Low intensity pulsed ultrasound for bone healing: a systematic review of randomised controlled trials

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Appendix 2_other functional.docx

Low intensity pulsed ultrasound for bone healing: a systematic review of randomised controlled trials

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ABSTRACT

Objective: To determine the efficacy of low intensity pulsed ultrasound (LIPUS) for healing of fracture or osteotomy.

Design: Systematic review and meta-analysis**.**

Data sources: MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials, and trial registries up to November 2016.

Study selection: Randomised controlled trials (RCTs) comparing LIPUS to sham device or no device in patients with any kind of fracture or osteotomy.

Review methods: Two independent reviewers identified studies, extracted data, and assessed risk of bias. A parallel guideline committee (*BMJ* Rapid Recommendation) provided input on the design and interpretation of the systematic review, including selection of patient-important outcomes. We assessed the quality of evidence using GRADE.

Results: We included 26 RCTs with a median sample size of 30 (range 8 to 501). The most trustworthy evidence came from four trials at low risk of bias including patients with tibia or clavicle fractures. Compared with sham device, LIPUS does not reduce time to return to work (percent difference: 2.7% later with LIPUS, 95% confidence interval [CI] 7.7% earlier to 14.3% later, moderate certainty) or the number of subsequent operations (risk difference: 3% reduction, 95% CI 7% reduction to 2% increase, moderate certainty). For pain, days to weight bearing, and radiographic healing, effects varied substantially between studies. For all three outcomes, trials at low risk of bias failed to demonstrate a benefit with LIPUS, while trials at high risk of bias suggested a benefit (interaction p<0.001). Considering only low risk of bias trials, LIPUS does not reduce days to weight bearing (4.8% later, 95% CI 4.0% earlier to 14.4 % later, high certainty), pain at 4 to 6 weeks (mean difference on 0-100 visual analogue scale: 0.94 lower,

95% CI 2.54 lower to 0.65 higher, high certainty), and days to radiographic healing (1.7% earlier, 95% CI 11.2% earlier to 8.8% later, moderate certainty).

Conclusions: LIPUS does not improve patient-important outcomes or radiographic bone healing.

Systematic review registration: PROSPERO CRD42016050965

What is already known of this topic?

Low intensity pulsed ultrasound (LIPUS) devices are marketed worldwide to accelerate recovery from a fracture or osteotomy.

Previous systematic reviews provided no definite conclusions about the effect of LIPUS on patient-important outcomes and radiographic healing.

What this study adds

With inclusion of the recently published TRUST trial, sufficient high quality data for patients with fresh fractures has accumulated to conclude that LIPUS fails to improve patient-important outcomes and radiographic healing.

INTRODUCTION

For over 20 years, patients have used low intensity pulsed ultrasound (LIPUS) as an adjunct therapy to improve bone healing. Based on radiographic outcomes, the US Food and Drug Administration and the UK National Institute for Health and Care Excellence NICE have approved LIPUS for fracture healing.[1, 2] Depending on country and device model, LIPUS devices currently cost between £1000-4000. In 2008, more than 20% of Canadian trauma surgeons regularly prescribed LIPUS to manage tibia fractures.[3] Sales from LIPUS amounted to approximately $250 million in 2006 in the US alone.[3, 4]

Within the last seven years, 10 systematic reviews have assessed the effectiveness of LIPUS for bone healing.[5-14] Because existing randomised controlled trials (RCTs) were limited by small sample size, risk of bias, inconsistent results, and failure to address patient-important outcomes, no review offered definitive conclusions. All reviews identified the need for additional RCTs.

This systematic review is part of the *BMJ* Rapid Recommendations project, a collaborative effort from the MAGIC research and innovation program (www.magicproject.org) and *The BMJ.* The aim of the project is to respond to new potentially practice-changing evidence and provide a trustworthy practice guideline in a timely manner.[15] In this case, the publication of the TRUST trial,[16] a multicentre trial that randomised 501 patients with tibia fractures from 43 North American centres to LIPUS or sham device, initiated the process. This systematic review informed a parallel guideline published in a multi-layered electronic format on *The BMJ*[17] and MAGICapp (www.magicapp.org/app#/guideline/1432).

Our objective was to assess whether LIPUS compared to sham device or no device improves patient important outcomes and radiographic healing in patients with any kind of fracture or osteotomy.

METHODS

Guideline panel and patient involvement

According to the *BMJ* Rapid Recommendations process,[15] a guideline panel provided critical oversight to the review and identified populations, subgroups, and outcomes of interest. The panel included six content experts (five orthopaedic or trauma surgeons and one physiotherapist), six methodologists (four of whom are also front-line clinicians), and four patients with lived experience with fractures (one of whom had used LIPUS). All patients received personal training and support to optimise contributions throughout the guideline development process. The patient panel members led the interpretation of the results based on what they expected the typical patient values and preferences to be, as well as the variation between patients.

Information sources

We searched MEDLINE, PubMed, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials up to 16 November 2016, using a combination of keywords and MeSH terms for fracture, orthopaedic surgical procedures, and ultrasound. Additional searches included trials registries clinicaltrials.gov and isrctn.com. An experienced research librarian designed the search strategies (appendix 1). Two independent reviewers scanned the references from eligible studies, related systematic reviews, and all studies citing eligible RCTs on Google Scholar.

Study selection

We included RCTs comparing LIPUS to a sham device or no device in patients with any type of fracture regardless of location (long-bone or other bone), type (fresh fracture, delayed union, non-union, or stress fracture), or clinical management (operative or non-operative). We included

any type of osteotomy, including distraction osteogenesis. We excluded trials that were published only as abstracts.

Two reviewers, independently and in duplicate, screened the titles and abstracts of identified articles and acquired the full text of any article that either reviewer judged to be potentially eligible. They independently applied the eligibility criteria to the full texts and, when consensus could not be reached, resolved disagreements through discussion or adjudication by a third reviewer.

Data collection

Two reviewers used standardised forms to independently abstract data; they resolved disagreements by discussion or involved a third reviewer when required. Extracted data included patient characteristics, fracture characteristics, clinical management, risk of bias, intervention details, statements about compliance with treatment, and outcomes.

Risk of bias assessment

Two reviewers independently assessed risk of bias using a modified Cochrane risk of bias instrument that includes response options of "definitely or probably yes" (assigned a low risk of bias) or "definitely or probably no" (assigned a high risk of bias).[18] On the study level, we assessed concealment of allocation, blinding of patients, and caregivers. For each outcome within studies, we assessed blinding of outcome assessors, loss to follow-up, and additional limitations. We considered ≥20% loss-to follow-up to represent a high risk of bias unless the investigators performed appropriate sensitivity analyses demonstrating the robustness of the

results. We categorised a trial as being at low risk of bias for a particular outcome if we identified no limitation for any risk of bias item.

Outcomes

Patients identified functional recovery (time to return to work and time to full weigh bearing), pain reduction, and number of subsequent fracture or osteotomy related operations (re-operation for operatively managed fracture and osteotomy) as the most important outcomes for patients considering LIPUS for bone healing. Because many clinicians currently base their management on time to radiographic healing, a surrogate outcome important only insofar as it influences patient experience, the panel requested its inclusion in our review. We extracted all outcomes that fell into these categories as well as ultrasound device-related adverse effects.

Synthesis of results

We pooled treatment effects of LIPUS on similar outcomes across eligible trials, regardless of clinical subgroups, focusing on complete case analysis. We calculated pooled estimates and associated 95% confidence intervals (CI) using random effects models for meta-analysis with three or more studies, and fixed-effects models for meta-analysis with two studies. We examined heterogeneity associated with all pooled analyses using both the X^2 test and I^2 statistic. SAS version 9.4, R version 3.1, and Review Manager 5.3 provided software for the statistical analysis.

For time-to-event outcomes, we pooled hazard ratios. For studies that did not apply methods of survival analysis, we considered time to event reported as a continuous variable (e.g. days to return to work) at the longest follow-up time. We used the relative effect measure ratio of means (mean LIPUS/mean control) in order to account for the baseline difference in fracture healing

depending on type of bone and (e.g. scaphoid, clavicle, tibia) and fracture or procedure (e.g. stress fracture or distraction osteogenesis). We pooled the natural logarithm of the ratio of means and presented the results as percentage difference (relative change). For studies that reported the proportion of patients who achieved the event at a specific time point, we calculated risk ratios.

When studies used different instruments to measure the same construct on a continuous scale, we converted all instruments to the most commonly used instrument among studies and then pooled results using the weighted mean difference.[19]

For the outcomes number of subsequent operations and device related adverse events, we calculated both risk ratios, which are preferable in case of varying baseline risks, and risk differences, which allow inclusion of studies with zero events in both groups.

In consultation with the expert and patient guideline panel, we pre-specified three subgroup hypotheses to explain heterogeneity of effects between studies: (1) LIPUS will show larger effects in high risk of bias studies, (2) LIPUS effects will differ based on clinical subgroups, and (3) LIPUS will show larger effects with greater patient compliance. In consultation with the six clinical experts on the parallel guideline panel, we classified eligible RCTs according to the following five clinical subgroups: (1) operatively managed fresh fractures, (2) non-operatively managed fresh fractures, (3) stress fractures, (4) non-union, and (5) osteotomy (including distraction osteogenesis). Because compliance was reported inconsistently, two reviewers independently categorised trials using response options of “definitely or probably high compliance” or “definitely or probably moderate compliance” using as a guide a definition of high compliance as at least 80% of patients applied LIPUS for at least 80% of the total time

prescribed. We conducted univariable tests of interaction to establish if the effect size from the subgroups differed significantly from each other, and, in order to test independence of subgroup effects, performed multivariable meta-regression in which we included risk of bias (high versus low), compliance with LIPUS treatment (high versus moderate), and clinical subgroups (as above) as independent variables in a single model.

Only one outcome, days to radiographic healing, included enough studies to perform all planned subgroup analysis. We assessed the credibility of significant subgroup effects using the criteria suggested by Sun et al.[20] Based on the finding that risk of bias appeared to independently explain the high heterogeneity in the outcome days to radiographic healing, we performed subgroup analysis by risk of bias for all outcomes.

The authors and the guideline panel achieved consensus in categorising the quality of evidence for all reported outcomes as high, moderate, low, or very low using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. In the GRADE approach, RCTs begin as high quality evidence but can be rated down due to: (1) risk of bias; (2) inconsistency; (3) indirectness; (4) imprecision; or, (5) publication bias.(21) We considered rating down for inconsistency if the magnitude and direction of effects were dissimilar, the confidence intervals had minimal overlap, the test of heterogeneity was significant, or the I^2 was high.[22] For outcomes with ten or more studies, we inspected symmetry of funnel plots and performed Egger's statistical test for publication bias.[23]

To calculate absolute effects, we applied the effect estimate from the meta-analysis to the control

arm of the TRUST trial, which enrolled patients with tibia fractures and had the largest sample size of any eligible study that was at low risk of bias. The approach to rating certainty of individual outcomes was fully contextualised: that is, in rating quality about any individual outcome, we took into account the findings on the other outcomes.

RESULTS

Search results

We identified 3489 potentially eligible abstracts, retrieved 42 studies in full text, and found 26 eligible RCTs (fig 1).[16, 24-50] Two RCTs, Handolin et al.[30, 31] and Emami et al.,[27, 28] provided two publications reporting on the same group of patients. There were no shared patients between the TRUST pilot [24] and the definitive trial.[16] Our registry search yielded four protocols of potentially eligible RCTs; three were completed or terminated but never published (JPRN-UMIN000002005, NCT00744861, ISRCTN90844675), and one is still ongoing (NCT02383160). Attempts to acquire the full text of another potentially eligible RCT,[51] reported in a recent systematic review,[11] were unsuccessful.

