematic Review and Meta-Analysis

**Number of studies:** N=23 (Randomized double-blind clinical trials n=13; meta-analysis n=7)

**Total number of patients:** n=842

**Comprehensive Literature search:**
- Electronic search (up to June 2010): MEDLINE, PubMed, EMBASE, Cumulative Index to Nursing and Allied Health, and Cochrane Library
- Manual Search

**Assessment of methodological quality:**

**Results:**

**Study quality:**
- Moderate (5-8 PEDro score): 15/23 studies
- Low (3-4 PEDro score): 3/23 studies
- Very low (1-2 PEDro score): 5/23 studies

**Effect LIPUS on bone-healing acceleration**
- 14/23 studies in favour of the LIPUS

**Ultrasound Devices**
- 21/23 studies: the Sonic

**Reviewer comments:**
- The review question and inclusion criteria were broad but clearly stated.
- Language restrictions raised the possibility that relevant studies were overlooked. For those studies which could not be pooled, a narrative
Question: To identify the clinical trials relevant to the effects of low-intensity pulsed ultrasound (LIPUS) on bone regeneration.

Funding: N/R

Data extraction:
- Patient demographics, inclusion and exclusion criteria, type of bone and fracture, fixation method, randomization, blinding of patients, clinicians and outcome assessors, control group, the treatment characteristics, assessment time and method and clinical outcomes.

Fixed or random effects:
Random effects models

Inclusion criteria:
- Human clinical trial studies (including randomized, controlled and noncontrolled, and cohort studies)
- All types of bones
- All types of fractures or reconstruction of bone deficiencies
- Using LIPUS as an intervention to at least one of the treatment groups
- All outcomes
- English studies.

Exclusion criteria:
- Animal studies
- Case report, review, or systematic reviews and meta-analyses
- Nonbone studies, including soft tissue or cartilage injuries
- Lack of fracture or bone deficiency
- Non-English articles.

Heterogeneity:
- Not reported

Accelerated Fracture-Healing System (Exogen, Smith & Nephew)
- 1/23 study: unknown device
- 1/23 study: Theramed101B System

The time of third cortical bridging:
- Standard Difference in Means = 2.263 (95%CI=0.183, 4.343), favouring LIPUS therapy

Author Conclusions:
LIPUS can stimulate radiographic bone healing in fresh fractures. Although there is weak evidence that LIPUS also supports radiographic healing in delayed unions and nonunions, it was not possible to pool the data because of a paucity of sufficient studies with similar outcome measures.


Number of studies:
- N = 7 LIPUS
- N = 8 ESTIM

Outcomes assessed:
- Pooled analyses for every

Excluded studies listed
- Characteristics of included studies are provided
- Scientific quality of included studies assessed and documented

Appropriate methods used to combine individual study findings
- Scientific quality of included studies assessed appropriately

Likelihood of publication bias assessed
- Conflicts of interest declared

Are results of study directly applicable to patient group targeted by guideline?
- Y

Clearly defined research question
- Y

Synthesis was appropriate given the diversity of the outcome measurements and clinical situations. A vote-counting approach was adopted, with some discussion of the characteristics of trials showing negative results. For the meta-analysis, heterogeneity was not tested and reported. In addition, the seven studies pooled only involved the treatment of two sites (tibia and radius). The generalizability of the meta-analysis could be improved. Given the nature of the synthesis and the study limitations, there is some concern over the reliability of the conclusion.
### Study design:
Systematic review and network meta-analysis

### Research Question:
To indirectly compare LIPUS with electrical stimulation (ESTIM) for fracture healing

### Funding:
One author is co-principal investigator of industry-partnered trial to explore effect of LIPUS on fracture healing (TRUST trial)

### Total number of patients:

### Comprehensive Literature search:
Examining Cochrane reviews (2012, 2014), Cochrane Bone, Joint and Muscle Trauma Group Specialised Register, Cochrane Central Register of Controlled Trials, Medline, Embase, trial registers and reference lists of all eligible articles

