External Assessment Centre report

Title: EXOGEN ultrasound bone healing system for long bone fractures with non-union or delayed healing

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Declared interests of the authors

None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

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1 Summary

Scope of the sponsor's submission

The sponsor proposes the use of EXOGEN Express for well aligned and stable fractures of the long bones at delayed union (after 3 months with no radiological evidence of healing) rather than routine observation followed by further surgery if necessary at diagnosis of non-union (failure of healing after 9 months). It is not clear whether this meets the requirements of the scope, which asks for a comparison of EXOGEN with surgical treatment. However, if current practice would be to not offer further surgery for uncomplicated delayed union fractures, then the comparison presented in the submission might be clinically appropriate. Clinical advice suggests that 'prophylactic' surgery for fractures of the long bones does sometimes take place between 3 and 9 months post-fracture, but that this varies according to expectations of individual healing times – for example, patients with fractures of the tibia or with indicators of impaired healing (e.g. smoking), might not be expected to heal until 6 months anyway, and so would be less likely to be offered surgery in advance of a diagnosis of non-union.

For non-union fractures, the submission presents a direct comparison between EXOGEN and surgery, and is therefore consistent with the scope.

Summary of clinical evidence submitted by the sponsor

Evidence for delayed union

The Schofer RCT of EXOGEN versus placebo reported healing rates of 65% versus 46% over four months of follow up. This difference was not statistically significant (hazard ratio 1.69, p=0.07). No device-related adverse events were reported in the EXOGEN arm of this study.

Estimates of the absolute rate of healing with EXOGEN are provided by registry data (Mayr 2000). For non-union, 90% of long bone fractures healed in a mean time of 4.4 months. Two other delayed union case series reported healing rates with EXOGEN: of 83% (Jingushi 2007), time to healing not reported; and 94% (Lerner et al. 2004) over a mean of 17 months.

Other outcomes requested in the scope ('return to painless weight bearing' and 'avoidance of surgery') were not reported.

No estimates of healing rates following surgery in people with delayed union fractures of long bones were identified.

Evidence for non-union

There was no direct comparative evidence of the effect on healing rates or other outcomes of interest for EXOGEN versus surgery in non-union fractures of long bones. However, independent estimates of healing rates for the two interventions were available from non-comparative case series.

The mean healing rate for non-union long bone fractures was reported in the Mayr analysis of EXOGEN registry data: 84% over a mean of 5.3 months. Other estimates ranged from 66% for a mixture of long bone fractures (Jinguishi et al. 2007) to 95% for radius/ulna fractures and 100% for tibia and tibia/fibula fractures (Mayr et al. 2000). No device-related adverse events were reported in the EXOGEN studies. Other outcomes requested in the scope ('return to painless weight bearing' and 'avoidance of surgery') were not reported, although in the context of non-union it is reasonable to suppose that patients whose fractures healed following use of EXOGEN would have otherwise required surgery.

For non-union long bone fractures treated by surgery, healing rates ranged from 62% to 100%, and healing time ranged from 9 weeks (Livani et al. 2010) to 24 weeks (Ring et al. 1997). There were some reports of time to weight bearing, but these may not be consistent with the scope. Further surgery and adverse events due to surgery were reported in some papers.

Summary critique of clinical evidence submitted by the sponsor

Delayed union

The EAC considers that the best estimate of the absolute rate of healing in patients with delayed union fractures treated with EXOGEN is 90% (87% to 92%) healed in a mean time of 4.4 months (Mayr 2000). This comes from a large registry database, with definitions of delayed union and non-union that match those in the scope, and with results reported separately for different long-bone and non long-bone fractures. Other estimates vary and are difficult to pool, due to differences in definitions and failure to report duration of follow up.

However, no evidence was available to estimate a comparable rate of healing with surgery. It is therefore not possible to compare EXOGEN with surgery in this population.

A sham-controlled randomised trial compared EXOGEN with delay in further surgery for a population of patients with fractures of the tibia (Schofer 2010). This trial failed to detect a significant improvement in the rate of healing with EXOGEN (hazard ratio 1.69 (p=0.07) over 4 months), although it was not powered to detect differences in healing rates, and it did report statistically

significant improvements in indicators of progression towards healing (bone mineral density and bone gap area). The applicability of these results to delayed union fractures is questionable, as the study included a large proportion of fractures which, under the definition of the scope, may be considered to be non-unions (failure of healing after 9 months).

Non-union

The EAC considers that the best estimate of the absolute rate of healing for non-union fractures treated with EXOGEN is 84% (80% to 89%), with a mean time to healing of about 5.3 months (Mayr 2000) – based on the same large registry database as the non-union estimate. As with delayed union, estimates from other studies vary and cannot be pooled.

Estimates of healing rates following surgery for non-union long bone fractures are available, but the evidence is of poor quality. The submission included a review of surgical case series, reporting healing rates from 62% to 100%, and healing times from 9 weeks to 124 weeks. However, the included studies differed in population, intervention and outcome, and it is not clear that they were identified systematically. The sponsor also cites Gebauer et al (2005), who report a mean healing rate of 86% based on 23 published studies of surgery in patients with non-union fractures (range 68% to 96%). But this did not appear to be based on a systematic review either, and it included some studies of non long bone fractures.

Adverse events

None of the EXOGEN studies included reports of any device-related adverse events. There are rare reports of localised pain or irritation following use of EXOGEN – possibly reactions to the contact gel – and isolated reports of possible interactions with implantable devices. In contrast, several surgery studies reported adverse events, including infections.

Summary of economic evidence submitted by the sponsor

The sponsor reviewed published economic evidence related to the scope. They found one study (Taylor 2009) that estimated the net cost of alternative treatment strategies for patients with fresh (out of scope) and non-union fractures of the tibia. This used a Markov model, with monthly cycles over a time horizon of one year. The other two studies (Kanakaris 2007 and Patil 2006) were non-comparative analyses, estimating the cost of surgical treatment for patients with non-union fractures of long bones.

The sponsor also submitted two models: one for delayed union and one for non-union. These models were adapted from the published model by Taylor

et al (2009). The sponsor concluded that EXOGEN is a cost-saving option for early use in delayed union and also as an alternative to surgery in non-union.

Summary critique of economic evidence submitted by the sponsor

The economic models submitted by the sponsor are of a good general standard. We found a few minor errors in coding and data entry. However, in adapting the Taylor model, the sponsor made some adjustments to modelling assumptions and parameters, some of which are more questionable. In particular, the method by which healing rates were extracted from the key clinical studies (Mayr and Schofer) and converted to monthly rates led to an overestimation of the likely relative effectiveness of EXOGEN compared with the control arm in the delayed union model.

The non-union model relies on an assumption of equal effectiveness for EXOGEN and surgery, for which there is only weak evidence. This model is also driven by the estimated cost of surgery itself, which is subject to uncertainty. The sponsor's estimate, based on clinical opinion, was higher than the relevant HRG-based reference costs.

Both models also increased the rate of infection and the cost of infections, compared with the results reported in Taylor (2009).

External Assessment Centre commentary on the robustness of evidence submitted by the sponsor

The EAC corrected errors in coding and data entry, and found that they made little difference to the results. However, changes to the methods for calculating monthly healing rates from the clinical studies for the delayed union model (Mayr and Schofer) meant that early use of EXOGEN in this context did not appear to be cost-saving – based on its preferred model, the EAC estimated that use of EXOGEN in delayed union costs approximately £500 more per patient than waiting and providing surgery at non-union if required.

We found the results of the non-union model to be more robust: with an estimated saving with EXOGEN of approximately £1,200 per patient compared with immediate surgery. EXOGEN remained cost-saving under a range of scenarios. Only under a 'worst case' scenario of the healing rate with EXOGEN (82%) and the relative risk of healing with surgery (2.5), did EXOGEN not appear to be a cost-saving alternative to surgery for non-union.

We also tested reductions in the rate and cost of infections, but found that these made little difference to the results – since the absolute number of patients developing an infection in any of the treatment arms is small.

2 Background

2.1 Overview and critique of sponsor's description of clinical context

The sponsor sets the clinical context by explaining that there are two versions of the EXOGEN ultrasound bone healing system that are applicable to the decision problem defined in the scope:

- EXOGEN Express, designed to treat delayed union fractures (no radiological evidence of healing after approximately 3 months). This delivers up to 150 daily treatments (nearly five months); and

- EXOGEN 4000+ designed for non-union fractures (failure of healing after 9 months), which delivers at least 191 days of treatment (over six months).

The devices are single use – one per patient – and non-rechargeable. They are designed to be used by the patient at home, although as noted in the scope, some patients might require assistance. The sponsor argues that there are no additional costs for consumables, tests or investigations, facilities, technologies or infrastructure required for delivery of the intervention. This may be reasonable, as the device appears to be simple to use, however there may be some opportunity costs associated with providing information to patients during routine appointments. If EXOGEN is successful at averting the need for further surgery, as claimed in the submission, it might present an opportunity for the NHS to redirect resources from these services.

The sponsor notes that the scope is limited to delayed and non-union fractures of the long bones: which were defined as the humerus, ulna, radius, femur, tibia and fibula for the purposes of this evaluation. These fractures reduce patients' quality of life and general well-being, and treatment can be complex and protracted, incurring high costs for the NHS.

The incidence of long bone fractures is estimated from Health Survey for England 2002-4 data (Donaldson *et al* 2008) at approximately 1.2 per 100 person years for men, and 0.8 per 100 for women. Assuming that around 5-10% of these fractures will not heal as expected (Rubin 2001), and an adult population of 40.2m, the sponsor estimates a potential treatment population 25,536 - 51,072 people per year. This estimate appears reasonable, although it is unclear how many patients would meet other criteria for use of the technology, including the size of inter-fragment gap (<10mm), and the stability and alignment of the fracture (Figure 1, p17).

The sponsor's proposed pathways of care with EXOGEN are outlined on p19-20 and in Figure 1 of the submission. These pathways and those for current

practice are further defined in the description of the cost model (p124-129) and Figure 7. However, there is some ambiguity in these descriptions: for example, Figures 1 and 7 do not distinguish between pathways for delayed and non-union, or explain how the two fit together. Our understanding of the current and proposed pathways outlined in the submission and consistent with the cost model are described below, and illustrated in Figure 1.

A) Current pathway of care

Patients have treatment immediately after fracture, with open or closed reduction, X-rays to verify alignment, immobilisation with a plaster or splint, and possibly insertion of internal or external fixings as appropriate. Those who do not show progress to healing by three months (delayed union) would not usually receive further surgery at this time, unless they had particular indications (e.g. unstable or mis-aligned fractures, or an inter-fragment gap of more than 10mm). If, however, the bone had failed to heal by nine months after the original injury (non-union), then further surgery would be required.

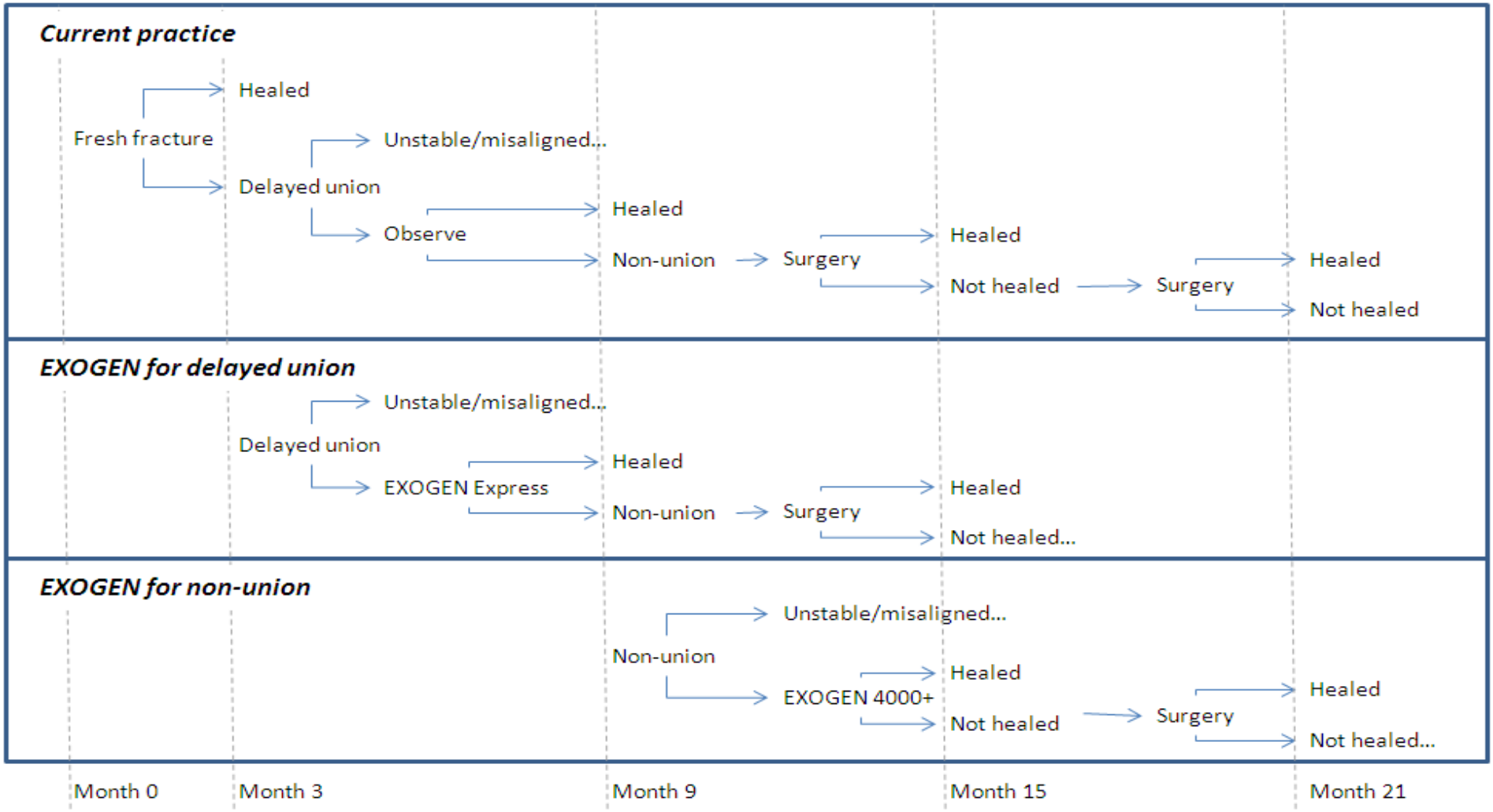
B) EXOGEN for delayed union

The sponsor suggests that the EXOGEN Express device should be used at the point of delayed union for patients with stable, well-aligned fractures, with a gap less than 10mm. The patient would use the device for 20 minutes per day, until their fracture heals or the device expires. Patients with non-union fractures following use of EXOGEN Express would have surgical treatment.

C) EXOGEN for non- union

The sponsor proposes use of the EXOGEN 4000+ device at the point of non-union for patients with stable, well-aligned fractures, with a gap less than 10mm. The device would be used daily for 20 minutes until healing or expiry of the device, followed by surgery if the fracture was still unhealed at that time (approximately six months after the point of non-union).

Figure 1. Illustration of care pathways



For delayed union, the effectiveness data and cost model presented in the submission compare EXOGEN Express with routine observation. It is not clear that this meets the requirements of the scope, which asks for a comparison of EXOGEN with surgical treatment. However, if current practice would be to not offer further surgery for uncomplicated delayed union fractures (stable and well-aligned), then the comparison presented in the submission might be clinically appropriate. Our understanding is that some patients would have surgery between 3 and 9 months, but that this would differ according to expectations of healing according to bone type and individual risk factors for impaired healing.

For non-union fractures, the submission does present a direct comparison between EXOGEN and surgery, and is therefore consistent with the scope.

An important aspect of the care pathway reflected in the costing model is the risk of post-surgical infection, particularly of 'deep' bone infections (osteomyelitis). Reducing the risk of infection by avoiding the need for further surgery is an element in the sponsor's argument that EXOGEN is clinically superior and cost-saving. Estimates of the incidence of infection and the costs of treating infections are discussed in section 3 below.

It should also be noted that the cost model presented relates only to the case of a tibia fracture initially treated by surgical insertion of an intramedullary (IM) nail. The sponsor chose to focus on Tibia fractures as they are a common cause of healing problems, and there is sufficient data to allow modelling. Though cost and patient impact do differ for other long bone fractures, the tibia is probably a reasonable exemplar – femoral non unions are more disabling and difficult to treat, but upper limb fractures are less so.

2.2 Overview of sponsor's description of ongoing studies

Ongoing studies – section 5.1 of sponsor's submission. The sponsor states that there are no ongoing studies relevant to the scope of the submission.