Study characteristics

Eligible trials enrolled patients with operatively managed fresh fractures (n=7); non-operatively managed fresh fractures (n=6); stress fractures (n=2); non-unions (n=3); and osteotomies (n=8), of which five were distraction osteogenesis (table 1). Most trials enrolled patients with tibia fractures or osteotomies (n=14). All but two trials applied LIPUS for 20 minutes every day either for a fixed period or until radiographic healing. Otherwise, one trial applied LIPUS for 15 minutes per day,[36] and another trial for 5 minutes every second day.[39] Fifteen RCTs (60%)

provided their control group with an inactive device that was indistinguishable from the active LIPUS. Only three trials (12%) were explicitly free of industry funding.[26, 42, 48]

Risk of bias

We contacted authors to resolve areas of uncertainty and successfully clarified details in five RCTs.[30, 31, 35, 37, 40] We considered six trials to be at low risk of bias,[16, 24, 27, 37, 46, 47] and the remaining 20 studies to be at high risk of bias (table 2). The main limitations were failure to report a method for allocation concealment (15 RCTs), unblinded patients (10 RCTs), caregivers or outcome assessors (10 RCTs), and high or unclear numbers of patients excluded from the analysis (13 RCTs; table 2).

Outcomes

Functional recovery

Only the TRUST trial assessed time to return to work using a time-to-event analysis, and found no significant effect (hazard ratio 1.11 favouring control, 95% CI 0.82 to 1.50; 343 patients).[16] Three trials assessed the number of days to return to work; the pooled effect was not significant (2.7% later return with LIPUS, 95% CI 7.7% earlier to 14.3% later; I^2=0%; 392 patients) (fig 2). We found no significant interaction with risk of bias (p=0.86). A fourth trial in patients with delayed union of tibia fracture provided insufficient data for inclusion in meta-analysis but found no significant difference in days to return to work.[50]

Only the TRUST trial assessed time to full weight bearing using a time-to event analysis, and found no significant effect (hazard ratio 0.87 in favour of LIPUS, 95% CI 0.70 to 1.08; 451 patients). Three trials assessed the number of days to full weight bearing. Overall results suggested no significant effect on full weight bearing with LIPUS but high heterogeneity (I^2=95%). The effect of the one trial at high risk of bias (40.0% earlier, 95% CI 48.4% to 30.3

earlier) differed significantly from the consistent results from the two trials at low risk of bias (4.8% later, 95% CI 4.0% earlier to 14.4% later; 483 patients; interaction p<0.001) (fig 3).

Appendix 2 presents results of other functional outcomes including return to leisure activities, return to household activities, return to pre-injury level of function, and physical function measured with a multidimensional questionnaire. None of these were significantly affected by use of LIPUS, nor did they show substantial inconsistency.

Pain reduction

Four trials assessed pain, two using a 100mm visual analogue scale[37, 49] and two using the subdomain "bodily pain" of the SF-36 instrument.[16, 24] After transforming of all results to a 100mm visual analogue scale, findings at 3 to 6 weeks follow-up showed no significant effect of LIPUS on pain reduction but high heterogeneity (I^2=97%). The effect of the one trial at high risk of bias (28.12 mm lower, 95% CI, 37.05 lower to 19.19 higher) differed significantly from the consistent results from the three trials at low risk of bias (0.93 mm lower, 95% CI 2.51 lower to 0.64 higher; 626 patients; I^2=0%; interaction p<0.001; fig 4). Two other studies assessed pain intensity and reported no difference at 5 months,[41, 49] but the data was insufficient for inclusion in meta-analysis.

Other outcomes for pain included pain intensity assessed at multiple time-points and number of painful days (appendix 3). None showed a significant effect of LIPUS, nor substantial inconsistency.

Number of subsequent operations

Ten trials reported the number of subsequent operations including three trials reporting zero events in both arms. Neither the pooled risk ratio (0.8 in favour of LIPUS, 95% CI 0.55 to 1.16; I^2=0%; 7 trials, 693 patients) nor the pooled risk difference (3% reduction with LIPUS, 95% CI 7% reduction to 2% increase; I^2=0%; 10 trials, 740 patients; fig 6) showed a significant effect. There was no significant interaction with risk of bias on either scale (risk ratio: p=0.75; risk difference: p=0.64).

Time to radiographic healing

Two trials used time-to-event analysis methods to assess time to radiographic healing,[16, 24] and showed no significant effect of LIPUS (hazard ratio 1.06 in favour of control, 95% CI 0.86 to 1.32; I^2=0%; 532 patients). Fifteen trials reported the number of days to radiographic healing. Overall results suggested accelerated radiographic healing with LIPUS (26% earlier, 95% CI 33.6% to 17.8% earlier; I^2=84.7%). The effect differed significantly between the 12 trials at high risk of bias (31.8% earlier; 95%CI 38.6% to 24.3% days earlier; I^2=77.8%; 446 patients) and the three trials at low risk of bias (1.7% earlier, 95% CI 11.2% earlier to 8.8% later, I^2=9.8%; 483 patients; interaction p<0.001; fig 6). This subgroup effect fulfilled 8 of 9 credibility criteria relevant to risk of bias as an explanation of heterogeneity (table 3). The effect did not differ significantly across clinical subgroups (p=0.13, fig 1 in appendix 4) or between high and moderate compliance with treatment (p=0.79, fig 2 in appendix 4). In our multivariable meta-regression, which included risk of bias, clinical subgroups, and compliance with treatment, the only significant effect modifier was the risk of bias (p=0.005).

Another RCT in patients with delayed union of tibia fracture reported only the proportion of healed fractures at 16 weeks and did not find a significant difference (65% in the LIPUS and 46% in the control arm, p=0.07; high risk of bias towards LIPUS due to serious imbalance in age of fracture at baseline).[44]

The funnel plot based on time to radiographic healing was not clearly asymmetrical and Egger's test for publication bias was not significant (p=0.25; fig 3 in appendix 4s).

Device related adverse effects

Seven studies reported explicitly the absence of any device-related adverse effects; two other studies reported mild transient skin irritations in 6 of patients. The pooled risk ratio based on these two studies (2.65 in favour of control, 95% CI 0.32 to 22.21; 129 patients) was not significant, nor was the pooled risk difference based on all nine trials (0%, 95% CI 1% reduction to 1% increase; I^2=0%; 839 patients; fig 7). We found no significant interaction with risk of bias on the risk difference scale (p=0.75).

DISCUSSION

Our systematic review demonstrated moderate quality evidence that LIPUS applied to patients with fractures or osteotomies has no effect on time to return to work or the number of subsequent operations (table 4). Overall results suggested a possible reduction of days to full weight bearing, pain, and days to radiographic healing, but with large variability between studies strongly associated with risk of bias as an effect modifier: only trials with high risk of bias demonstrated benefit. Based on RCTs at low risk of bias, we found high quality evidence that LIPUS has no effect on pain reduction, days to full weight bearing, or device-related adverse effects, and moderate quality evidence that LIPUS has no effect on days to radiographic healing (table 4).

Our results are consistent with other systematic reviews in concluding that most RCTs addressing LIPUS therapy are poorly reported, lack patient important outcomes, and are at high risk of bias.[5-14] Our systematic review, however, differs from previous systematic reviews in several important aspects. First, we include the recently published TRUST trial,[16] by far the largest trial addressing LIPUS therapy for bone healing, which reported a number of patient-important outcomes. Second, our choice of outcomes and interpretation of findings was informed by a guideline panel including patients with lived experience with fractures in the context of BMJ Rapid Recommendations. Patients considered functional recovery, pain reduction and operations as critical outcomes, while expressing little interest in the commonly reported surrogate outcome of radiographic healing. Third, we used optimal statistical approaches, and in particular the ratio of means to combine days to radiographic healing, return to work, or full weight bearing across studies. This relative effect measure is most appropriate in the context of LIPUS where the average time to recovery differs substantially between clinical subgroups. For

instance, a lower grade stress fracture is likely to heal much faster than a complicated tibia fracture. It is not surprising, therefore, that previous meta-analyses found high heterogeneity when they used absolute mean differences to pool across studies.[8, 11, 12]

Finally, we used the GRADE approach to assess the quality of evidence, taking into account the results of subgroup analysis based on risk of bias: when effects differed significantly between high and low quality trials, we based our conclusions on trials at low risk of bias. Our approach of limiting conclusions to low risk of bias trials depends on our judgement of risk of bias; however, our ratings of risk of bias were consistent with those of a previous Cochrane systematic review.[5] Further, most trials judged to be at high risk of bias had limitations in more than one domain, and some had additional sources of bias including baseline imbalance or unclear clustering when patients had more than one fracture or surgery. Applying our risk of bias judgments as an effect modifier met 8 of 9 relevant criteria for a credible subgroup analysis (table 3).

The primary limitation of our review is the failure of most trials to measure or report patient-important outcomes. Of the 26 eligible trials, 11 reported, in sufficient detail for inclusion in meta-analysis, outcomes that patient consider critical for decision making.[16, 24, 25, 27, 29-31, 35, 37, 39, 46, 47] Of these, the only four trials that contributed substantial data were either conducted in patients with operatively managed fresh tibia fracture[16, 24, 27] or conservatively managed clavicle fracture.[37] One could question the extent to which our results apply to populations not included at all (such as children) or underrepresented (stress fractures, non-union, and osteotomies) in the eligible trials. Qualitative subgroup effects (e.g. no benefit in one

subgroup and important benefit in another) are, however, unusual. In the absence of evidence to the contrary, it is therefore reasonable to apply our results to these populations. Our subgroup analysis and meta-regression for radiographic healing found no effect modification based on clinical subgroups. Certainly, the burden of proof regarding the effect of LIPUS in children and underrepresented populations rests with those who might postulate a benefit.

In conclusion, moderate to high quality evidence demonstrates that LIPUS fails to accelerate return to work, return to full weight bearing, pain, or the need for subsequent operation. If one gives highest credibility to combined effects from all available RCTs, low quality evidence would suggest a large reduction in time to radiographic healing. If, however, one gives higher credence to low risk of bias trials, moderate to high quality evidence suggests that LIPUS not only has no effect on patient-important outcomes, but also fails to accelerate radiographic healing.

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Competing interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work. We acknowledge that JWB, DHA, and GHG were co-authors of the TRUST trial, which was supported in part by an industry grant from Smith & Nephew, a manufacturer of LIPUS devices. No other relationships or activities that could appear to have influenced the submitted work.

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Contributors

JWB, RAS, GHG and POV conceived the study idea. SS and JWB coordinated the systematic review. SS wrote the first draft of the manuscript. RC designed the search strategy. LL, AK, RC, and SS screened abstracts and full texts. LL, AK, RAS, TA, and SS acquired the data and judged risk of bias in the studies. SS, JWB and DHA performed the data analysis. DHA and GHG provided statistical advice. SS, RAS, POV, JWB and GHG interpreted the data analysis. All

authors critically revised the manuscript. SS had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical approval

Not required.

Data sharing

All data informing the study is freely available in the appendices.

Data access

All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Patient involvement

Four patient representatives were full members of the guideline, and contributed to the selection and prioritisation of outcomes, values and preferences assessments, and critical feedback to the protocol for the systematic review and the BMJ Rapid Recommendations manuscript.

