Low intensity ultrasound treatment for acceleration of bone fracture healing - Exogen™ bone growth stimulator

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Assessment report

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The Medical Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

This report was prepared by the Medical Services Advisory Committee (MSAC) with the assistance of Dr Adèle Weston, Mr Peter Davey, Mr Dominic Tilden and Mr Dan Jackson of M-TAG Pty Ltd. The report was endorsed by the Commonwealth Minister for Health and Ageing on 5 February 2002.

Publication approval number

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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This report summarises the efficacy, safety and cost-effectiveness of Exogen™ bone growth stimulator, a low-intensity ultrasound treatment (LIUS) for the acceleration of bone healing, on the basis of the currently available evidence. The use of LIUS as a home-based therapy for tibial, distal radius and scaphoid fresh fractures and fracture non-union is considered in the context of the Australian healthcare setting.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, taking into account access and equity. MSAC adopts an evidence-based approach, based on reviews of the scientific literature, other information sources and clinical expertise.

MSAC's terms of reference and membership are listed in Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer affairs and health administration.

The quality of evidence available for the current review was variable. Randomised controlled trial evidence (National Health and Medical Research Council (NHMRC) level II) was available regarding the efficacy of LIUS in the treatment of fresh tibial, distal radius and scaphoid fractures. These studies were undertaken relative to appropriate comparator treatments. In contrast, only low-level patient case series and registry evidence (NHMRC level IV) was available regarding fractures exhibiting non-union. In the case of non-union, no direct comparisons with active interventions such as surgery have been undertaken.

MSAC's assessment of low-intensity ultrasound (LIUS)

Clinical need

Approximately 26,000 treatments are currently rendered annually to Australian adults for the treatment of fresh fractures of the tibia, radius and scaphoid. Treatments include cast immobilisation and closed or open reduction, with or without internal fixation. Closed and grade I open fractures, for which LIUS is indicated, are most often treated with cast immobilisation, although the use of intramedullary rods is relatively common for tibial fractures. Failure to respond to treatment can result in non-union with implications for the patient's quality of life and functional capacity, together with financial costs to both patient and government. While current Australian treatment practice is relatively successful, tibial fractures are more likely to fail to unite than distal radius or undisplaced scaphoid fractures.

Safety

The intervention appears safe for use in adults on the basis of available evidence and clinical experience to date. However, LIUS should not be used prior to skeletal maturation. The use of LIUS in patients with pacemakers is contraindicated.

Effectiveness

On the basis of the evidence currently available, it is not possible to conclude that LIUS is consistently more efficacious than other treatments of fresh fractures. We identified only two high quality, randomised, placebo-controlled studies (Kristiansen *et al*, 1997; Emami *et al*, 1999) conducted in distal radius and tibial fractures, respectively. The results of these studies are contradictory.

With respect to the treatment of fractures exhibiting non-union, only poorly controlled patient registry or case series data are currently available. It is concluded that this represents minimally acceptable, low-level evidence to support the efficacy of LIUS for treatment of non-unions. This conclusion is restricted to patients with radiologically confirmed fracture non-union who have failed previous treatment. Importantly, this conclusion is made only in comparison with no further treatment, which is an inappropriate comparator in the Australian setting. It is therefore not possible to evaluate comparative effectiveness against current Australian treatments of fracture non-union.

Cost-effectiveness

The incremental costs per quality-adjusted life-year gained for LIUS treatment of fresh tibial, distal radius and scaphoid fractures were $106,601, $501,699 and $641,060, respectively. The cost-effectiveness of LIUS in each of the indications reviewed in the assessment does not compare favourably with a range of other common healthcare interventions.

Recommendation

MSAC recommended that on the basis of the evidence available on low intensity ultrasound treatment for acceleration of bone fracture healing, public funding should not be supported for this procedure.

- The Minister for Health and Ageing accepted this recommendation on 5 February 2002 -

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of Exogen™ bone growth stimulator[1], a low-intensity ultrasound (LIUS) for the treatment of bone fractures. This review encompasses treatment of:

- fresh fractures of the tibia, radius and scaphoid; and
- fractures that have exhibited non-union.

MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the current evidence relating to the safety and effectiveness of LIUS in the treatment of bone fractures.

[1] Exogen™ is a registered trademark of Smith and Nephew Surgical Pty Ltd.

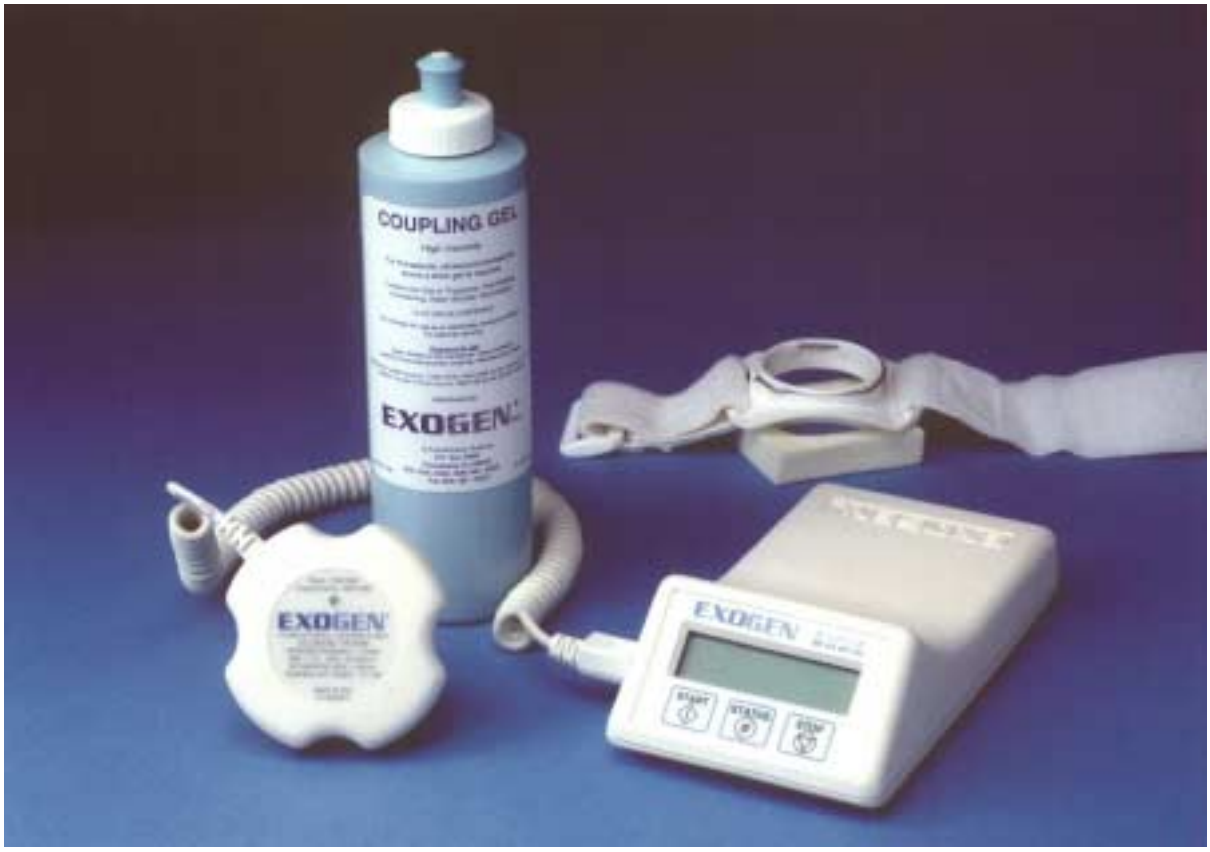
Background

Low-intensity ultrasound

The procedure

Therapeutic low-intensity ultrasound (LIUS) is delivered by a non-invasive, portable device fitted with a treatment probe. The probe head is held in place at the fracture site with a cast mounting. For the treatment of older fractures (ie non-unions) where a cast is no longer in use, the device is held in place with a Velcro® strap during treatment. In both situations, coupling gel is used to prevent disruption of the ultrasound signal between probe and skin.

Figure 1 Photograph of Exogen unit and components (courtesy of Smith and Nephew Surgical Pty Ltd)



The unit delivers acoustic radiation in the form of pulsed, low-intensity ultrasound (sine wave) in accordance with programmed specifications. The intensity is considerably lower than that delivered by conventional ultrasound equipment used for the treatment of soft-tissue injury. Specifications of the LIUS unit reviewed in this assessment are indicated in Table 1.

Table 1 LIUS technical specifications in comparison with conventional therapeutic ultrasound

Output parameter	LIUS[a]	Conventional ultrasound unit
Effective radiating area (cm^2)	3.88	5
Beam non-uniformity ratio	2.16	< 8
Frequency (MHz)	1.5	0.75 — 3.0
Pulse period (μs)	200	2,000
Interval period (μs)	800	8,000
Duty cycle	20	20
Spatial-averaged temporal-averaged intensity (mW/cm^2)	30	100–3,000
Spatial-peak temporal-averaged intensity (mW/cm^2)	65	< 24,000

Source: Warden *et al*, 2000.
[a]Output of the EXOGEN device is presented as indicative of LIUS.

The average intensity of the ultrasound together with the beam non-uniformity ratio determine the extent to which tissue temperature is elevated during treatment. Therefore, the lower output characteristics of LIUS allow it to be fixed in a stationary position during operation without substantial elevation of tissue temperature. This removes the need for the probe to be continually moved by a skilled operator, as required for treatment with conventional ultrasound. The unit is typically programmed by the supplier to deliver a 20-minute session of LIUS, after which it automatically ceases to deliver an output. The normal treatment regimen consists of one 20-minute session per day. An internal data logger records compliance.

Research in animal models has suggested that LIUS has the potential to accelerate bone healing (Reuter *et al*, 1984; Pilla *et al*, 1990; Zorlu *et al*, 1998), although no acceptable dose-response information is available to date. The exact mechanism is poorly understood but may be related to the delivery of micro-mechanical stress to the bone which results in more rapid calcium deposition and osteogenesis.

LIUS is intended as a home-based procedure, performed by the patient without the direct supervision of a medical or health professional. Instructions regarding the correct use of the device are given to the patient by the medical practitioner prior to despatch of the unit.

Intended purpose

LIUS is indicated as a therapeutic intervention to accelerate healing of bone fractures in skeletally mature individuals. However, the current assessment focuses on those fracture types for which clinical trial efficacy data are available, namely closed and/or grade I open fresh fractures of the tibia, distal radius and scaphoid and existing fractures exhibiting non-union.

Clinical need / burden of disease

Fresh fractures

The incidence of fractures in Australia can be estimated from retrospective survey data and population-based studies. Where no information is available for the Australian population, it is necessary to consider epidemiological reports from other nations. Where possible, data are corrected to the current Australian demographic profile.

The National Health Survey, conducted by questionnaire in 1995, estimated the total fracture prevalence in Australia to be 100,000 at the time of the survey. Of these, 84,500 fractures occurred in adults over 15 years of age, equating to a point prevalence of 56 per 10,000 individuals. This should not be interpreted as an annual incidence, as it relates only to injuries current at the time of the survey, rather than over a one-year period. As a typical fracture is likely to be present for 3–6 months, the annual incidence could be two- to four-fold higher (approximately 112–224 per 10,000). No information regarding fracture type was reported.

While these retrospective, patient-reported, questionnaire data are less reliable and informative than data derived from patient records, they do provide an estimate of the total number of fractures in Australia at any one point in time.

The most comprehensive fracture incidence data for the Australian population is derived from the Geelong Osteoporosis Study, conducted in a contained adult (>35 years old) population of 109,923. Data on patients aged <35 years were not collected. All fractures occurring in this population were recorded and radiologically verified. When demographically extrapolated to the entire population, the authors estimate that in 1996 approximately 83,238 fractures (94 / 10,000 per year) occurred in Australians over 35 years of age (Sanders *et al*, 1999a). Tibial fractures occurred at an annual rate of 2 / 10,000 while wrist fractures were more common, occurring at a rate of approximately 11 / 10,000 (Table 2).

Table 2 Estimated annual incidence of tibial and distal radius fractures in the Australian population (>35 years of age)[a]

Fracture site	Rate/10,000 – women	Rate/10,000 – men	Rate/10,000 – total
Tibia[b]	2	2	2
Distal radius	17	4	11

[a]Adjusted to age and gender distribution of the 1996 Australian population.
[b]On the basis of recorded proportions of fibula and tibia fractures in Australia, it was estimated that 30% of the lower leg fractures reported by Sanders *et al* (1999a) were tibial fractures.

These data are comparable to fracture rates reported in a large comprehensive analysis of fracture epidemiology conducted in the adult population of Edinburgh, Scotland (risk population 575,600; Singer *et al*, 1998). The annual incidence of all fractures was 140 / 10,000 in individuals older than 15 years, while the incidence of fractures of specific interest to the current assessment are tabulated below (Table 3). The higher rates reported in the Scottish study when compared with the Australian study can be explained by the wider age range in the Scottish study, which included the high risk 15–25 year old group.