We identified one ongoing study listed in the ClinicalTrials.gov register that is *potentially* of relevance – the **TRUST** trial, NCT00667849. This is a multinational randomised placebo-treatment controlled clinical trial to evaluate the EXOGEN Bone Healing System for adults with tibial fractures treated with intramedullary nailing. Estimated enrolment is 500 patients and outcomes include time to healing, followed up to 12 months. It is sponsored by Smith and Nephew, and is stated to be due to complete in December 2012. Dijkster et al (2011) report an analysis for 51 patients from the TRUST feasibility trial, assessing the effect of adding clinical notes to radiographs in adjudication of fracture healing. It is not explicitly stated in the clinical trial register, or in

Dijkster *et al* 2011, but it appears that the sample largely or wholly comprises patients with fresh fractures. If so, this study would fall outside the scope of this current assessment.

The **PUSH-IT** trial (ISRCTN90844675), which is registered in the Current Controlled Trials register as completed but has not yet reported, is a randomised comparison of adjuvant EXOGEN compared with a 'standard of care' control after intramedullary nailing of tibia fractures. This study is sponsored by the German Employer's Liability Insurance for the Administrative Professions. Again, it appears that this study relates wholly or largely to fresh fractures, and so is out of scope.

We therefore agree with the sponsor's conclusion that there are no ongoing studies relevant to the scope of this evaluation.

2.3 Critique of sponsor's definition of the decision problem

Population

The scope defines the population as: "patients with long bone fractures with non-union (failure of healing after 9 months) or delayed healing (no radiological evidence of healing after approximately 3 months)."

The sponsor specifies that the long bones to include in this evaluation are: humerus, ulna, radius, femur, tibia and fibula (Glossary p10).

In their summary of included papers (Table B3, page 34), the sponsor lists 9 clinical studies of EXOGEN and 10 of surgery, although they later excluded one of the EXOGEN studies (Pigozzi 2004) as only 2 out of 15 patients had a fracture of a long bone. The population characteristics for the remaining 18 studies are summarised in Table 1 below.

The studies were conducted in 12 countries, but none in the UK. This might potentially limit applicability of the findings to patients treated in an NHS context. For example, differing practice in treating the initial fracture might possibly influence clinical features of delayed union and non-union fractures, making them more or less amenable to ultrasound treatment.

The mean age of study participants was around 30-50 years, but there was a wide range (13 to 92).

The EXOGEN studies included patients with fractures classified as delayed union (3 studies), non-union (4 studies) and both (2 studies). However, definitions of delayed union (DU) and non-union (NU) varied between studies,

and often differed from the definitions in the scope. For example, Schofer *et al* defined delayed union as a "lack of clinical and radiologic evidence of union, bony continuity or bone reaction at the fracture site for no less than 16 weeks from the index injury or the most recent intervention" (Schofer 2010). But 51 of the 101 patients in this trial had fractures that had not healed for over 9 months at study entry, and would therefore appear to fit the scope definition of non-union. No subgroup analysis comparing results for delayed union and non-union fractures was presented. The Schofer trial is an important study, as it is the only sizeable randomised controlled trial of EXOGEN, and it is a key input to the costing model for delayed union. However, its applicability to this context is unclear, because under the definition of the scope it included a large proportion of patients with non-union fractures (failure of healing after 9 months).

The other main source of effectiveness evidence used in the costing model comes from a registry of patients treated with EXOGEN, reported in Gebauer (2005) and Mayr (2000). The EXOGEN registry uses definitions of delayed and non-union, which are consistent with those in the scope.

The surgery case series - included for comparison with the largely uncontrolled EXOGEN studies – all related primarily to non-union fractures, although a few included patients with unhealed fractures of less than 9 months duration.

The studies included a mix of different long bone fractures, and some included other bones as well (where possible these data have been excluded from the summary of study outcomes). However, the only randomised evidence relevant to the scope relates to the tibia (Schofer 2010): although (Rutten 2008) report a small RCT of fibula, this did not include any outcomes specified in the scope. There is no direct evidence of the effectiveness of EXOGEN compared with surgery in patients with delayed union or non-union fractures of other long bones. For this reason, the costing model is restricted to tibia fractures. It may be questioned how generalisable the clinical evidence and cost estimates are to long bones other than the tibia, although this might be a reasonable exemplar.

Table 1. Summary of patient populations for included clinical studies

Study	Country	Long bone	Delayed / non-union	Mean fracture age (months)	Mean patient age (years)
EXOGEN STUDIES					
Schofer 2010 *	Germany	Tibia	DU/NU?	13 51/101>9m	43 (14-70)
Rutten 2008	Netherlands	Fibula	DU	6-11 2/13>9m	42-63
Lerner 2004	Israel	Femur, tibia, radius/ulna, humerus	DU	6 (1-38)	19-48
Jingushi 2007	Japan	Femur, tibia, humerus, radius, ulna	DU/NU	19 (3-159)	40 (14-83)
Mayr 2000 *	Germany	Femur, tibia, fibula, radius, ulna, humerus	DU/NU	951 3-9m 366 >9m	20 - 71
Gebauer 2005 *	Germany & Austria	Tibia, fibula, femur, humerus, radius, ulna	NU	>8	23-86
Nolte 2001	Netherlands	Humerus, radius, ulna, femur, tibia, fibula	NU	15 (6-34) 5/21<9m	18-90
Romano 1999	Italy	Tibia, humerus, femur	NU (septic)	8-30 1/13<9	28-78
SURGERY STUDIES					
Bellabarba 2002	USA	Femur	NU	10 (3-25)	48 (18-92)
Birjandinejad 2009	Iran	Femur, tibia	NU	-	31 (18-52)
Cacchio 2009	Italy	Femur, tibia, ulna, radius	NU	11	43
Friedlaender 2001	USA	Tibia	NU	33	34
Khalil 2010	Egypt	Ulna	NU		42
Lin 2010	Taiwan	Humerus	NU	>6m	42 55
Livani 2010	Brazil	Humerus	NU	>8m	38 (18-74)
Razaq 2010	Pakistan	Femur	NU	-	40
Ring 1997	USA	Femur	NU	17 (6-68)	35 (13-81)
Wu 2003	Taiwan	Tibia	NU	22 (10-48)	34 (19-58)

* Clinical evidence used in costing model

Intervention

The technology described in section 2 of the submission (p14) relates to the EXOGEN ultrasound bone healing system, as specified in the scope. Two versions of the device are available; the **EXOGEN Express** designed for delayed union fractures, and limited to 150 20 minute treatments; and the **EXOGEN 4000+** designed for non-union fractures, which delivers a minimum of 191 20 minute treatments.

The sponsor submitted certification of approval by: the Medical Devices Bureau of Canada; the Australian Department of Health and Ageing Therapeutic Goods Administration; the British Standards Institution; the US Food and Drug Administration; EC Medical Devices Directive CE marking; BSI Management Systems Japan.

The intervention studies reported in the submission, and those informing the cost analysis, all relate to versions of the EXOGEN device (sometimes under the name of SAFHS).

Comparator(s)

The comparators specified in the scope were surgical treatment, including internal and external fixation, with or without bone grafting. The interventions and comparators for studies included in the submission are summarised in Table 2 below.

The submission did not identify any studies directly comparing EXOGEN with surgery for people with delayed or non-union fractures of the long bones.

The Schofer trial compared the use of EXOGEN with a sham device (Schofer 2010). Most of the participants in this study had previously received surgery (including intramedullary (IM) nailing, locking screws, external fixation, osteosynthesis place and supplemental bone graph), but patients who had revision surgery or reoperations at the fracture site within four months were excluded. Schofer *et al*, does not, therefore, provide direct evidence for the requested comparison of EXOGEN vs. surgery.

So, as noted above, the sponsor's cost model does not compare EXOGEN with immediate surgery at the point of delayed union. Instead it is assumed that both groups would have received surgical intervention shortly after the time of injury, and EXOGEN is compared with routine observation at the point of delayed union followed by further surgery for both groups at the point of non-union if required.

Table 2. Summary of study design, interventions and comparators for included clinical studies

Study	Delayed/ non-union	Study design	Intervention	Comparator
EXOGEN STUDIES				
Schofer 2010	DU/NU?	RCT	EXOGEN	Sham device
Rutten 2008	DU	RCT	EXOGEN	Sham device
Lerner 2004	DU	Case series	EXOGEN	
Jingushi 2007	DU/NU	Case series	EXOGEN	
Mayr 2000	DU/NU	Case series	EXOGEN	
Gebauer 2005	NU	Case series	EXOGEN	
Nolte 2001	NU	Case series	EXOGEN	
Romano 1999	NU	Case series	EXOGEN	
SURGERY STUDIES				
Bellabarba 2002	NU	Case series	Plate & screws	
Birjandinejad 2009	NU	Case series	Plate & screws after IM nailing	
Cacchio 2009	NU	RCT	Surgery	Shock Wave* *
Friedlaender 2001	NU	RCT	Surgery + rhOP-7	Surgery + autograft
Khalil 2010	NU	Case series	Contour plate	
Lin 2010	NU	Prospective comparison	Surgery + allograft	Surgery + autograft
Livani 2010	NU	Case series	Plating	
Razaq 2010	NU	Case series	Exchange nailing	
Ring 1997	NU	Case series	Wave plate	
Wu 2003	NU	Case series	Reaming bone grafting	

* Outside scope

For non-union, the sponsor argues that case series of patients treated with EXOGEN alone can provide sufficient evidence of effectiveness – since one would not expect *any* healing in these patients in the absence of treatment. Therefore, non-union patients may provide their own control – the studies are referred to as 'self-paired' (Gebauer 2005, Jingushi 2007, Nolte 2004 and Romano 1999).

However, this self-paired data does not provide evidence of the relative effectiveness of surgery and EXOGEN in non-union. The sponsor therefore had to rely on estimates of the absolute healing rate from separate case series of surgery and EXOGEN. This approach is vulnerable to bias due to differences between the study populations and contexts.

The sponsor's cost model for non-union bases the estimated healing rate with EXOGEN on registry data reported in Mayr (2000), and assumes equal effectiveness for surgery in this population. The latter assumption is based on

a comparison of a subset of local registry data presented by Gebauer *et al* (2005) and the pooled result of a review of published case series of non-union surgery presented in the same paper. However, this review did not appear to be systematic (no search strategy was presented), and it included studies of non long-bone as well as long-bone fractures. The sponsor also presented their own review of the non-union surgery case series literature. This did use a systematic strategy to identify and select studies (section 7.1 and 7.2, p27-32), but it is not clear that all relevant studies were retrieved: "EXOGEN data was identified first and then surgical data was matched as closely as possible to the methodologies and design of the relevant papers" (p28). The assumption of equal effectiveness for surgery and EXOGEN in non-union fractures is based on weak non-comparative evidence. If surgery were to be more effective than EXOGEN at this point in the pathway, then the sponsor's conclusion that EXOGEN is dominant for non-union fractures might not be justified. We therefore tested changes to the relative risk of healing with surgery compared with EXOGEN in our sensitivity analysis.

Outcomes

Outcomes requested in the scope are:

- Bridging on radiograph (3 out of 4 cortices bridged);
- Fracture healing time;
- Return to painless weight bearing;
- Avoidance of further surgery; and
- device-related adverse events.

The availability of these outcomes is reported in Table 3. Most studies reported healing rates and healing times, however reporting of the other outcomes was sparse. The sponsor mentions the lack of accepted methods for diagnosing delayed and non-union fractures, including differing time thresholds and clinical and radiographic criteria (section 3.4 p18). This complicates the assessment of outcomes in the clinical studies.

Table 3. Summary of reported outcomes for included clinical studies

Study	Bridging on radiograph	Healing rate	Healing time	Painless weight bearing	Further surgery	Adverse events
EXOGEN STUDIES						
Schofer 2010	No[3]	Yes	No	No	No[2]	Yes
Rutten 2008	No[3]	No	No	No	No	No
Lerner 2004	No[3]	Yes	Yes	No	No	No
Jingushi 2007	Yes	Yes[1]	No	No[1]	No[2]	No
Mayr 2000	No[3]	Yes	Yes	No	No[2]	No
Gebauer 2005	No[3]	Yes[1]	Yes	No[1]	No[2]	No
Nolte 2001	No[3]	Yes	Yes	No	No[2]	No
Romano 1999	No[3]	Yes	Yes	No	Yes	No
SURGERY STUDIES						
Bellabarba 2002	No[3]	Yes	Yes	No	Yes	Yes
Birjandinejad 2009	No[3]	Yes	Yes	No	Yes	Yes
Cacchio 2009	Yes	Yes	No	No	No	Yes
Friedlaender 2001	Yes	Yes	No	Yes	Yes	Yes
Khalil 2010	Yes	Yes	Yes	No	Yes	Yes
Lin 2010	No[3]	Yes	Yes	No	Yes	No
Livani 2010	Yes	Yes	Yes	No	No	Yes
Razaq 2010	No[3]	Yes	Yes	No	No	Yes
Ring 1997	No[3]	Yes	Yes	Yes	Yes	Yes
Wu 2003	No[3]	Yes	Yes	No	No	Yes

1 Definition of 'healing' in these studies included painless weight bearing, although time to painless weight bearing was not reported.

2 Non-union fractures that healed with EXOGEN are unlikely to have healed if EXOGEN had not been used. Healing rates for non-union fractures reported in these studies are therefore suggestive of avoidance of further surgery.

3 Not reported separately from other criteria of healing.

Cost analysis

The sponsor's cost models deviated from that requested in the scope in several ways.

- ***Comparison between EXOGEN and surgery***
  The non-union model compared immediate surgery with EXOGEN, followed by further surgery for both groups after six months if needed. This reflects the comparison requested in the scope. However, the delayed union model compared use of EXOGEN at 3 months with no further intervention at this time, followed by surgery at nine months if required. This does not directly address the comparison asked for in the scope, although it might be a relevant comparison if current clinical practice is to not offer further surgery until 9 months post-fracture.

- ***NHS and PSS Perspective***
  The cost models only included NHS costs. It is argued that this is a conservative approach, and that inclusion of personal social service

costs would only increase the estimated cost savings with EXOGEN. This is a fair point.

- ***Time horizon sufficiently long to reflect differences***
  The cost models only followed patients for a 12-month time horizon, which will not capture all differences in costs and health consequences.

  In the delayed union model, the sponsor assumes that a greater proportion of fractures will be healed by 12 months when patients are treated with EXOGEN. This implies that a greater proportion of costs will be omitted for the non-EXOGEN arm, so the short time horizon will tend to bias results against EXOGEN.

  However, for the non-union model, the impact of the short time horizon is much more uncertain. Although the sponsor assumes equal rates of healing with EXOGEN and surgery, they also assume a higher infection rate with surgery, which leaves a greater proportion of the cohort unhealed after 12 months in the surgery arm. As argued above, this would tend to bias the cost estimates against EXOGEN. But evidence supporting the assumption of equal effectiveness is poor. In sensitivity analyses where surgery is assumed to give a better healing rate, the bias from the short time horizon would be favouring EXOGEN.

- ***Sensitivity analyses***
  The model does not include probabilistic sensitivity analysis, which would have been helpful in understanding the overall extent and impact of uncertainty over model parameters. The deterministic sensitivity analysis presented in the submission is also very limited. The only parameters that were varied were the healing rate with EXOGEN and the comparator, and the monthly rate of infection (which was only increased, not decreased). We argue below that there are other important sources of uncertainty, and extend the sensitivity analysis of the cost models.

- ***Scenario analysis for risk sharing scheme***
  Not presented. The EAC does not have sufficient information to estimate the impact of this scheme ourselves.

Subgroups

The results of the clinical studies are summarised separately for non-union and delayed healing fractures, as requested in the scope. However, results are not presented for different long bone fractures, and the cost model only estimates results for tibia fractures.

It is noted in section 9.6.1, that the Taylor (2009) economic evaluation, on which the sponsor's cost model is very largely based, reported a subgroup analysis for patients with fresh fractures at high risk of delayed healing and increased infection rates – exemplified by smokers.

Special considerations, including issues related to equality

The scope notes that because treatment with EXOGEN is self-administered, some patients might need assistance in using the technology.

The submission does not identify any further equalities issues.

3 Clinical evidence

3.1 Critique of the sponsor's search strategy

Identification of studies

The sponsor points to the variability in diagnosis and treatment of non-union fractures and problems with the quality of study design which raises difficulty in searching. Their stated intention is to minimise the possibility of bias and allow a fair comparison between EXOGEN and surgical intervention.

Under the heading "Literature Search Strategy" the sponsor describes their approach to searching. Of the suggested databases (section 10.1 Appendix) the sponsor chose to search only one (MEDLINE via PubMed) which risks them increasing rather than minimising the possibility of bias. A more comprehensive search would have been achieved by including MEDLINE In-Process, EMBASE and the Cochrane Library. The EAC tested this by recreating the sponsors search strategies as closely as possible on EMBASE and CENTRAL.