### Assessment of methodological quality:
- Guidelines proposed by Landis and Koch for assessing inter-rater agreement for categorical data
- Risk of bias assessed using a modified Cochrane risk of bias instrument

### Data extraction:
- Two pairs of reviewers extracted data independently and in duplicate
- Extracting data on patient characteristics, intervention, control device details, union rates, frequency and timing of outcomes

### Fixed or random effects:
Random-effects

### Inclusion criteria:
All published randomised controlled trials (RCTs) enrolling patients with a fresh fracture or an existing delayed union or non-union who were randomly assigned to LIPUS or ESTIM as well as a control group

### Results:

#### Effect of LIPUS on rate of fracture union
- Low quality evidence showed LIPUS had no significant effects on improving healing rates at 3 months (RR 1.01, 0.90 – 1.13), 6 months (1.17, 0.97 – 1.41) or 12 months (RR 1.06, 0.85 – 1.31).
- Other comparisons of ESTIM, another type of bone stimulator, show no change to fracture healing rates as well

#### Author Conclusions:
Potential but non-significant benefit of LIPUS at 6 months.
Overall neither LIPUS nor ESTIM (compared with standard care) were effective in improving union rates in fresh fracture populations.

<p>| Review that extracts evidence base largely from Cochrane reviews, and trial registers, and up and coming trials. | Y |
| Limited to studies that included union rates only | N |
| LIPUS not the main focus of this paper. | Y |
| Independent search not done, studies not included not discussed in detail. | N |
| High quality analyses done, however there is potential for bias in the design: 1- | Y |</p>
<table>
<thead>
<tr>
<th>Heterogeneity:</th>
<th>Conflicts of interest declared</th>
</tr>
</thead>
<tbody>
<tr>
<td>• $X^2$ test and $I^2$ and Tau² statistics</td>
<td>Are results of study directly applicable to patient group targeted by guideline?</td>
</tr>
<tr>
<td>• Interpreted using guidelines proposed by the Cochrane Handbook</td>
<td></td>
</tr>
</tbody>
</table>

All standard meta-analyses performed with RevMan software, and Microsoft Excel 2011 for network meta-analyses.
### Reference and study design

**Busse et al. (2014)**

Trials, 15(1), 206.

**Study design:**
A multicenter, concealed, blinded randomized trial

**Research Question:**
To explore the feasibility of a definitive trial to establish the role of LIPUS for tibial fracture healing, specifically: to determine recruitment rates in individual centers, adherence to study protocol and data collection procedures, our ability to achieve close to 100% follow-up rates.

### Participants

<table>
<thead>
<tr>
<th>Number of patients:</th>
</tr>
</thead>
<tbody>
<tr>
<td>n= 51 patients</td>
</tr>
</tbody>
</table>

**Inclusions criteria:**
Skeletally mature men or women with an open or closed tibial fracture amenable to intramedullary nail fixation.

**Exclusions (n=433):**
Fracture extended into the joint, non-intramedullary nail operative treatment or conservative treatment, < 18 years old, patient could not comply with protocol, concomitant injury, problems anticipated with follow-up, treating surgeon refused to randomize patient, approached for consent > 14 days from operative treatment, patient already in a completing study, pathological fractures, circumferential/open wound that precludes placement of ultrasound at the fracture site, grade IIIb or IIIc fracture, surgical delay of >14 days.