Table 3 Estimated annual incidence of tibial and distal radius fractures in Edinburgh population adjusted to Australian demographics (>15 years of age)[a]

Fracture site	Rate/10,000 – women	Rate/10,000 – men	Rate/10,000 – total
Tibia	2	4	3
Distal radius	28	12	20

[a]Singer *et al* (1998); age and gender adjusted by Australian population demographics

Sanders *et al* (1999b) have projected fracture numbers based on the ageing Australian population. If modified to include the 15–35 years age group (according to Singer *et al*, 1998), it is possible to estimate the total pool of tibial and distal radius fractures in 2001. Table 4 summarises this estimation. It should be noted that the incidence of wrist fractures has the potential to increase considerably in the future due to the ageing population and the high incidence of wrist fractures in elderly women.

Table 4 Estimated annual number of tibial and distal radius fractures in Australian adults in 2001

Fracture site	Estimate of number of fractures occurring in Australians (>35 years of age)[a]	Estimate of number of fractures occurring in Australians (>15 years of age)[b]
Tibial[c]	2,026	4,573
Distal radius	10,669	18,192

[a]Sanders *et al* (1999b).
[b]Sanders *et al* (1999b), modified by the addition of 15–35-year-old incidence according to Singer *et al* (1998).
[c]On the basis of recorded fibula and tibia fracture proportions in Australia, it was estimated that 30% of the lower leg fractures reported by Sanders *et al* (1999a) were tibial fractures.

In summary, on the basis of the available epidemiological evidence, it is estimated that the total number of tibial fractures in Australia in 2001 will be approximately 4,600 while the number of distal radius fractures will be approximately 18,200.

There are currently no published epidemiological reports relating specifically to scaphoid fractures. Studies undertaken in Denmark and Norway report the annual incidence of scaphoid fractures in the total population to be 2/10,000 (Brondum *et al*, 1992) and 4/10,000 (Hove, 1999). If a rate of 3/10,000 were applied to Australians over the age of 15 years, this would equate to approximately 4,200 fractures.

Non-union

Fractures that fail to heal (non-unions) have implications for a patient's quality of life and functional capacity, together with financial costs to both patient and government due to reduced productivity and cost of further medical and/or social care. Epidemiological estimates of fracture non-union of as high as 39% have been reported (Foulk *et al*, 1995); however, a rate of 4–10% is a more common observation (Heppenstell, 1980; Oni *et al*, 1988; Brondum *et al*, 1992; Duppe *et al*, 1994; Wei *et al*, 1999). It is difficult to obtain an accurate epidemiological estimate of the incidence of fracture non-union in Australia as reports are confounded by variations in treatment practice and definition of non-union, as well as by inadequate follow-up. However, to some extent the incidence of fracture non-union can be inferred from the number of services provided for fracture non-unions (see below). It is possible that this may underestimate the true incidence as some fracture non-unions remain undiagnosed or untreated.

Existing procedures

Fresh fractures

In support of the epidemiological estimates, the number of tibial, distal radius and scaphoid fracture treatments currently performed within the Australian healthcare system can be approximated. Data are derived from: i) statistics documenting services reimbursed according to the Medicare Benefits Schedule (MBS), which includes private patients treated in hospitals and non-hospital treatments of private and public patients; and ii) statistics from the National Hospital Morbidity Database (NHMD) on treatments undertaken in public hospitals on 'admitted' public patients (Australian Institute of Health and Welfare).

The main exclusions are public hospital patients who are not admitted (ie outpatients and some emergency department patients). A proportion of patients referred to hospital outpatient clinics will have been captured by Medicare statistics if they received initial treatment from their general practitioner; however, the proportion of emergency department patients formally admitted to hospital will vary according to the nature of the fracture and the hospital.

Hence, the total numbers derived from these sources approximate the number of treatments for which the government would be *potentially* liable should LIUS be reimbursed, but may be an underestimate.

This approach assumes that there is not likely to be an increase in the total number of treatable fractures due to the availability of this technology *per se*, although it is acknowledged that a shift in the provision of fracture treatments between sectors of the health system is possible. Tables 5, 6 and 7 indicate the MBS services rendered in 1999–2000 and NHMD data on public hospital procedures performed in 1998–1999[2,3], identified by the ICD-10-AM block number and descriptor under which related procedure codes are grouped.

All relevant item and block numbers relating to non-articular fractures of the shaft of tibia and distal end of radius[4] are included, although the descriptors used are not completely consistent between the source databases. Nevertheless, in combination, the two sources reflect the majority of tibial, distal radius and scaphoid fracture treatments performed within Australia annually. LIUS is indicated only in the treatment of fractures of mature bone, and consequently, is not suitable for use in children. Therefore, only services rendered to adults over 15 years are presented.

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[2] Hospital data for 1999–2000 are currently unavailable.

[3] MBS services are limited to Medicare benefits paid on a fee-for-service basis and therefore exclude services to public patients in public hospitals. In contrast, the public hospital procedure statistics presented here include only public patients in public hospitals, but excludes those not formally admitted to hospital. Services reimbursed by the Commonwealth Department of Veterans' Affairs for private patients are not included in this approximation. Inclusion of this group would result in minimal increase in the total.

[4] For completeness, services rendered for all radial shaft fractures are included, whether or not they were specified as distal.

Table 5 Annual number of publicly funded treatment services rendered for tibial shaft fractures in Australia (>15 years of age)

Medicare item number ***Description of fracture treatment***	**Medicare services rendered July 1999–June 2000**		**ICD-10-AM block number** ***Description of fracture treatment***	**Public hospital services[a] July 1998–June 1999**
47561 *Treatment of fracture of tibial shaft by cast immobilisation, where item 47564, 47567, 47570 or 47573 do not apply*	430		1495[b] *Immobilisation of fractured tibia*	26
47564 *Treatment of fracture of tibial shaft, by closed reduction, with or without treatment of fibular fracture*	186		1509 *Closed reduction of shaft of tibia*	673
47566[c, d] *Treatment of fracture of tibial shaft, by intramedullary fixation and cross fixation*	217		1510[c, e] *Open reduction of shaft of tibia* (includes use of intramedullary rod)	821
47565[c, d] *Treatment of fracture of tibial shaft, by internal fixation or external fixation*	168		1521[c, d, f] *Internal fixation of fractured tibia or femur with reconstruction*	10
47570[d] *Treatment of fracture of tibial shaft, by open reduction, with or without fibular fracture*	33			
Total	**1,034**			**1,530**

[a]Includes only public patients admitted to public hospitals. Source: Australian Institute of Health and Welfare.
[b]Number of services adjusted to reflect that approximately 30% of recorded lower leg fractures are tibial fractures.
[c] Likely to include both treatment of fresh fractures and that of non-unions.
[d]LIUS is unlikely to replace these services in treatment of fresh fractures.
[e]Open reduction and fixation with an intramedullary rod maps to codes in this block.
[f]Assumes 50% refer to tibia.

Table 6 Annual number of publicly funded treatment services rendered for radius fractures in Australia (>15 years of age)

Medicare item number ***Description of fracture treatment***	**Medicare services rendered July 1999–June 2000**		**ICD-10-AM block number** ***Description of fracture treatment***	**Public hospital services[a] July 1998–June 1999**
47360 *Treatment of fracture of distal end of radius or ulna, by cast immobilisation, where item 47363 or 47366 do not apply*	6,300		1421 *Immobilisation of fractured distal and shaft of radius or ulna (Non surgical treatment of fracture of shaft and distal radius)*	82
47363 *Treatment of fracture of distal end of radius or ulna, by closed reduction*	726		1427 *Closed reduction of fracture of radius*	4,085
47366[b] *Treatment of fracture of distal end of radius or ulna, by open reduction*	58		1429[b] *Open reduction of fracture of radius*	1147
47369 *Treatment of fracture of distal end of radius: Colles', Smith's or Barton's, by cast immobilisation, where item 47372 or 47375 do not apply*	2,280			
47372 *Treatment of fracture of distal end of radius: Colles', Smith's or Barton's, by closed reduction*	2,341			
47375[a] *Treatment of fracture of distal end of radius: Colles', Smith's or Barton's, by open reduction*	712			
47378 *Treatment of fracture of radius or ulna shaft, by cast immobilisation, where item 47381, 47384, 47385 or 47386 do not apply*	734			
47381 *Treatment of fracture of radius or ulna shaft, by closed reduction undertaken in the operating theatre of a hospital or approved day hospital facility*	39			
47384[b] *Treatment of fracture of radius or ulna shaft, by open reduction*	125		1432[b] *Open reduction of fracture of shaft of radius or ulna with dislocation*	27
47387 *Treatment of fracture of radius and ulna shafts, by cast immobilisation, where item 47390 or 47393 do not apply*	249			
47390 *Treatment of fracture of radius and ulna shafts, by closed reduction undertaken in the operating theatre of a hospital or approved day hospital facility*	151		1431 *Reduction of fracture of shaft of radius and ulna*	268
47393[a] *Treatment of fracture of radius and ulna shafts, by open reduction*	115			
Total	**13,830**			**5,609**

[a]Includes only public patients admitted to public hospitals. Source: Australian Institute of Health and Welfare.
[b]LIUS is unlikely to replace these services in treatment of fresh fractures.

Table 7 Annual number of publicly funded treatment services rendered for scaphoid fractures in Australia (>15 years of age)

Medicare item number ***Description of fracture treatment***	**Medicare services rendered July 1999–June 2000**		**ICD-10-AM block number** ***Description of fracture treatment***	**Public hospital services[a] July 1998–June 1999**
47354 *Treatment of fracture of carpal scaphoid, not being a service to which item 47357 applies*	3,546		1452[b] *Closed reduction of fracture of carpus*	42
47357 *Treatment of fracture of carpal scaphoid by open reduction*	151		1455[b] *Open reduction of fracture of carpus*	157
Total	**3,697**			**199**

[a]Includes only public patients admitted to public hospitals. Source: Australian Institute of Health and Welfare.
[b]Number of services adjusted to reflect scaphoid fractures contributing 85% of total carpal fractures.

The tables above include only services rendered to individuals over 15 years of age as LIUS is indicated only in skeletally mature individuals. Approximately 55% of total fracture services are rendered to non-skeletally mature children or adolescents, and are therefore not included within the tables above. A second over-represented group are postmenopausal women, in whom the incidence of fractures is higher than other mature men and women. However, this group is included as they fall within the indication currently under review.

In the context of the populations captured by the two source databases and the somewhat imprecise nature of the item descriptors, it is estimated that the number of tibial, distal radius and scaphoid fracture treatments rendered annually to Australians >15 years old is about 26,000 (approximately 2,600, 19,400 and 3,900, respectively). In total, 49% of services rendered for tibial fractures involved open reduction and/or internal fixation, compared with only 11% and 8% of the services for radius and scaphoid fractures, respectively.

It is apparent that treatment varies according to the setting in which it is delivered. With respect to Medicare-reimbursed services (which included treatment in the general practice surgery), the majority of fresh tibial and distal radius fractures are currently treated with cast immobilisation alone, with a proportion requiring closed reduction (Tables 5 & 6). Fewer are treated with open reduction and internal fixation in this setting. In contrast, fractures treated within the public hospitals typically require closed reduction prior to cast immobilisation and a considerable number require open reduction and fixation. Although not categorised separately in the hospital statistics, expert clinical opinion confirms that a considerable number of tibial fixations undertaken in the hospital setting are by intramedullary rod. Typically, these are categorised within ICD-10-AM block number 1510. According to the available statistics, the majority of scaphoid fractures receive first-line treatment outside the public hospital setting (at the general practitioner or in a private hospital) and are therefore reimbursed by Medicare (Table 7). However, the number of public hospital treatments may be underestimated in this indication as many scaphoid fractures may be treated in the emergency department without the patient being formally admitted. Nevertheless, the annual number of scaphoid fractures estimated from available treatment statistics (3,900) is not dissimilar to the epidemiological estimate (4,200).

The statistics tabulated above include all patients to whom a specific service has been rendered, irrespective of the characteristics and severity of the fracture. Therefore, included in the total will be comminuted and more complex open fractures that fall beyond LIUS indications, together with patients in whom a self-administered, home-based treatment is not appropriate. Similarly, some items in Table 5 may have been rendered for the treatment of a non-union fracture (eg item number 47565).

As a result, despite the aforementioned emergency department omissions, these statistics are likely to somewhat overestimate the number of services that are potentially replaceable by LIUS for the treatment of simple fresh fractures. When considering only those services clinically indicated for treatment with cast immobilisation (with or without closed reduction), this is reduced to approximately 1,300 tibial[5], 17,300 distal radius and 3,600 scaphoid services. It is these services that most closely represent fractures for which LIUS is indicated.

Non-unions

In the absence of adequate Australian epidemiological data on the incidence of fracture non-union, it is useful to review the number of services provided for treatment of this indication. The total number of services rendered by Medicare for non-unions is relatively small, although more common in tibial fractures than distal radius or scaphoid fractures.

In contrast to fresh fractures, non-unions are typically treated with a bone graft and fixation, while an implantable bone growth stimulator is used more rarely. Table 8 indicates the number of these services reimbursed by Medicare from July 1999 to June 2000, although it is conceivable that a significant number of these services relate to treatment of more severe fresh fractures. In contrast to fresh fracture treatment above, very few of the Medicare services likely to be rendered for non-union are rendered to children under 15 years.

[5]In Australia, a significant number of tibial fractures meeting the LIUS indication will currently be treated by fixation with an intramedullary rod (ie included within ICD-10 item 1510). It is not possible to estimate this number and, for simplicity, only those treated conservatively are included here. Therefore, this number may underestimate the true number of tibial fractures meeting the LIUS indication.