Transparency declaration

SS is guarantor and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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TABLES

Table 1, Study characteristics

Author Year	Bone	Type of fracture / surgery	% open fracture	Management	% women	Mean age	N randomised		Sham device	Dose and duration of LIPUS therapy	Maximum follow-up	Explicitly free of industry funding
							LIPUS	No ultrasound				
Busse 2014[24]	Tibia	Fresh fracture	27%	Operative	24%	40	23	28	Yes	20 min daily until radiographic healing	1 year	No
Busse 2016[16]	Tibia	Fresh fracture	23%	Operative	31%	40	250	251	Yes	20 min daily until radiographic healing	1 year	No
Dudda 2011[25]	Tibia	Distraction osteogenesis	NA	Operative	11%	39	16	20	No	20 min daily until radiographic healing	35 weeks	No
El-Mowafi 2005[26]	Tibia	Distraction osteogenesis	NA	Operative	0%	35	10	10	No	20 min daily until radiographic healing	12 months	Yes
Emami 1999[27, 28]	Tibia	Fresh fracture	13%	Operative	25%	37	15	17	Yes	20 min/day for 75 days	20 weeks	No
Gan 2014[29]	Tibia, fibula, metatarsal	Stress fracture	0%	Non-operative	83%	30	15	15	Yes	20 min/day for 28 days	12 weeks	No
Handolin 2005a[30, 31]	Lateral malleolus	Fresh fracture	0%	Operative	47%	42	11	11	Yes	20 min/day for 42 days	12 weeks	No
Handolin 2005b[32]	Lateral malleolus	Fresh fracture	0%	Operative	56%	40	15	15	Yes	20 min/day for 42 days	18 months	No
Heckman 1994[33]	Tibia	Fresh fracture	4%	Non-operative	19%	33	48	49	Yes	20 min/day until radiographic healing	140 days	No
Kamath 2015[45]	Tibia and femur	Fresh fracture	0%	Operative	NR	36	33	27	No	20 min/day for 1 month	16 weeks	No
Kristiansen 1997[34]	Distal radius	Fresh fracture	0%	Non-operative	84%	56	40	45	Yes	20 min/day for 70 days	140 days	No
Leung 2004[35]	Tibia	Fresh fracture	47%	Operative	11%	35	16	14	Yes	20 min/day for 4 months	5 months	No
Liu 2014[36]	Distal radius	Fresh fracture	NR	Non-operative	36%	67	41	40	No	15 min/day for at least 12 weeks	At least 12 weeks	No
Lubbert 2008[37]	Clavicle	Fresh fracture	0%	Non-operative	16%	38	61	59	Yes	20 min/day for 28 days	8 weeks	No
Mayr 2000[38]	Scaphoid	Fresh fracture	0%	Non-operative	17%	37	15	15	No	20 min/day until radiographic healing	120 days	No
Patel 2014[39]	Mandible	Fresh fracture	NR	Non-operative	25%	15-35	14	14	No	5 min every second day for 24 days	5 weeks	No
Ricardo 2006[40]	Scaphoid	Non-union	NA	Operative	0%	27	10	11	Yes	20 min/day until radiographic healing	4 years	No
Rue 2004[42]	Tibia	Stress fracture	0%	Non-operative	50%	19	Probably 20	Probably 20	Yes	20 min/day until radiographic healing	NR	Yes
Rutten	Tibia	Non-union	0%	Operative	70%	41-63	10	10	Yes	20 min/day for 5	5 years	No

2012[41]										months		
Salem 2014[43]	Tibia	Distraction osteogenesis	NA	Operative	14%	30	12	9	No	20 min/day until radiographic healing	NR	No
Schofer 2010[44]	Tibia	Non-union	NA	Operative	24%	44	51	50	Yes	20 min/day for 16 weeks	16 weeks	No
Schortinghuis 2005[46]	Mandible	Distraction osteogenesis	NA	Operative	75%	65	4	4	Yes	20 min/day for 4 weeks	30 months	No
Schortinghuis 2008[47]	Mandible	Distraction osteogenesis	NA	Operative	NR	56	5	4	Yes	20 min/day for 6 weeks	44 months	No
Tsumaki 2004[48]	Tibia	Distraction osteogenesis	NA	Operative	81%	68	21 knees	21 knees	No	20 min/day until radiographic healing	NR	Yes
Urita 2013[49]	Ulna and radius	Osteotomy (shortening)	NA	Operative	63%	48	14	13	No	20 min/day until radiographic healing or 12 weeks	24 weeks	No
Zacherl 2009[50]	Hallux valgus	Osteotomy (deformity correction)	NA	Operative	85%	53	26 toes	26 toes	Yes	20 min/day for 42 days	1 year	No

Table 2, Risk of bias

Author Year	Concealment of treatment allocation	Patients blinded	Caregivers blinded	Outcome assessors blinded	No other bias detected	Loss to follow-up (%) for outcome radiographic healing unless specified otherwise
Busse 2014[24]	Yes	Yes	Yes	Yes	Yes	2%
Busse 2016[16]	Yes	Yes	Yes	Yes	Yes	19% for radiographic healing, 11% for return to work, 9% for weight bearing
Dudda 2011[25]	No	No	No	No	Yes	Unclear, assumed to be 0
El-Mowafi 2005[26]	No	No	No	No	Yes	5%
Emami 1999[27, 28]	Yes	Yes	Yes	Yes	Yes	3%
Gan 2014[29]	No	Yes	Yes	Yes	Yes	23% (pain)
Handolin 2005a[30, 31]	No	Yes	Yes	Yes	Yes	5%
Handolin 2005b[32]	No	Yes	Yes	Yes	Yes	Not included in meta-analysis
Heckman 1994[33]	Yes	Yes	Yes	Yes	Yes	31%
Kamath 2015[45]	No	No	No	Yes	Yes	Not included in meta-analysis
Kristiansen 1997[34]	Yes	Yes	Yes	Yes	Yes	Unclear, assumed to be 0
Leung 2004[35]	No[a,b]	No[b]	No[b]	No[b]	No[c]	Unclear, assumed to be 0
Liu 2014[36]	No	No	No	yes	No[d]	Unclear, assumed to be 0
Lubbert 2008[37]	Yes	Yes	Yes	Yes	Yes	16%
Mayr 2000[38]	No	No	No	Yes	Yes	0
Patel 2014[39]	No	No	No	No	Yes	Unclear, assumed to be 0
Ricardo 2006[40]	No	Yes	Yes	Yes	Yes	Unclear, assumed to be 0
Rue 2004[42]	No	Yes	Yes	Yes	Yes	Unclear, probably 35%
Rutten 2012[41]	Yes	Yes	Yes	Yes	Yes	45%
Salem 2014[43]	No	No	No	No	Yes	Unclear, assumed to be 0
Schofer 2010[44]	Yes	Yes	Yes	Yes	No[e]	Unclear, assumed to be 0
Schortinghuis 2005[46]	Yes	Yes	Yes	Yes	Yes	0 for subsequent operation
Schortinghuis 2008[47]	Yes	Yes	Yes	Yes	Yes	0 for subsequent operation
Tsumaki 2004[48]	Yes	No	No	No	No[f]	Unclear, assumed to be 0
Urita 2013[49]	No	No	No	Yes	Yes	Unclear, assumed to be 0
Zacherl 2009[50]	No	yes	yes	yes	No[g]	Not included in meta-analysis

[a] quasi-randomised based on sequence of admission
[b] Inactive device was distinguishable from active device
[c] Unadjusted clustering, 30 fractures of 28 patients were randomized
[d] Implausibly narrow confidence intervals
[e] Prognostic imbalance: non-union fractures in LIPUS arm were considerably older
[f] Bilateral surgery – one tibia was randomised to LIPUS and one to no treatment. We assumed a correlation of 0.5 in our analyses of days to radiographic healing
[g] 52 toes of 44 patients but clusters not reported, standard deviations not reported

Table 3, Credibility of subgroup effects for risk of bias for the outcome days to radiographic healing

Criteria[20]	Rating (yes means higher credibility)
Is the subgroup variable a characteristic measured at baseline or after randomization?	Not applicable for risk of bias
Is the effect suggested by comparisons within rather than between studies?	No, between studies
Was the subgroup effect specified a priori?	Yes, specified in our protocol
Was the direction of the subgroup effect specified a priori?	Yes, we expected a larger effect for studies at high risk of bias
Is there indirect evidence that supports the hypothesized interaction (biological rationale)?	Not applicable for risk of bias
Was the subgroup effect one of a small number of hypothesized effects tested?	Yes, one of three
Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	Yes, significant in univariable subgroup analysis ($p<0.001$)
Is the significant subgroup effect independent?	Yes, significant in multivariable meta-regression ($p<0.01$)
Is the size of the subgroup effect large?	Yes, 31.8% acceleration in high risk of bias trials versus 1.7% acceleration in low risk of bias trials
Is the interaction consistent across closely related outcomes within the study?	Yes, risk of bias explained heterogeneity in outcomes weight bearing and pain
Is the interaction consistent across studies?	Yes, high risk of bias studies consistently showed large effects, low risk of bias studies small effects

Table 4, GRADE Summary of Findings table

Outcome	Study results and measurements	Absolute effect estimates		Quality of evidence	Narrative Summary
		No ultrasound	LIPUS		
Days to return to work	% Difference: 2.7% (95% CI, -7.7% to 14.3%) in days, lower better Based on data from 392 patients in 3 studies	**200 days (Mean)**	**205 days (Mean)**	**Moderate** Due to serious imprecision	LIPUS probably has little or no impact on time to return to work
		Difference: 5 days later (95% CI, 15 earlier to 20 later)			
Days to full weight bearing	% Difference: 4.8% (95% CI, -4.0% to 14.4%) in days, lower better Based on data from 483 patients in 2 high quality studies	**70 days (Mean)**	**73 days (Mean)**	**High**	LIPUS has no impact on time to full weight bearing
		Difference: 3 days earlier (95% CI, 3 earlier to 10 later)			
Pain reduction Follow up 4 to 6 weeks	Mean difference: -0.93 (95% CI -2.51 to 0.64) 0 to 100 visual analogue scale, lower better, minimal important difference: 10-15 Based on data from 626 patients in 3 high quality studies	**40 (Mean)**	**39 (Mean)**	**High**	LIPUS has no impact on pain reduction
		Difference: 1 lower (95% CI 3, lower to 1 higher)			
Subsequent operations Follow up 8 weeks to 44 months	Risk difference: -3% (95% CI, -7% to 2%) Based on data from 740 patients in 10 studies	**160 per 1000**	**130 per 1000**	**Moderate** Due to serious imprecision	LIPUS probably has little or no impact on subsequent operation
		Difference: 30 fewer (95% CI, 70 fewer to 20 more)			
Days to radiographic healing	% Difference: -1.7% (95% CI, -11.2% to 8.8%) in days, lower better Based on data from 483 patients in 3 high quality studies	**150 days (Mean)**	**147 days (Mean)**	**Moderate** Due to serious imprecision	LIPUS probably has little or no impact on time to radiographic healing
		Difference: 3 days earlier (95% CI, 17 earlier to 13 later)			
Device-related adverse effects Follow up 5 to 52 weeks	Risk difference: 0% (CI 95% -1% to 1%) Based on data from 839 patients in 9 studies	**0 per 1000**	**0 per 1000**	**High**	LIPUS has no impact on device-related adverse effects
		Difference: 0 fewer (95% CI, 10 fewer to 10 more)			

FIGURES

Figure 1, Flow diagram of studies included in review of low intensity pulsed ultrasound compared with sham device or no device for patients with fracture or osteotomy