The sponsor states that they also searched CRD databases but the meta-analyses they found were not within scope. Ideally, sources for searching for reviews and meta-analyses would include HTAi Vortal, TRIP database and general internet searches which would have located appraisals by health insurers, of which there are a number on this topic.

The searches were conducted on 12th April 2012 and were divided into two strands – search 1 looking at the technology and search 2 looking at surgery for delayed/non-union fractures of long bones. The EAC replicated the sponsor's searches (detailed in section 10.1) as closely as possible, resulting in similar yields to those obtained by the sponsor. The searches appeared to have pinpointed the topic areas required and to be broad enough to retrieve most relevant studies. There is some duplication of terms in the EXOGEN strategy but this would not affect the outcome.

The surgery search has not included the term delayed union so may have missed some references. Because of the volume of literature yielded by this search when using [ALL FIELDS], a decision has been made to restrict the search to title only. This pragmatic decision makes sense although again risks missing some references. Given the non-comparative nature of the evidence on surgery for non-union, this might potentially bias the results.

The searches were limited to the years 1992-2012, presumably relating to the years the technology has been in use. There was also a limit to English language publications only, which introduces a risk of bias, particularly since the technology is widely used internationally. When running searches on

EMBASE and CENTRAL the EAC did not use a language limit to avoid this risk.

The sponsor states that “identified literature from PubMed searches was used to source additional clinical literature and background literature”.....but do not clarify how this was done. The EAC assumes this may have been by reference list searching or using the “related articles” feature in PubMed.

The sponsor also states that “due to the large number of publications identified using the PubMed search terms, additional selection criteria were identified and used to screen articles.” The process is illustrated in the two flow diagrams (figs 2 and 3) under “Records screened”. Although not stated clearly, it seems that Tables B1 and B2 list the criteria used in the screening process for published and unpublished studies respectively.

The sponsor used reference searching as a means of supplementing the searches. The EAC agrees this is a reliable way of locating additional relevant papers.

The sponsor states that “EXOGEN data was identified first and then surgical data was matched as closely as possible to the methodologies and design of the relevant papers”. It is not quite clear what is meant by this –that the study designs used in the EXOGEN studies were then searched for in the papers identified by the surgical searches.

In conclusion, although the sponsor did not always follow recommended practice in searching for clinical evidence, we obtained a similar yield on repeating and extending their search strategy. However, we do consider that there is a potentially serious risk of bias from the use of post-hoc adjustment of the search strategy for the surgery studies.

Unpublished studies

No unpublished studies were identified. Sources listed are internal post-market vigilance and the annual report compiled for the FDA, together with a Google search. These searches could have been more extensive (pipeline sources, conference and annual meeting abstracts and trials registers) although admittedly the sponsor is likely to be aware of any unpublished studies relating to their own technology.

NB It would have been helpful if the list of references at the end of the submission had included titles.

3.2 Critique of the sponsor's study selection

Most inclusion criteria used for the selection of studies in the sponsor's submission Table B1 are consistent with the decision problem, and therefore are considered by the EAC to be appropriate. Patients included were adults with non-union or delayed unions in long bones. Studies included were published studies based on data collections after 1992. The included outcomes were healing rate and healing time but some other outcome measures (e.g. return to painless weight bearing, avoidance of further surgery, and device-related adverse events) specified in the scoping document were not featured in the sponsor's inclusion criteria.

The exclusion criteria used for the selection of studies were reasonable. It excluded fresh fractures or fracture healing complications in children. As EXOGEN is not suitable for skeletally-immature patients, the EAC thinks it is sensible to exclude children from the study population. Interventions not in the scope or lacking healing data were also excluded. Studies having fewer than 12 patients were excluded (and meanwhile studies having 12 or more patients in each series were included). This is rather a low cut-off, and the EAC noted that the smallest sample size of submitted studies was 13 (Rutten et al. 2008) and another study (Pigozzi et al. 2004) with only 2 long bone fracture patients was excluded. Studies in any language other than English were also excluded. The EAC thinks this is sensible decision and the submission did include studies undertaken in non-English speaking countries. Retrospective study design was excluded but it was not clear why the sponsor excluded this type of studies.

The same inclusion and exclusion criteria were applied to identify both published and unpublished studies. The sponsor included a total of 18 published studies in their submission, and no unpublished studies.

3.3 Included and excluded studies

Nineteen clinical studies were identified as relevant in the sponsor's submission: 9 studies of EXOGEN (delayed union and non-union patients) and 10 of surgery (non-union patients only). These studies are presented in Table 4 below (adapted from Table B3 of the sponsor's submission).

Despite listing it in Table B3, the sponsor excluded one study (Pigozzi 2004) as only 2 of the 15 patients had a long bone fracture. Therefore there were 18 studies included in the final submission.

The sponsor noted that they found no direct comparisons of EXOGEN and surgery. Therefore, they conducted separate searches for EXOGEN and surgical interventions in a way that the EXOGEN data was identified first and

then surgical data was matched as closely as possible to the methodologies and designs of the relevant papers. As noted above, it is unclear what this means, and we suggest that all studies that met the inclusion criteria should have been included, and that the match was not necessary.

There were 4 RCTs, including: two comparing EXOGEN with placebo (sham device) in delayed union of long bone fractures; one comparing surgery with shockwave in long bone non-union fractures; and one comparing two different types of graft in surgery for non-union patients. Another study (Lin 2010) was a non-randomised comparative study between surgery plus allograft or surgery plus autograft. The comparisons in the surgical studies are not relevant to the decision problem defined in the scope. We therefore treat these as case series for the purpose of this evaluation.

The remaining 13 studies are case series. The sponsor noted that four of these studies for non-union fractures (Gebauer 2005, Jingushi 2007, Nolte 2001 and Romano 1999) are 'self-paired' studies, where the comparator was the non-union patients themselves, based on the assumption of no or minimal (5%) healing rate with no treatment.

Table 4. List of relevant published studies in sponsor's submission (Table B3 p34)

Primary study reference	Population	Intervention	Comparator
EXOGEN STUDIES			
Schofer 2010	DU/NU?	EXOGEN	placebo
Mayr 2000	DU/ NU	EXOGEN	-
Gebauer 2005	DU/NU	EXOGEN	-
Jingushi 2007	NU	EXOGEN	-
Lerner 2004	DU	EXOGEN	-
Nolte 2001	NU	EXOGEN	-
Romano 1999	NU (septic)	EXOGEN	-
Rutten 2008**	DU	EXOGEN	placebo
Pigozzi 2004 *	NU	EXOGEN	-
SURGERY STUDIES			
Bellabarba 2002	NU	Plate & screws	-
Birjandinejad 2009	NU	Plate & screws after IM nailing	-
Cacchio 2009	NU	Surgery	Shockwave
Friedlaender 2001	NU	rhBMP-7	Autograft
Khalil 2010	NU	Contour plate	-
Lin 2010	NU	Surgery plus Allograft	-
Livani 2010	NU	plating	-
Razaq 2010	NU	Exchange nailing	-
Ring 1997	NU	Wave plate	-
Wu 2003	NU	Reaming bone grafting	-

* Listed, but excluded by the sponsor – not long bone.

** Excluded by the EAC - outcomes outside scope.

We did not identify any relevant studies that had been excluded from the sponsor's submitted clinical evidence

The EAC excluded one study from the sponsor's submission (Rutten 2008), because it did not report outcome measures defined in the scope, but only indicators of progression to healing (bone mineral density, osteoid thickness).

3.4 Overview of methodologies of all included studies

The sponsor's submission included summaries of the methods used for each of the included studies. We have reviewed these summaries (Appendix A: Clinical study methods). An overview of the EAC critique of the included studies is provided below for delayed union (Table 5) and for non-union studies (Table 6). Key findings are summarised below:

Evidence for delayed union

- All four included studies of delayed union involved use of EXOGEN. One of these studies was a randomised trial comparing EXOGEN with placebo (Schofer 2010). The largest of the case series, analyses data from a registry of patients treated with EXOGEN (Mayr 2000).

- Although many of the participants in the included delayed union studies would have received surgical intervention shortly after injury, surgery was not used at the time of delayed union. Therefore, we cannot estimate the effectiveness of surgery for delayed union on the basis of this evidence.

Evidence for non-union

- Estimates of healing rates with EXOGEN and with a variety of surgical interventions are available from 15 case series (Table 6). The largest of these studies is the report by Mayr (2000), summarising healing rates and times from the EXOGEN registry.

- The sponsor argues that, since no or minimal healing of non-union fractures is expected without further intervention, evidence of healing from case series is reasonably robust – patients effectively provide their own 'control (the studies are 'self-paired'). However, independent case series cannot provide direct evidence for the effectiveness of EXOGEN compared with surgery.

- Indirect comparison of absolute healing rates from separate case series is potentially biased, due to differences between study populations and contexts.

Heterogeneity between studies

- Definitions of delayed union or non-union varied between studies. Some of these definitions may not be consistent with the scope. For example, Schofer (2010) defined delayed union as 'lack of clinical and radiological evidence … for no less than 16 weeks', Jingushi (2007) mentioned ' union…not being observed more than 3 months', Lerner (2004) used 'no radiographic evidence of fracture callus was noted median 6 months (ranged 4 – 38 months)'.

- The patient population varied between studies in terms of age, fracture age, fracture types and smoking status.

- Studies were conducted in 12 countries, and did not include the UK. This evidence might not be transferable to an NHS context if patient characteristics, clinical practice, or other context differs in other healthcare systems.

- The position of long bone fractures varied between studies. The most commonly examined were tibia and femur.

Table 5. Summary of methods for delayed union studies

Study	Patient population	Country	Age, fracture age	Long bone type	Study design	Sample size
EXOGEN STUDIES						
Schofer 2010*	Lack of clinical and radiologic evidence of union, bony continuity or bone reaction at the fracture site for no less than 16 weeks from the index injury or the most recent intervention.	Germany	For EXOGEN group: mean age 42.6, SD 14.6 Mean fracture age 60.3, SD 61.0 weeks.	Tibia shaft	RCT (EXOGEN vs. placebo)	51 EXOGEN vs. 50 placebo
Mayr 2000 *	SAFHS worldwide prescription registry of delayed union patients (3 - 9 months post-fracture); Similar patients from local clinic.	Germany	Fracture age ranged from 146 - 163days.	Humerus, Radius-ulna, femur, tibia/tibia-fibula	Prospective case series (registry)	654 EXOGEN from registry; (42 from local clinic)
Jingushi 2007 *	Union or radiogical bone reaction not being observed more than 3 months after the most recent operation	Japan	Mean age 40.4. Mean fracture age 18.9 month (3-159)	Femur, tibia, humerus, radius, and ulna	Case series	40 EXOGEN
Lerner 2004	Patients with severe compound high-energy limb injuries and varying degreess of bone comminution and soft-tissue loss. No radiographic evidence of racture callus appearance was noted 4 - 38 (median 6) months after prolonged fixation time.	Israel	Age ranged from 19 - 48 yrs.	Femur, tibia, radius/ulna, humerus	Case series	16 EXOGEN

* Studies involved both delayed union and non-union

Table 6. Summary of methods for non-union studies

Study	Patient population	Country	Age, fracture age	Long bone type	Study design	Sample size
EXOGEN STUDIES						
Mayr 2000	SAFHS worldwide prescription registry of non-union patients (the failure of a healing process 9 months post-fracture).	Germany	Fracture age ranged from 435 - 871 days.	Humerus, radius/radius-ulna, femur, tibia/tibia-fibula	Prospective case series (registry)	256 EXOGEN
Gebauer 2005	Established non-union (minimum fracture age 8 months), radiographic indicated the healing process had stopped for at least 3 months; a minimum of 4 months without surgical intervention before EXOGEN.	Germany and Austria	Age ranged 23 - 86 yrs.	Tibia, femur, ulna, fibula, humerus	Case series (self-paired)	51 EXOGEN
Jingushi 2007	Non union defined as additional operative treatment being indicated for the case (different from the scope) .	Japan	Mean age 40.4. Mean fracture age 18.9 month (3-159)	Femur, tibia, humerus, radius, and ulna	Case series	32 EXOGEN
Nolte 2001	Patients had a failure of the fracture to unite at a minimum of 6 months from fracture, radiographic healing had not progressed or had stopped for a minimum period for 3 months before EXOGEN. The interval between the last operative procedure and EXOGEN was 3 months minimum.	Netherlands	Average age 47 yrs (range 18 - 90). Average fracture age 61 weeks (range 25 - 137 weeks).	Humerus, radius, ulna, femur, tibia/fibula	Case series (self-paired), assuming 5% healing rate for non-union without any interventions	22 EXOGEN
Romano 1999	Patients with septic non-unions: sufficiently stable; infection controlled with antibiotics; sufficient vascularisation; and skin covering	Italy	28-78 years	Tibia, humerus, femur	Case series	15 fractures (13 long bones)

Study	Patient population	Country	Age, fracture age	Long bone type	Study design	Sample size
SURGERY STUDIES						
Bellabarba 2002	Consecutive patients with non-union o the distal femur. Non-union was defined as failure of frature union at 6 month of the absence of pregrossive healing on 3 consecutive monthly radiographs.	USA	Mean age 48 yrs (ranged 18 - 92). Interval from injury to non-union 10 months (ranged 3 - 25)	distal femur	Prospective consecutive study	20 surgery (plate and screws)
Birjandinejad 2009	Non-union patients after IM nailing of femoral and tibial fracture. Infected non-unions were excluded. No definition for non-union.	Iran	Mean age 31.4 yrs (ranged 18 - 53).	femur and tibia	case series	38 surgery (plate and screws augmentation following IM nailing)
Cacchio 2009	Long bone non-union and skeletal maturity patients. Non-union was defined as a fracture that did not show any progress toward healing on radiographs made at 1 month intervals for at least 6 months following treatment.	Italy	Mean age 42.8 yrs (SD 6.3), duration of non-union 11.5 (SD 4.9).	Femur, tibia, ulna, radius	RCT	42 surgery (vs. 84 shockwave)
Friedlaender 2001	Tibial non-union patients where non-union was defined as 9 months duration of the non-united fracture with no evidence of progressive healing over the previous 3 months. Patients judged for internal fixation along and patients with infection were excluded.	USA	Mean age 34 yrs (SD 11), 57% smoking, median non-union duration 33 months.	tibia	RCT - partially blinded	124 surgery (61 autograft vs. 63 authograft)
Khalil 2010	Ununited proximal ulna fracture.	Egypt	Mean age 41.7 yrs.	ulna	case series	21 surgery (contour plate)

Study	Patient population	Country	Age, fracture age	Long bone type	Study design	Sample size
Lin 2010	Patients with humeral shaft non-union of greatter than 6 months duration.	Taiwan	Mean age 42.2 yrs (SD 18.4 for autograft group), 55.3 (SD 23.5 for allograft group)	humerus	prospective, comparative cohort study	65 surgery (plus allograft/ autograft)
Livani 2010	Patients with humeral shaft fracture who had no clinical, radiological or bone scan signs of healing after 8 months.	Brazil	Mean age 37.53 yrs (range 18 - 74).	Humerus	Case series	15 surgery (anterior plating)
Razaq 2010	Consecutive patients of non-union fractures shaft of femur and had less than 1cm shortening with no segmental bone defect, and a radio lucent line of the non-union, and had been previously treated by IM nail.	Pakistan	Mean age 38.8 yrs (SD 13.8)	Femur	case series	43 surgery (exchange IM nailing)
Ring 1997	Consecutive complex un-united fractures of the femoral shaft patients.	USA	Mean age 35 yrs (13 - 81), mean duration of non-union before the surgery was 17 months (6 - 68).	Femur	case series	42 surgery (wave-plate combined with bone grafting)
Wu 2003	Patients sustained tibial shaft aseptic non-unions after plating. 2)	Taiwan	Median age 34 (19-58). Median of time from injury to current treatment was 1.8 yrs (0.8 - 4.	tibia	case series	31surgery (reaming and IM nai)

3.5 Overview and critique of the sponsor's critical appraisal

The sponsor critically appraised each included study. The EAC reviewed the sponsor's critical appraisals, and comments for each study are provided in Appendix B.