Table 8 Annual number of publicly funded treatment services rendered for non-union fractures in Australia (>15 years of age)[a]

Medicare item number *Description of fracture treatment*	Medicare services rendered July 1999–June 2000		ICD-10-AM block number *Description of fracture treatment*	Public hospital services[b] July 1998–June 1999
48206 *Bone graft of tibia*	326		1513 *Bone graft to tibia*	80
48209[c] *Bone graft of tibia with internal fixation*	112		1461[d] *Bone graft of wrist, metacarpal or phalanx*	119
48227 *Bone graft of radius or ulna with internal fixation of one or both bones*	121		1435[d] *Bone graft of forearm*	81
48224 *Bone graft of radius or ulna*	68			
48221 *Bone graft of radius and ulna with internal fixation of one or both bones*	37			
48218 *Bone graft of radius and ulna*	5			
48230 *Bone graft of scaphoid for non-union*	23			
48233 *Bone graft of scaphoid for non-union, both internal fixation*	218			
47920 *Implanting of bone growth stimulator (not specific to bone)*	5			
Total	**915**			**280**

[a]Only data for tibia, radius and scaphoid are presented. Will overestimate treatment for fracture non-unions as includes bone grafts undertaken for non-fracture indications (eg tumours).
[b]Includes only public patients in public hospitals.
[c]See also item 47565 in Table 5 previously.
[d]Represents an overestimate of scaphoid and distal radius non-union, as inclusive of other sites.

The number of services provided for non-unions is only 4.6% of that for fresh fractures. Given the potential overestimation of non-union services, this percentage provides an upper-bound estimation of the proportion of fractures that fail to heal in the Australian healthcare setting.

The likelihood of non-union is considerably higher following a tibial fracture than after a distal radius or scaphoid fracture. A high degree of soft-tissue injury and/or displacement will increase the likelihood of non-union. In the case of tibia fractures, a concurrent fracture of the fibula will also increase this risk.

Comparator

Consideration of the comparator treatment is made in light of the treatment patterns described above. These are somewhat specific to the treatment setting. In the Medicare setting, which includes the general practice surgery, the use of LIUS for the treatment of

fresh tibial, distal radius and scaphoid fractures should be compared with cast immobilisation (with or without closed reduction). LIUS treatment should not be compared with treatment involving open reduction or fixation for three reasons: 1) only a small proportion of the fracture treatments rendered involve open reduction and/or fixation, representing just 14% of the total services itemised in Tables 5, 6 and 7; 2) these treatments are predominantly rendered for more complicated fractures for which treatment with LIUS is not indicated; and 3) a proportion of these services will have been rendered for the treatment of existing fractures (eg non-unions).

Similarly, in the public hospital setting, cast immobilisation is the appropriate comparator treatment for distal radius and scaphoid fractures. However, with regard to tibial fractures, open reduction with intramedullary rod fixation is also a relevant comparator treatment.

The comparator for the treatment of fracture non-union is less clear, but on balance the most common treatment for tibial, radius and scaphoid fractures that have failed to heal after 20 or 30 weeks is currently open reduction and internal fixation (ORIF) with bone grafting. However, it should be noted that continuation of conservative treatments such as cast immobilisation will not appear in the services tabulated above. Nevertheless, surgical ORIF intervention with bone grafting is considered the most common treatment of non-union in the publicly funded Australian healthcare sector. Therefore, the use of LIUS in non-union fractures should be compared with open reduction and internal fixation with bone grafting, both with respect to efficacy and cost.

Marketing status of the device

Exogen, a branded LIUS, is listed on the Australian Register of Therapeutic Goods with the Therapeutic Goods Administration (TGA). The TGA listing number is AUSTL 61521. Furthermore, Exogen is approved for marketing by the US Food and Drug Administration for use in fracture non-union together with specific fresh fractures of the tibia and distal radius. Marketing approval is limited to treatment of skeletally mature individuals who are being managed by closed reduction and cast immobilisation. Exogen is also approved for marketing in Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, Japan, Luxembourg, Norway, Spain, Sweden, Switzerland, the Netherlands, and the United Kingdom.

Current reimbursement arrangement

LIUS is currently not reimbursed by Medicare in Australia. The equivalent reimbursement committee in the United States (Health Care Financing Administration) has not granted reimbursement for the treatment of fresh fractures and has limited reimbursement to non-union fractures meeting specific criteria, including no radiological evidence of progression in healing over a 90-day period *and* documented failure of at least one surgical intervention. LIUS is currently reimbursed by the Japanese and Dutch governments for the treatment of non-union fractures.

Approach to assessment

MSAC reviewed the available literature regarding the use of LIUS and convened a supporting committee to review the evidence and provide expert opinion.

Review of literature

A search of the medical literature spanning 1966 to October, 2000 was conducted. Primary literature databases searched were Medline, HealthSTAR, DARE, Cochrane, EMBASE and Econlit using the terms 'ultrasound' and 'fracture/s', narrowed by the subheadings 'ultrasonic therapy' and 'fracture healing' when available. Only articles published in English, German or French were reviewed. Further information was sourced from international health technology assessment agencies, evidence-based medicine databases and references cited in publications previously retrieved. Additional material was provided by the applicant**.** In addition, bibliographies and reference lists were manually searched.

Publications relating to ultrasound as a therapy for bone fractures were selected for further review while those relating to diagnostic use of ultrasound were excluded. Studies reporting on fewer than 10 patients or using an animal model were not included in the review. Additional case series data from patient registries were reviewed as low-level evidence. Non-systematic review articles that did not present original data were excluded.

After applying these inclusion and exclusion criteria, six published papers and three case series or registry reports were included in the review. These are listed in Appendix C. Where additional data were obtained from the original study reports, this is noted. Duplicated publications (where a total or partial overlap of data occurred) were noted as such. A list of excluded papers is also presented in Appendix C, together with the reason for exclusion.

The evidence presented in the selected studies was assessed and classified according to the National Health and Medical Research Council (NHMRC) revised hierarchy of evidence shown in Table 9. Studies were reviewed with respect to their subject population, methodology (limitation of study bias, appropriate use of statistics, appropriate choice of outcome measures) and ultimately their efficacy and safety outcomes.

Table 9 NHMRC levels of evidence

I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test and post-test

Source: NHMRC.

The subject populations and methodologies of the selected studies appear in detail in Appendix D. Key outcomes are detailed in the results section of this report.

For the purposes of this review, the primary outcome measure reviewed was time to healing, defined as independent radiological confirmation of bridging of three of four cortices. Where data are available, a dichotomous variable reflecting proportion of patients healed at a standardised time point was reviewed.

Expert advice

A supporting committee including members with expertise in orthopaedic surgery, radiology, general practice and public health was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the supporting committee is provided at Appendix B.

Results of assessment

The quality of the evidence available to support the use of LIUS in the treatment of fractures varies considerably with respect to indication. While randomised controlled studies have been conducted in the treatment of fresh fractures, only case series data exist to support use in non-unions.

For the purposes of this review, safety issues will be considered simultaneously for both fresh and non-union fractures. Evidence relating to efficacy and subsequent calculations of cost-effectiveness will be considered individually.

Is it safe?

There have been no reports of adverse events related to the use of LIUS in human clinical trials. Post-marketing registry data report isolated incidents of skin rash caused by sensitivity to the coupling gel, which resolved by changing to an alternative coupling medium.

Theoretical concerns regarding the use of therapeutic ultrasound relate to overheating of the tissue and potential disruption of the interface between soft tissue and bone. Animal and human studies of conventional therapeutic ultrasound (as used by physiotherapists) have indicated that muscle temperature can be elevated to as high as 41.5°C (Gersten, 1958; Ward and Robertson, 1996). Although the frequency may be similar, the lower average intensity of the pulsed ultrasound signal in LIUS appears to minimise the possibility of tissue heating. However, there are currently no published studies reporting the direct measurement of temperature during the use of LIUS, as has been undertaken with conventional ultrasound. Since there are no data available, subclinical deep-tissue consequences cannot be ruled out in humans. The signal intensity cannot be changed by the patient or the medical practitioner.

Until further information is available, the following precautionary guidelines should be observed.

- The safety of this device in pregnant or nursing women has not been established, and therefore use in this group is not recommended.
- The device should not be used in the case of mal-aligned fractures as it will not correct the alignment.
- The effects of LIUS on skeletally immature bone is unknown and therefore use of this treatment in children is not recommended
- Active implantable devices such as pacemakers may be adversely affected by the operation of LIUS and therefore the use of LIUS in these patients is contraindicated.

Information currently available indicates that LIUS does not appear to have any detrimental effects upon the position or composition of metal orthopaedic implants, even with continued exposure (Lotsova, 1979; Skoubo-Kristiansen, 1982). As the

frequency of LIUS is outside the range of human and animal hearing, it is unlikely that LIUS will cause auditory discomfort or damage.

Is it effective?

Fresh fractures

Table 10 presents a summary of the published clinical evidence meeting the inclusion criteria for review. More detailed information regarding patient characteristics, fracture characteristics, methodology and results is tabulated in Appendix D. The quality of each study was reviewed by two independent assessors using a modification of the Cochrane Collaboration Musculoskeletal Injuries Review Group quality assessment tool (Handoll and Madhok, 2000). This tool is designed to assess the minimisation of bias in study design, conduct and analysis. There was close agreement between assessors and the mean score is presented in Table 10.

Table 10 Summary of clinical evidence of LIUS treatment of fresh fractures

Level of evidence	Author/study design	Patient and fracture characteristics (see Appendix D for details)	Primary outcomes	Evidence quality score (total possible = 33)
Level I	None available			
Level II	Heckman *et al* (1994)[a] Randomised, double-blind, placebo-controlled trial	Closed and grade 1 open tibial fractures	Improvement in time to healing when LIUS + cast immobilisation was compared with placebo + cast immobilisation: 102 days vs 190 days, 46% improvement Proportion not healed at 20 weeks: 15% vs 62% Proportion not healed at 30 weeks: 0% vs 21%	22
	Emami *et al* (1999)[a] Randomised, double-blind, placebo-controlled trial	Closed and grade 1 open tibial fractures	No difference in time to healing when LIUS + intramedullary rod was compared with placebo + intramedullary rod: 155 days vs 125 days, 24% poorer Proportion not healed at 20 weeks: 33% vs 12% Proportion not healed at 30 weeks: 27% vs 12%	30
	Kristiansen *et al* (1997)[a] Randomised, double-blind, placebo-controlled trial	Closed distal radius (Colles) fractures	Improvement in time to healing when LIUS + cast immobilisation was compared with placebo + cast immobilisation: 64 days vs 87 days, 26% improvement Proportion not healed at 20 weeks: 0% vs 0% Proportion not healed at 30 weeks: 0% vs 0%	26
	Mayr et al (2000a) Randomised, open, controlled trial[b]	Stable scaphoid fractures	Improvement in time to healing[c] when LIUS + cast immobilisation was compared with cast immobilisation alone (no placebo): 42 vs 60 days, 30% improvement Proportion not healed at 20 weeks: 0% vs 0% Proportion not healed at 30 weeks: 0% vs 0%	19
Level III	None available			
Level IV	None available			

[a]The data presented by the reviewer in this table for the Heckman, Emami and Kristiansen studies are those of the independent radiologist for 3/4 cortices healed and are therefore different to those reported in the respective publications, which referred primarily to assessments made by the principal investigator. Only core group (evaluable) data are included for both Heckman and Kristiansen, where patient attrition was considerable (31% and 28%, respectively). An intention-to-treat analysis has been performed by the reviewer and is presented in Appendix D. Individual data were obtained from clinical study reports.
[b]Mayr *et al* (2000a) was not placebo controlled.
[c]For Mayr, 70% radiological healing is used for 'time to healing'. However, it was necessary to use clinical healing to calculate the proportion healed at 20 and 30 weeks, as this 70% radiological healing was not reported in this manner and individual data were not available.

The studies reviewed in this assessment investigated three different fracture sites with inherently different healing characteristics, or utilised a different comparator. For this

reason, it was considered inappropriate to pool the study results and therefore no meta-analysis has been conducted. This assessment will therefore summarise the efficacy data for each fracture type individually, prior to summarising the efficacy of the technology in fresh fractures generally.

The efficacy of LIUS in the treatment of distal radius fractures is supported by only one study to date (Kristiansen *et al*, 1997). This study was undertaken primarily in older female patients, which reflects the profile of patients with distal radius fractures in Australia. However, care should be taken in extrapolating the results to the general population. A large proportion of patients were lost to follow-up (28%). When an intention-to-treat (ITT) analysis was undertaken by the reviewer, the difference in treatment effect of LIUS relative to control was reduced from 26% to 18%. Therefore, confirmation of the magnitude of the treatment effect by further independent research would strengthen the study conclusions. Nevertheless, this evidence is considered sufficient to cautiously support the efficacy of LIUS in the treatment of closed distal radius fractures in this distinct patient population.

With respect to tibial fractures, the efficacy of LIUS is not sufficiently supported by quality research. While the results of Heckman *et al* (1994) suggest a positive treatment effect of LIUS over and above cast immobilisation, this study has methodological limitations, including block randomisation, inconsistent patient management and a large patient drop-out rate (31%). Furthermore, a second randomised controlled trial conducted in patients with tibial fractures showed no beneficial effect of LIUS (Emami *et al*, 1999). In fact, the direction of the treatment effect favoured placebo in this well-controlled independent study, despite studying a similar fracture population to that of the Heckman study.