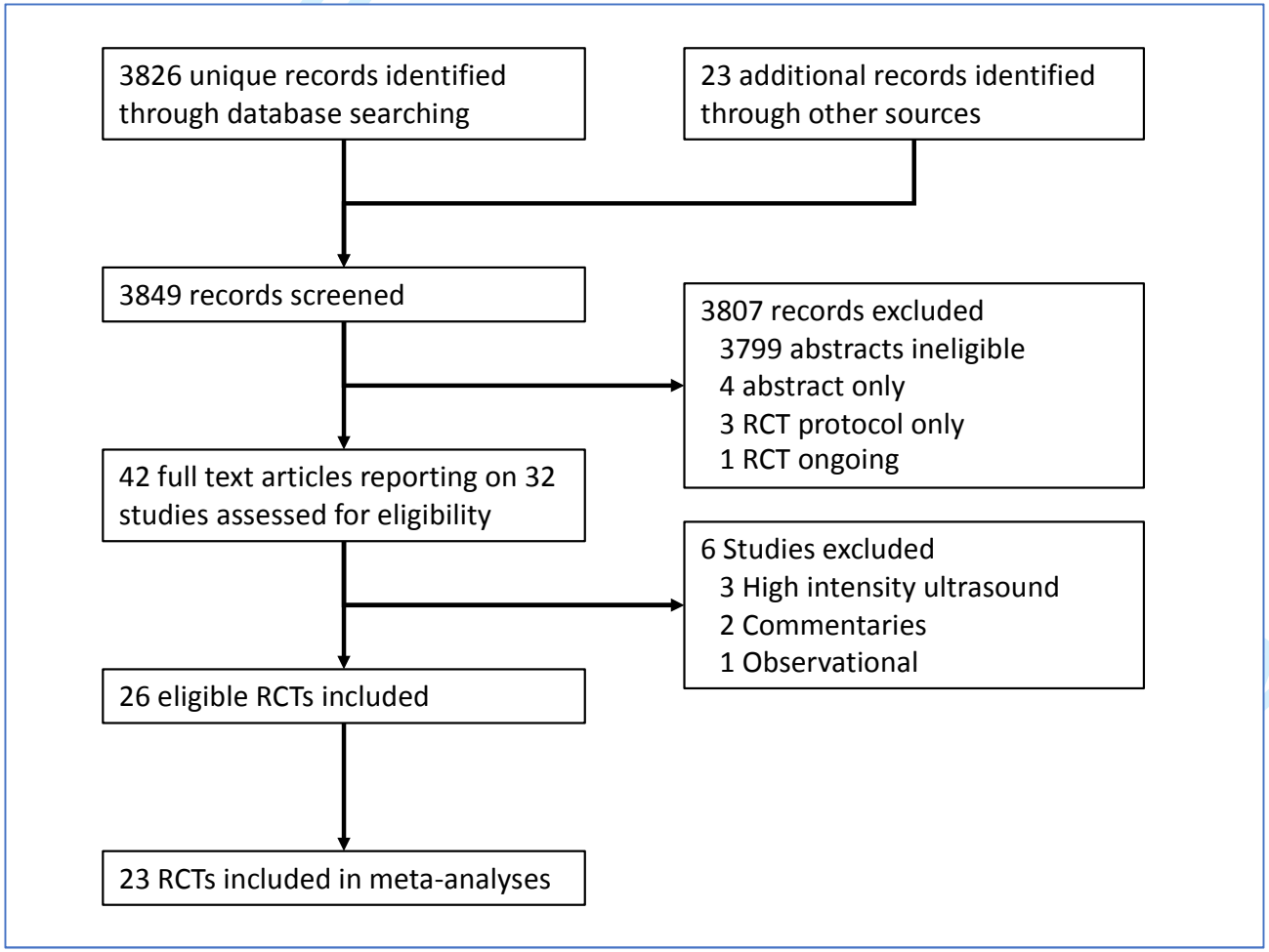
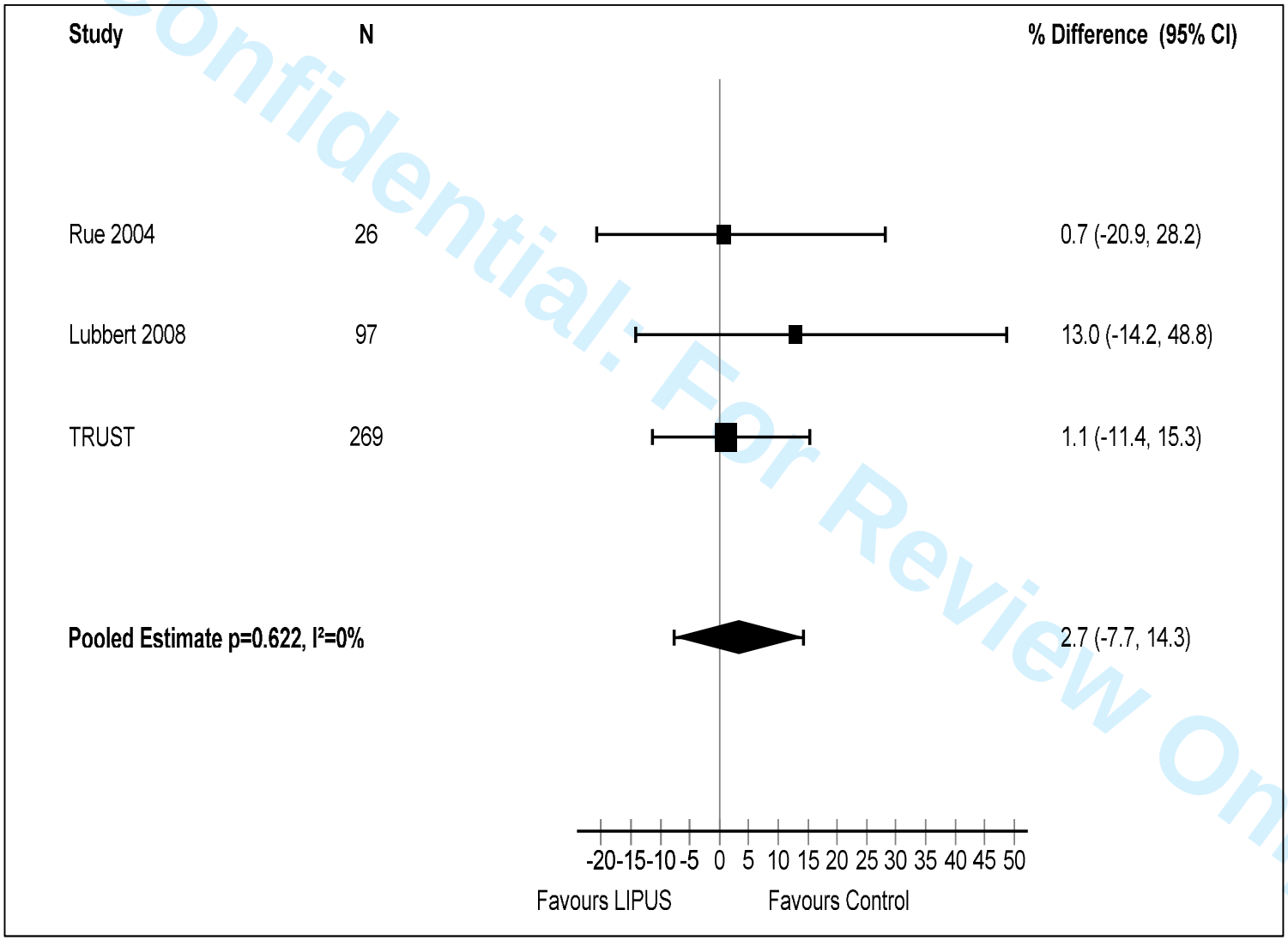
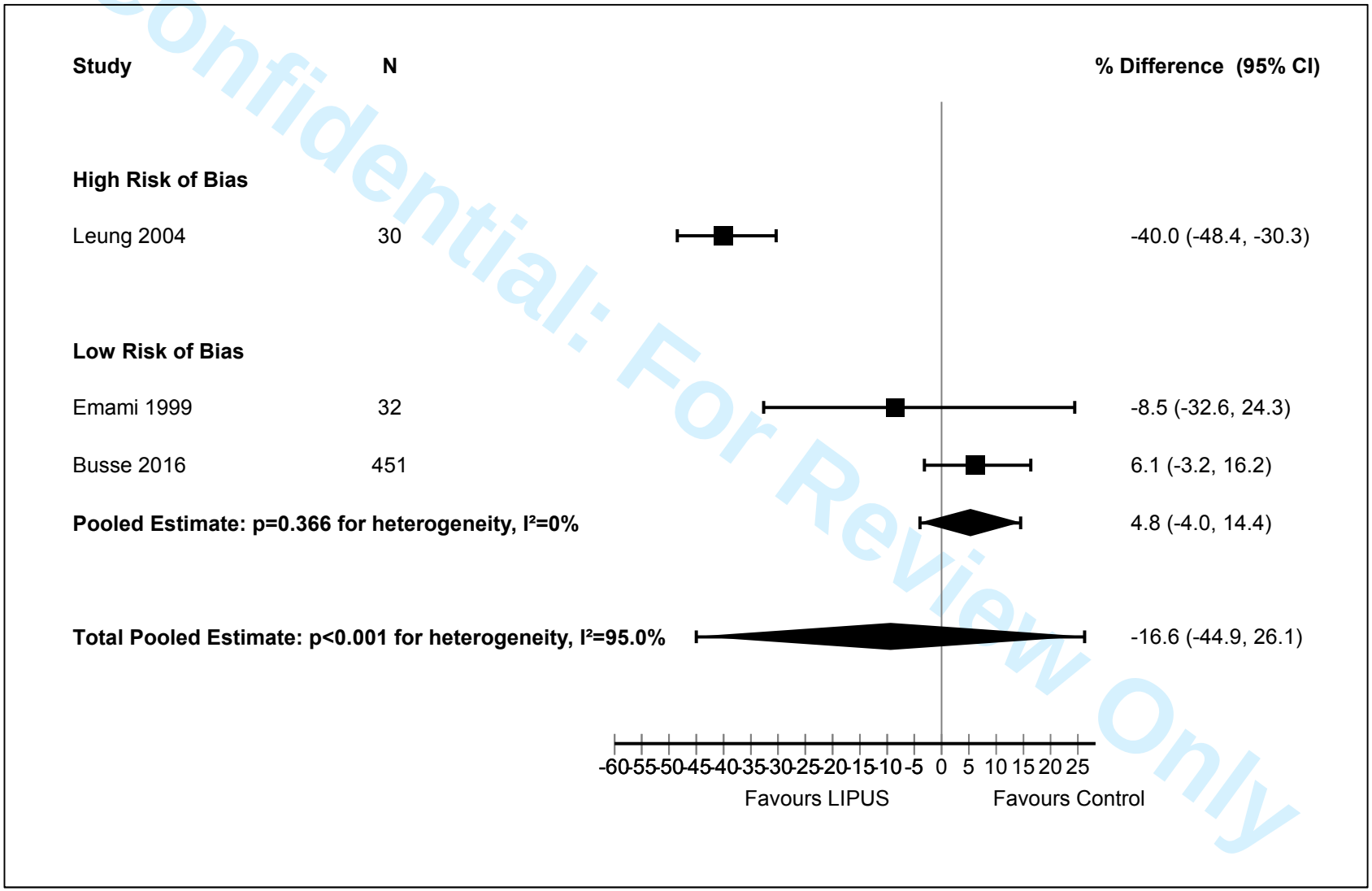


Figure 2, Forest plot for percent difference of days to return to work for low intensity pulsed ultrasound (LIPUS) compared with Control (sham device or no device)



Study	LIPUS			Control			Weight, % (log ratio of means, random effects)	Clinical subgroup
	N	Mean	SD	N	Mean	SD		
Rue 2004	14	56.2	19.6	12	55.8	15.5	19.6	Stress fracture of tibia
Lubbert 2008	50	17.0	11.0	47	15.05	11.0	15.0	Non-operatively managed fresh fracture of clavicle
Busse 2016	139	202.9	108.6	130	200.7	113.5	65.4	Operatively managed fresh fracture of tibia

Figure 3, Forest plot for percent difference of days to full weight bearing for low intensity pulsed ultrasound (LIPUS) compared with Control (sham device or no device), by risk of bias. Interaction p<0.001



Study	LIPUS			Control			Weight, % (random effects)	Clinical subgroup
	N	Mean	SD	N	Mean	SD		
Leung 2004	16	65.1	14.7	14	108.5	21.0	34.4	All operatively managed fresh fracture of tibia
Emami 1999	15	45.5	18.9	17	49.7	23.1	30.1	
Busse 2016	228	76.9	38.5	223	72.5	35.5	35.4	

Figure 4, Forest plot for mean difference of pain reduction, all instruments transformed to 0-100 visual analogue scale, by risk of bias. Interaction p<0.001