3.6 Results

The submission included a summary of outcomes for each of the included studies, which we critiqued (see Appendix C). Our summary of the results of the clinical studies is provided in Table 7 for delayed union and Table 8 for non-union. Key findings are summarised below:

Evidence for delayed union

- The Schofer RCT of EXOGEN versus placebo reported healing rates of 65% versus 46% over four months of follow up. This difference was not statistically significant (hazard ratio 1.69, p=0.07).
- The analysis of EXOGEN registry data for delayed union (Mayr 2000), found that 90% of long bone fractures healed in a mean 4.4 months.
- The other two delayed union studies reported healing rates with EXOGEN of 83% (Jingushi 2007), time to healing not reported; and 94% (Lerner et al. 2004) over a mean of 17 months.
- Other outcomes requested in the scope were not reported.

Evidence for non-union

- The mean healing rate for non-union long bone fractures reported in the Mayr analysis of EXOGEN registry data was 84% over a mean of 5.3 months. Other estimates ranged from 66% for a mixture of long bone fractures (Jinguishi et al. 2007) to 95% for radius/ulna fractures and 100% for tibia and tibia/fibula fractures (Mayr et al. 2000). There were no reports for other outcomes requested in the scope.
- For non-union long bone fractures treated by surgery, healing rates ranged from 62% to 100%, and healing time ranged from 9 weeks (Livani et al. 2010) to 24 weeks (Ring et al. 1997). There were some reports of time to weight bearing, but these are not consistent with the scope. Further surgery and adverse events due to surgery were reported in some papers.

Table 7. Summary of outcomes of delayed union studies

Study	Healing rate	Healing time	Return to painless weight bearing	Avoidance of further surgry	Device related adverse events
EXOGEN STUDIES					
Schofer 2010	65% (33/51) for EXOGEN, 46% (23/50) for placebo. Hazard ratio:1.69 (p=0.07) Over 16 weeks.	Not reported	not reported	not reported	not reported
Mayr 2000	76% (Humerus 41/54), 94%(Radius-ulna 49/52), 81% (Ulna 35/43), 87%(femur (85/98), 92%(tibia 350/380), 96% (fibula, 26/27) Total 90% (586/654)	125 days(humerus, SD 11.7), 115 (Radius-ulna, SD 9.3), 130 (Ulna, SD 15.3), 140 (femur (SD 8.3), 138 (tibia SD 4.5), 113(fibula, 9.6). Mean 4.4 months	not reported	not reported	not reported
Jingushi 2007	82.5%(33/40)	Not reported separately for DU and NU	not reported	not reported	not reported
Lerner 2004	94% (15/16)	Mean bone union time 75 weeks (34 - 224)	not reported	not reported	not reported

Table 8. **Summary of outcomes of non-union studies**

Study	Healing rate	Mean Healing time	Return to painless weight bearing	Avoidance of further surgry	Device related adverse events
EXOGEN					
Mayr 2000	69% (humerus, 33/48); 95% (radius/ulna 21/22); 86% (femur 57/66); 88% (tibia-fibula 105/120) Total 84% (216/256)	174 days (humerus, SD 19.5); 117 (radius/ulna, SD 16.1); 157 (femur, SD 10.3); 166 (tibia-fibula, SD 10.6) Mean 5.3 months	no report	no report	no report
Gebauer 2005	90% (46/51) for long bones, 85% (57/67) for all fractures.	178 days (86- 375) for long bone fractures, 168 days for all fractures.	no report	no report	none
Jingushi 2007	66% (21/32, not clear when the cut-off time point was)	219days (56-588 for all delayed and non-union fractures)	no report	no report	no report
Nolte 2001	100% (10/10,Tibia-tibia/fibula), 80%(femur, 4/5), 80% (radius-radius/ulna, 4/5), 100% (other long bones, 2/2). Duration was 2 years.	144 days(Tibia-tibia/fibula), 185(femur), 139 (radius-radius/ulna, 4/5), 153 (other long bones, 2/2)	no report	no report	None
Romano 1999	62% (8/13 tibia, humerus, femur)	95 to 181 days (3 still in treatment at time of report)	no report	no report	no report

Study	Healing rate	Mean Healing time	Return to painless weight bearing	Avoidance of further surgry	Device related adverse events
SURGERY					
Bellabarba 2002	100% (20/20)	14 weeks (range 12 -20)	no report	0	1 patient developed a deep postoperative wound infection. 1 patient developed a postoperative superficial frmoral deep vein thrombosis. Average estimated blood loss was 245 milliliters (ranged 100 - 400 mililiters)
Birjandinejad 2009	94.7 % (36/38, femur& tibia), 100% (25/25, femoral), 84.6% (11/13 tibia)	4.78 months (range 1 - 6)	no report	2 required further surgery	1 wound infection
Cacchio 2009	52%(21/41, 3 months followup), 74%(28/38, 6 months), 87%(33/38, 12 months), 95% (35/37, 24 months)	no report	no report but used two functional status questionnaires	no report	7% (3/42), 2 wound infections, 1 radial nerve neuropraxia.
Khalil 2010	90% (19/21)	9.6 weeks (8 - 12)	no report	2 required further surgery	No deep infection, ulna neoritis and metal failure were recorded
Lin 2010	95% v 93%;	18.8 v 20.1 weeks	no report	2 required further surgery	

Study	Healing rate	Mean Healing time	Return to painless weight bearing	Avoidance of further surgry	Device related adverse events
Friedlaender 2001	74% (authograft) and 62% (OP1)(bridging in at least three of four views) at 9 months followup	no report	85%(52/61) in autograft group and 81%(51/63) in OP1 group fulled weight bearing with less than severe pain at 9 months followup	10% patients in autograft group and 5% in OP1 group received surgical re-treatment	All patients experienced adverse events and 44% patients in each treatment group had serious event but none of which were related to their bone grafts. 13 arthralgia lower leg, 17 multiple sites pain, 15 acute or sub-acute osteomyelitis lower leg, 59 pyrexia, 37 vomiting, 26 postoperative infection, 59 mecgabucak complication of internal orthopaedic device, 13 hematoma complicating a process
Livani 2010	100% (15/15) - Callus formation and cortical continuity as evidence of radiological union.	9 weeks (6 - 18). Followup to 68 weeks (12 - 68).	no report but mentioned good functional outcome in all patients who returned to work with no limitations on daily activities.	no	No infection or any other clinical complications developed.
Razaq 2010	91% (39/43)	5 months (SD 1.5)	no report	no report	3 discolor, 8 pain, 6 sweling

Study	Healing rate	Mean Healing time	Return to painless weight bearing	Avoidance of further surgry	Device related adverse events
Ring 1997	98%(41/42)	6 months (3 - 18)	41 at followup (12 - 66 months)	4 patients required further procedure (not very clear though)	2 infections, 1 draining fisula
Wu 2003	100 %(31/31)	4.5 months (median, 3 - 7.5)	no report but stated that all patients could walk without aid postoperatively.		No deep infection, rotational or angular deformity or shortening reported.

3.7 Adverse events

Description of the adverse events reported by the sponsor

Does the EAC believe that the adverse events reported by the sponsor raise any safety concerns for the technology being evaluated? What is the opinion of Expert Advisers to NICE?

The search strategy for adverse events is listed in section 10.2 (appendix 2). The implication is that the PubMed EXOGEN search was used to locate adverse events data, where ideally EMBASE, the Cochrane Library and MEDLINE In Process should also have been used. Additionally internal EXOGEN complaint databases were searched, although no further details of these are given.

Under section 7.7.3 the sponsor is required to describe all adverse events associated with the technology in national regulatory databases MHRA and FDA (MAUDE) and this has been done. Four adverse events recorded are described. The period April 2011 – April 2012 was searched on the MAUDE database but there is no explanation of why the search should be limited in this way.

No device- related adverse events were reported in the EXOGEN studies

Adverse events reported in surgery studies are listed below:

Cacchio 2009

The rate of adverse effects in the surgical group was 7% (three of forty-two). Two cases of wound infection were observed, both in the lower limb. The infections healed after surgical debridement and antibiotic therapy. There were no deep infections in this series. A radial nerve neurapraxia was noted in a patient in the surgical group with a non-union of the distal third of the humerus.

Friedlaender 2001

All patients in the autograft group had pain at the donor site following the operative procedure, and more than 80% judged their postoperative pain as moderate or severe. Furthermore, more than 20% of patients had persistent pain, mild or moderate in nature, at their 6-month visit, and approximately 13% had persistent pain at the donor site 12 months following the operative procedure. Forty-four percent of both groups had serious adverse events, none of which were considered related to the OP-1 implant or the bone autograft. Osteomyelitis was reported at the fracture site in 21% of patients following treatment with bone autograft but in only 3% of those receiving OP-1 ($p = 0.002$).

Bellabarba 2002

One case of deep infection from a patient with previous osteomyelitis and one case of superficial deep vein thrombosis

Birjandinejad 2009

No serious adverse events were reported

Khalil 2010

Six patients noticed hardware prominence. Two had it removed immediately and one developed an ulcer which was treated conservatively prior to removal. No deep infection, neuritis or metal failure were recorded.

Lin 2010

Immediately after surgery, 43% of patients in the autograft group reported pain and limited mobility at the donor site. At one year 14% reported persistent pain or paraesthesia. No patient had deep infection, implant breakage, post-op fracture or heterotopic ossification

Livani 2010

No infection or clinical complication developed. One patient had limitations described as Elbow flexion deficit (10°); elbow varus (10°); shoulder elevation 120°, moderate deficit of shoulder MR.

Razaq 2010

No major surgical complications were noted, although discolouration, pain and swelling were reported in 7%, 18.6% and 14% respectively. No other adverse events are reported

Ring 1997

There were two cases of deep infection, both occurred in patients with a previous infection. Five of the patients in the cohort required an additional surgical procedure and there was one amputation.

Wu 2003

No deep infections or other complications were reported

Description of adverse events in national regulatory databases

The sponsor conducted a one year search (April 2011 – April 2012) of US FDA MAUDE database, from which they identified four recorded instances of EXOGEN adverse events. There were three instances of skin complaints, which is noted in the EXOGEN instructions for use document:

> "Some patients have experienced mild skin irritation caused by skin sensitivity to the coupling gel. Resolution can be obtained by a change of coupling medium to mineral oil or glycerin."

There was one report of increased chest pain due to potential interference with cardiac pacemaker, which is also a stated precaution in the IFU

> "The operation of active, implantable devices, such as cardiac pacemakers may be adversely affected by close exposure to the EXOGEN device. The physician should advise the patient or other person in close proximity during treatment to be evaluated by the attending cardiologist or physician before starting treatment with the EXOGEN device."

The sponsor noted that over this one-year period, approximately 55,000 EXOGEN devices were used by patients in the USA.

Review of MAUDE data from August 1995 to March 2012 submitted by the sponsor identified a number of other reports of localised pain or irritation, and one other report of a pacemaker that stopping working during use of the device (although, of course, it is unknown whether this was in any way related to use of the device).

Overview of the safety of the technology.

There are no significant safety concerns regarding EXOGEN in relation to the scope. No device-related adverse effects were reported in the clinical studies. The MAUDE registry includes some reports of localised pain or irritation associated with use of the device, and isolated concerns over the potential for interference between the device and implantable devices.

In contrast, there is well-known potential for adverse events associated with surgery, including the risk of infection, which can have serious consequences.

3.8 Description and critique of evidence synthesis and meta-analysis carried out by the sponsor

The sponsor did not undertake any meta-analysis in their submission. They stated that this would not be appropriate because of the lack of controls and heterogeneity of outcome measurements, patient cohorts and fracture types,

surgery interventions, and baseline characteristics. Having reviewed the submitted papers, the EAC agree that any formal meta-analysis would not be appropriate.

3.9 Additional work carried out by the External Assessment Centre in relation to clinical evidence

We have presented a qualitative summary of the evidence above.

3.10 Conclusions on the clinical evidence

- There is no direct evidence comparing EXOGEN with surgery in the treatment of either delayed or non-union long bone fractures.

Evidence for delayed union

- The EAC considers that the best estimate of the absolute rate of healing in patients with delayed union fractures (across all long bones) treated with EXOGEN is 90% (87% to 92%) healed in a mean time of 4.4 months (Mayr 2000). These estimates come from a large registry study that used a definition of delayed union that matched that in the scope, with a breakdown of results for different long bones. Other estimates vary and are difficult to pool because of failure to report the duration of follow up.

- However, no evidence was available to estimate a comparable rate of healing with surgery. It is therefore not possible to compare EXOGEN with surgery in this population.

- There is some evidence to compare EXOGEN with no further treatment at the onset of delayed union (3 months) followed by surgery if required for non-union (9 months). A sham-controlled randomised trial (Schofer 2010), failed to detect significant improvement in the rate of healing with EXOGEN (hazard ratio 1.69 (p=0.07) over 4 months), although it did report significant improvement in indicators of progression towards healing (bone mineral density and bone gap area).

- Although the comparison with placebo is not strictly relevant to the scope, the EAC considers that it might well be clinically appropriate *if* surgery is not usually offered until the point of non-union. If so, then evidence from the Schofer trial is crucial. This appears to be a well-conducted study, but we note two key limitations:

    - Firstly, the trial included patients with fractures that under the scope definition would be defined as non-unions as well as delayed union fractures - approximately half the participants

entered the study with a fracture that had not healed in 9 months or longer. One might expect a greater relative risk of healing with EXOGEN compared with placebo in non-union fractures than in delayed union fractures – since, the latter may still heal without further intervention but the former will not. But this is uncertain, since healing rates with EXOGEN might also differ between non-union and delayed union fractures. The applicability of the Schofer results to delayed union fractures is therefore questionable.

- Secondly, the Schofer trial was not powered to detect differences in healing rates. The primary outcomes of this trial were BMD and gap at fracture site (assessed by CT scan).

- No evidence was identified for the outcomes of 'return to painless weight bearing' or 'avoidance of further surgery', as requested in the scope.

Evidence for non-union

- The EAC considers that the best estimate of the absolute rate of healing for non-union fractures (across all long bones) treated with EXOGEN is 84% (80% to 89%), with a mean time to healing of about 5.3 months (Mayr 2000). These estimates come from the large registry dataset, which used appropriate definitions of non-union, and reported results separately for different long bones. As with delayed union, estimates from other studies vary and cannot be pooled.

- Estimates of the healing rate following surgery for non-union long bone fractures are available, but the evidence is of poor quality:

  - The sponsor reviewed surgical case series, reporting healing rates from 62% to 100%, and healing times from 9 weeks to 124 weeks. However, the included studies differed in population, intervention and outcome, and it is not clear that they were identified systematically.

  - The sponsor also cites Gebauer et al (2005), who report a mean healing rate of 86% based on 23 published studies of surgery in patients with non-union fractures (range 68% to 96%). However, this does not appear to be based on a systematic review, and some studies included non long bone fractures.

- For the costing model, the sponsor assumes equal healing rates in non-union patients treated with EXOGEN or surgery. This appears to be

based on Gebauer *et al*, who compared their estimate from the literature with healing rates for their local registry patients treated with EXOGEN; also 86%. In the absence of better information, the EAC considers that equal effectiveness in non-union fractures is a reasonable starting assumption, but it is clearly possible that healing rates could differ. If EXOGEN were to be less effective than surgery at non-union, then it could not be dominant in this context. We therefore tested this in sensitivity analysis.

- As noted above, it might be argued that evidence from the Schofer placebo-controlled trial of EXOGEN could be applied to a non-union population. However, the comparison is not clinically appropriate for this group, as they could not be left for a further four months without any treatment. And without subgroup analysis, the relative risk in non-union patients is also uncertain.

- No estimates of 'return to painless weight bearing' or 'avoidance of further surgery' were available for non-union patients treated with EXOGEN, although if treated successfully these patients would likely have required surgery if not treated with EXOGEN.

Adverse events

- None of the EXOGEN studies included reports of any device-related adverse events. There are rare reports of localised pain or irritation following use of EXOGEN – possibly reactions to the contact gel – and isolated reports of possible interactions with implantable devices.

- Several surgery studies reported adverse events, including infections.

The EAC did not identify any relevant clinical studies, published or unpublished, that were not included in the sponsor's submission.

Of the 19 studies listed by the sponsor, we consider that 2 are not relevant to the scope: as noted by the sponsor, one study initially included did not relate to fractures of the long bones (Pigozzi 2004); and we excluded one (Rutten 2009) because it did not report any outcomes requested in the scope.

The remaining studies all reported healing rates for relevant populations and interventions. There was uncertainty over these reported healing rates for three main reasons: firstly the assessment of healing (clinical or radiographic) differed between studies; secondly the definitions of delayed union and non-union varied, and were not always consistent with scope; and thirdly, the duration of follow-up was often unclear, making comparison of healing rates across studies difficult.

Discussion of sponsor interpretation of clinical evidence

The sponsor provides a summary of principal conclusions from the clinical data (p102):

'EXOGEN shows heal rates of approximately 90% in delayed unions, and 86% in non-unions, with faster progression to healing than placebo in the delayed union, and a similar time healing when compared to surgery (152 – 192 days) in the case of non-union'.