An explanation for this inconsistency in study findings is not immediately obvious. Although the LIUS intervention was the same in the two studies (20 min/day), in the Heckman *et al* study it was compared with cast immobilisation while in the Emami *et al* study it was compared with treatment with an intramedullary rod, which allows early weight-bearing. It is possible that the mechanical stress imposed by early weight-bearing overshadows any advantage of LIUS. It is also conceivable that presence of metal minimises the effect of the ultrasound, although experimental findings in animals do not support this explanation (Wang *et al*, 1994). In addition, the Emami *et al* study contained only a small number of smokers in comparison with the previous two studies, and the presence of an interaction effect between smoking and response to LIUS has been suggested (Cook *et al*, 1997).

To date, only one study has been conducted in scaphoid fractures (Mayr *et al*, 2000a). This study was not placebo-controlled, so both patients and treatment providers were aware of the nature of treatment. Assessments of healing status were made by three radiologists blind to treatment intervention, although all were in agreement in only 61% of scans. While the study results suggest accelerated healing, it is not possible to conclude greater efficacy than cast immobilisation on the basis of this unblinded study alone.

When considering LIUS technology for the treatment of fresh fractures generally, there is a trend toward a faster time to healing in response to LIUS in comparison with current treatment options, particularly when compared with cast immobilisation. However, on the basis of the evidence currently available, it is not possible to conclude that LIUS offers a consistent advantage with respect to the treatment of all fresh fractures. We conclude that there are currently only two high-quality, well-designed studies (Kristiansen

et al, 1997; Emami *et al*, 1999) and the results of these studies are contradictory. For this reason, while it can be tentatively concluded that there is evidence of efficacy in distal radius fractures, it is not possible to extend this conclusion to the treatment of fresh fractures in general.

Non-union fractures

With respect to non-union fractures, only level IV evidence exists. Details of these case series and registry studies are summarised in Table 11 and presented in more detail in Appendix D.

Table 11 Summary of clinical evidence of LIUS treatment of non-union fractures

Level of evidence	Author/study design	Patient and fracture characteristics (see Appendix D for detail)	Primary outcomes[a] Results in core group comleting treatment with IIUS (not ITT)
Level I	None available		
Level II	None available		
Level III	None available		
Level IV	Gebuaur *et al* (1998) (Germany) Case series reports using retrospective self-control	n = 41 (core group assessed at nine months) Radiographically verified non-union > nine months post-fracture Excluding: spine, skull, tumour-related fractures 63% initial surgical intervention 61% subsequent surgical intervention Surgery permitted up to three months prior to LIUS intervention	Results in core group completing treatment with LIUS (20 minutes/day) (not ITT): Proportion of patients healed in nine months: 83% Median time to healing[b]: 153 days (5.1 months)
	Albers *et al* (1999) (Netherlands) Case series reports using retrospective self-control	n = 24 (core group assessed at nine months) Radiographically verified non-union >nine months post-fracture Excluding: spine, skull, tumour-related fractures 67% initial surgical intervention 42% subsequent surgical intervention Surgery permitted up to three months prior to LIUS intervention	Proportion of patients healed in nine months: 83% Median time to healing[b]: 116 days (3.9 months)
	Heppenstell *et al* (1999) (US) Registry case series reports using retrospective self-control	n = 313 (core group assessed at nine months) > Nine months post-fracture Excluding: spine, skull, tumour-related fracture 34–77% initial surgical intervention[c] 47% subsequent surgical intervention Surgery permitted up to three months prior to LIUS intervention No radiographic verification of non-union or healing	Proportion of patients healed in nine months: 74% Median time to healing[b]: 140 days (4.7 months)

[a]Only results of the core group are available, thus a large proportion of patients who did not complete treatment are excluded from the analysis, introducing considerable potential for bias in the study results.
[b]Median of healed patients only.
[c]Initial treatment was unknown for 43% of patients.

The results of the three studies reviewed in this assessment appear to suggest that LIUS promotes healing in established non-unions, although the average time to healing remains substantial (approximately a further five months). However, these case series studies do not have a parallel control group, nor are they blinded. Therefore, it is not possible to make a direct comparison with either no further treatment or with alternative treatments. Despite the assertions of the authors, the potential for bias in an unblinded case series with retrospective, self-control is considerable. In the largest case series

contributing in excess of 80% of patients (Heppenstell, 1999), considerable data relating to previous fracture management were unavailable and patients commencing LIUS treatment did not have radiographic confirmation of non-union. As surgery was permitted up to three months prior to the LIUS intervention, a delayed response obtained during this 'control' period (post-surgery), could have inflated the success rate of LIUS. Furthermore, the quality of the outcome assessment was poor, in some cases relied on patient reporting.

Interpretation of the findings of these studies is made more difficult due to the heterogeneous nature of the patients. Considerable variation was present with respect to fracture site, initial fracture severity, initial fracture treatment and the number of subsequent surgical interventions. A large proportion of patients had received at least one surgical intervention. On this basis, it is not appropriate to apply these findings to patients requiring treatment for the initial diagnosis of fracture non-union immediately subsequent to conservative treatment. To assess the comparative efficacy in this indication, it would be necessary to directly compare LIUS with ORIF as first subsequent treatment upon confirmation of non-union. In fact, on the basis of the study populations investigated, any efficacy conclusions are more applicable to patients having failed at least one prior surgical intervention for non-union.

Interpretation of the case series and registry data for treatment of non-unions is made in the context of expert opinion that fractures more than nine months old that have ceased healing are unlikely to heal without further treatment. There is also considerable potential study bias. Therefore, we cautiously conclude that there is minimally acceptable, low-level, indirect evidence to support the efficacy of LIUS in patients with established non-unions who have failed previous surgical intervention, in comparison with no further treatment.

However, this limited conclusion of efficacy is made with reference to LIUS alone and should not be interpreted as a comparison with other non-union interventions such as further immobilisation, ORIF or other treatments. To date, no clinical trials have directly compared LIUS with other interventions typically used in the treatment of fracture non-unions. A prospective, randomised comparison of LIUS against surgical intervention is required to make such a comparison. In conclusion, there is currently no evidence to support superior efficacy of LIUS when compared with existing Australian treatment of fracture non-unions.

What are the economic considerations?

An assessment of the cost-effectiveness of LIUS in the treatment of fresh tibia, radius and scaphoid fractures was conducted. Each evaluation was undertaken on the results of randomised, placebo-controlled trials.

- The economic evaluation of fresh tibia fractures was based on the study by Heckman *et al* (1994).
- The economic evaluation of fresh radius fractures was based on the study by Kristiansen *et al* (1997).
- The economic evaluation of fresh scaphoid fractures was based on the study by Mayr *et al* (2000a).

Each evaluation presents direct and indirect costs of LIUS treatment relative to no LIUS treatment. To estimate value-for-money, the costs were assessed together with the health outcomes to derive cost-effectiveness and cost-utility ratios. Estimates of value-for-money should be interpreted in the context of the quality of health outcome evidence used. In particular, the large drop-out rate and subsequent analysis of evaluable patients is likely to overestimate the relative efficacy of LIUS and therefore its value-for-money.

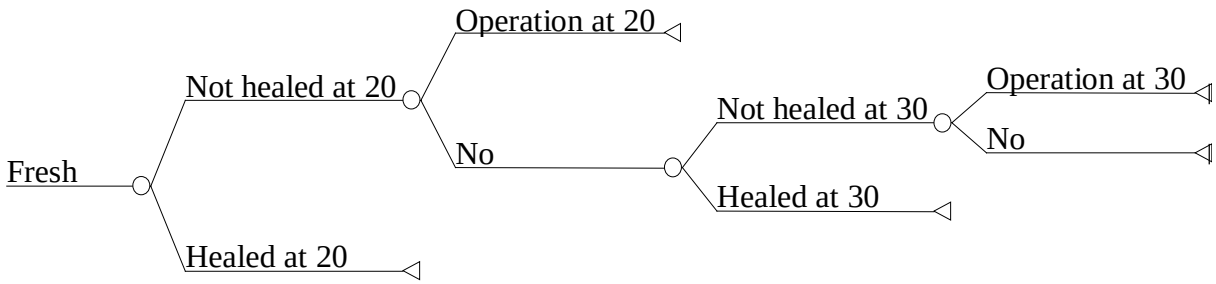
Cost-effectiveness analyses

Fresh tibia fractures

The cost of LIUS per patient ($4,995) was obtained from the applicant's submission. LIUS has the potential to decrease the number of re-operations necessary for delayed and non-union fractures. The applicant has estimated the total healthcare cost of open reduction surgery at $6,663.85. This cost is applied to the economic evaluation; however, it is likely that this amount overestimates the true cost of surgery in this setting.

Figure 2 presents a clinical pathway for patients with fresh fractures. This pathway has been used to determine the number and cost of re-operations with and without LIUS. The probabilities of following a particular course through this pathway are based on the rate of healing reported in the Heckman *et al* (1994) study. It is assumed the probabilities of operation at 20 and 30 weeks are 50% and 75%, respectively, for those who have not healed at this stage.

Figure 2 Clinical pathway after a fresh fracture



By applying the clinical trial data to the clinical pathway in Figure 2, Table 12 determines the proportion of patients with and without LIUS who would require an operation. This table shows that LIUS is associated with additional direct healthcare costs of $2,904 per patient.

Table 12 Direct healthcare costs by treatment group

	LIUS	Placebo	Incremental
Cost of initial therapy			
Cost of LIUS	$4,995	$0	$4,995
Cost of surgery			
Cost per surgical intervention	$6,664	$6,664	
Patients with operations at 20 weeks (%)	8%	31%	
Patients with operations at 30 weeks (%)	0%	8%	
Total operations (%)	8%	39%	
Expected cost of surgery per patient	$500	$2,591	–$2,091
Total direct healthcare costs	$5,495	$2,591	$2,904

The costs of initial assessment and casting were not considered in the economic evaluation as these costs would be common to both interventions. It is possible that LIUS may lead to a decrease in the use of consultations because patients are healing faster and the follow-up required is not as long. However, it is unlikely that these cost savings would be large[6].

Indirect costs attributable to work time lost were also estimated. The calculation of these costs is based on the average weekly wage in Australia (Australian Bureau of Statistics, 2000). This is consistent with the 'friction cost method'. This method recognises that not all work days lost are productive work days; it assumes that 80% of work days lost are productive work days (Brouwer and Koopsmanchap, 1998).

The calculated number of work days lost is based on the percentage of the total time to healing reported in the studies. National Occupational Health and Safety Commission data suggest that on average, 36 work days are lost with lower limb related injuries[7]. The placebo arm of the Heckman *et al* (1994) study reported 190 days to healing. Therefore, it is assumed that work days lost comprise 19% (36/190) of the total days to healing. Table 13 calculates the number and value of work days lost in each of the treatment arms. Based on the results of the Heckman *et al* (1994) study, LIUS could save up to $2,124 in productivity losses associated with fresh tibia fractures.

Table 13 Indirect costs due to fresh tibia fractures by treatment group

Parameter	LIUS	Placebo	Incremental
Time to healing (days per patient)	102	190	
Work days lost (per patient)[a]	19	36	
Productive value of one work day lost	$127.39	$127.39	
Expected value of work days lost (indirect cost)	$2,462	$4,586	–$2,124

[a]Work days lost as a proportion of time to healing is 19%.

The total cost of treatment per patient (with and without LIUS) is presented in Table 14.

[6]For example, the mean improvement of 58 days implies a saving of less than two consultations if patients are reviewed once a month.

[7]This may be an underestimate of absence from work for younger workers who work in manual occupations. The findings of this report, however, would remain unchanged.

Table 14 Total cost per patient by treatment group in fresh tibia fractures

Cost item	LIUS	Placebo	Incremental
Direct healthcare costs	$5,495	$2,591	$2,904
Indirect costs	$2,462	$4,586	–$2,124
Total cost	**$7,957**	**$7,177**	**$780**

The economic evaluation considered the following outcomes of treatment:

- mean time to healing
- proportion of patients with healed fracture at 20 weeks
- proportion of patients with healed fracture at 30 weeks

Data for these outcomes were derived directly from the clinical trials and are presented in Table 15. For the purposes of the economic evaluation, the primary outcome measure was time to healing, defined as independent radiological confirmation of bridging of three of four cortices. Efficacy results were presented in Table 10.

Table 15 Outcomes of treatment in fresh tibia fractures (Heckman *et al*, 1994)

Outcome	LIUS	Placebo	Incremental
Mean time to healing (days)	102	190	–88
Proportion of patients with healed fracture at 20 weeks	85%	38%	47%
Proportion of patients with healed fracture at 30 weeks	100%	79%	21%

Table 16 presents the incremental cost-effectiveness ratios for LIUS in fresh tibia fractures. The indicative economic evaluation found that the incremental cost of LIUS per additional day with healed fracture was between $9 and $33. The incremental cost per additional patient healed at 30 weeks was between $3,715 and $13,830.