**Follow-up:**
1 year

**Drop outs:** 6 in control group and 2

### Intervention

**Intervention:**

- Active LIPUS treatment group (n=23)
- Sham LIPUS control group (n=28)

### Outcome measure

| Physical Component Summary (PCS) score: time × treatment interaction, P = 0.27 |
| Health Utilities Index-III (HUI-III): time × treatment interaction, P = 0.31 |
| Radiographic Union Scale for Tibial Fractures (RUST) score: time × treatment interaction, P = 0.53 |

### Validity/applicability (SIGN check list)

| Question clearly defined? |
| Randomisation? |
| Concealment? |
| Blinding? |
| Similar at baseline? |
| Treatment is the only difference between group |
| Valid and reliable outcome measurement |
| Drop-outs < 20%? |
| Intention to treat? |
| Generalizability? |

| YES |
| YES |
| YES |
| YES |
| YES |
| Can’t say |
| YES |
| YES |
| YES |

### Conclusions

**Author’s conclusion:**
Our pilot study identified key issues that might have rendered a definitive trial unfeasible. By modifying our protocol to address these challenges we have enhanced the feasibility of a definitive trial to explore the effect of LIPUS on tibial fracture healing.

**Reviewer comments:**
It is a well-designed pilot study of a full trial and was partially funded by the ultrasound device manufacturers. Most results were not significant between groups, but the statistical power was weak due to small sample size. Considering the limitations and the main purpose of this trial, the results should be interpreted with caution. The author indicated that the full trial had been completed. Conclusive evidence may be available when the full trial...
and the degree to which patients complied with treatment.

**Funding:**
A research grant from the Canadian Institutes of Health Research, and an industry grant from Smith & Nephew.

---

**Gan et al, 2014**
Clinical Journal of Sports Medicine, 24(6), 457–460

**Study design:**
Double-blinded randomised placebo-controlled trial

**Research Question:**
To evaluate the effectiveness of low-intensity pulsed ultrasound

<table>
<thead>
<tr>
<th>Number of Participants</th>
<th>LIPUS in treatment group received machine: US at 1.5%±5% MHz, burst width 100%±10ms at cycle of 1.0%±10% mHz. Placebo received sham device identical in appearance and weight. Subject to use at home,</th>
<th>6 Clinical parameters: nightpain, pain at rest, when performing ADLs, when walking, running, or jogging. Tenderness at BSI site.</th>
<th>Question clearly defined?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan et al, 2014</td>
<td>23 participants with Grade II – IV stress injury diagnosed by MRI. Injury to either the Postero-medial tibia, fibula, 2nd, 3rd, 4th metatarsal, subject of all sporting levels Recruited from sports medicine clinics/practitioners in metropolitan Sydney.</td>
<td>Radiological parameters: MRI grade and bone marrow edema size of each BSI</td>
<td>Randomisation?</td>
<td>Not clear</td>
</tr>
<tr>
<td>Inclusion Criteria:</td>
<td>Participants with II, III or IV bone stress injury (BSI, stress fracture IV, seen from fracture line in MRI)</td>
<td></td>
<td>Concealment?</td>
<td>Yes</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>Exclusion criteria:</td>
<td>Blinding?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LIPUS in treatment group received machine: US at 1.5%±5% MHz, burst width 100%±10ms at cycle of 1.0%±10% mHz. Placebo received sham device identical in appearance and weight. Subject to use at home,</td>
<td>Similar at baseline?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of Participants</td>
<td>Treatment is the only difference between group</td>
<td>Treatment is the only difference between group</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>23 participants with Grade II – IV stress injury diagnosed by MRI. Injury to either the Postero-medial tibia, fibula, 2nd, 3rd, 4th metatarsal, subject of all sporting levels Recruited from sports medicine clinics/practitioners in metropolitan Sydney.</td>
<td>Valid and reliable outcome measurement</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inclusion Criteria:</td>
<td>Reviewer comments:</td>
<td>Valid and reliable outcome measurement</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Participants with II, III or IV bone stress injury (BSI, stress fracture IV, seen from fracture line in MRI)</td>
<td>Selective cohort of participants makes RCT susceptible to selection bias, small sample sizes and subjective clinical parameters utilized may affect quality of the conclusions of the study.</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria:</td>
<td>Fractures across different bones from different sporting levels may have introduced heterogeneity into sample.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Due to small sample sizes and potential for selection bias this RCT has been graded as 1-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Funding:
A research grant from the Canadian Institutes of Health Research, and an industry grant from Smith & Nephew.