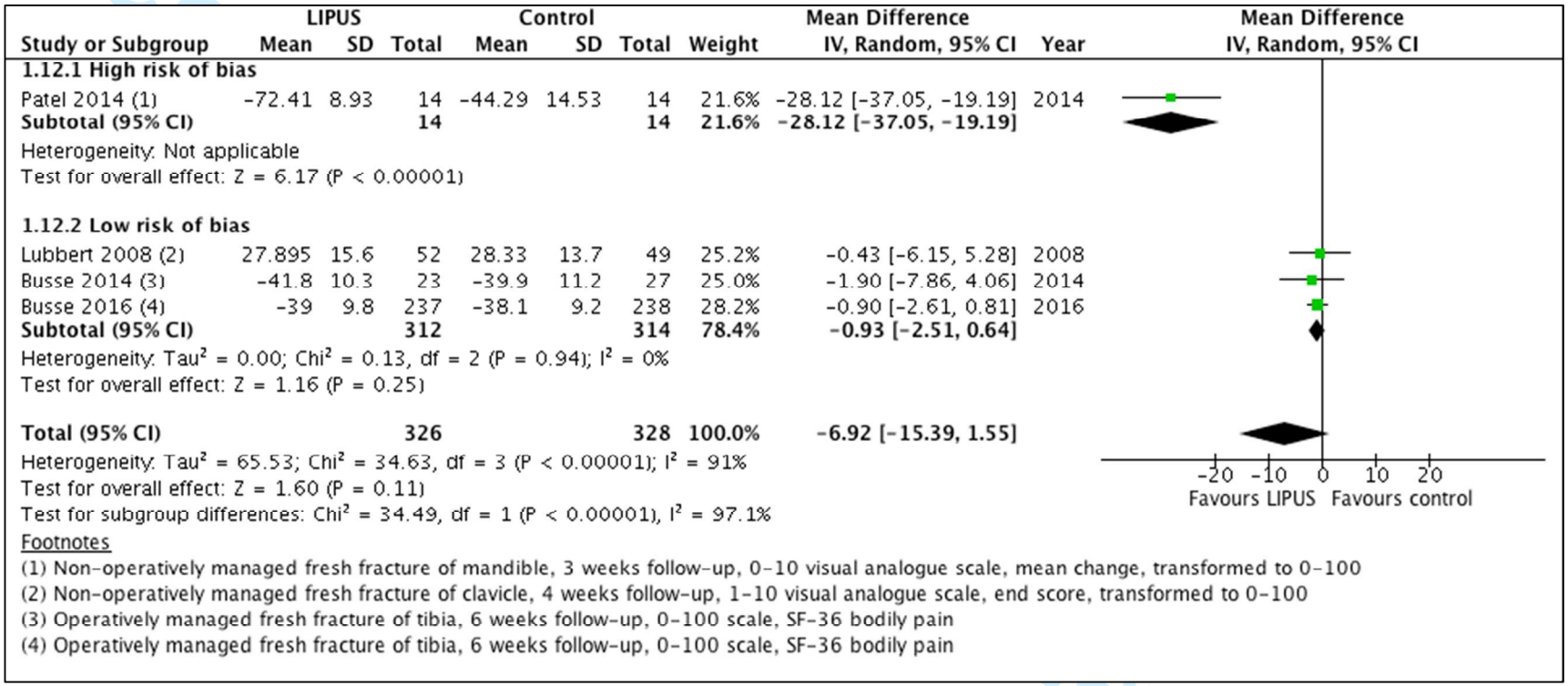
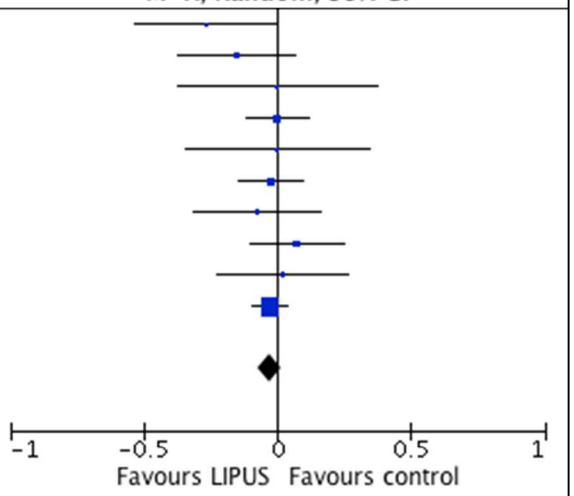


Figure 5, Forest plot for risk difference for low intensity pulsed ultrasound (LIPUS) compared with Control (sham device or no device) of number of subsequent fracture-related operations

Study or Subgroup	LIPUS Events	LIPUS Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Emami 1999 (1)	1	15	5	15	2.9%	-0.27 [-0.54, 0.00]	1999
Leung 2004 (2)	0	15	2	13	4.4%	-0.15 [-0.37, 0.06]	2004
Schortinghuis 2005 (3)	0	4	0	4	1.5%	0.00 [-0.37, 0.37]	2005
Handolin 2005a (4)	0	15	0	15	14.4%	0.00 [-0.12, 0.12]	2005
Schortinghuis 2008 (5)	0	5	0	4	1.8%	0.00 [-0.34, 0.34]	2008
Lubbert 2008 (6)	5	52	6	49	14.1%	-0.03 [-0.15, 0.10]	2008
Dudda 2011 (7)	2	16	4	20	3.7%	-0.08 [-0.31, 0.16]	2011
Patel 2014 (8)	1	14	0	14	6.7%	0.07 [-0.11, 0.25]	2014
Busse 2014 (9)	6	23	6	25	3.5%	0.02 [-0.22, 0.27]	2014
Busse 2016 (10)	28	217	32	205	47.0%	-0.03 [-0.09, 0.04]	2016
Total (95% CI)		**376**		**364**	**100.0%**	**-0.03 [-0.07, 0.02]**	
Total events	43		55				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.15$, df = 9 (P = 0.73); $I^2 = 0\%$

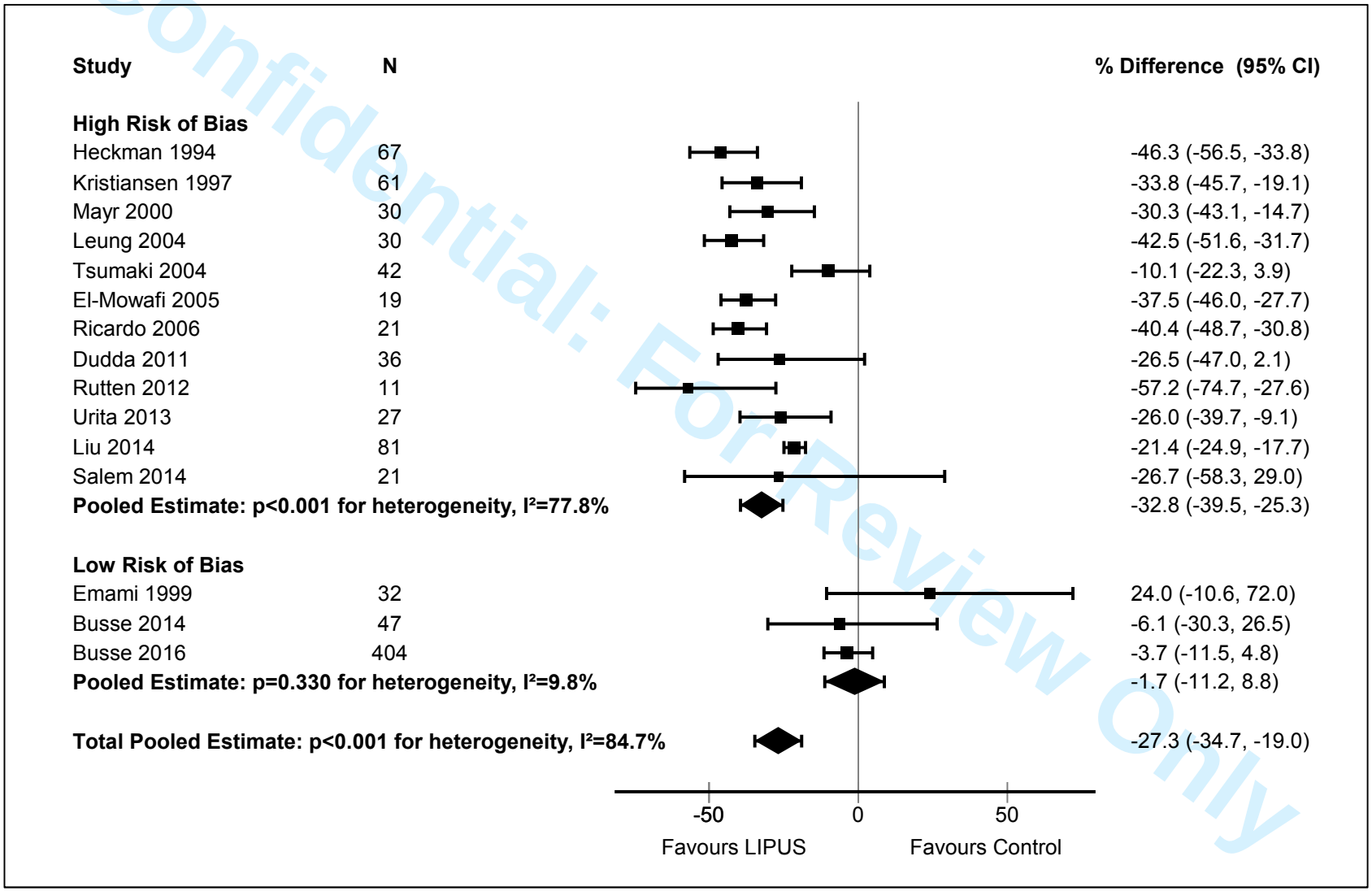
Test for overall effect: Z = 1.21 (P = 0.23)



Footnotes

(1) Operatively managed fresh fracture of tibia, 20 weeks follow-up
(2) Operatively managed fresh fracture of tibia, 9 months follow-up
(3) 30 months follow-up
(4) Operatively managed fresh fracture of ankle, 12 weeks follow-up
(5) 44 months follow-up
(6) Non-operatively managed fresh fracture of clavicle, 8 weeks follow-up
(7) Osteotomy (distraction osteogenesis) of tibia, 35 weeks follow-up
(8) Non-operatively managed fresh fracture of mandible, 5 weeks follow-up
(9) Operatively managed fresh fracture of tibia, 52 weeks follow-up
(10) Operatively managed fresh fracture of tibia, 52 weeks follow-up

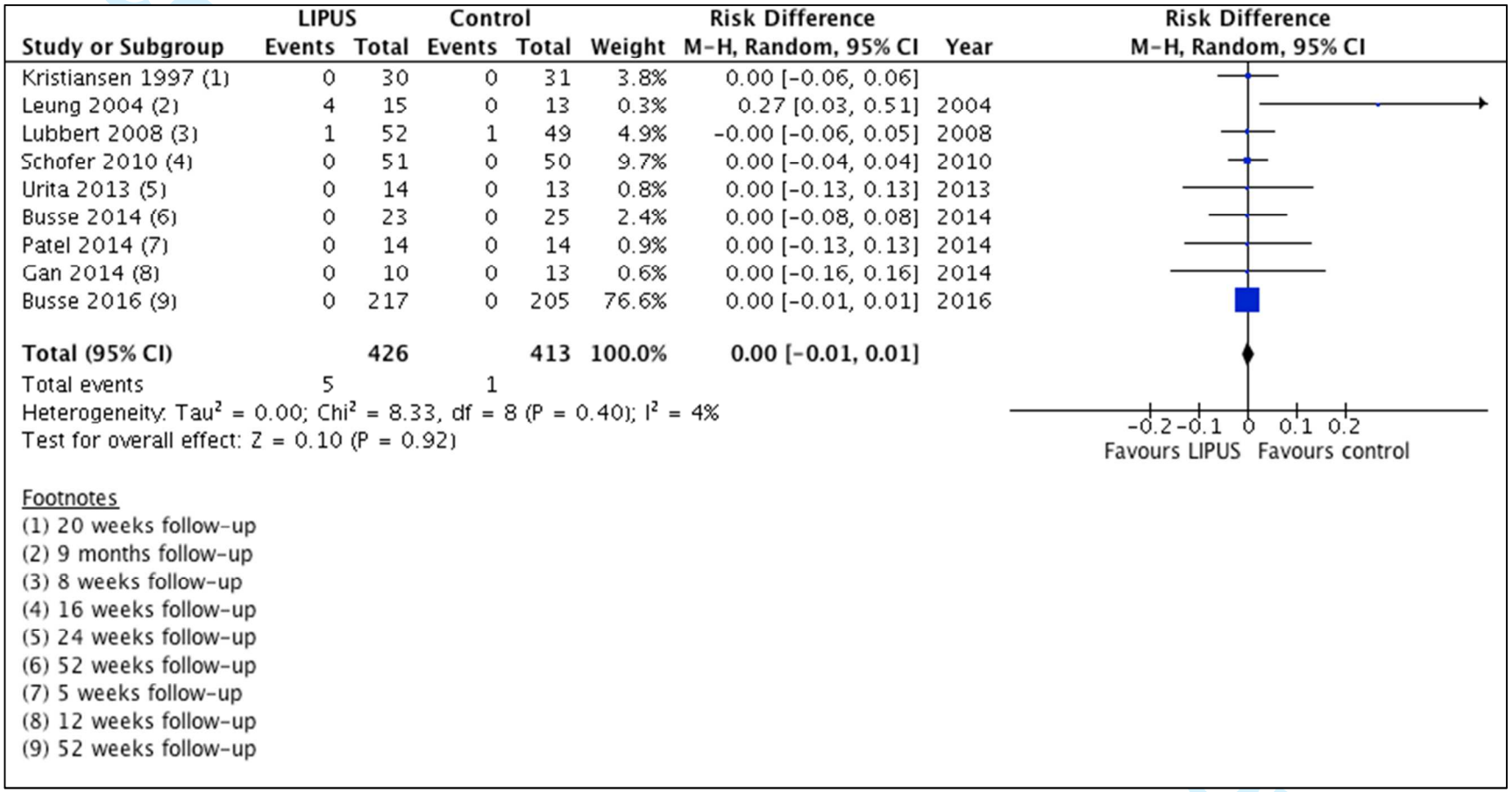
Figure 6, Forest plot for percent difference for low intensity pulsed ultrasound (LIPUS) compared with Control (sham device or no device) of days to radiographic healing, by risk of bias. Interaction p<0.001