Table 16 Incremental cost effectiveness of LIUS in fresh tibia fractures

	Incremental cost[a]	Incremental benefit[b]	Incremental cost-effectiveness
Ratios with only direct healthcare costs			
Cost per additional day with healed fracture	$2904	88 days	$33
Cost per additional patient healed at 20 weeks	$2904	47%	$6179
Cost per additional patient healed at 30 weeks	$2904	21%	$13,830
Ratios including indirect costs			
Cost per additional day with healed fracture	$780	88 days	$9
Cost per additional patient healed at 20 weeks	$780	47%	$1660
Cost per additional patient healed at 30 weeks	$780	21%	$3715

[a]Table 14
[b]Table 15

Fresh radius fractures

The methodology of this evaluation is equivalent to that of fresh tibia fractures.

The applicant's estimate of the cost of LIUS per patient of $4,995 was used. In the Kristiansen *et al* (1997) study, all patients (both LIUS and non-treated) were healed by 20 weeks, resulting in no savings in operation costs. Indirect costs were estimated on the basis that 58% (50/87) of time to healing represented lost work days[8]. The total cost per patient, with and without LIUS, is presented in Table 17.

Table 17 Total cost per patient by treatment group

Cost item	LIUS	Placebo	Incremental
Treatment cost	$4,995	$0	$4,995
Expected cost of re-operations	$0	$0	$0
Indirect costs	$4,709	$6,401	–$1692
Total cost	**$9,704**	**$6,401**	**$3,303**

The preliminary economic evaluation considered mean time to healing as the primary outcome of treatment. Data for these outcomes were derived directly from the clinical trial and are presented in Table 18.

Table 18 Outcomes of treatment in fresh radius fractures (Kristiansen *et al,* 1997)

Outcome	LIUS	Placebo	Incremental
Mean time to healing (days)	64	87	–23

Table 19 presents the incremental cost-effectiveness of LIUS in the treatment of fresh radius fractures. The incremental cost per additional day with a healed fracture was between $144 and $217.

Table 19 Incremental cost-effectiveness of LIUS in fresh tibia fractures

Treatment	Incremental cost[a]	Incremental benefit[b]	Incremental cost-effectiveness
Ratios with only direct healthcare costs			
Cost per extra day with a healed fracture	$4,995	23 days	$217
Ratios including indirect costs			
Cost per extra day with a healed fracture	$3,303	23 days	$144

[a]Table 17
[b]Table 18

Fresh scaphoid fractures

The methodology of this evaluation is equivalent to that of the evaluations in fresh tibia and radius fractures.

[8]Workers compensation data suggest that the average number of work days lost with arm-related injuries is 50 days per case. This compares with 87 days to healing in the placebo arm of the Kristiansen *et al* trial (50/87 = 58%).

Again, the applicant's estimate of the cost of LIUS per patient was used ($4,995). In the Mayr *et al* (2000a) study, all patients (both LIUS and non-treated) were healed by 20 weeks, meaning there were no operation costs[9]. Indirect costs were estimated on the basis that 58% of time to healing are work days lost[10]. The total cost per patient, with and without LIUS, is presented in Table 20.

Table 20 Total cost per patient by treatment group

Cost item	LIUS	Placebo	Incremental
Treatment cost	$4,995	$0	$4,995
Expected cost of re-operations	$0	$0	$0
Indirect costs	$3,090	$4,415	–$1,324
Total cost	**$8,085**	**$4,415**	**$3,671**

The preliminary economic evaluation considered mean time to healing as the primary outcome of treatment. Data for these outcomes were derived directly from original study reports and are presented in Table 21.

Table 21 Outcomes of treatment in scaphoid fractures (Mayr *et al*, 2000a)

Outcome	LIUS	Placebo	Incremental
Mean time to healing (days)	42	60	–18

Table 22 presents the incremental cost-effectiveness of LIUS. This indicative economic evaluation found the incremental cost of LIUS per day with a healed fracture is between $204 and $278.

Table 22 Incremental cost effectiveness of LIUS in scaphoid fractures

Treatment	Incremental cost[a]	Incremental benefit[b]	Incremental cost-effectiveness
Ratios with only direct healthcare costs			
Cost per extra day with a healed fracture	$4,995	18 days	$278
Ratios including indirect costs			
Cost per extra day with a healed fracture	$3,671	18 days	$204

[a]Table 20.
[b]Table 21.

Delayed and non-union fractures

The quality of evidence relating to the comparative efficacy of LIUS in this patient population is poor, for the following reasons.

- There are no controlled trials.
- It is unclear to what extent the case series data correspond with other non-blinded studies of surgery.

[9]Healing determined by removal of cast (see Table 10).
[10]Assume the same as for radius fractures.

- Only 8,980 of 18,642 fractures were used to assess the efficacy of LIUS.
- Confirmation of non-union at inclusion and the measurement of fracture healing at completion of LIUS were lacking in objectivity in the largest patient registry.

Given the similarity of relative costs for LIUS and surgery and the substantial uncertainty regarding relative efficacy, the case for cost-effectiveness could not be investigated. However, it is likely that surgical intervention has a more immediate impact than LIUS and that time to healing is reduced. Therefore, it could be hypothesised that indirect costs and other healthcare costs will be higher when LIUS is used instead of surgery in this patient population.

Cost-utility analyses

The cost-effectiveness ratios make it difficult to compare the relative cost-effectiveness of LIUS with other healthcare interventions. Indicative cost-utility analyses were conducted to determine how the cost-effectiveness of LIUS compares with other healthcare interventions. This is possible by use of a single metric combining life-years and quality of life. The cost-utility analysis determines the quality-adjusted life-years (QALYs) resulting from each intervention and calculates the incremental cost per QALY gained. QALYs are calculated by weighting the length of life by the utility value associated with that life. For example, a year of life with breast cancer may be equivalent to 0.65 QALYs. In this case, 0.65 is a utility value. By convention, the utility value for perfect health is 1 and for death is 0.

Indicative utility values for tibia, radius and scaphoid fractures were estimated using the Assessment of Quality of Life instrument (AQoL). The AQoL is a validated multi-attribute utility instrument (Hawthorne *et al*, 1999). The quality of life domains that were considered to be affected by tibia, radius or scaphoid fractures included independent living, sleeping, pain and discomfort. The utility values derived and applied to the indicative cost-utility analyses are presented in Table 23. The utility value for radius and scaphoid fractures are assumed to be the same. The utility value for life without a fracture is 1.

Table 23 Indicative utility values for fracture health states

Health state	Utility value
Fresh tibia fracture	0.887
Fresh radius fracture	0.842
Scaphoid fracture	0.842

Table 24 presents the utility values alongside a number of published utility values for a range of health conditions. Utility values can vary depending on the definition of the health state, the study design, the utility instrument used, and a number of other factors. The utility values applied in this indicative cost-utility analysis imply that the quality of life associated with a fractured tibia or radius is better than that for a fractured hip, but worse than unstable angina. At face value, this would seem reasonable.

Table 24 Published utility values for a range of health states

Health state	Utility value	Source	Utility valuation instrument
Second and later years after suffering an acute myocardial infarction	0.950	Nease *et al* (1995)	Rating scale, TTO and standard gamble
Unstable angina	0.950	Nease *et al* (1995)	Rating scale, TTO and standard gamble
First year after suffering a non-hip fracture	0.925	Jönsson *et al* (1995)	Assumption
Second and later years after suffering a hip fracture	0.900	Jönsson *et al* (1995)	Assumption
Fractured tibia	**0.887**	**Indicative estimate**	**AQoL**
First year after suffering an acute myocardial infarction	0.870	Oldridge *et al* (1991)	
Fractured radius	**0.842**	**Indicative estimate**	**AQoL**
Scaphoid fracture	**0.842**	**Indicative estimate**	**AQoL**
Hip fracture	0.800	Jönsson *et al* (1995)	Assumption

TTO – time trade off

Total QALYs for each patient are determined by assigning the relevant utility value to time to healing and a utility value of 1 for the remainder of the year. Tables 25–27 calculate the total QALYs per patient by treatment group in each of the three settings (fresh tibia, radius and scaphoid fractures, respectively). Note that these calculations assume the quality of life of a healed fracture is 1, representing perfect health. It is possible that patients do not return to perfect health following a fracture, meaning the incremental quality-of-life benefit of LIUS therapy could be overestimated.

Table 25 Total QALYs by treatment group – fresh tibia fractures

Parameter	LIUS	Placebo	Incremental
Days to healing	102	190	
Utility value – not healed	0.887	0.887	
Days healed (up to one year)	263	175	
Utility value – healed	1.000	1.000	
Total QALYs	0.968	0.941	0.027

Table 26 Total QALYs by treatment group – fresh radius fractures

Parameter	LIUS	Placebo	Incremental
Days to healing	64	87	
Utility value – not healed	0.842	0.842	
Days healed (up to one year)	301	278	
Utility value – healed	1.000	1.000	
Total QALYs	0.972	0.962	0.010

Table 27 Total QALYs by treatment group – fresh scaphoid fractures

Parameter	LIUS	Placebo	Incremental
Days to healing	42	60	
Utility value - Not healed	0.842	0.842	
Days healed (up to one year)	323	305	
Utility value - Healed	1.000	1.000	
Total QALYs	0.982	0.974	0.008

The direct healthcare costs of LIUS for the cost-utility analyses are those used in the earlier cost-effectiveness analyses. However, for methodological reasons, indirect costs are not considered in cost-utility analysis. Including indirect costs in these evaluations has the potential to 'double count' the benefits of LIUS. This is because utilities are considered to capture the benefits of early return to work. Table 28 presents the incremental costs per QALY of LIUS in tibia, radius and scaphoid fractures.

Table 28 Incremental cost per QALY ratios of LIUS

Treatment	Incremental costs[a]	Incremental QALYs[b]	Incremental cost per QALY
LIUS in fresh tibia fractures	$2,904	0.027	$106,601
LIUS in fresh radius fractures	$4,995	0.010	$501,699
LIUS in scaphoid fractures	$4,995	0.008	$641,060

[a]Tables 14, 17, 20.
[b]Tables 25, 26, 27.

Table 29 presents the incremental cost per QALY ratios for a range of healthcare interventions estimated in published Australian cost-utility analyses. The values calculated in this indicative evaluation suggest that use of LIUS in fresh tibia, radius and scaphoid fractures is less cost-effective than a range of other common healthcare interventions.

Table 29 Incremental cost per QALY of a range of healthcare interventions

Therapy	Incremental cost per QALY (A$)	Source
Intensive care of infants (birth weight 500–999g)	$5,360	VICSG[a] (1997)
Childhood immunisation against Hib disease	$6,930	McIntyre *et al* (1994)
Cochlear implant for children	$5,070–11,100	Carter and Hailey (1999)
Mammography screening	$16,355	Hall *et al* (1992)
Cochlear implant for profoundly deaf adults	$11,790–38,150	Carter and Hailey (1999)
LIUS in fresh tibia fractures	**$106,601**	**This evaluation**
LIUS in fresh radius fractures	**$501,699**	**This evaluation**
LIUS in scaphoid fractures	**$641,060**	**This evaluation**

[a]VICSG: Victorian Infant Collaborative Study Group (1997).

Sensitivity analyses were performed and are presented in Table 30. Sensitivity analysis calculates the incremental cost per QALY gained using different assumptions than used in the base case analyses above. Even under the most favourable conditions, the cost-effectiveness of LIUS fails to compare well with the cost-effectiveness of other healthcare interventions.

Table 30 Sensitivity analysis

Variable	Incremental cost per QALY gained		
	Tibia fractures	Radius fractures	Scaphoid fractures
Base case[a]	$106,601	$501,699	$641,060
Utility values of fracture health states decreased by:			
0.1	$56,554	$307,242	$392,587
0.2	$38,485	$221,420	$282,926
Probability of operations for patients not healed at 20 weeks:			
75%	$87,491	$501,699	$641,060
100%	$68,382	$501,699	$641,060
Probability of operations for patients not healed at 30 weeks:			
100%	$100,180	$501,699	$641,060
Cost of operations:			
Increased by 20% ($7,997)	$91,248	$501,699	$641,060
Decrease by 20% ($5,331)	$121,950	$501,699	$641,060

[a]Base case refers to the primary analysis presented earlier in this section.

Conclusions

Approximately 26,000 treatments are currently rendered annually to Australian adults for fractures of the tibia, radius and scaphoid. Lack of treatment or failure to respond to treatment can result in non-union. Delayed healing, non-union and the sequelae of unresolved non-union have implications for patient quality of life and functional capacity, as well as incurring financial costs affecting both the patient and government (ie cost of further medical and/or social care and reduced productivity). However, current treatment practice in Australia (reduction, cast immobilisation or fixation) is relatively successful. It is estimated that fewer than 5% of these fractures require treatment for non-union after the expected time for healing, although this may be higher for complex tibial fractures.

Safety

LIUS appears safe for use in adults on the basis of the evidence and clinical experience available to date. However, this intervention should not be used prior to skeletal maturation. No publications were located that reported direct measurements of deep-tissue temperature changes in human subjects using the LIUS specifications currently under investigation. The use of LIUS in patients with pacemakers is contraindicated.

Effectiveness

On the basis of the evidence currently available, it is concluded that LIUS offers no consistent advantage in the treatment of fresh fractures in general. Only two high-quality, randomised, placebo-controlled trials have been reported (Kristiansen *et al*, 1997; Emami *et al*, 1999) and the results of these studies were contradictory.