- We broadly agree with the absolute healing rates quoted for EXOGEN, and think that the most reliable estimates are 90% and 84% for delayed and non-union respectively (Mayr 2000)

- The claim that EXOGEN achieves faster progression to healing than placebo in delayed union is not strictly justified, since the only trial (Schofer 2010) also included patients who according to the scope definition had non-union fractures, and although intermediate measures of bone healing (BMD and bone gap) were significantly better in the EXOGEN-treated group, differences in healing rates were not significant.

- It is difficult to compare rates of healing with surgery and with EXOGEN in non-union fractures, due to different follow-up.

"EXOGEN treatment has no known device related adverse events"

- Certainly, no adverse effects were reported in the included clinical trials, and reports of possible device-related adverse effects from the MAUDE database were scarce.

"Surgical management of non-unions in long bones produces good results and is an appropriate management option. The healing rates of 73% - 100% seen at six months in the individual trials are supported by other literature excluded from the searches performed."

- The EAC found that although most surgery studies reported high rates of healing, it is difficult to summarise across these studies due to failure to differences in length of follow-up.

"Surgery has complications – within the individual studies the immediate complications are reported as DVT, infection (deep and superficial), haematoma and poor range of movement (ROM). Longer term complications included requirement for further surgery (hardware removal), persistent non-union and in the case of bone grafting persistent donor site pain. Even in the

case of achieving union of fractures through surgery, removal of metalwork added further surgical intervention to patient management "

- We agree that some major complications were reported in the surgery studies.

It was also asserted that for EXOGEN:

'A reduced time to healing compared with surgery, particularly with reference to delayed union'.

- The foundation for this statement is unclear, as no direct or indirect evidence was presented for surgery in delayed unions.

"The avoidance of surgical intervention to achieve comparable clinical outcomes. Similar healing rates and time to healing are reported." And

"Use of the EXOGEN ultrasound bone healing system may reduce the need for high cost surgical intervention. Assuming the heal rates reported, EXOGEN has the potential to reduce 86% of the operations that are currently performed on stable, well-aligned delayed or non-union fractures

- The EAC agrees that there is the potential for cost savings, and avoidance of complications, if EXOGEN were to reduce the need for surgery.

- There is no direct clinical evidence that early use of EXOGEN in delayed union would avoid rates of further surgery. However the EAC notes that there is indirect evidence for this claim, based on intermediate healing outcomes (outside the scope) in a mixed delayed union and non-union population.

- Similarly in non-union, there is no direct comparative data supporting the claim that EXOGEN would reduce rates of surgery. There is indirect evidence from case series, showing broadly comparable rates of healing, although differences between the studies make this difficult to interpret. If surgery was more effective in this population, it is possible that the use of EXOGEN would further delay definitive treatment.

"There is less clarity regarding the impact of EXOGEN on a quicker return to weight bearing and normal daily living as compared with surgery."

- We agree, as no evidence was found for these outcomes with EXOGEN, and no comparative data in relation to surgery.

4 Economic evidence

4.1 Published economic evidence

Critique of the sponsor's search strategy

The search methods for economic evidence are detailed in section 8.1 of the submission and details of the strategies are appended in section 10 Appendix 3. The strategy was run on PubMed only. A broader strategy using MEDLINE and EMBASE combined with economic filters would have been advisable. The EAC recreated the sponsor's strategy and ran it on EMBASE to establish whether any relevant studies had been missed.

The sponsors did not search NHS EED or EconLit as recommended. However the EAC tested this and can confirm no additional relevant studies were found by searching these two databases.

A minimal economic filter (economic* or cost*) was used in combination with the EXOGEN and Surgery strategies discussed previously to pinpoint relevant economic evidence. Truncation of these two terms was not used in the EXOGEN search which may have narrowed the search slightly. A more detailed economic filter may have located additional relevant literature. The EAC tested a filter of this type on MEDLINE and located 170 studies although this sensitivity would have been to the detriment of precision in the search (a lot of irrelevant papers to be screened to locate any extra relevant ones). In addition we might assume that economic studies would have been set aside during the sponsor's screening process, serving as an internal "filter".

The searches were again limited to English language only. The EAC searches did not impose this limit to test whether any studies may have been missed in this way. As with the searches for clinical evidence a date limit of 1992-2012 was used.

The sponsor again used cited reference searching to identify additional studies.

Internal Smith and Nephew databases and Google searching were also used to locate unpublished material.

The results of the economic searches are illustrated in a flow chart (fig. 6). 6 studies were identified from "other sources" – possibly the methods described above but this could be made more transparent.

Critique of the sponsors study selection

The sponsor used specified inclusion and exclusion criteria to select health economic studies for inclusion in their review. The criteria were consistent with the scope, and also with those used to select clinical evidence.

Included and excluded studies

The sponsor included three economic studies (see Table 9).

Table 9. Included economic studies

Study		Design	Population	Intervention(s)
Taylor 2009	UK	Cost effectiveness analysis - Markov model using published data	Fresh and non-union tibia fractures	Fresh: Casting, IM nailing, EXOGEN and casting (for fresh fractures). NU: Exogen vs. Surgery
Kanakaris 2007	UK	Cost study (secondary)	Non-union fractures of humerus, tibia, femur	Surgery
Patil 2006	UK	Cost study (audit of 41 cases)	Non-union of tibia and femur	Surgery

Overview of methodologies of all included economic studies

One study (Taylor 2009) was a cost minimisation study, estimating the net cost of alternative treatment strategies for patients with fresh (out of scope) and non-union fractures of the tibia. The analysis was based on a Markov model, with monthly cycles over a time horizon of one year. The non-union analysis compared EXOGEN with surgery. Parameter estimates were obtained from published sources.

The other two studies (Kanakaris 2007 and Patil 2006) were non-comparative analyses, estimating the cost of surgical treatment for patients with non-union fractures of long bones.

Overview and critique of the sponsor's critical appraisal

The economic studies were reviewed using the BMJ checklist for appraising economic evaluation studies (Drummond and Jefferson 1996).

Does the sponsor's review of economic evidence draw conclusions from the data available?

The submission included a summary of the findings of the three studies. Taylor et al concluded that for non-union fractures, the dominant strategy is to delay surgery and try a course of ultrasound therapy first. Based on published literature they concluded that this would give an equivalent healing rate to immediate surgery, at lower cost (£6718 for surgery compared with £3926 for EXOGEN). The model developed for this published paper was adapted for use in the submission.

Kanakaris et al estimated the total cost of treating aseptic non-union long bone fractures, using 'gold standard' treatment over a six month period. They estimated the cost of treating humerus, femur and tibia fractures at £15,566, £17,200 and £16,330 respectively.

Patil et al conducted a 'bottom up' costing for 41 complex non-union tibia or femur fractures treated surgically with the Ilizarov procedure. The estimated a mean cost per patient of £29,204.

4.2 De novo cost analysis

Patients

Two cost models were submitted by the sponsor: one for non union and one for delayed union (adapted from the model by Taylor et al, mentioned above). Both analyses were restricted to fractures of the tibia. The submission highlighted the complexity involved in creating a cost model for each fracture site, lack of good sources of data and the high incidence of healing problems in tibial fractures as reasons for focusing on this group.

We note that the results from these analyses are not necessarily generalisable to other long bones. Nevertheless, expert opinion suggests that the tibia might offer a reasonable reflection of likely costs in fractures of other long bones. The submitted models could potentially be adapted for other long bone fractures.

Technology

- Delayed union: EXOGEN Express at diagnosis of delayed union, followed by surgery if the fracture does not heal within 6 months (9 months post fracture).

- Non union: EXOGEN 4000+ at diagnosis of non-union, followed by further surgery if the fracture does not heal within six months.

Comparator(s)

- Delayed union: no further intervention at diagnosis of delayed union, followed by surgery if the fracture does not heal within 6 months (at non-union).

- Non union: Surgery at diagnosis of non-union, followed by further surgery if the fracture does not heal within a further 6 months.

Model structure

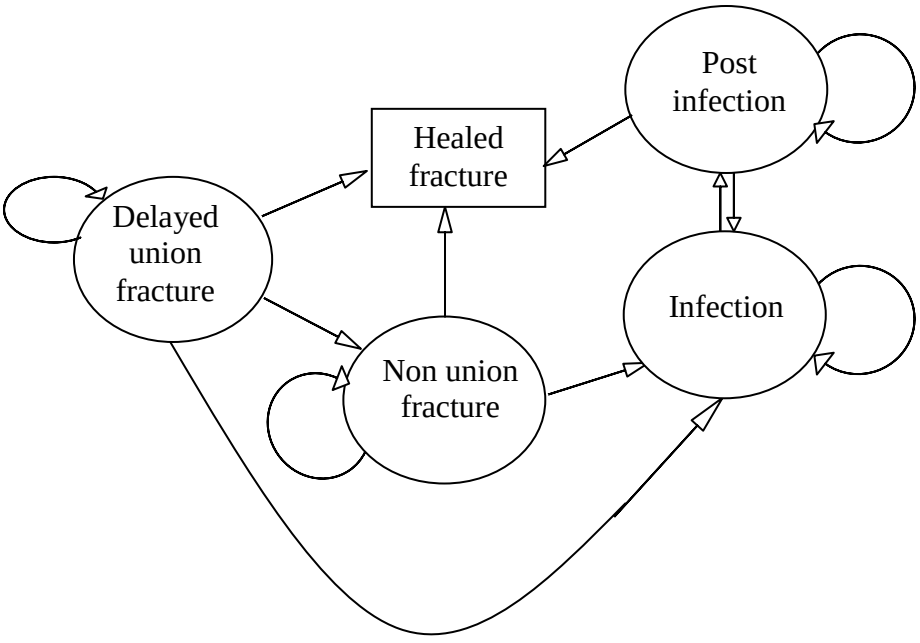
The overall schematic provided in the submission (Figure 7) seems to accurately represent the clinical pathway of care, although there are some issues around the translation of this into excel format for analysis. Interpretation of the modelling was hampered somewhat by the failure to provide separate diagrams for the delayed union and non union models.

A Markov model, with a time horizon of one year and monthly cycles was used to conduct the cost analysis. Markov diagrams showing the health states and transitions included in the delayed union and non-union models are shown below.

Delayed union model

There are 5 health states, and all members of the cohort begin in the delayed union state. It is assumed that surgical intervention (IM nailing) has occurred previous to delayed healing, shortly after the fracture.

Figure 2. Model structure for delayed union



The model is run twice: once for the EXOGEN arm, where patients start using the EXOGEN Express device at the beginning of the modelling period; and once for the control arm, where patients are assumed to have no further treatment (observation only) until the time of non-union.

In subsequent cycles, patients can move to healed (an absorbing state), infection, or after six-months in the model, to non-union. Following infection a staged revision surgery process begins, with the administration of intravenous (IV) antibiotics and removal of metalwork. It is considered that the infection will take a minimum amount of time to clear up (2 months) at which point revision surgery will take place. Patients can become re-infected having previously moved into the post infection state.

After six months of a delayed union fracture not healing and no infection occurring, the patient progresses to non union fracture, where further surgery takes place. In subsequent cycles, non-union patients may heal or acquire an infection.

The submitted model assumes that there is a minimum time to heal of 2 months from baseline in both arms, but this does not seem realistic, given that the initial surgery will have taken place 3 months previously – this appears to be a left over assumption for the earlier version of the model designed for evaluation of treatments for fresh fractures. Conversely, the submitted model did not assume any minimum time to healing following revision surgery after six months.

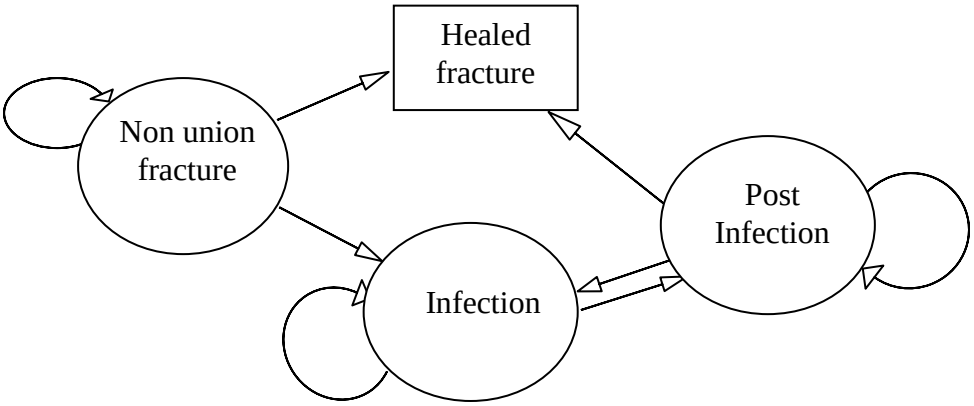
Non union model

The Markov model for non union fractures can be characterised in a similar fashion, but all patients begin in the non union fracture health state. Patients in the EXOGEN arm receive treatment with the ultrasound technology from baseline, whilst patients in the comparator arm receive surgery at baseline.

In both arms, if healing has not occurred after six months in the non union fracture health state, it is assumed that further surgery is performed.

In the surgery arm, patients are at risk of infection from the onset of non-union and also if they have further revision surgery after six months in the non-union state. However, the submitted non-union model assumes that no infection can occur in the EXOGEN arm. This seems appropriate for the first six-month period, when patients in this arm have not been recently exposed to the risk of infection from surgery (they last had surgery 9 months previously for a fresh fracture). However, it does not seem correct for patients who fail to heal after a 6 months in the non-union state.

Figure 3. Model structure for non-union



The non-union model assumes a 2-month minimum time to healing from the start of EXOGEN treatment, and initial surgery. However, it does not apply this same delay after revision surgery at 6 months.

Clinical parameters and variables

Clinical parameters in the model come from a variety of sources as outlined in section 9.2 of the submission.

Monthly healing rates, converted from 6 month rates, are used to determine transition from delayed union and non union health states into the healed state. In the delayed union model, the healing rate in the EXOGEN arm is based on the 65% healing at 16 weeks from Schofer (2010) and that in the Surgery arm is based on 92% healing (tibia/tibia-fibula) at approximately 4 months in Mayr (2000). These rates were extended over a 6 month period by assuming a simple linear assumption (e.g. 69% healed over six months = 65% *6/4)

In the non-union model, healing rates for both the EXOGEN and surgery arms come from Gebauer et al (2005), estimated to be 86% for 6 months.

The models use an infection rate of 1.4%, based on a 2011 HPA report inform transition from delayed and non union states into infection. This rate was calculated from 7,580 cases of reductions of long bone fracture where 104 led to readmissions. This rate is applied as a monthly rate in the submitted models and the EAC questions the validity of this approach. It would be more appropriate to have applied this as a one-off probability in the first month after infection, given that the median and inter quartile range time to infection in the HPA data falls within the first month, and to do a sensitivity on a higher rate.

The sponsor used expert advisers to provide a check of face validity of modelling and the clinical pathway defined. They also offered validation of

model inputs and in particular resource use. However, the submission does not give any details about how this expert opinion was elicited.

The time horizon chosen for both models was one year. There seems to be little justification as to why this is the case, but for both models this does lead to a majority of fractures having healed by the end of the time period.

Resource identification, measurement and valuation

Resource use was identified from the clinical pathway defined in section 9.1.4 of the submission. For surgical interventions, the resource use involved in the procedures was broken down into individual components, to each of which a unit cost was applied, to construct a total cost. Estimates of resource use were informed by clinical opinion, and it is not clear how this was elicited, or whether published data might have been available to inform these estimates.

The process involved in dealing with infection was taken from Cierny (2003) and resource use identified from a range of sources including expert opinion. Information from the NICE hip fracture guideline (CG124) is used to inform the components of theatre time and bed stay. The EAC questions whether these estimates are reflective of usual care for patients with long bone fractures, due to the different demographic of patients with hip and long bone fractures and their different clinical needs. In Taylor (2009) they identify that the antibiotics administered to patients with an infection can be delivered on an outpatient basis, which is less costly than the IV inpatient antibiotics assumed in the sponsor's submitted cost models. The EAC would also suggest that there might be some routinely available reference costs that could be used, which would provide good costs estimates applicable to the NHS. This could be explored as a sensitivity analysis.

The estimates of resource use for routine observations applicable to the health states in the model are not clearly outlined. There is no reference to the source of this information. The valuation of resource use that occurs in each health state was provided from published sources where possible. Physiotherapy costs are taken from NICE guideline CG124, the cost of a GP visit and wheelchair from Curtis (2010), and an outpatient visit from NHS reference costs. The cost of crutches and an X-ray were acquired from expert opinion. The EAC feels that for the latter especially, a more robust estimate could be gained from published sources.