---

**Level of evidence: 1-**

---

Reviewer comments:
Selective cohort of participants makes RCT susceptible to selection bias, small sample sizes and subjective clinical parameters utilized may affect quality of the conclusions of the study. Fractures across different bones from different sporting levels may have introduced heterogeneity into sample. Due to small sample sizes and potential for selection bias this RCT has been graded as 1-
(LIPUS) for the improvement of lower limb bone stress injuries in a civilian population

**Funding:**
Supported by the Australian Sports Commission, Surgical Synergies Pty Ltd, equipment loaned from Surgical Synergies Pty Ltd. One author received consultancy fee from IMED radiology for reporting MRI scans.

<table>
<thead>
<tr>
<th>Lower limb BSI to navicular, fifth metatarsal, anterior tibia, femoral neck or pubic rami as these have a high incidence of delayed/malunion. Also femoral neck and pub rami excluded because of anticipated difficulty in accurate placement of LIPUS at correct site. (n = 7 excluded)</th>
<th>20min/day for 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sham: 13</strong></td>
<td><strong>Treatment: 10</strong></td>
</tr>
<tr>
<td><strong>Device</strong> Melmak (manufactured by Melmak GmbH in Diessen, Germany and distributed for use by Surgical Synergies Pty Ltd.)</td>
<td><strong>Author Conclusions:</strong> Low –intensity pulsed ultrasound was found not to be an effective treatment for the healing of lower limb bone stress injuries in this study. However this was measured over a relatively short duration of 4 weeks in a small, mostly female population</td>
</tr>
</tbody>
</table>

**Parameters:**
- 6 clinical parameters (night pain, pain at rest, when performing ADLs, when walking, running, or jogging. Tenderness at BSI site. |

| Drop-outs < 20%? | Yes |
| Intention to treat? | Yes |
| Generalisability? | No |

**Level of evidence:** 1-
7.2 Appendix 2: Cigna and Aetna guidelines for LIPUS use

7.2.1 Cigna Medical Necessity Guidelines (Revised 15/8/2014)

ULTRASOUND BONE GROWTH STIMULATOR (HCPCS code E0760)

An ultrasound bone growth stimulator is considered medically necessary for ANY of the following indications:

- As an adjunct to closed reduction and immobilization for ANY of the following acute fracture indications:
  - closed or grade I open, tibial diaphyseal fractures
  - closed fractures of the distal radius (Colles’ fracture)
  - closed fractures when there is suspected high risk for delayed fracture healing or nonunion as a result of either of the following:
    - poor blood supply due to anatomical location (e.g., scaphoid, 5th metatarsal)
    - at least one comorbidity where bone healing is likely to be compromised (e.g., smoking, diabetes, renal disease)

- Nonunion of fractures when ALL of the following criteria are met:
  - treatment is for nonunion of bones other than the skull or vertebrae (e.g., radius, ulna, humerus, clavicle, tibia, femur, fibula, carpal, metacarpal, tarsal, or metatarsal)
  - fracture gap is ≤ 1 cm
  - nonunion is not related/secondary to malignancy
  - it is ≥ three months from the date of injury or initial treatment
  - fracture nonunion is documented by at least two sets of appropriate imaging studies separated by a minimum of 90 days confirming that clinically significant fracture healing has not occurred

- Nonunion of a stress fracture when ALL of the following criteria are met:
  - it is ≥ three months from initial identification of the stress fracture
  - failure of a minimum of 90 days of conventional, nonsurgical management (e.g., rest, bracing)
  - radiograph imaging studies at least 90 days from the initial identification of the stress fracture demonstrates a fracture line that has not healed

NOT MEDICALLY NECESSARY: ULTRASOUND

An ultrasound bone growth stimulator for ANY other indication, including ANY of the following, is considered experimental, investigational or unproven and not medically necessary:

- as part of the acute treatment (i.e., preoperative, immediately postoperative) of any fracture requiring open reduction and internal fixation (ORIF)
- fresh fractures (other than for the above listed indications)
- stress fracture

7.2.2 Aetna Clinical Policy Bulletin for Bone Growth Stimulators (Revised 4/6/2014)

Full review on which this policy is based on can be found at:
http://www.aetna.com/cpb/medical/data/300_399/0343.html

However it should be noted that that this review does not report the grade of the strength or quality of evidence the policy is made on.