With respect to the treatment of fractures exhibiting non-union, there is currently no high-quality evidence to support the efficacy of LIUS. There is low-level evidence that LIUS is efficacious in patients with radiologically confirmed fracture non-union who have failed previous treatment, when compared with no further treatment. However, this is an unrealistic comparison and it is not currently possible to evaluate the effectiveness relative to other Australian treatments of fracture non-union.

Cost-effectiveness

The cost-effectiveness of LIUS in each of the indications reviewed in the assessment does not compare favourably with a range of other common healthcare interventions.

Recommendation

MSAC recommended that on the basis of the evidence available on low intensity ultrasound treatment for acceleration of bone fracture healing, public funding should not be supported for this procedure.

- The Minister for Health and Ageing accepted this recommendation on 5 February 2002 -

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC), and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or Affiliation
Mr Stephen Blamey (Chair)	general surgery
Professor Bruce Barraclough	general surgery
Professor Syd Bell	pathology
Dr Paul Craft	clinical epidemiology and oncology
Professor Ian Fraser	reproductive medicine
Associate Professor Jane Hall	health economics
Dr Terri Jackson	health economics
Ms Rebecca James	consumer health issues
Professor Brendon Kearney	health administration and planning
Mr Alan Keith	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Ageing
Associate Professor Richard King	internal medicine
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Mr Lou McCallum	consumer health issues
Emeritus Professor Peter Phelan	paediatrics
Dr Ewa Piejko	general practice
Dr David Robinson	plastic surgery
Professor John Simes	clinical epidemiology and clinical trials

Professor Richard Smallwood	Chief Medical Officer, Commonwealth Department of Health and Ageing
Professor Bryant Stokes	neurological surgery, representing the Australian Health Ministers' Advisory Council
Associate Professor Ken Thomson	radiology
Dr Douglas Travis	urology
Professor David Weedon	pathology (Chair until 24/08/01)
Ms Hilda Bastian	consumer health issues (Member until 24/08/01)
Dr Ross Blair	vascular surgery (New Zealand)(Member until 24/08/01)
Dr Paul Hemming	general practice (Member until 24/08/01)

Appendix B Supporting committee

Supporting committee for MSAC application 1030 Exogen bone growth stimulator

Dr Terri Jackson (Chair) MA, PhD Senior Research Fellow Monash University Health Economics Unit Melbourne	Member of MSAC
Dr Frank Burke MBBS, FRACR Radiologist, Melbourne	Nominee of the Royal Australian and New Zealand College of Radiologists
Dr Brian Kable BA, MBBS, FRACGP General Practitioner, Brisbane	Nominee of the Royal Australian College of General Practitioners
Mr Craig Mills MBBS, Dip Anat, FRACS(Orth) Specialist Orthopaedic Surgeon Royal Melbourne Hospital, Melbourne	Nominee of the Royal Australasian College of Surgeons
Dr John Primrose MBBS (Hons), FRACR Senior Medical Adviser Health Access and Financing Division Department of Health and Aged Care	Medical adviser to MSAC
Mr Victor Reid Engineer (Ret.)	Nominee of the Consumers' Health Forum
Dr David Robinson MBBS, FRCS, FRACS President of Senior Medical Staff Association Princess Alexandra Hospital, Brisbane	Member of MSAC

Appendix C Included/excluded studies

Table 31 Published papers included in review

First author	Year of publication	Journal	Comments
Mayr	2000a	Handchirurgie, Mikrochirurgie and Plastic Chirurgie	
Mayr	2000b	Archives of Orthopaedic and Trauma Surgery	Report on case series data (review has used original study reports)
Emami	1999	Journal of Orthopaedic Trauma	
Kristiansen	1997	Journal of Bone and Joint Surgery	(In addition, review has used material from original study reports)
Cook	1997	Clinical Orthopaedics and Related Research	Duplicate data
Heckman	1994	Journal of Bone and Joint Surgery	(In addition, review has used material from original study reports)

Table 32 Case series/registry reports included in the review

First author	Year of report	Origin
Albers	1999	Netherlands case series data
Gebauer	1998	German case series data
Heppenstell	1999	US registry data

Table 33 Published papers excluded from review (only English/French/German language studies listed)

First author	Year of publication	Journal	Reason for exclusion
Fujioka	2000	Journal of Hand Surgery	< 10 patients
Warden	2000	Calcified Tissue International	Review
Brand	1999	Iowa Orthopaedic Journal	< 10 patients
Marsh	1999	British Medical Bulletin	Review
Sato	1999	Journal of Ultrasound Medicine	< 10 patients
Parvizi	1999	Journal of Orthopaedic Research	Non-human
Sun	1999	Journal of Biomedical Materials Research	Non-human
Mayr	1999	Unfallchirurg	< 10 patients
Hadjiargyrou	1998	Clinical Orthopaedics and Related Research	Review
Jensen	1998	Medicine and Science in Sport and Exercise	< 10 patients
Frankel	1998	Surgical Technology International VII	Review
Brighton	1998	Clinical Orthopaedics and Related Research	Conference symposium
Zorlu	1998	American Journal of Physical Medicine and Rehabilitation	Non-human
Spadaro	1998	Ultrasound in Medicine and Biology	Non-human
Nussbaum	1998	Journal of Hand Therapy	Review
Heckman	1997	American Journal of Orthopedics	Review (conference presentation)
Yang	1996	Journal of Orthopaedic Research	Non-human
Baggs	1996	Lancet	News
Wang	1994	Journal of Orthopaedic Research	Non-human

Table 33 Published papers excluded from review (only English/French/German language studies listed) (continued)

First author	Year of publication	Journal	Reason for exclusion
McClure	1992	Physical Therapy	< 10 patients
Tsai	1991	Chinese Journal of Physiology	Non-human
Tsai	1992a	Chinese Journal of Physiology	Non-human
Tsai	1992b	Chinese Journal of Physiology	Non-human
Pilla	1990	Journal of Orthopaedic Trauma	Non-human
Klug	1986a	European Journal of Nuclear Medicine	Non-human
Klug	1986b	Zeitschrift fur Experimentelle Chirurgie, Transplantation, und Kunstliche Organe	Non-human
Klug	1986c	Beitrage zur Orthopadie und Traumatologie	Not low-intensity ultrasound
Leitgeb	1985	Biomedizinische Technik	Non-human
Reuter	1984	Zeitschrift fur Experimentelle Chirurgie, Transplantation, und Kunstliche Organe	Non-human
Dyson	1983	Ultrasound in Medicine and Biology	Non-human
Klug	1983	Beitrage zur Orthopadie und Traumatologie	Non-human
Skoubo-Kristensen	1982	Archives of Physical Medicine and Rehabilitation	Non-human
Smolenski	1981	Zeitschrift for Arzliche Fortbildung	Review
Veihelmann	1981	Aktuelle Traumatologie	Non-human
Ejubs	1981	Beitrage zur Orthopadie und Traumatologie	Non-fracture indication
Muller	1979	Beitrage zur Orthopadie und Traumatologie	Review
Patrick	1978	Physiotherapy	Review
Downer	1975	Veterinary Clinics of North America	Non-human
Lehmann	1974	Clinical Orthopaedics and Related Research	Review
Davis	1973	New Zealand Veterinary Journal	Non-human
Dumoulin	1973	Electrodiagnostic Therapie	Non-fracture indication
Nikolova	1969	Munchener Medizinische Wochenschrift	Not low-intensity ultrasound
Knoch	1967	Zentralblatt for Chirurgie	Non-human

Author	Study design	Comments	Outcomes (mean ± SD)
Mayr et al (2000a) **Level II**	Randomised, controlled, prospective trial. Single centre (Augsburg, Germany). Patients and treating orthopaedic surgeon were not blinded with respect to treatment. Fracture characteristics: Stable, non-dislocated fracture through waist of scaphoid (AO classification B1 and B2) Excluding: unstable fractures, bone pathology, > 10 days post fracture Intervention: Active: cast immobilisation + LIUS (20 minutes/day) Placebo: cast immobilisation Patient characteristics: ITT: Active 15, Control 15 Evaluable: Active 15, Control 14 Male: 83% Mean age: 37 ± 14 years Smoking status: No data Note: Characteristics are not reported according to group. Authors state that there were no significant differences. Outcome measures: Clinical healing time – time from start of treatment to removal of cast (determined by unblinded treating surgeon). Healing assessed by CT scan.	No placebo-ultrasound provided. Patients and orthopaedic surgeon not blinded to treatment. First assessment at 28 days (42 in some) and then assessed at consistent 14-day intervals thereafter. Healing defined as time at which orthopaedic surgeon discontinued immobilisation. The surgeon was not blinded to treatment group. Therefore, the key outcome measure was not blinded. This outcome is reported as the primary outcome by the investigators. CT scans taken at this time were then blindly reviewed by two radiologists, and the level of agreement between treating orthopaedic surgeon and the radiologists was compared statistically. All assessors agreed on assessment of healing in 61% of scans. For the purposes of the current review, analysis was considered as ITT as only one patient was not evaluable. Note: Time to 70% healing on CT scan is used by the reviewer as a proxy for the primary review outcome measure of 3/4 cortices healed	Active (n = 15) Control (n = 14) Radiological healing (CT scan) (days): time to 70% healing Active 42 ± 11 Control 60 ± 22 $p < 0.05$ Clinical healing (days): time to removal of cast Active 43 ± 19 Control 62 ± 11 $p < 0.01$ Delayed union (not clinically healed by specified time): % healed at 10 weeks Active 100% Control 78% % healed at 12 weeks Active 100% Control 86% % healed at 20 weeks Active 100% Control 100% % healed at 30 weeks Active 100% Control 100%

Author	Study design	Comments	Outcomes (mean ± SD)
Emami et al (1999) **Level II**	Randomised, double-blind, placebo-controlled, prospective trial. Single centre (Uppsala, Sweden). Fracture characteristics: Closed (88%) and Grade I open (12%) Excluding: severely comminuted fractures, multiple fractures Intervention: Active: Intramedullary rod + LIUS (20 min/day) Placebo: Intramedullary rod (+ placebo LIUS) Patient characteristics: ITT 33 Active / Placebo Evaluable 15 / 17 Male 67% / 82% Mean age (years) 39.9 / 34.3 Fibular fracture 80% / 76% Smoking status: Smokers 7% / 6% Non-smokers 93% / 94% Outcome measures: Blind assessment by site investigator: -- clinical healing (unaided weightbearing + walking) Blind assessment by independent radiologist and orthopaedic surgeon: -- time to first visible callus -- 3 of 4 cortices healed	Immediate partial weightbearing permitted with crutches. Assessment consistently at three-week intervals until healing. For the purposes of the current review, analysis was considered as ITT as only one patient was not evaluable.	Active (n = 15) Placebo (n = 17) **Radiographical healing (days)** First visible callus: Independent radiologist Active 40 ± 12 Placebo 37 ± 12 $p = 0.44$ Orthopaedic surgeon Active 37 ± 12 Placebo 33 ± 12 $p = 0.20$ Three bridged cortices: Independent radiologist Active 155 ± 85 median=113 Placebo 125 ± 45 median=112 $p = 0.76$ Orthopaedic surgeon Active 128 ± 50 Placebo 114 ± 37 $p = 0.40$ Delayed union (not radiologically healed by 20 weeks): Independent radiologist Active 5 (33%) Placebo 2 (12%) Not Significant Orthopaedic surgeon Active 4 (27%) Placebo 2 (12%) Not Significant Delayed union (not radiologically healed by 30 weeks): Independent radiologist Active 4 (27%) Placebo 2 (12%) Not Significant Orthopaedic surgeon Active 1(7%) Placebo 1 (6%) Not Significant

Author	Study design	Comments	Outcomes (mean ± SD)
Kristiansen et al (1997) **Level II**	Randomised, double-blind, placebo-controlled, prospective trial. Multicentre (nine sites in US, one in Israel). Fracture characteristics: Closed, dorsally angulated, metaphyseal fracture of the distal radius (within 4 cm of tip) (Colles fractures) that could be satisfactorily reduced with one closed reduction and below-elbow cast Intra-articular involvement of radiocarpal or radio-ulnar joints and concomitant ulnar styloid process fractures were acceptable Excluded: Chauffeur, Barton, Smith fractures Intervention: Active: cast immobilisation + LIUS (20 minutes/day) Placebo: cast immobilisation (+ placebo LIUS) Patient characteristics: Active / Placebo ITT 40 / 45 Evaluable 30 / 31 Male 20% / 13% Mean age (years) 54 / 58 Ulna styloid process fracture 67% / 58% Frykman score 5.2 / 4.4 Smoking status: Ex/current smokers 20%; Non-smokers 64%; Unknown 16% Outcome measures: Blind assessment by principal investigator and independent radiologist: -- 3 of 4 cortices healed -- 4 of 4 cortices healed	Statistics performed upon evaluable population only (referred to by author as core group). The results of the ITT analysis are not presented in full by the investigators. Twenty-four of the randomised patients not evaluable (28%). Discontinuous and unequal intervals between assessments of healing (ie only at scheduled visits at 1, 2, 3, 4, 5, 6, 8, 10, 12 and 16 weeks). Results in 'clumping' of healing times and has the potential to overestimate magnitude of difference between means. Patient smoking status documented retrospectively 5--8 years later. One or more authors are affiliated with the manufacturer, Exogen. A declaration of conflict of interest is made in the published article. Note: ITT analysis performed by reviewer using time to healing for all randomised fractures from raw data, applying 140 days in the case of patients unable to be evaluated	Active (n = 30) Placebo (n = 31) **Radiographical healing (days)** Three bridged cortices: Principal investigator Active 51 ± 22 Placebo 77 ± 28 $p < 0.0005$ Independent radiologist Active 64 ± 15 Placebo 87 ± 34 $p < 0.005$ Note: When ITT analysis was performed: Independent radiologist Active 81 ± 34 Placebo 99 ± 36 $p < 0.05$ Four bridged cortices: Principal investigator Active 61 ± 19 Placebo 98 ± 29 $p < 0.0001$ Independent radiologist Active 70 ± 16 Placebo 110 ± 30 $p < 0.0001$ Delayed union (not radiologically healed by 20 weeks): Principal investigator Active 0 (0%) Placebo 0 (0%) Independent radiologist Active 0 (0%) Placebo 0 (0%) Delayed union (not radiologically healed by 30 weeks): Principal investigator Active 0 (0%) Placebo 0 (0%) Independent radiologist Active 0 (0%) Placebo 0 (0%)