The submission states that non procedure costs are the same in both arms. Although unit costs are the same, the resources used in the non union model actually differ between the arms. This has the effect of increasing the costs of each health state in the Surgery arm (in all health states by £100). Furthermore, in Table C7 of the submission (p.137) health state costs for "not

healed, not infected" health states are said to be £255. This cost is not used at any stage in the modelling. In the excel model, depending on which of health states the patients are in, the value of this differs and the submission does not suggest this is the case.

Unit costs included in the model for non union surgery, revision surgery and staged revision were estimated using a micro-costing approach to incorporate different components of cost. The unit costs and their sources are displayed below. Again, the EAC suggests that Reference Cost data might be a more suitable source for an estimate of the cost of surgery.

Costs used in submitted models

Surgery- £3,437

- NICE Guideline CG 124 unless otherwise stated
- 4.9 days bed stay (HES W28.1) - £1184.28
- 3 hours surgery - £957
- 1 pre-op prophylaxis antibiotic= £14.50
- BNF - Injection, powder for reconstitution, vancomycin (as hydrochloride), for use as an infusion, 1-g vial
- Long IM nail - £1175.40
- Iliac bone graft - £106.33 (additional 20 min theatre time) ref 45 St. John (2003)

GP visit-£41

- Curtis L (2010). Unit Costs of Health and Social Care 2010. Personal Social Services Research Unit: University of Kent.
- Table 10.8b: General Practitioner - unit costs.
- Per clinic consultation lasting 17.2 minutes, excluding direct care staff costs, without qualification costs.

Outpatient visit- £137

- NHS Reference Costs 2012-2013.
- NHS Trusts Outpatient Attendances
- 110T - Trauma & Orthopaedics: Trauma

Cost of treatment of infection (including revision surgery) – £14,527

- Staged admission and treatment for chronic osteomyelitis:
- Removal of implant and debridement = 3 hours theatre (expert opinion) = £957 (NICE CG124)
- Temporary fixator = £1050 (personal communication Smith & Nephew)
- Minimum 21 days bed stay = £5075.49 (NICE CG124) NHS trust communication infection control guidelines

- IV antibiotic (source NHS prescription services May 2012, Flucloxacillin 1g powder= £4.90 per vial, 8g per day) = £823.00

Assuming cleared infection:

- Further 3 hours surgery = £957
- Antibiotic Prophylaxis = £14.50
- Synthetic bone graft and /or DBM = £448 (data on file idata Orthopaedic biomaterials report)
- Simple external ring fixator = £2,520 (personal communication Smith & Nephew)
- Average 11.1 days bed stay (W.30.4 apllication of external ring fixation to bone, NEC) = £2682.76
- **Total = £14,527**

Note - this estimate is much higher than that in the Taylor et al study (which was based on HRG costs).

The sponsor notes two published cost estimates:

- Patil 2006 (ref 34) describes limb salvage procedure costs to be approximately £30,000

- Thakar 2010 (ref 36) states mean cost of treating deep infection is £22,846

However, these relate to particularly complex cases are not reflective of mean costs across the all cases.

Drugs for infection-£50 expert opinion

Cost of X-ray- £70 expert opinion

Wheelchair (per month)- £14

- Curtis L (2010). Unit Costs of Health and Social Care 2010. Personal Social Services Research Unit: University of Kent.
- Table 7.2: NHS Wheelchairs
- Unit cost per active user per chair per year.

Crutches- £35

- Based on expert opinion from 2005, inflated to 2010 prices.

Physiotherapy- £200

- NICE guideline 124
- Combination of Physiotherapy and Occupational therapy
- Health Economics report - Appendix H table 98
- 8.5 hours per patient p. 572

Technology and comparators' costs

Cost of EXOGEN used in the models differed from that stated in the sponsor submission.

EXOGEN 4000+ (non union)- £2,562.50 +VAT- Smith & Nephew

- @20% VAT = £512.50
- Total cost = £3,075
- Cost of EXOGEN used in modelling £2,667

EXOGEN Express (delayed union) = £999.38- Smith &Nephew

- @ 20% VAT = £199.88
- Total cost = £1,199.26
- Cost of EXOGEN express used in modelling = £998

Sensitivity analysis

The submission includes details of deterministic sensitivity analysis carried out to explore parameter uncertainty and the effect this has on the incremental cost of EXOGEN. One way and two way analyses were conducted varying the healing rates for EXOGEN and Surgery. The rate of infection was also varied.

For EXOGEN, values for the healing rate were used to reflect a 10% or 20% reduction compared with the base case. For surgery, healing rates were increased by 5% and 10%. By varying the values either alone or in combination, "best" and "worst" case scenarios are examined.

It is not clear why these values were chosen, nor is it clear why they were not uniform across the two groups, giving very arbitrary analysis. It would have been more appropriate to base the sensitivity analysis on the range of results reported in included studies. The submission does however test the impact of varying the healing rate across a fairly large range to explore the sensitivity of base case results to changes.

The Infection rate was varied from the base case value of 1.4% to 5.1%, and justification of this was not provided, though it may bear relation to the rate noted for high risk patients such as smokers (Castillo 2001).

There were few details provided around what might be considered another important set of variables in the model- costs inputs. Although in isolation

changing one of these, e.g. cost of surgery might have a small impact; incorporating uncertainty in a multi-way analysis might show greater sensitivity.

It is stated that "The model was relatively insensitive to variation in all other parameters", but these wider sensitivity analyses were not presented in the submission.

4.3 Results of de novo cost analysis

Base-case analysis results

Results from the sponsor's basecase models are reported in Table 10 and Table 11 below, for delayed union and non-union respectively. These results suggest that EXOGEN is cost-saving in both contexts. The EAC confirmed that the results reported in the submission match the output of the submitted models.

Table 10 Base case analysis results: delayed union model

Intervention	Mean cost per patient
EXOGEN Express	£4,290
Control (routine observation)	£4,974
EXOGEN vs control	-£684

Table 11 Base case analysis results: non-union model

Intervention	Mean cost per patient
EXOGEN 4000+	£4,647
Surgery	£6,957
EXOGEN vs Surgery	-£2310

Sensitivity analysis results

The sponsor varied the healing rate with EXOGEN and with surgery and also the rate of infection in sensitivity analysis.

- Non-union model: The findings were relatively insensitive to the parameter changes tested. EXOGEN remained cost saving for non-union in all scenarios tested.

- Delayed union model: EXOGEN ceased to appear cost-saving when the difference in healing rates between EXOGEN and the control arm was reduced. In the base case, the six-month healing rates were

assumed to be 69% for the control group and 92% for EXOGEN. When the rate for EXOGEN was reduced to 82.8%, its estimated cost was very similar to that of the no intervention control. And if the difference was further reduced, EXOGEN became more expensive than the control.

The EAC re-ran these sensitivity analyses, and confirmed that the results were consistent with those reported in the submission.

Subgroup analysis

Not reported

Model validation

The sponsor notes that the submitted models are adaptations of a published model (Taylor 2009), and was subject to peer review as part of the publication process. They note that the model was also subject to 'internal validation', and that the clinical pathways were derived through consultation with expert clinical advisors, but no details are given.

4.4 Interpretation of economic evidence

The sponsor quotes the conclusion for the published cost analysis (Taylor 2009), on which the submitted models are based:

> " From an NHS perspective, adjunctive ultrasound offers a cost-effective choice for patients at particular risk of non-union, and for non-union fractures which are stable and well-aligned."

The sponsor goes on to claim that "the de novo analysis, based on updated treatment costs and revised infection rates supports this conclusion. Any assumptions adopted in the analysis are believed to be conservative, suggesting that the potential savings presented may be underestimated." (p152).

4.5 Additional work undertaken by the External Assessment Centre in relation to economic evidence

The EAC reviewed the assumptions built into the sponsor's model in relation to available evidence and expert opinion. We considered that a number of assumptions are not justified. By reviewing the Excel formulae, we also identified a number of what we consider to be errors in the coding of the model. We summarise below the changes that we made to the submitted models, and how we tested them in sensitivity analysis.

Costs

- The prices entered in the spreadsheets differed from those stated in the submission. We have confirmed that the correct prices are £2,562.50 + VAT for EXOGEN 4000+ and £999.38 + VAT for EXOGEN Express.

- VAT was not added to the prices in the model, and depending on the perspective this may or may not be appropriate. We conduct a sensitivity analysis in which we add VAT both to the cost of EXOGEN and to other consumables in the model.

- As noted previously, the submission indicates a health state cost of £255 for individuals who are "not healed-not infected" and that costs do not differ between arms (p137). The models however have different cost for delayed union and non union patients in this state based on resource estimates in the model. Not knowing the combination of resource usage that yields £255 per month, we have used the resource use already stated in the model. In the non union model these health state cost also differ between arms. We understand that these differences were not intended, and have corrected them (assuming one day per month physiotherapy for both EXOGEN and surgery arms).

- The cost of surgery in the submitted models is estimated by a 'bottom up' costing based on expert opinion about the likely use of resources. The EAC maintained the sponsor's estimate of the cost of surgery (£3,437) in our main analyses, but tested the effect of using Reference Cost estimates in sensitivity analysis: with a lower estimate of the cost of surgery £2,349 (weighted mean of HRG codes HD24A, HD24B elective with CC/with major CC); and an upper estimate of £4,126 (HRG code of HA99Z).

Healing rates for delayed union model

- The methods used to calculate healing rates from the clinical data are not explained in the submission. We understand that in the delayed

union model, the 6-month healing rate for the control arm is taken from the control arm of the Schofer trial, multiplied by 6/4 to adjust it from 4 to 6 months (0.46*6/4=0.69). A more appropriate method for extrapolating this data would be to assume a constant hazard rate.

- The healing rate for the EXOGEN arm in the delayed union model is taken from the Mayr registry paper (92% for tibia/tibia-fibula delayed union fractures at a mean follow up of 138 days). This figure was not adjusted from the average 4.5 months to six-months.

- No justification is given for using two separate data sources, rather than the comparative evidence that is available from the Schofer trial. A direct comparison of 4-month healing rates from the trial would give 0.46 for the control arm versus 0.65 for the EXOGEN arm. This appears reasonable for the comparison in the delayed union model, although approximately half of the patients in the Schofer trial would be classified as non-union cases, based on the definition in the scope.

- An alternative approach would be to take the baseline healing rate with EXOGEN from the Mayr paper (0.92 at approximately 4 months), dividing by the relative effect for EXOGEN vs no further treatment from Schofer (hazard ratio 1.69) to yield an indirect estimate of the healing rate without EXOGEN (0.78). The EAC considers this to be a more appropriate approach, as the population from the registry is more likely to be applicable to the general delayed union population. However, we conduct a sensitivity analysis using the Schofer data for both arms.

- The delayed union model includes an assumption that there is a minimum time to healing, though this is not discussed in the submission. Following expert advice, we assume that this should apply following surgery (which in this model may occur for patients in either arm who have not healed by 9 months). We conduct sensitivity analysis to test the impact of removing this minimum time to healing assumption.

- A final assumption that we make is about the onset of the effects of EXOGEN on healing (applying a similar 2 month delay in the benefits of EXOGEN as for surgery), and in the persistence of the effects of EXOGEN after treatment has been completed at 4 months. Again, we test the impact of these assumptions in sensitivity analysis.

Healing rates for non-union model

- The non-union model assumes equal healing rates for surgery and EXOGEN based on the Gebauer paper. We accepted this as a starting

assumption, but tested the impact of changing the relative risk of healing for surgery compared with EXOGEN – given the lack of comparative evidence on this point.

- In our main analysis, we take the healing rate for EXOGEN from the Mayr registry data (88% for tibia/tibia-fibula fractures over approximately 6 months).

- We noted and rectified that the non-union model contains an error in months 7, 8 and 9, when the total number of people in the cohort increases above the initial 1,000.

Infection rates and costs

- In our main analyses, we used an estimated post-surgical infection rate of 2.6%. This reflects reported infections (74 cases) identified during the inpatient stay or subsequently through readmission following operations for reduction of long bone fractures in 2864 patients at raised risk of infection (index score 1-3) (HPA 2011, Table 2 p9). Though unlikely to capture all surgical site infections, it is also very unlikely that this rate would recur for every month post surgery. We therefore include this as a one-off rate of infection following any surgery in our main analyses.

- Taylor et al (2009) estimate the risk of infection based on an analysis of Medicare claims data. This gave an annual rate of osteomyelitis as 4.95%, which equates to approximately 0.42% per month. We used this as a recurring monthly rate after surgery, as an alternative to the one off 2.6% HPA rate.

- The sponsor's non-union model assumed that there is no risk of infection in patients treated with EXOGEN, which might be appropriate for the first six months (as patients in this arm do not have further surgery during this time). But it is not justified for patients whose fractures do not heal with EXOGEN and who go on to have revision surgery after a further six months.

- The sponsor's models use a bottom-up costing approach to estimate the NHS cost of treating infections. This assumes that all patients with an infection have a 'deep' or 'major' infection, such that they require intravenous antibiotics, incurring a 3 week inpatient stay in addition to the costs of revision surgery: total cost £14,527 (p138). This appears at odds with estimates from the HPA report (Figure 4, p15), which indicates that 48.7% of infections following reduction of long bone fracture are 'superficial'. The published version of the model (Taylor et

al 2009), assumed that after an initial inpatient stay, patients with an infection could be discharged and complete the antibiotics on an outpatient basis (estimated at £3,210 in 2006 prices). This seems to be a more realistic estimate, as least for those patients with superficial infections. We therefore estimated a cost of infection comprising £14,527 for the 51% of patients with deep infections, and an updated reference cost value (£3,109 for HRG code HD23) for the remaining 49% with superficial infections.

4.6 Results of EAC sensitivity analysis

EAC results - Non Union

The following changes were made to the submitted non-union model:

- Healing rates taken as 88% after 6 months from Mayr.
- Relative risk for surgery compared with EXOGEN = 1.0
- Two-month minimum time to healing for both EXOGEN and surgery at baseline, and for further surgery at 6 months
- Removal of double counting of individuals in months 7,8 and 9.
- Allowing infection in EXOGEN arm following surgery at 6 months.
- Changing costs to reflect non union resource use at baseline, rather than that of fresh fracture.
- Price of EXOGEN changed from £2667 to £2562.50
- Infection rate 2.6% in first month following surgery (at 9 months post fracture for the surgery arm, and for both groups if they have not healed after a further six months) and 0% up until repeat surgery
- Cost of infection weighted using for £14,527 for 51% deep infections and HRG £3,108 for 49% superficial infections = £8,932.
- Resource use - physiotherapy same between arms.

The results of this analysis are shown in Table 13 below. This suggests that EXOGEN would be cost saving compared with immediate surgery for non-union.

Table 12. EAC main model non-union: mean cost per patient

Model	EXOGEN	Surgery	Cost difference
EAC main analysis	£5,688	£6,852	-£1,164

There is uncertainty over the relative healing rate for surgery compared with EXOGEN. We therefore tested this in sensitivity analysis (Table 13). This shows that the magnitude of the estimated cost savings declines as surgery becomes more effective than EXOGEN. However, even if the healing rate

with surgery is over twice that with EXOGEN, the latter still appears to be cost saving. This is because EXOGEN is considerably cheaper than surgery.

Table 13. EAC non-union model: varying RR surgery compared with EXOGEN

Relative risk	EXOGEN	Surgery	Cost difference (EXOGEN - Surgery)
0.5	£5,688	£8,309	-£2,621
1.0	£5,688	£6,852	-£1,164
1.5	£5,688	£6,274	-£586
2.0	£5,688	£6,029	-£341
2.5	£5,688	£5,915	-£227

We conducted a two-way sensitivity analysis, varying the baseline healing rate with EXOGEN (95% confidence interval from Mayr 2000 study) and the relative risk of healing with surgery compared with EXOGEN. This results are quite stable, only if we reduce the healing rate with EXOGEN to its lower limit, and the relative risk of healing with surgery to its upper limit does EXOGEN become more expensive than surgery.

Table 14. EAC non-union model: baseline healing rate with EXOGEN and RR with surgery

	Cost difference per patient (EXOGEN – surgery)		
Relative risk surgery vs EX	EX Lower CI 82%	EX Mean rate 88%	EX Upper CI 93%
0.5	-£2,692	-£2,621	-£2,448
1.0	-£1,167	-£1,164	-£1,160
1.5	-£465	-£586	-£749
2.0	-£129	-£341	-£598
2.5	£40	-£227	-£532

Other sensitivity analyses conducted on the non-union model are reported in Table 15. EXOGEN remained cost-saving in this context under all scenarios tested.