Days to Radiographic Healing	LIPUS			Control			
Study	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Weight, % (random effects)**
Heckman 1994	33	102.0	27.6	34	190.0	106.7	7.0
Kristiansen 1997	30	51.0	21.9	31	77.0	27.8	7.2
Emami 1999	15	155.0	85.2	17	125.0	45.4	5.1
Mayr 2000	15	43.2	10.9	15	62.0	19.2	7.1
Leung 2004	16	80.5	21	14	140	30.8	7.7
Tsumaki 2004[a]	21	49.7	18.2	21	55.3	16.8	8.1
El-Mowafi 2005[b]	10	30.0	3.0	9	48.0	9.8	8.1
Ricardo 2006	10	56.0	10.1	11	94.0	15.9	8.1
Dudda 2011[b]	16	32.8	13.1	20	44.6	26.8	5.1
Rutten 2012	4	80.0	28.0	7	187.0	100.5	2.9
Urita 2013	14	57.0	10.0	13	77.0	26.0	7.1
Liu 2014	41	32.0	2.6	40	40.8	5.1	9.4
Salem 2014[b]	12	33.0	16.0	9	45.0	34.0	2.6
Busse 2014	23	151.7	59.9	24	161.6	101.2	5.5
Busse 2016	209	143.2	62.6	195	148.7	63.9	9.0

[a] Bilateral – one tibia was randomized to active and one to control. We assumed a correlation of 0.5 in our analyses
[b] Days per cm distraction

Figure 7, Forest plot for risk difference for low intensity pulsed ultrasound (LIPUS) compared with Control (sham device or no device) of ultrasound device related adverse effects



Footnotes

(1) 20 weeks follow-up
(2) 9 months follow-up
(3) 8 weeks follow-up
(4) 16 weeks follow-up
(5) 24 weeks follow-up
(6) 52 weeks follow-up
(7) 5 weeks follow-up
(8) 12 weeks follow-up
(9) 52 weeks follow-up

Appendix 1. Literature search strategies

MEDLINE (Ovid)

1 Fracture Healing/
2 Bony Callus/
3 bone remod*.mp.
4 exp Fractures, Bone/
5 fracture*.mp.
6 exp Orthopedic Procedures/
7 or/1-6
8 Ultrasonic Therapy/ or Ultrasonic Waves/
9 LIPUS.mp.
10 8 or 9
11 7 and 10

EMBASE (Ovid)

1 exp fracture healing/
2 callus/
3 bone remod*.mp.
4 exp fracture/
5 (Fracture* and (bone* or osteo* or verteb* or bony or extremity)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
6 exp orthopedic surgery/
7 or/1-6
8 exp ultrasound therapy/ or ultrasound.mp. or ultrasonic.mp. or LIPUS.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
9 exp echography/
10 8 or 9
11 7 and 10
12 limit 11 to ("therapy (maximizes sensitivity)" or "therapy (maximizes specificity)" or "therapy (best balance of sensitivity and specificity)")

CINAHL (Ebsco)

Query
S12 S11 Limiters - Clinical Queries: Therapy - High Sensitivity, Therapy - High Specificity, Therapy - Best Balance
S11 S6 AND S10

S10 S8 OR S9
S9 (MH "Ultrasonic Therapy")
S8 "LIPUS" or "ultrasound"
S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6
S6 (MH "Orthopedic Surgery+")
S5 "fracture*"
S4 bone remod*
S3 (MH "Bone Remodeling+")
S2 (MH "Fracture Healing")
S1 (MH "Fractures+")

Cochrane Library (Wiley)
#1 MeSH descriptor: [Fracture Healing] explode all trees
#2 MeSH descriptor: [Bony Callus] explode all trees
#3 MeSH descriptor: [Fractures, Bone] explode all trees
#4 bone remod*:ti,ab,kw (Word variations have been searched)
#5 fracture*:ti,ab,kw (Word variations have been searched)
#6 MeSH descriptor: [Orthopedic Procedures] explode all trees
#7 osteotom*
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 MeSH descriptor: [Ultrasonic Therapy] explode all trees
#10 ultrasound:ti,ab,kw (Word variations have been searched)
#11 or #9 or #10
#14 #8 and #11 in Trials

PubMed
Search (Therapy/Broad[filter]) AND ((((fracture) AND ultrasound)) AND (((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)))

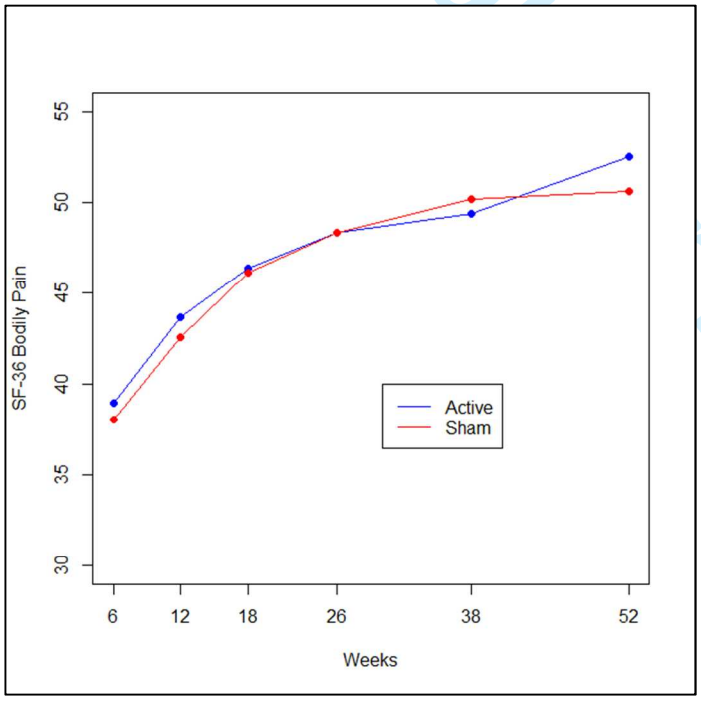
Trials registry search in Clinical Trials.gov service of the U.S. National Institutes of Health and World Health Organization International Clinical Trials Registry Platform Search Portal (Search term: low intensity pulsed ultrasound)

Appendix 3. Other pain outcomes

The following outcome was reported in two studies: 1) TRUST Investigators writing group, Busse JW, Bhandari M, Einhorn TA, et al. Re-evaluation of low intensity pulsed ultrasound in treatment of tibial fractures (TRUST): randomized clinical trial. *BMJ (Clinical research ed)* 2016;355:i5351., and 2) Busse JW, Bhandari M, Einhorn TA, et al. Trial to re-evaluate ultrasound in the treatment of tibial fractures (TRUST): a multicenter randomized pilot study. *Trials* 2014;15:206.

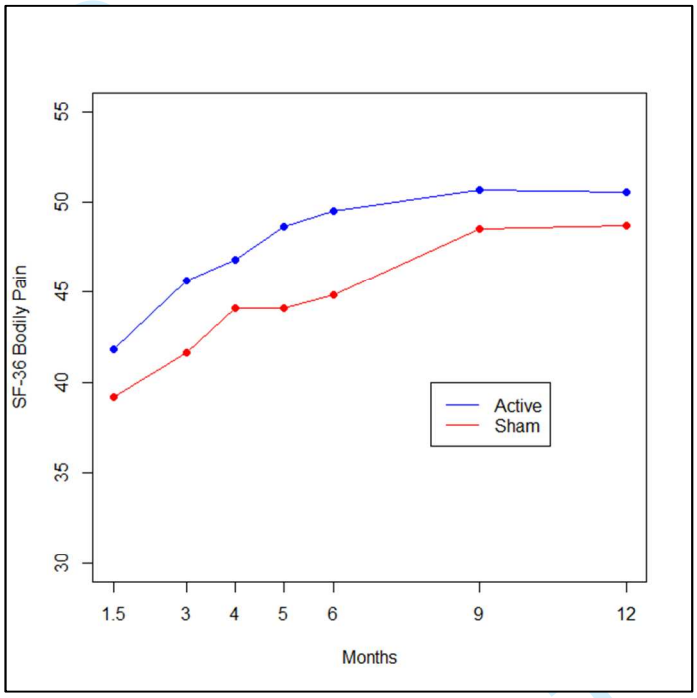
Pain intensity, continuous, multiple time points (unpublished data), subdomain bodily pain of the SF-36 instrument

Fig 1, Busse et al. (2016), unpublished material: Unadjusted repeated measures analyses examining Short Form 36 Bodily Pain (SF-36 Bodily Pain) in the Active (LIPUS device) and Sham (sham device)



N ranging from 475 at 6 weeks to 301 at 52 weeks

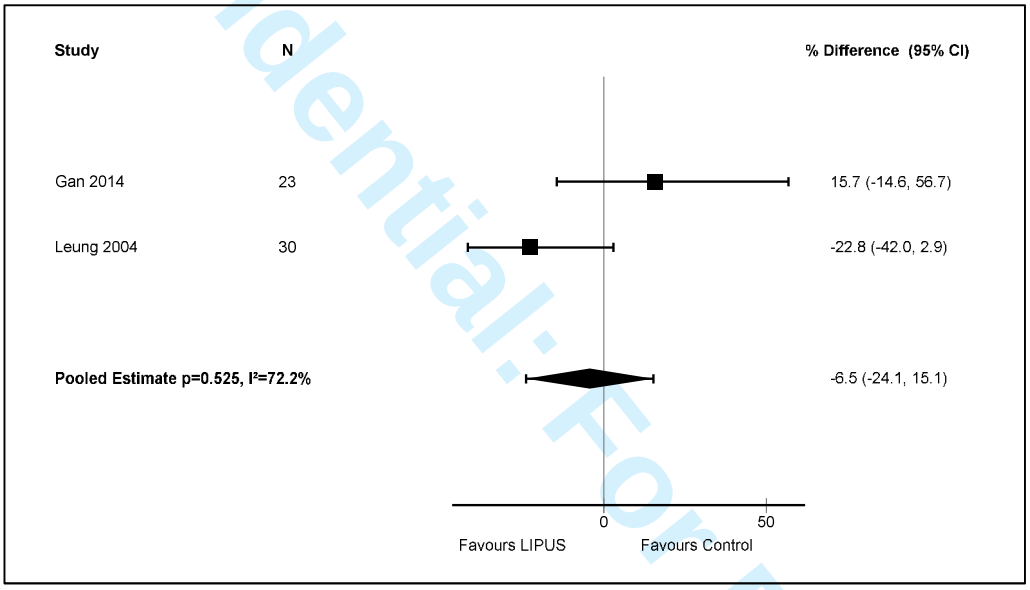
Fig 2, Busse et al. (2014), unpublished material. Unadjusted repeated measures analyses examining Short Form 36 Bodily Pain (SF-36 Bodily Pain) in the Active (LIPUS device) and Sham (sham device)



N ranging from 50 at 6 weeks to 43 at 1 year

The following outcome was reported in two studies: 1) Gan TY, Kuah DE, Graham KS, Markson G. Low-intensity pulsed ultrasound in lower limb bone stress injuries: a randomized controlled trial. *Clin J Sport Med* 2014;24:457-60., and 2) Leung KS, Lee WS, Tsui HF, Liu PP, Cheung WH. Complex tibial fracture outcomes following treatment with low-intensity pulsed ultrasound. *Ultrasound Med Biol* 2004;30:389-95.