1. Ultrasonic osteogenesis stimulator
   A. Aetna considers the use of an ultrasonic osteogenesis stimulator (e.g., an ultrasonic accelerated fracture healing device) medically necessary durable medical equipment (DME) to accelerate healing of fresh fractures, fusions, or delayed unions at either of the following high-risk sites:
     1. Fresh fractures, fusions, or delayed unions of the shaft (diaphysis) of the tibia that are open or segmental; or
2. Fresh fractures, fusions, or delayed unions of the scaphoid (carpal navicular); or
3. Fresh fractures, fusions, or delayed unions of the 5th metatarsal (Jones fracture).

This system uses pulsed ultrasound to speed healing. Fractures on these sites are difficult to heal because of poor vascular supply.

B. Aetna considers an ultrasonic osteogenesis stimulator medically necessary for non-unions, failed arthrodesis, and congenital pseudarthrosis (pseudoarthrosis) of the appendicular skeleton if there has been no progression of healing for 3 or more months despite appropriate fracture care.

C. Aetna considers an ultrasonic osteogenesis stimulator experimental and investigational for fractures, failed fusions, or non-unions of the axial skeleton (skull and vertebrae) because the effectiveness of SAFHS in these fractures has not been determined.

D. Aetna considers an ultrasonic osteogenesis stimulator experimental and investigational for all other indications, including avascular necrosis of the femoral head, calcaneal apophysitis (Sever disease), Charcot arthropathy, pathological fractures due to malignancy (unless the neoplasm is in remission), stress fractures, and talar dome lesion following osteochondral autograft transfer system (OATS) because the medical literature does not support its use for these indications.

7.2.3 Medicare and Medicaid guidelines


Ultrasonic Osteogenic Stimulators

A. General

An ultrasonic osteogenic stimulator is a noninvasive device that emits low intensity, pulsed ultrasound. The device is applied to the surface of the skin at the fracture site and ultrasound waves are emitted via a conductive coupling gel to stimulate fracture healing. The ultrasonic osteogenic stimulators are not be used concurrently with other non-invasive osteogenic devices.

Indications and Limitations of Coverage

Ultrasonic Osteogenic Stimulators

B. Nationally Covered Indications

Effective January 1, 2001, ultrasonic osteogenic stimulators are covered as medically reasonable and necessary for the treatment of nonunion fractures. In demonstrating non-union fractures, CMS expects:

- A minimum of 2 sets of radiographs, obtained prior to starting treatment with the osteogenic stimulator, separated by a minimum of 90 days. Each radiograph set must include multiple views of the fracture site accompanied with a written interpretation by a physician stating that there has been no clinically significant evidence of fracture healing between the 2 sets of radiographs; and,
- Indications that the patient failed at least one surgical intervention for the treatment of the fracture.
- Effective April 27, 2005, upon reconsideration of ultrasound stimulation for nonunion fracture healing, CMS determines that the evidence is adequate to conclude that noninvasive ultrasound stimulation for the treatment of nonunion bone fractures prior to surgical intervention is reasonable and necessary. In demonstrating non-union fractures, CMS expects:
- A minimum of 2 sets of radiographs, obtained prior to starting treatment with the osteogenic stimulator, separated by a minimum of 90 days. Each radiograph set must include multiple views of the fracture site accompanied with a written interpretation by a physician stating that there has been no clinically significant evidence of fracture healing between the 2 sets of radiographs.

C. Nationally Non-Covered Indications
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 non-invasive osteogenic devices.
Ultrasonic osteogenic stimulators for fresh fractures and delayed unions remains non-covered.
(This NCD last reviewed June 2005.)