Table 15. EAC non-union model: other sensitivity analysis

Sensitivity analysis	EXOGEN	Surgery	Cost difference (EXOGEN - Surgery)
No delay in onset of healing	£5,046	£6,224	-£1,178
VAT on devices and consumables	£6,199	£7,123	-£924
Annual risk of infection 4.9%	£5,652	£6,734	-£1,082
HRG cost of infection (£3,108)	£5,635	£6,638	-£1,002
HRG cost of surgery (£2,350)	£5,527	£5,601	-£74
HRG cost of surgery (£4,126)	£5,735	£7,589	-£1,854

EAC results - Delayed Union

The following changes were made to the delayed union model:

- Allowing infection in EXOGEN arm following further surgery for patients who have not healed after 6 months (9 months post-fracture)
- Changing costs to apply to delayed union resource use (as per model) at baseline, not fresh fracture.
- Price of EXOGEN changed from £998 to £999.38
- Infection rate 2.6% in first month following surgery (for patients in both arms whose fractures fail to heal by 9 months post-fracture) and then 0% in subsequent cycles
- Cost of infection weighted using for £14,527 51% deep and HRG £3,108 for 49% superficial = £8,932.

The EAC estimated results for eight scenarios reflecting different sources of healing rates (Mayr for EXOGEN and relative risk from Schofer vs. Schofer alone), and different assumptions about the minimum time to healing following surgery and EXOGEN (no delay vs. two-month delay before healing is observed), and the persistence of relative benefits of EXOGEN (persistence vs. no persistence of enhanced healing rate between end of EXOGEN treatment at 4 months and further surgery if needed at 6 months).

Model 1
Assumes healing rate with EXOGEN of 92% at four months (Mayr) and hazard ratio for EXOGEN versus placebo 1.69 (Schofer)

A- 2 month delay, no persistence of benefit of EXOGEN beyond 4 months
B- 2 month delay, persistence of benefit of EXOGEN beyond 4 months
C- No delay, no persistence of benefit of EXOGEN beyond 4 months
D- No delay, persistence of benefit of EXOGEN beyond 4 months

Model 2
Uses Schofer healing rates for both arms: 46% for controls and 65% for EXOGEN group over four months.

A- 2 month delay, no persistence of benefit of EXOGEN beyond 4 months
B- 2 month delay, persistence benefit of EXOGEN beyond 4 months
C- No delay, no persistence of benefit of EXOGEN beyond 4 months
D- No delay, persistence of benefit of EXOGEN beyond 4 months

The monthly and cumulative healing rates for these scenarios over the 12 month time horizon are shown in Figure 4 and Figure 5.

Figure 4. EAC delayed union models 1A to 1D: EXOGEN healing rate (Mayr), hazard ratio (Schofer)

DU model 1A		Months since fracture												
		3	4	5	6	7	8	9	10	11	12	13	14	15
CONTROL	Hazard rate		0.38	0.38	0.38	0.38	0.38	0.38	-	-	0.49	0.49	0.49	0.49
	% per month		31%	31%	31%	31%	31%	31%	0%	0%	39%	39%	39%	39%
	% healed	0%	31%	53%	68%	78%	85%	89%	89%	89%	94%	96%	98%	99%
								0%	0%	0%	39%	63%	77%	86%
	Source		Mayr EXOGEN / RR Schofer								Gebauer surgery			
EXOGEN	Hazard rate		0.38	0.38	0.89	0.89	0.38	0.38	-	-	0.49	0.49	0.49	0.49
	% per month		31%	31%	59%	59%	31%	31%	0%	0%	39%	39%	39%	39%
	% healed	0%	31%	53%	81%	92%	95%	96%	96%	96%	98%	99%	99%	99%
								0%	0%	0%	39%	63%	77%	86%
	Source		=control		Mayr EXOGEN		=control				Gebauer surgery			

DU model 1B		Months since fracture												
		3	4	5	6	7	8	9	10	11	12	13	14	15
CONTROL	Hazard rate		0.38	0.38	0.38	0.38	0.38	0.38	-	-	0.49	0.49	0.49	0.49
	% per month		31%	31%	31%	31%	31%	31%	0%	0%	39%	39%	39%	39%
	% healed	0%	31%	53%	68%	78%	85%	89%	89%	89%	94%	96%	98%	99%
								0%	0%	0%	39%	63%	77%	86%
	Source		Mayr EXOGEN / RR Schofer								Gebauer surgery			
EXOGEN	Hazard rate		0.38	0.38	0.89	0.89	0.89	0.89	-	-	0.49	0.49	0.49	0.49
	% per month		31%	31%	59%	59%	59%	59%	0%	0%	39%	39%	39%	39%
	% healed	0%	31%	53%	81%	92%	97%	99%	99%	99%	99%	100%	100%	100%
								0%	0%	0%	39%	63%	77%	86%
	Source		=control		Mayr EXOGEN						Gebauer surgery			

DU model 1C		Months since fracture												
		3	4	5	6	7	8	9	10	11	12	13	14	15
CONTROL	Hazard rate		0.38	0.38	0.38	0.38	0.38	0.38	0.33	0.33	0.33	0.33	0.33	0.33
	% per month		31%	31%	31%	31%	31%	31%	28%	28%	28%	28%	28%	28%
	% healed	0%	31%	53%	68%	78%	85%	89%	92%	95%	96%	97%	98%	99%
								0%	28%	48%	63%	73%	81%	86%
	Source		Mayr EXOGEN / RR Schofer								Gebauer surgery			
EXOGEN	Hazard rate		0.63	0.63	0.63	0.63	0.38	0.38	0.33	0.33	0.33	0.33	0.33	0.33
	% per month		47%	47%	47%	47%	31%	31%	28%	28%	28%	28%	28%	28%
	% healed	0%	47%	72%	85%	92%	95%	96%	97%	98%	99%	99%	99%	99%
								0%	28%	48%	63%	73%	81%	86%
	Source		Mayr EXOGEN				=control				Gebauer surgery			

DU model 1D		Months since fracture												
		3	4	5	6	7	8	9	10	11	12	13	14	15
CONTROL	Hazard rate		0.38	0.38	0.38	0.38	0.38	0.38	0.33	0.33	0.33	0.33	0.33	0.33
	% per month		31%	31%	31%	31%	31%	31%	28%	28%	28%	28%	28%	28%
	% healed	0%	31%	53%	68%	78%	85%	89%	92%	95%	96%	97%	98%	99%
								0%	28%	48%	63%	73%	81%	86%
	Source		Mayr EXOGEN / RR Schofer								Gebauer surgery			
EXOGEN	Hazard rate		0.63	0.63	0.63	0.63	0.63	0.63	0.33	0.33	0.33	0.33	0.33	0.33
	% per month		47%	47%	47%	47%	47%	47%	28%	28%	28%	28%	28%	28%
	% healed	0%	47%	72%	85%	92%	96%	98%	98%	99%	99%	99%	100%	100%
								0%	28%	48%	63%	73%	81%	86%
	Source		Mayr EXOGEN								Gebauer surgery			

Figure 5. EAC delayed union models 2A to 2D: healing rates for both groups from Schofer

DU model 2A		Months since fracture												
		3	4	5	6	7	8	9	10	11	12	13	14	15
CONTROL	Hazard rate		0.15	0.15	0.15	0.15	0.15	0.15	-	-	0.49	0.49	0.49	0.49
	% per month		14%	14%	14%	14%	14%	14%	0%	0%	39%	39%	39%	39%
	% healed	0%	14%	27%	37%	46%	54%	60%	60%	60%	76%	85%	91%	94%
								0%	0%	0%	39%	63%	77%	86%
	Source		Schofer placebo								Gebauer surgery			
EXOGEN	Hazard rate		0.15	0.15	0.37	0.37	0.15	0.15	-	-	0.49	0.49	0.49	0.49
	% per month		14%	14%	31%	31%	14%	14%	0%	0%	39%	39%	39%	39%
	% healed	0%	14%	27%	49%	65%	70%	74%	74%	74%	84%	90%	94%	96%
								0%	0%	0%	39%	63%	77%	86%
	Source		Schofer placebo		Schofer EXOGEN		Schofer placebo				Gebauer surgery			

DU model 2B		Months since fracture												
		3	4	5	6	7	8	9	10	11	12	13	14	15
CONTROL	Hazard rate		0.15	0.15	0.15	0.15	0.15	0.15	-	-	0.49	0.49	0.49	0.49
	% per month		14%	14%	14%	14%	14%	14%	0%	0%	39%	39%	39%	39%
	% healed	0%	14%	27%	37%	46%	54%	60%	60%	60%	76%	85%	91%	94%
								0%	0%	0%	39%	63%	77%	86%
	Source		Schofer placebo								Gebauer surgery			
EXOGEN	Hazard rate		0.15	0.15	0.37	0.37	0.37	0.37	-	-	0.49	0.49	0.49	0.49
	% per month		14%	14%	31%	31%	31%	31%	0%	0%	39%	39%	39%	39%
	% healed	0%	14%	27%	49%	65%	76%	83%	83%	83%	90%	94%	96%	98%
								0%	0%	0%	39%	63%	77%	86%
	Source		Schofer placebo			Schofer EXOGEN					Gebauer surgery			

DU model 2C		Months since fracture												
		3	4	5	6	7	8	9	10	11	12	13	14	15
CONTROL	Hazard rate		0.15	0.15	0.15	0.15	0.15	0.15	0.33	0.33	0.33	0.33	0.33	0.33
	% per month		14%	14%	14%	14%	14%	14%	28%	28%	28%	28%	28%	28%
	% healed	0%	14%	27%	37%	46%	54%	60%	71%	79%	85%	89%	92%	94%
								0%	28%	48%	63%	73%	81%	86%
	Source		Schofer placebo								Gebauer surgery			
EXOGEN	Hazard rate		0.26	0.26	0.26	0.26	0.15	0.15	0.33	0.33	0.33	0.33	0.33	0.33
	% per month		23%	23%	23%	23%	14%	14%	28%	28%	28%	28%	28%	28%
	% healed	0%	23%	41%	54%	65%	70%	74%	81%	87%	90%	93%	95%	96%
		0%						0%	28%	48%	63%	73%	81%	86%
	Source		Schofer EXOGEN				Schofer placebo				Gebauer surgery			

DU model 2D		Months since fracture												
		3	4	5	6	7	8	9	10	11	12	13	14	15
CONTROL	Hazard rate		0.15	0.15	0.15	0.15	0.15	0.15	0.33	0.33	0.33	0.33	0.33	0.33
	% per month		14%	14%	14%	14%	14%	14%	28%	28%	28%	28%	28%	28%
	% healed	0%	14%	27%	37%	46%	54%	60%	71%	79%	85%	89%	92%	94%
								0%	28%	48%	63%	73%	81%	86%
	Source		Schofer placebo								Gebauer surgery			
EXOGEN	Hazard rate		0.26	0.26	0.26	0.26	0.26	0.26	0.33	0.33	0.33	0.33	0.33	0.33
	% per month		23%	23%	23%	23%	23%	23%	28%	28%	28%	28%	28%	28%
	% healed	0%	23%	41%	54%	65%	73%	79%	85%	89%	92%	94%	96%	97%
		0%						0%	28%	48%	63%	73%	81%	86%
	Source		Schofer EXOGEN								Gebauer surgery			

Our preferred scenario is model 1A because we believe that:

a) the best estimate of the healing rate with EXOGEN is the registry data reported by Mayr *et al*;

b) the best estimate of relative healing rates with EXOGEN compared with no further treatment until non-union is the Schofer trial;

c) it is reasonable to assume that healing following surgery or start of EXOGEN treatment will not usually be observed within two months (clinical opinion);

d) it is conservative to assume that EXOGEN does not continue to enhance the background healing rate once ultrasound treatment has finished after four months (the duration of follow-up in the Schofer trial).

Results for the main EAC analyses for delayed union fractures of the tibia are shown in Table 16. Under the EAC preferred model (1A), using EXOGEN at this time point is estimated to be about £500 more expensive per patient than waiting and treating surgically at non-union if necessary. For most scenarios, EXOGEN is not cost saving in this context. The only real exception is with model 2B: where we assume that healing with EXOGEN is not observed until month 2, that it climbs quickly to 65% at four months, and continues at this faster rate until month six (when any remaining unhealed patients have surgery).

Table 16. EAC main analysis delayed union: mean cost per patient

Model			EXOGEN	Control (placebo)	Cost difference (EX vs control)
Healing rates at four months: 92% EXOGEN (Mayr), RR 1.69 (Schofer)					
1A	delay	no persistence	£3,033	£2,529	£504
1B	delay	persistence	£2,899	£2,529	£370
1C	no delay	no persistence	£2,835	£2,384	£451
1D	no delay	persistence	£2,772	£2,384	£388
Healing rates: 65% EXOGEN and 45% control (Schofer)					
2A	delay	no persistence	£4,674	£4,571	£103
2B	delay	persistence	£4,181	£4,571	-£390
2C	no delay	no persistence	£4,212	£4,024	£188
2D	no delay	persistence	£4,009	£4,024	-£15

Table 17 shows the results of a two-way sensitivity analysis on the EAC preferred model (1A), in which we vary both the baseline healing rate with EXOGEN (between 95% confidence limits from Mayr) and the relative risk of healing with EXOGEN compared with control (from Schofer). Results are not sensitive to these changes, and EXOGEN remains more costly than waiting to see if the patient heals without further intervention.

Table 17. EAC delayed union: sensitivity analysis on healing rate with EXOGEN and RR

Relative risk (Ex vs control)	Cost difference per patient (EXOGEN – control)		
	EX lower CI	EX mean rate	EX upper CI
	89%	92%	95%
1.0	£999	£999	£999
1.7	£405	£504	£621
2.0	£114	£239	£395

Other sensitivity analyses on version 1A of the EAC model are presented in Table 18. EXOGEN remained more expensive than the comparator under all of the scenarios tested.

Table 18. EAC delayed union: other sensitivity analyses

Sensitivity analysis	EXOGEN	Control	Cost difference (EX vs control)
VAT on devices and consumables	£3,243	£2,557	£686
Risk of infection annual rate of 4.9%	£3,032	£2,527	£505
Use of HRG cost of infection	£3,027	£2,512	£515
Cost of surgery (£2,350)	£2,994	£2,418	£576
Cost of surgery (£4,126)	£3,058	£2,599	£459

4.7 Conclusions on the economic evidence

The economic models submitted by the sponsor are of a good general standard. We found a few minor errors in coding and data entry – probably inherited from when the model was adapted from the published (Taylor 2009) evaluation of fresh fractures. But these make little difference to the results.

However, in adapting the published model, the sponsor made a number of other adjustments to modelling assumptions and parameters, some of which the EAC considers to be potentially misleading. In particular, the method by which healing rates were extracted from the key clinical studies (Mayr and Schofer) and converted to monthly rates led to an overestimation of the likely relative effectiveness of EXOGEN compared with the control arm in the delayed union model. On changing these assumptions, we found that EXOGEN did not appear to be cost-saving in this context.

We found the results of the non-union model to be more robust. Under the EAC preferred model, the use of EXOGEN followed by surgery only if needed after a further 6 months was estimated to save about £1,200 per patient compared with immediate surgery in patients with non-union fractures of the tibia. EXOGEN remained cost-saving under a wide range of scenarios. There is some uncertainty over this result, due to uncertainty over two key drivers of the non-union cost model. Firstly, the model is somewhat sensitive to changes in assumptions about the relative effectiveness of surgery

compared with EXOGEN, and it should be noted that the clinical evidence supporting the basecase assumption of equal effectiveness is of poor quality. Secondly, the magnitude of the cost saving with EXOGEN model depends on the estimated cost of surgery.

We were initially concerned that the submitted models overestimated the incidence of infection (taking what appears to be a rate over approximately three months post surgery from the HPA, and applying it monthly) and also that they overestimated the cost of infections (assuming that they would all require an inpatient stay of one month). However, we found that these assumptions actually make little difference to the results – since the absolute number of patients developing an infection in any of the treatment arms is small.

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

The additional analyses undertaken by the EAC did change the results as reported in the submission. Early treatment with EXOGEN (at 3 months post fracture) did not appear to be cost saving under the EAC assumptions.

Results were more robust for later treatment of non-union fractures (at 9 months post fracture), and the EAC did conclude that use of EXOGEN in this context is likely to be cost-saving, although there is some uncertainty over this conclusion due to uncertainty over the relative effectiveness of surgery and ultrasound in this context and over the cost of surgery itself.

5 Conclusions

The clinical evidence is generally weak. There is one large registry study (Mayr 2000), which provides quite robust estimates of absolute healing rates with EXOGEN for delayed union and non-union fractures of different long bones, and one randomised controlled trial comparing EXOGEN with placebo in a mixed population of patients with delayed and non-union fractures of the tibia. Other available evidence comes from case series, which are difficult to summarise due to differences in the reporting of outcomes. There is a lack of evidence on other outcomes of interest.