Fig 3, Forest plot percent difference for low intensity pulsed ultrasound (LIPUS device) compared with Control (sham device or no device) for pain duration, number of days with tenderness



Appendix 4. Additional analyses

Fig 1, Forest plot for percent difference for low intensity pulsed ultrasound (LIPUS device) compared with Control (sham device or no device) for days to radiographic healing, by clinical subgroups. Interaction p=0.13

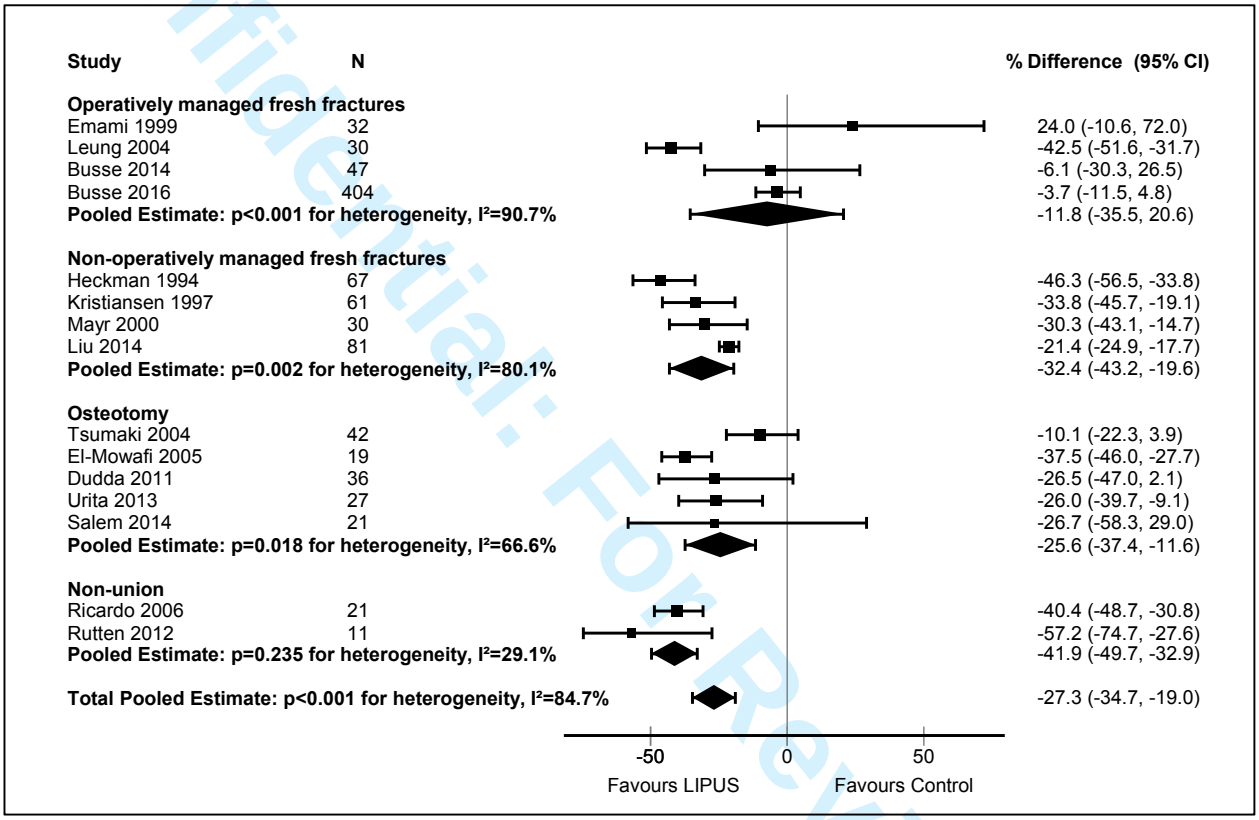


Fig 2, Forest plot for percent difference for low intensity pulsed ultrasound (LIPUS device) compared with Control (sham device or no device) for days to radiographic healing, by compliance. Interaction p=0.99

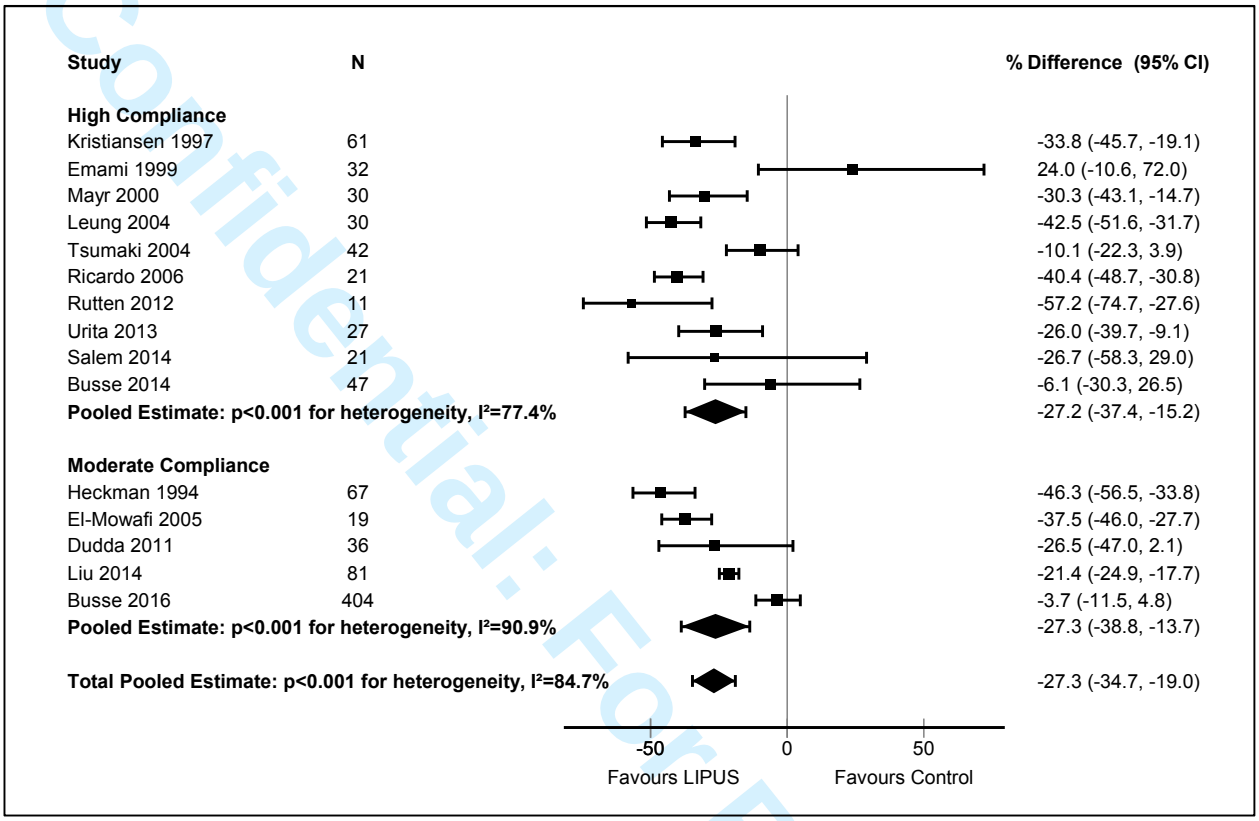
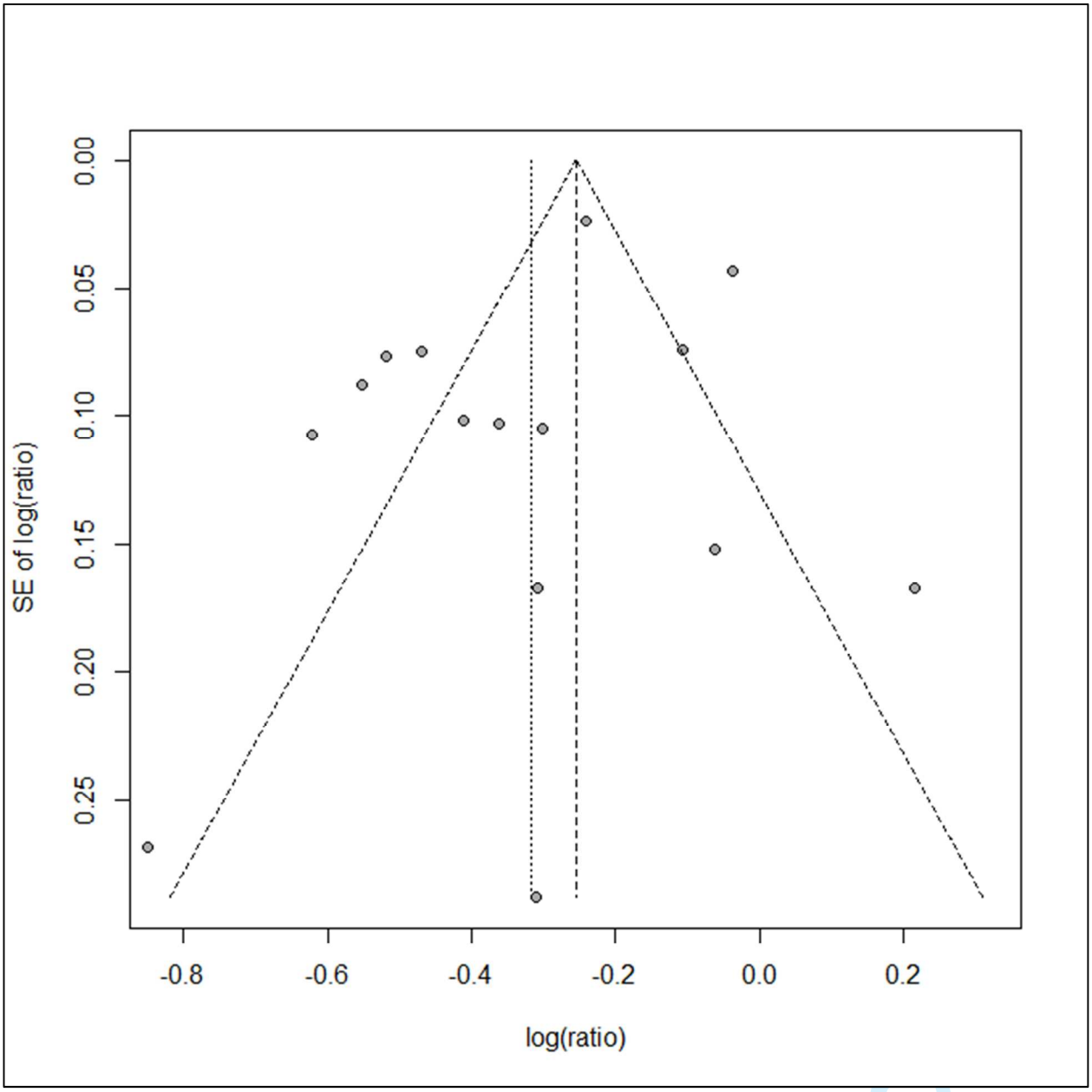


Fig 3, Funnel plot for days to radiographic healing. Egger's linear regression test for asymmetry of the funnel plot: p=0.251



Low intensity pulsed ultrasound (LIPUS) for bone healing: a clinical practice guideline

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Does low intensity pulsed ultrasound (LIPUS) accelerate recovery in adults and children who have experienced bone fractures or osteotomy (cutting of a bone)? Prompted by a recent large multi-centre randomized trial in adults with tibial fractures, an expert panel rapidly produced these recommendations based on a linked systematic review.

(MAIN INFOGRAPHIC)

We recommend against the use of low intensity pulsed ultrasound (LIPUS) for adults and children with fractures or osteotomy

Around 38% of people have a fracture at some point in their life. Each year this is around 3.6 per 100 people of all ages.[1] Five to 10 percent experience delayed healing or non-union.[2] Bones can also be broken for medical reasons; osteotomy is a procedure whereby a bone is cut to shorten, lengthen, or to change its alignment. Although osteotomy is performed infrequently, the bone is subject to the same healing problems as traumatic fractures and may require more extensive recovery for bone healing.[3]

Bone stimulators such as LIPUS and electro-magnetic field therapy might promote bone healing by stimulating bone growth (osteogenesis) in long or other bones following:

- fracture managed with or without surgery, or
- osteotomy.