Author	Study design	Comments	Outcomes (mean ± SD)
Heckman et al (1994) **Level II**	Randomised, double-blind, placebo-controlled trial, retrospectively compiled from two studies. Multicentre (16 sites in US, one in Israel). Fracture characteristics: Closed (95%) or grade 1 open (5%) tibial shaft fractures that could be treated effectively by closed reduction and cast immobilisation Mean maximum fracture gap: 4 mm Mean length of fracture: 4 cm Excluded: long fractures, large displacements, fractures of metaphysis, most comminuted fractures Intervention: Active: cast immobilisation + LIUS (20 minutes/day) Placebo: cast immobilisation (+ placebo LIUS) Patient characteristics: ITT: Active 48, Placebo 49 Evaluable: Active 33, Placebo 34 Male: Active 76%, Placebo 85% Mean age (years): Active 36, Placebo 31 Fibular fracture: Active 73%, Placebo 88% Smoking status: Ex/current smokers: Active 33%, Placebo 38% Non-smokers: Active 27%, Placebo 15% Unknown: Active 39%, Placebo 47% Outcome measures: Blind assessment by principal investigator and independent radiologist: -- 3 of 4 cortices healed -- Endosteal healing	Combination of data from two studies with inconsistency in instructions to patients re weight-bearing. Statistics performed upon evaluable population only (referred to by author as core group). The results of the ITT analysis are not presented in full by the investigators. Thirty of the randomised patients not evaluable (31%). One patient treated with placebo healed at 502 days (independent radiologist). This is likely to heavily skew the mean results. Furthermore, not clear if an assessment was made between 365 (52-week scheduled assessment) and 502 days. No median results reported. Discontinuous and unequal intervals between assessments of healing (ie only at scheduled visits at 4, 6, 8, 10, 12, 14, 20, 33 and 52 weeks. Results in clumping of healing times and has the potential to overestimate the magnitude of the differences between means. One or more authors are affiliated with the manufacturer, Exogen. A declaration of conflict of interest is made in the published article. NB: ITT analysis performed by reviewer using time to healing for all randomised fractures from raw data, applying 140 days in the case of patients unable to be evaluated.	Active (n = 33) Placebo (n = 34) **Radiographical healing (days):** <u>Three bridged cortices:</u> Principal investigator Active 89 ± 21 Placebo 148 ± 77 $p = 0.0001$ Independent radiologist Active 102 ± 28 Placebo 190 ± 107 $p = 0.0001$ Note: When ITT analysis is performed: Independent radiologist Active 117 ± 40 Placebo 165 ± 83 $p < 0.001$ (excl patient healed at 502 days) Active 117 ± 40 Placebo 158 ± 68 $p < 0.001$ <u>Endosteal healing:</u> Principal investigator Active 117 ± 49 Placebo 167 ± 81 $p = 0.002$ Independent radiologist Active 171 ± 78 Placebo 271 ± 114 $p = 0.0001$ <u>Delayed union (not radiologically healed by 20 weeks):</u> Principal investigator Active 1 (3%) Placebo 15 (44%) $p < 0.01$ Independent radiologist Active 5 (15%) Placebo 21 (62%) $p < 0.01$ <u>Delayed union (not radiologically healed by 30 weeks):</u> Principal investigator Active 0 (0%) Placebo 5 (15%) $p < 0.01$ Independent radiologist Active 0 (0%) Placebo 7 (21%) $p < 0.01$

Author	Study design	Comments	Outcomes (mean ± SD)
Gebauer *et al* (Mayr) 1998 **German case series data** **Level IV**	Case series data of LIUS use in non-unions in Germany, July 1995–April 1997. No parallel control group. Fracture characteristics (core group only): Radiographically verified non-union of all bones other than those below Minimum nine months post-fracture No surgical intervention in previous three months 63% had initial surgical intervention 61% received subsequent surgical intervention Excluding: spine, skull, tumour-related fractures Intervention: Active: LIUS (20 minutes/day) (aligned with plastic fixture and Velcro strap). No change to any existing fixation Patient characteristics: 41 (core group only) Age: 47 ± 2.4 years Variety of previous interventions, conservative and surgical Outcome measures: Dichotomous only: healed or not healed at nine months follow-up	No parallel control group. Not possible to directly compare against other treatment of non-unions. Large potential for bias in patient selection. Furthermore, only patients completing LIUS treatment were reviewed in the analysis. Interpretation of the statistical analysis is limited by the quality of the control. Retrospective use of initial healing period as control, for the post non-union treatment period. This ignores any differences in the underlying, ongoing biological processes. Post hoc comparison of groups healing and not healing was conducted. Timing of follow-up not exact. Factors significantly different between those healing and not healing: - Majority of fractures failing to heal (5/7) were more than five years old - Mean fracture age 3531 ± 838 days in unhealed group vs 981 ± 236 days in the healed group (p = 0.02) - Median fracture age 4737 days in unhealed group vs 426 days in the healed group	34/41 (82.9%) healed in nine months Mean heal time (of healed group) = 160 ± 10 days Median = 153 days

Author	Study design	Comments	Outcomes (mean ± SD)
Albers et al 1999 **Netherlands case series data** **Level IV**	Case series data of LIUS use in non-unions in the Netherlands, November 1995–May 1997. No parallel control group. *Fracture characteristics (core group only*): Radiographically verified non-union of all bones other that those below Minimum nine months post-fracture No surgical intervention in previous three months 67% had initial surgical intervention 42% received subsequent surgical intervention Excluding: spine, skull, tumour-related fractures Intervention: Active: LIUS (20 minutes/day) (aligned with plastic fixture and Velcro strap). No change to any existing fixation Patient characteristics: 24 patients (core group only) Age: 47 ± 4.2 years Variety of previous interventions, conservative and surgical Outcome measures: Dichotomous only: healed or not healed at nine months follow-up	No parallel control group. Not possible to directly compare against other treatment in non-unions. Large potential for bias in patient selection. Furthermore, only patients completing LIUS treatment were reviewed in the analysis. Interpretation of the statistical analysis is limited by the quality of the control. Use of initial healing period as control, for the post non-union treatment period. This is not valid due to differences in the underlying, ongoing biological processes. Post hoc comparison of groups healing and not healing was conducted. Timing of follow-up not exact. Fracture age was not significantly different between healed and not healed patients. Median fracture age 591 days in not healed vs 454 days in the healed group.	20/24 (83.3%) healed in nine months Mean heal time (of healed group) = 140 ± 13 days Median = 116 days

Author	Study design	Comments	Outcomes (mean ± SD)
Heppenstell et al 1999 **US case registry** **Level IV**	Registry data of LIUS use in non-unions in the US, October 1994–October 1996. No parallel control. Fracture characteristics (core group only): Minimum nine months post-fracture No surgical intervention in previous three months 34% had initial surgical intervention (43% initial treatment unknown) 47% received subsequent surgical intervention Excluding: spine, skull, tumour-related fractures Intervention: Active: LIUS (20 minutes/day) (aligned with plastic fixture and Velcro strap). No change to any existing fixation Patient characteristics: 313 patient (core group only) Age: 44 ± 1 years Variety of previous interventions, conservative and surgical Outcome measures: Dichotomous only: healed or not healed at nine months follow-up Outcome was obtained principally from the investigator follow-up forms, or if these reports were not available, from follow-ups with the investigator's office or directly with the patient.	No parallel control group. Not possible to directly compare against other treatment in non-unions. Large potential for bias in patient selection. Furthermore, only patients completing LIUS treatment were reviewed in the analysis. Interpretations of the statistical analysis is limited by the quality of the control. Use of initial healing period as control, for the post non-union treatment period. This is not valid due to differences in the underlying, ongoing biological processes, particularly in this study as non-union was not confirmed radiographically prior to commencement of LIUS. Previous surgery was permitted up to three months prior and the study design allows for delayed outcome from surgery to be attributed to LIUS. Post hoc comparison of groups healing and not healing was conducted. Timing of follow-up not exact. Fracture age between the healed and not healed groups: - Mean fracture age 752 ± 93 days in unhealed vs 626 ± 51 days in the healed group (p = 0.01) Median 475 vs 403 days Trend toward LIUS being more successful in males (79%) than females (69%), p = 0.06. The large proportion of patients for whom nature of initial treatment was unknown makes accuracy of other measures, such as fracture age, questionable. Quality of outcome measurement data is questionable (healing assessed by contacting patient if other data were unavailable). Independent radiographic review not conducted.	232/313 (74%) healed in nine months Mean heal time (of healed group) = 152 ± 4.2 days Median = 140 days

Abbreviations

AIHW	Australian Institute of Health and Welfare
AQoL	Assessment of Quality of Life instrument
ICD-10-AM	International Classification of Diseases, version 10 – Australian modification
ITT	intention-to-treat
LIUS	low-intensity ultrasound
NHMD	National Hospital Morbidity Database
NHMRC	National Health and Medical Research Council
QALYs	Quality-adjusted life-years
ORIF	open reduction and internal fixation

References

Albers RGH, Patka P, Janssen IMC, van der Krans A, Frey JJ, Ryaby JP & McCabe J (1999). 'Pulsed low-intensity ultrasound: an effective treatment of non-union.' (The Netherlands Study). Unpublished Clinical Study Report provided by Exogen, Inc.

Australian Bureau of Statistics (2000). *Average weekly earnings, 2000* [Internet] Commonwealth of Australia. Available from: http://www.abs.gov.au/ausstas/abs%40.nsf/e8ae5488b59682000131612/ea302c0e69dd4cd2ca2568a90013934d!OpenDocument [Accessed: July 2000].

Australian Institute of Health and Welfare (1999). *National hospital morbidity database, 1999*. [Internet] Australian Institute of Health and Welfare. Available from: http://www.aihw.gov.au/publications/health/ahs98-9 [Acessed: Oct 2000].

Baggs AC (1996). 'Portable bone-growth stimulators go domestic in USA.' *Lancet*, 347, 1474.

Brand JC Jr, Brindle T, Nyland J, Caborn DN & Johnson DL (1999). 'Does pulsed low intensity ultrasound allow early return to normal activities when treating stress fractures? A review of one tarsal navicular and eight tibial stress fractures.' *Iowa Orthopaedic Journal*, 19, 26–30.

Brighton CT (1998). Breakout session 4: 'Biophysical enhancement'. *Clinical Orthopaedics and Related Research*, 355, S357–58.

Brondum V, Larsen CF & Skov O (1992). 'Fracture of the carpal scaphoid: frequency and distribution in a well-defined population.' *European Journal of Radiology*, 15, 118–22.

Brouwer W & Koopmanschap M (1998). 'How to calculate indirect costs in economic evaluations.' *Pharmacoeconomics* 13, 563–66.

Carter R & Hailey D (1999). 'Economic evaluation of the cochlear implant.' *International Journal of Technology Assessment in Health Care*, 15(3), 520–30.

Cook SD, Ryaby JP, McCabe J, Frey JJ, Heckman JD & Kristiansen TK (1997). 'Acceleration of tibia and distal radius fractures healing in patients who smoke.' *Clinical Orthopaedics and Related Research*, 337, 198–207.

Davis PE (1973). 'Toe and muscle injuries of the racing greyhound.' *New Zealand Veterinary Journal*, 21, 133–46.

Downer AH & Spear VL (1975). 'Physical therapy in the management of long bone fractures in small animals.' *Veterinary Clinics of North America*, 5, 157–64.

Dumoulin J & de Bisschop G (1973). [Electrotherapy of osteo-articular disorders due to injury][French]. *Electrodiagnostic Therapie*, 10, 18–26.

Duppe H, Johnell O, Lundborg G, Karlsson M & Redlund-Johnell I (1994). 'Long-term results of fracture of the scaphoid. A follow-up study of more than thirty years.' *Journal of Bone and Joint Surgery*, 76-A, 249–52.

Dyson M & Brookes M (1983). 'Stimulation of bone repair by ultrasound.' *Ultrasound in Medicine and Biology*, Suppl 2, 61–66.

Ejubs LJ, Gromak GB, Ose VP, Birzniek IM, Stepanova AA & Jodzevica HP (1981). [The use of ultrasonics in the operative management of post-traumatic osteomyelitis][German]. *Beitrage zur Orthopadie und Traumatologie*, 28, 229–31.