Guidance from independent organisations on LIPUS for bone healing is scarce. The U.S. Food and Drug Administration (FDA) approved LIPUS for fracture healing in 1994, and for treatment of established non-unions in 2000.[4] The National Institute for Health and Care Excellence (NICE) issued a statement in 2010 supporting the use of LIPUS to reduce fracture healing time and provide clinical benefit, particularly in circumstances of delayed healing and fracture non-union.[5]

A Canadian survey of 450 trauma surgeons in 2008 found that 45% of respondents were using bone stimulators to manage tibial fractures. Of those, about half used electro-magnetic field therapy and the other half used LIPUS.[6] Global revenues for bone stimulators were about 400 million USD in 2004.(7) In 2007, sales from LIPUS were around 250 million in the US alone (personal communication, Jason Busse, 2016). Costs vary across countries, each device costing between 1,300 to 5,000 USD each (based on US and UK). To what extent the use of LIPUS and its associated costs and sales have increased or decreased over the past years remains uncertain in the absence of available data.

How the recommendation was created (BOX)

The Rapid Recommendations team believed that the TRUST trial, when considered in context of the full body of evidence, could change practice.[7]

Our international guideline panel included orthopaedic and musculoskeletal trauma surgeons, physiotherapists, general internists, methodologists, and people with lived experience of bone fractures including one who used LIPUS (appendix 1). No person had financial conflicts of interest; intellectual and professional conflicts were minimised and managed according to *BMJ* Rapid Recommendations standards (appendix 2).

The panel followed the *BMJ* Rapid Recommendations procedures for creating a trustworthy recommendation[8, 9] and applied the GRADE system to critically appraise the evidence and move from evidence to recommendations (appendix 3).[10] The panel considered the balance of benefits, harms, and burdens of the procedure, the quality of evidence for each outcome, the typical and expected variation in patient values and preferences, resources, feasibility, and acceptability.[11] Recommendations can be strong or weak, for or against a course of action. We place a very low value on speculative benefits. Thus, when available evidence suggests no benefit, or only very low quality evidence suggests benefit, and moderate or high quality evidence demonstrates appreciable adverse effects, burden, or cost, the panel would make strong recommendations against an intervention.

The panel considered research from linked teams who conducted:

- a rapid systematic review the effects of LIPUS added to standard care, for a variety of fractures and osteotomies where LIPUS was applied, which informed the recommendation,[12] and
- a systematic literature search on patients' values and preferences, which did not identify any relevant studies.

Given that the TRUST trial demonstrated no effect of LIPUS, the panel decided that there was no need for a systematic review of observational studies reporting typical (prognostic) outcomes of patients without LIPUS therapy.

The guideline panel members identified that the important outcomes for patients with bone fractures or osteotomy considering LIPUS for bone healing were:

- functional recovery (time to return to work and time to full weight bearing),
- pain,
- subsequent operations, and
- complications.

Radiographic healing was considered to represent a less important outcome for patients. It was included as many clinicians likely consider radiographic healing to inform their management decisions.

The evidence

A new RCT on the use of LIPUS for tibial fracture healing

The TRUST randomised controlled trial published in *The BMJ* 25 October 2016 found that the addition of LIPUS to standard care did not improve functional recovery or accelerate radiographic healing at one year compared to a sham device, in 501 adult patients undergoing surgery for fresh tibial fracture.[7]

A systematic review of LIPUS for all fracture healing

The data from TRUST were included in a linked systematic review of LIPUS compared to sham or no device on patient-important outcomes and radiographic fracture healing in patients with a fracture or osteotomy. The researchers identified 26 randomised trials (1565 adult patients).[12] The systematic review provides evidence of moderate to high certainty that LIPUS has little or no impact on functional recovery (e.g., time to return to work or time to full weight bearing), pain, the number of subsequent operations, or time to radiographic healing (Infographics 1). From the nine trials reporting adverse events, there was high certainty that there is no risk of device-related adverse events.

For some patient-important outcomes (return to work, time to full weight bearing, and number of subsequent operations) our certainty is moderate rather than high because the confidence intervals included important benefit and harm. The observed heterogeneity in the effect sizes between trials for time to weight bearing, pain, and radiographic healing was explained by considering risk of bias: studies with serious methodological limitations suggested a benefit, while studies without such limitations did not (see subgroup analyses in the linked systematic review).[12] We therefore base our conclusions on the trials with low risk of bias. The estimates for typical (prognostic) outcomes for patients not treated with LIPUS were based on the control arm of the TRUST trial which enrolled patients with tibia fractures in the US and Canada and was at low risk of bias. Infographic 2 shows details about the trials and characteristics of included patients.

INFOGRAPHIC 2: PATIENT AND TRIAL CHARACTERISTICS (26 trials, 1565 adult patients)

	Median	Range
Number of patients enrolled	30	8 to 501
Mean Age	39.5	19 to 68
Sex (% women)	25%	0% to 84%
Type of fractures or osteotomies (number of studies)	Operatively managed fresh fractures (7 trials, 3 low risk of bias), non-operatively managed fresh fractures (6 trials; 1 low risk), stress fractures (2 high risk), non-union (3 high risk), osteotomy (8 trials; 2 low risk), mostly affecting the tibia (14 trials; 3 low risk).	
Comparator	All patients received standard post-fracture or post-operative care without (9 studies) or with a sham device (17 studies).	
Exclusion criteria	Most studies excluded patients with infections, multiple fractures, pathologic fractures, or large gap between bone ends after fixation.	
Funding	3 of 26 trials were explicitly free from industry funding.[13-15]	
Patient involvement	No trials involved patients in design or conduct.	

Understand the recommendations

Based on best current evidence demonstrating that LIPUS does not improve patient-important outcomes or radiographic healing, we issue a strong recommendation against LIPUS for patients with bone fractures or osteotomy. The panel unanimously agreed that the moderate-to-high certainty in a lack of benefit – through a systematic review of 26 trials – combined with high costs of treatment, represents an inefficient use of limited health care resources.

Trials including patients with stress fractures, non-union, and osteotomies were either at high risk of bias or did not contribute relevant outcome data to the systematic review, and no trials included children. Evidence for these types of fractures as well as for children, therefore, is indirect. The trials we used to inform the recommendation studied patients with fresh tibial and clavicle fractures managed operatively. The panel considered to what extent evidence from adults with tibial and clavicle fracture would apply to children and adults with different types of

fracture. We judged that although it is indirect it is applicable and did not downgrade our certainty in the evidence.[16]

Working from first principles, the panel found no compelling anatomic or physiologic reason why LIPUS would be likely beneficial in these other patient populations. For example, osteotomies have the same biological response as in traumatic fractures. If LIPUS on fresh fractures is not able to decrease the incidence of non-unions, it is very unlikely that it exerts a beneficial effect in the conversion of these non-unions into healed bones. Paediatric fractures typically heal faster and have lower rates of non-union; any benefit of LIPUS for children is likely be smaller than for adults.

Practical issues

Patients with fractures may experience pain and limited mobility, particularly in the first 2 to 3 months. Driving and physical activity is limited during the recovery period. Infographic 3 outlines the key practical issues for those considering LIPUS as an adjunct therapy in the management of bone fractures.

INFOGRAPHIC 3: PRACTICAL ISSUES

	Low intensity pulsed ultrasound (LIPUS)
PROCEDURE	• Patient operated device. • Portable device that emits ultrasound that cannot be heard or felt. • A probe (also called transducer) is applied to area of fracture, directly on skin using a gel to conduct the ultrasound. • If a cast is used, a window can be created to give access to the area. • Used for 20 minutes each day for 14 to 140 days or until healing.
TESTS & VISITS	• Device usually obtained from orthopaedic clinic or directly from the manufacturer. • A prescription from a family physician or orthopaedic surgeon is typically required. • Follow up is the same for patients using LIPUS.
ADVERSE EFFECTS & INTERACTIONS, ANTIDOTE	• The gel used for the probe may rarely result in skin irritation. • Should not be used in proximity to a cardiac

	pacemaker.
COST & ACCESS	• The LIPUS device costs about 1,300 – 5,000 USD; some devices can be re-used. • Health insurance may or may not cover the cost of the device.
TRAVEL & DRIVING	• Device can be cumbersome to travel with and may require authorization for transport in cabin luggage.

Values and Preferences

The panel agreed in advance upon what would constitute an important benefit of LIPUS for the key patient-important outcomes, and decided how patient values and preferences might vary between persons. Our systematic search did not identify any studies to inform these values and preference judgements (appendix 4).

Guided by patients on our panel, we believe that most people want at least moderate quality evidence, for at least a possibly important benefit in functional recovery time or pain to make the time and expense of using LIPUS worth it. The limited compliance in the TRUST trial supports our assessment that LIPUS can be burdensome to patients during their compromised clinical state.[7]

Costs and resources

LIPUS is expensive, and given its lack of benefit on patient-important outcomes and radiographic healing, it does not represent an efficient use of health resources for individuals or health funders. Health care organisations that currently pay for LIPUS may reasonably choose to stop reimbursements based on best current evidence and our strong recommendation against LIPUS.

Future research

It is unlikely that new trials will change the interpretation of the evidence: LIPUS does not improve bone healing, time to return to work, or other patient important outcomes (GRADE high to moderate quality of evidence). Fracture research should further focus on other interventions that have a greater probability to speed up healing, whereas for treatment of non-unions alternatives should be compared to the current gold standard that are used to initiate a bone healing response, such as operative stabilization with or without autologous bone grafts. Research should also address de-implementation strategies for the use of LIPUS for bone healing, where a better understanding of other, cognitive or political factors that facilitate or hinder de-implementation is warranted.[17]

Box. How patients were involved in the creation of this article

Four people with lived experience of bone fractures, one of whom had used LIPUS, were full panel members, participated in the teleconferences and email discussions, and met all authorship criteria. These panel members identified important outcomes and led the discussions about values and preferences. Return to work or regular activities and pain were weighed as of higher importance for patients than radiographic healing. The panel identified key practical issues including concerns with cost and access to LIPUS, as well as the burden of therapy. In light of the lack of efficacy, one patient panel member remarked and the others agreed that discussing LIPUS would unnecessarily take valuable time from the patient-clinician encounter, which is often already too short.

Box. What you need to know

- LIPUS is frequently used for bone healing for people who have had fractures or osteotomy
- LIPUS is expensive
- A new trial and linked systematic review provides moderate to high certainty evidence to support a strong recommendation against the use of LIPUS for bone healing
- Further research is unlikely to alter the evidence
- Healthcare administrators and funders may consider de-implementation of LIPUS as a performance indicator in quality improvement initiatives

Box. Linked articles in this *BMJ* Rapid Recommendations cluster

• Systematic review of LIPUS for bone healing after fracture or osteotomy	
	Review of all available randomised trials that assessed LIPUS versus sham device or no device that informed the recommendation
	Schandelmaier S, Kaushal A, Lytvyn L, et al. Low intensity pulsed ultrasound for bone healing: systematic review of randomized controlled trials. *BMJ (submitted)* 2016.
• Recommendation and decision aids in MAGICapp online platform	
	Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices
	www.magicapp.org

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Footnote

This *BMJ* Rapid Recommendation article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between the MAGIC group (www.magicproject.org) and *The BMJ*. A summary is offered here and the full version including decision aids is on the MAGICapp (www.magicapp.org), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation of recommendations to allow contextualisation of recommendations and to reduce duplication of work. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact *The BMJ* for permission to reuse content in this article.

Data supplements on bmj.com

Infographic 1: Summary of recommendations and evidence

Appendix 1: Rapid Recommendation panel members
Appendix 2: Full list of authors' declarations of interests
Appendix 3: Methodology for development of *BMJ* Rapid Recommendations
Appendix 4: Values and preferences search for literature
Appendix 5: The full information available on the MAGICapp

Competing interests

All authors have completed the *BMJ* Rapid Recommendations interests form. The *BMJ* Rapid Recommendations team judged that no panel member declared financial, professional, or academic interests that precluded authorship. The declared interests for each panel member are in the supplementary appendix. No panel members declared any financial conflicts of interest related to this clinical question, specifically no financial ties to the bone stimulators industry. B Mollon uses bone stimulators in practice. T Agoritsas, RAC Siemieniuk, B Mollon, S Schandelmaier, L Lytvyn, and PO Vandvik participated in writing the complementary systematic reviews that formed the evidence base for this guideline. B Mollon was a co-author on a systematic review on this topic published in *The BMJ* in 2009, for which R Poolman wrote the editorial. No other panel member has previously formally made statements regarding LIPUS. This article was edited by H MacDonald at *The BMJ* who had no relevant financial or intellectual interests.

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This study was unfunded.

Ethics committee approval

Not applicable.

Transparency declaration

R Poolman affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.