Emami A, Petren-Mallmin M & Larsson S (1999). 'No effect of low-intensity ultrasound on healing time of intramedullary fixed tibial fractures.' *Journal of Orthopaedic Trauma*, 13, 252–57.

Foulk DA & Szabo RM (1995). 'Diaphyseal humerus fractures: natural history and occurrence of non-union.' *Orthopedics*, 18, 333–35.

Frankel VH (1998). 'Results of prescription use of pulse ultrasound therapy in fracture management.' *Surgical Technology International*, VII, 389–93.

Fujioka H, Tsunoda M, Noda M, Matsui N & Mizuno K (2000). 'Treatment of ununited fracture of the hook of hamate by low-intensity pulsed ultrasound: a case report.' *Journal of Hand Surgery*, 25, 77–79.

Gebauer G, Mayr E, Orthner E, Frey J, Ryaby JP & McCabe J (1998). 'Efficacy of low-intensity ultrasound to heal non-union.' (A German study). Unpublished Clinical Study Report provided by Exogen, Inc.

Gersten JW (1958). 'Effect of metallic objects on temperature rises produced in tissue by ultrasound.' *American Journal of Physical Medicine*, 37, 75-82

Hadjiagyrou M, McLeod K, Ryaby JP & Rubin C (1998). 'Enhancement of fracture healing by low intensity ultrasound.' *Clinical Orthopaedics and Related Research*, 355, S216–29.

Hall J, Gerard K, Salkeld G & Richardson J (1992). 'A cost-utility analysis of mammography screening in Australia.' *Social Science and Medicine*, 34(9), 993–1004.

Handoll HHG & Madhok R [Cochrane Collaboration Musculoskeletal Injuries Review Group] (2000). 'Conservative interventions for treating distal radial fractures in adults' (Cochrane Review). In: The Cochrane Library, Issue 2. Oxford: Update Software.

Hawthorne G, Richardson J & Osborne R (1999). 'The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health-related quality of life.' *Quality of Life Research*, 8(3), 209–24.

Heckman JD, Ryaby JP, McCabe J, Frey JJ & Kilcoyne RF (1994). 'Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound.' *Journal of Bone and Joint Surgery*, 76, 26–34.

Heckman JD (1997). 'Factors that affect fracture healing.' *American Journal of Orthopedics*, 26, 161–64.

Heckman JD & Sarasohn-Kahn J (1997). 'The economics of treating tibia fractures. The cost of delayed union.' *Bulletin/Hospital for Joint Diseases*, 56, 63–72.

Heppenstell RB, ed. (1980). *Fracture treatment and healing*. WB Saunders, Philadelphia, PA..

Heppenstell RB, Frey JJ, Ryaby JP & McCabe J (1999). 'The treatment of non-unions with pulsed, low-intensity ultrasound.' Unpublished Clinical Study Report provided by Exogen, Inc.

Hove LM (1999). 'Epidemiology of scaphoid fractures in Bergen, Norway.' *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery*, 33, 423–26.

Jensen JE (1998). 'Stress fracture in the world class athlete: a case study.' *Medicine and Science in Sports and Exercise*, 30, 783–87.

Jönsson B, Christiansen C, Johnell O & Hedbrandt J (1995). 'Cost-effectiveness of fracture prevention in established osteoporosis.' *Osteoporosis International*, 5, 136–42.

Klug W, Franke WG & Schulze M (1986a). [Animal experimental scintigraphic observations of the course of secondary fracture healing without and with ultrasound stimulation] [German]. *Zeitschrift fur Experimentelle Chirurgie, Transplantation und Kunstliche Organe*, 19, 185–95.

Klug W & Knoch HG (1986b). [Quantification of biophysical studies of fracture healing following ultrasound stimulation of distal radius fractures][German]. *Beitrage zur Orthopadie und Traumatologie*, 33, 384–91.

Klug W, Franke WG & Knoch HG (1986c). 'Scintigraphic control of bone-fracture healing under ultrasonic stimulation: an animal experimental study.' *European Journal of Nuclear Medicine*, 11, 494–97.

Klug W (1983). [Stimulation of fracture healing by ultrasound – animal experiment study][German]. *Beitrage zur Orthopadie und Traumatologie*, 30, 670–80.

Knoch HG (1967). [Conservative treatment possibilities with ultrasonics in delayed callus formation][German]. *Beitrage zur Orthopadie und Traumatologie*, 14, 720–23.

Kristiansen TK, Ryaby JP, McCabe J, Frey JJ & Roe LR (1997). 'Accelerated healing of distal radius fractures with the use of specific, low intensity ultrasound.' *Journal of Bone and Joint Surgery*, 79, 961–73.

Lehmann JF, Warren CG & Scham SM (1974). 'Therapeutic heat and cold.' *Clinical Orthopaedics and Related Research*, 99, 207–45.

Leitgeb N, Lasser W & Schuy S (1985). [Stability of ultrasound osteosynthesis][German]. *Biomedizinische Technik*, 30, 44–48.

Lotsova EI (1979). 'Effect of ultrasound on the strength of metal fixing pins for fractured bones.' *Mekhanika Kompozitnykh Materialov* (translated abstract available only), 3, 548–49.

Marsh DR & Li G (1999). 'The biology of fracture healing: optimising outcome.' *British Medical Bulletin*, 55, 856–69.

Mayr E, Rudzki MM, Borchardt B, Hausser H & Ruter A (2000a). [Does pulsed low-intensity ultrasound accelerate healing of scaphoid fractures?][German]. *Handchir Mikrochir Plast Chir*, 32, 115–122.

Mayr E, Frankel V & Ruter A (2000b). 'Ultrasound – an alternative healing method for nonunions?' *Archives of Orthopaedic and Trauma Surgery*, 120, 1–8.

Mayr E, Wagner S, Ecker M & Ruter A (1999) 'Ultrasound therapy for nonunions. Three case reports.' [German]. *Unfallchirurg*, 102, 191–96.

McClure PW & Flowers KR (1992). 'Treatment of limited shoulder motion: a case study based on biomechanical considerations.' *Physical Therapy*, 72, 929–36.

McIntyre P, Hall J & Leeder S (1994). 'An economic analysis of alternatives for childhood immunisation against *Haemophilus influenzae* type b disease.' *Australian Journal of Public Health*, 18(4), 394–400.

Muller T & Wehner W (1979). [Current state and prospectives of ultrasonic osteosynthesis surgery of accidental injuries][German] *Beitrage Ortho Trauma*, 26, 570–76.

Australian Bureau of Statistics (1995). *National Health Survey (1995) Injuries, Australia.* Australian Bureau of Statistics catalogue reference 4384.0, ABS, Canberra.

National Health and Medical Research Council (1999). *A guide to the development, implementation and evaluation of clinical practice guidelines.* NHMRC, Australia.

National Occupational Health and Safety Commission (2000). *The National Workers' Compensation Statistics database, 1997/8 data.* [Internet] National Occupational Helath & Safety Commission. Avaliable from: http://nohsc.info.au.com/site.taf?go=assisted&_UserReference=08FA7028FB38405A3C44AAC2 [Accessed Oct 2000].

Nease RF Jr, Kneeland T, O'Connor GT *et al*. (1995). 'Variation in patient utilities for outcomes of the management of chronic stable angina. Implications for clinical practice guidelines.' *Journal of the American Medical Association*, 273(15), 1185–90.

Nikolova L (1969). [Physical therapy in the rehabilitation of bone fracture complications][German]. *Munchener Medizinische Wochenschrift*, 111: 592–99.

Nussbaum E (1998). 'The influence of ultrasound on healing tissues.' *Journal of Hand Therapy*, 11, 140–47.

Oldridge N, Guyatt G, Jones N *et al*. (1991). 'Effects on quality of life with comprehensive rehabilitation after acute myocardial infarction.' *American Journal of Cardiology*, 67(13), 1084–89.

Oni OOA, Hui A & Gregg PJ (1988). 'The healing of closed tibial shaft fractures. The natural history of union with closed treatment.' *Journal of Bone and Joint Surgery*, 70-B, 787–90.

Parvizi J, Wu CC, Lewallen DG, Greenleaf JF & Bolander ME (1999). 'Low intensity ultrasound stimulates proteoglycan synthesis in rat chondrocytes by increasing aggrecan gene expression.' *Journal of Orthopaedic Research*, 17, 488–94.

Patrick MK (1978). 'Applications of therapeutic pulsed ultrasound.' *Physiotherapy*, 64, 103–4.

Pilla AA, Mont MA, Nasser PR, Khan SA, Figueiredo M, Kaufman JJ & Siffert RS (1990). 'Non-invasive low-intensity pulsed ultrasound accelerates bone healing in the rabbit.' *Journal of Orthopaedic Trauma*, 4, 246–53.

Reuter U, Strempel F, John F & Knoch HG (1984). 'Modification of bone fracture healing by ultrasound in an animal experiment model.' *Zeitschrift fur Experimentelle Chirurgie, Transplantation, und Kunstliche Organe*, 17, 290–97.

Sanders KM, Seeman E, Ugoni AM, Pasco JA, Martin TJ, Skoric B, Nicholson GC & Kotowicz MA (1999a). 'Age- and gender-specific rate of fractures in Australia: a population-based study.' *Osteoporosis International*, 10, 240–47.

Sanders KM, Nicholson GC, Ugoni AM, Pasco JA, Seeman E & Kotowicz MA (1999b). 'Health burden of hip and other fractures in Australia beyond 2000. Projections based on the Geelong Osteoporosis Study.' *Medical Journal of Australia*, 17, 467–70.

Sato W, Matsushits T & Nakamura K (1999). 'Acceleration of increase in bone mineral content by low-intensity ultrasound energy in leg lengthening.' *Journal of Ultrasound Medicine*, 18, 699–702.

Singer BR, McLauchlan GJ, Robinson CM & Christie J (1998). 'Epidemiology of fractures in 15,000 adults: the influence of age and gender.' *Journal of Bone and Joint Surgery*, 80 B, 243–48.

Skoubo-Kristiansen E & Sommer J (1982). 'Ultrasound influence on internal fixation with a rigid plate in dogs.' *Archives of Physical Medicine and Rehabilitation*, 63, 371–73.

Smolenski U, Callies R & Dietze C (1981). [Local symptoms and the aim of therapy as starting points of physical therapy in traumatology][German]. *Zeitschrift fur Arztliche Fortbildung*, 75, 701–4.

Spadaro JA & Albanese SA (1998). 'Application of low-intensity ultrasound to growing bone in rats.' *Ultrasound in Medicine and Biology*, 24. 567–73.

Sun JS, Tsuang YH, Lin FH, Liu HC, Tsai CZ & Chang WH (1999). 'Bone defect healing enhanced by ultrasound stimulation: an in vitro tissue culture model.' *Journal of Biomedical Materials Research*, 46,253–61.

Tsai CL, Chang WH, Liu TK & Song GM (1991). 'Ultrasound can affect bone healing both locally and systemically.' *Chinese Journal of Physiology*, 34, 213–22.

Tsai CL, Chang WH & Liu TK (1992a). 'Preliminary studies of duration and intensity of ultrasonic treatments on fracture repair.' *Chinese Journal of Physiology*, 35, 21–26.

Tsai CL, Chang WH, Liu TK & Song GM (1992b). 'Ultrasonic effect on fracture repair and prostaglandin E2 production.' *Chinese Journal of Physiology* 35: 27–34

Veihelmann D & Grozinger D (1981). [Animal experimental studies on "bonewelding" by ultrasound (author's transl)][German]. *Aktuelle Traumatologie*, 11, 203–9.

Victorian Infant Collaborative Study Group (VICSG) (1997). 'Economic outcome for intensive care of infants of birthweight 500–999 g born in Victoria in the post-surfactant era.' *Journal of Paediatrics and Child Health*, 33(3), 202–208.

Wang SJ, Lewallen DG, Bolander ME, Chao EYS, Ilstrup DM & Greenleaf JF (1994). 'Low intensity ultrasound treatment increases strength in a rat femoral fracture model.' *Journal of Orthopaedic Research*, 12, 40–47.

Ward AR & Robertson VJ (1996). 'Comparison of heating of nonliving tissue produced by 45 kHz and 1 MHz frequency ultrasound machines.' *Journal of Orthopaedic and Sports Physical Therapy*, 23, 258–66.

Warden SJ, Bennell KL, McMeeken JM & Wark JD (2000). 'Acceleration of fresh fracture repair using the sonic accelerated fracture helaing system (SAFHS): a review.' *Calcified Tissue International*, 66, 157–63.

Wei SY, Born CT, Abene A, Ong A, Hayda R & DeLong WG Jr (1999). 'Diaphyseal forearm fractures treated with and without bone graft.' *J Trauma – Injury, Infection & Critical Care*, 46, 1045–48.

Yang KH, Parvizi J, Wang SJ, Lewallen DG, Kinnick RR, Greenleaf JF & Bolander ME (1996). *Journal of Orthopaedic Research*, 14, 802–809.

Zorlu U, Tercan M, Ozyazgan I, Taskan I, Kardas Y, Balkar F & Ozturk (1998). 'Comparative study of the effect of ultrasound and electrostimulation on bone healing in rats.' *American Journal of Physical Medicine and Rehabilitation*, 77, 427–32.