It is clear that EXOGEN carries a much lower risk of adverse effects than surgery. Surveillance data indicates that around 1.4% of patients undergoing surgical reduction of a long bone fracture (2.6% of patients with risk factors for

infection) will develop an infection, around 51% of which are serious deep infections (HPA 2010/11). In contrast, reports of adverse reactions possibly related to the use of EXOGEN are rare.

Delayed union

There is no evidence – direct or indirect - comparing healing rates with EXOGEN and surgery in the treatment of delayed union fractures of long bones. This means that it is not possible to evaluate the comparison requested in the scope. However, the sponsor does present a comparison between early use of EXOGEN (at three months) and observation followed by surgery at non-union (nine months) if necessary. This might be a clinically appropriate comparison if surgery would not usually be offered for delayed union fractures. This comparison relies on evidence from the Schofer sham-controlled randomised trial, and it should be noted that this study did not find a significant difference in healing rates, although it was not powered for this outcome, and it did find significant improvements in indicators of progression to healing (outside the scope). It should also be noted that the Schofer trial included a mix of patients with fractures that would be classified as delayed union and non-union under the scope definition, and did not present a subgroup analysis. It is therefore difficult to know to what extent the results apply to the specific context of delayed union. The trial data also relates to tibia fractures only, so there is some uncertainty over effects for fractures of other long bones.

The costing model for delayed union presented by the sponsor found a small cost-saving of £684 on average per patient associated with the early use of the EXOGEN system. However, this result was not robust to sensitivity analysis conducted by the EAC. We found that different (legitimate) methods of estimating healing rates from the available clinical data reversed the conclusions. Under our best estimate, early use of EXOGEN for delayed union was around £500 more expensive than waiting for surgery at non-union.

Non union

There is no direct comparative evidence for outcomes of interest for EXOGEN versus surgery in non-union fractures of long bones. There is a fair estimate of the absolute healing rate with EXOGEN from a large registry study, and supportive evidence from other smaller non-comparative case series. There are also estimates of the healing rate with surgery from case series. Although these non-controlled studies provide reasonable evidence of effectiveness for each intervention, it is difficult to gauge the size of their relative effect.

For the non-union costing model, the sponsor assumes equal healing rates with EXOGEN and surgery. Together, this assumption and the sponsor's

estimate of the cost of surgery yield a cost-saving for EXOGEN of about £2310. This is a much larger difference than in the delayed union model, which is not surprising given that the proposed pathway for non-union assumes that EXOGEN will directly displace the need for further surgery. The EAC best estimate of the cost-saving with EXOGEN versus surgery in non-union is lower than that of the sponsor: £1,164 cost saving on average per patient. This makes the results of the non-union model somewhat susceptible to uncertainty over the relative effectiveness and costs of EXOGEN and surgery.

6 Implications for research

Comparative evidence for the relative clinical and cost effectiveness of EXOGEN and surgery for the treatment of non-union long bone fractures is lacking. This could be provided by a randomised trial, or if this is not feasible in the non-union population comparative observational data could be of used.

Corroboration of the results of the Schofer trial, with further randomised studies of the clinical and cost-effectiveness of early use of EXOGEN in delayed union would also be valuable. Evidence for long bones other than the tibia would help to establish generalisability.

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Appendix A: Clinical study methods

The below are sponsor's summary of methodology for individual studies and the EAC's comments in the last right column. The sponsor's submission are in grey and the EAC's comments in black.

Study name Schofer 2010	Improved healing response in delayed unions of the tibia with low-intensity pulsed ultrasound: results of a randomized sham-controlled trial	Comments by the EAC
Objectives	Test the hypothesis that in comparison to a placebo, 16 consecutive weeks of LIPUS treatment would accelerate the progression to healing as evidenced by quantitative radiographic measurements of bone mineral density (BMD) and the reduction in the size of the residual gap area.	Agree
Location	Six centres in Germany	Agree
Design	Multicentre randomized sham-controlled trial	Agree
Duration of study	16 weeks	Agree
Sample size	101	Agree
Inclusion criteria	All adult patients who had sustained a tibial shaft fracture that subsequently showed inadequate progress toward healing (i.e., delayed union) and provided informed consent.	Agree
Exclusion criteria	Patients who were pregnant had a revision or reoperation at the fracture site within 16 weeks of enrollment, had a deep wound infection, or had excessive malalignment.	Agree
Method of randomisation	Treatment was assigned randomly to each subject on a 1:1 basis in blocks of six and randomization was stratified within each clinical site. The randomization code was developed using a computer random number generator. The investigators, subjects and sponsor were blinded to the random allocation sequence prior to initiation of treatment and throughout the entire duration of this study.	Agree
Method of blinding	A sham device was used.	Agree

Intervention(s) (n =51) and comparator(s) (n =50)	n=51 (EXOGEN group) n=50 (sham group)	Agree
Baseline differences	Age, female, fracture age, distribution of fracture age, open fracture, surgical treatment, smoking status.	Agree
Duration of follow-up, lost to follow-up information	16 weeks	Agree
Statistical tests	For each of five stochastically completed data sets, analysis of covariance (ANCOVA) was used to estimate a treatment group contrast that controlled for the baseline value of the clinical endpoint as well as clinical site. Subject baseline characteristics were summarized using frequency and percentage distributions or descriptive statistics, as appropriate. Proportions were compared using the Chi-square test with Yates' continuity correction or Fisher's exact test. Continuous variables were compared using the two sample t-test.	Agree
Primary outcomes (including scoring methods and timings of assessments)	*Change in BMD between pre-treatment and 16 weeks:* Results from the descriptive 'completers' analysis of observed cases are expressed on the log scale in order to allow comparison of ES between BMD and gap area. The mean (SD) changes from pre-treatment to 16 weeks follow-up in log BMD were 0.87 (0.67) HU and 0.57 (0.38) HU for active- and sham-treated groups, respectively (t-test, p = 0.014) (Figure 1). The difference in these means, divided by the pooled standard deviation results in a standardized ES of 0.53 (95% CI 0.09 to 0.97). The corresponding mean changes (SD) in log gap area were -0.131 (0.072) mm2 and -0.097 (0.070) mm2 for active and sham groups, respectively (p = 0.034) resulting in a standardized effect size of comparable absolute value (ES = -0.47, 95% CI -0.91 to -0.03).	Agree

Secondary outcomes (including scoring methods and timings of assessments)	*Change in gap area at the fracture site:* A statistically significant benefit of LIPUS treatment was realized in terms of mean reduction in bone gap area based on log transformed data using multiple imputation methods (1-sided, p = 0.014). The exponentiated difference in log mean changes was 0.974 (90% CI 0.956 to 0.993) reflecting proportionally smaller average gap area. For untransformed data, the group difference in mean adjusted changes from baseline in bone gap area was -0.457 mm2 (90% CI -0.864 to -0.049) with 1-sided p = 0.03 similarly reflecting a smaller expected gap area in LIPUS-treated subjects compared to controls.	Plus, healing rates were 65% (33/51) for EXOGEN, 46% (23/50) for placebo in 16 weeks follow-up. .

Study name Rutten 2008	Low-intensity pulsed ultrasound increases bone volume, osteoid thickness and mineral apposition rate in the area of fracture healing in patients with a delayed union of the osteotomized fibula	Comments by the EAC
Objectives	Investigate how LIPUS affects bone healing at the tissue level in patients with a delayed union of the osteotomized fibula, by using histology and histomorphometric analysis to determine bone formation and bone resorption parameters	Agree
Location	Single centre in the Netherlands	Agree
Design	Randomised, double-blind, placebo controlled	Agree
Duration of study	4 months	Agree
Sample size	13 patients	Agree
Inclusion criteria	Patients with fibular delayed union 6 months post- High tibial osteotomy (HTO)	
Exclusion criteria	Patients with union of the fibula post - HTO	Not mentioned in the paper
Method of randomisation	Computerised randomisation	Agree
Method of blinding	A sham device was used	Agree
Intervention(s) (n =) and comparator(s) (n =)	EXOGEN = 7 Placebo = 6	Agree
Baseline differences	None reported	The paper reported age, gender, smoking status, fracture age and delayed union type of the two treatment group but no statistical test was reported, probably due to the small sample size.
Duration of follow-up, lost to follow-up information	2- 4 months – no loss to follow-up	Agree
Statistical tests	Statistical analysis of the data was performed using a Student's independent t-test (two-tail). The values of the histomorphometric parameters are expressed as mean ± SEM. A p-value of b 0.05 is considered significant.	Agree but due to the small sample size these test did not make much sense.

Primary outcomes (including scoring methods and timings of assessments)	1) area of new bone formation, 2) area of cancellous bone, and 3) area of cortical bone.	Agree Therefore this study did not include any outcome measures in the scope.
Secondary outcomes (including scoring methods and timings of assessments)	None	Agree

Summary of methodology for randomised controlled trials - SURGERY

Study name Cacchio 2009	Extracorporeal Shock-Wave Therapy Compared with Surgery for Hypertrophic Long-Bone Non-unions	Comments by the EAC
Objective	Compare the results of extracorporeal shock-wave therapy produced by two different devices with those of surgical treatment in the management of long-bone non-union.	Agree
Location	Multicentre in Italy	Agree
Design	Randomised, double-blind, controlled	Agree
Duration of study	6 months	Agree
Patient population	156	Agree
Sample size	126	Agree
Inclusion criteria	long-bone non-union and skeletal maturity.	Agree
Exclusion criteria	bone tumours, pathologic fractures, infected non-unions, breakage of fixation devices, an implanted pacemaker, blood coagulation disorders, use of anticoagulant drugs, and pregnancy.	Agree
Intervention(s) (n =) and comparator(s) (n =)	SWT (1)= 42, SWT (2) = 42 Surgery = 42	Agree
Baseline differences	None reported	No significant differences were found between study groups, in terms of age, gender, duration of non-union, type of non-union, pain score, DASH score and LEFS score.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Active follow up over 24 months 15 patients were lost to follow up	Agree

Statistical tests	To test the primary end point, a two-sided chi-square test was carried out to compare the success rate at six months in the extracorporeal shock-wave therapy groups with that in the surgery group; the level of significance was 5%. To test the secondary end points, a two-way analysis of variance, with the group as the between-subjects factor and time as the within-subjects factor, was used to assess whether there were significant differences in the DASH, LEFS, and visual analogue scale scores among the three groups and between the preoperative and scheduled follow-up time points within each group. A Tukey post hoc comparison was used to assess significant differences between mean values when a significant main effect and interaction were found. The model for all of the analyses included the main effects of treatment, time, and the treatment · time interaction. Significance levels for multiple comparisons were adjusted with the Bonferroni procedure. The level of significance was set at $p < 0.05$.	Agree
Primary outcomes (including scoring methods and timings of assessments)	Radiographic healing - callus bridged the non-union site on all four cortices	Agree. Radiographic test of healing was assessed at 6 months.
Secondary outcomes (including scoring methods and timings of assessments)	Clinical results – The DASH questionnaire for the patients with an upper-limb non-union and the LEFS questionnaire for the patients with a lower-limb non-union.	Agree

Study name Friedlaender 2001	**Osteogenic Protein-1 (Bone Morphogenetic Protein-7) in the Treatment of Tibial Non-unions: A Prospective, Randomized Clinical Trial Comparing rhOP-1 with Fresh Bone Autograft***	**Comments by the EAC**
Objective	Comparison the clinical and radiographic results with this osteogenic molecule and those achieved with fresh autogenous bone.	Agree
Location	Multicentre USA	Agree
Design	controlled, prospective, randomized, partially blinded,	Agree
Duration of study	24 months, primary endpoint 9 months	Agree
Patient population	Adults with non-unions	Adults with tibial non-unions
Sample size	124 fractures	122 patients (2 patients had two non-union fractures)
Inclusion criteria	Each patient had a tibial non-union, as based on a 1988 FDA guidance document definition requiring 9 months duration of the non-united fracture with no evidence of progressive healing over the previous 3 months	Agree

Exclusion criteria	Patients who, in the judgment of their treating orthopaedic surgeon, were candidates for internal fixation alone (generally reaming and an intramedullary rod), were excluded, as were patients with clinically apparent infection at the fracture site. 1. Patients who do not meet the study inclusion criteria. 2. Patients who are skeletally immature. 3. Patients unable or unwilling to fulfil the follow-up requirements. 4. Patients with severely compromised soft-tissue coverage at the non-union site, sufficient to impair bone healing. 5. Patients with non-unions resulting from pathological fractures (neoplasia, metabolic bone disease). 6. Patients receiving radiation, chemotherapy, immunosuppression, or chronic steroids. 7. Patients who are or could become pregnant during the study or who are breastfeeding. 8. Patients with active infection systemically or at the site of non-union. 9. Patients receiving other investigational treatment. 10. Patients with congenital or synovial pseudarthrosis of the tibia. 11. Patients with complete neuropathy that would interfere with walking or appreciation of pain. 12. Patients with non-unions of multiple bones (other than the tibia). 13. Patients with a known autoimmune disease. 14. Patients with known sensitivity to collagen.	Agree
Intervention(s) (n =) and comparator(s) (n =)	Surgery plus rhOP-1 = 63 fractures Surgery plus autograft = 61 fractures	Agree but note that both treatments involved surgical interventions using different material.
Baseline differences	These two randomly assigned populations were similar in most respects, including age, sex ratio, duration of non-union, and the number of prior surgical interventions. There was, however, a statistically higher prevalence of atrophic non-unions (41 compared with 25%, p = 0.048) and a strong trend toward more smokers (74 compared with 57%, p = 0.057) in the OP-1 group.	Agree

How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	These criteria were evaluated at 1, 2, 3, 6, 9, 12, and 24 months following surgery, and the primary end-point of the study was the 9-month visit. No loss to follow-up	Agree
Statistical tests	Analyses of efficacy outcomes were conducted with use of a chi-square test, and a p value of ≤ 0.05 was considered statistically different. Differences in the frequency of adverse events were evaluated by a two-tailed chi-square or Fisher's exact test, as appropriate. Comparison of the means of operative blood loss was performed with a Student t test. For the length of stay and operative time, Wilcoxon rank sum tests were performed, which are appropriate for variables that are not normally distributed. A p value of ≤ 0.05 for analysis of safety variable was considered significant.	Agree
Primary outcomes (including scoring methods and timings of assessments)	Assessment criteria included the severity of pain at the fracture site, the ability to walk with full weight-bearing, the need for surgical re-treatment of the non-union during the course of this study, plain radiographic evaluation of healing, and physician satisfaction with the clinical course.	Healing had two definitions in this study, one is radiographic evidence of bone bridging on at least one view, and the other was bridging in at least three of four views. The second definition was consistent with the scope. Also, the fully weight-bearing criteria was under the condition of 'less than severe pain' which was different from painless weight bearing as defined in the scope.
Secondary outcomes (including scoring methods and timings of assessments)	Not stated which is primary and which secondary	

Summary of methodology, observational studies - EXOGEN

Study name Gebauer 2005	**Low-Intensity Pulsed Ultrasound: Effects on Non-unions**	**Comments by the EAC**
Objective	To study the efficacy of EXOGEN low-intensity pulsed ultrasound on non-union cases with a minimum fracture age of 8 months.	Agree
Location	Germany and Austria	Agree
Design	Self-paired control study where the control is the patient's own history of failed treatments.	The self-paired study assumed a 5% healing rate for non-union patients without any interventions.
Duration of study	22 months	168 days of EXOGEN treatment duration. 402 days long term telephone follow-up.
Patient population	Consecutively entered German and Austrian population of fractures, of all fracture ages, who were prescribed the use of EXOGEN as an alternative to surgery, based on the patient's decision. All the non-union fractures were consecutively entered into the study, provided the patient did not decide on a surgical revision of the non-union.	Agree
Sample size	85 treated non-union cases. 67 cases met the study inclusion criteria	Agree
Inclusion criteria	• Established non-union defined as a fracture with a minimum age of 8 months from the fracture date • Radiographic assessments displaying a clearly visible fracture line, before and at the start of EXOGEN treatment indicating that the fracture healing process had not progressed or had stopped for at least 3 months before the start of EXOGEN treatment • A minimum period of 4 months without surgical intervention before EXOGEN.	Agree

Exclusion criteria	• Patients who were not skeletally mature • Women who were pregnant or nursing • Patients who could not comply with their physicians' instructions • Fractures that were malaligned, grossly unstable, actively infected or had extensive bone loss	Agree
Intervention(s) (n =) and comparator(s) (n =)	EXOGEN (n=67) Non-union (n=67)	The comparator non-union group was the patients themselves as self-pair.
Baseline differences		This is not relevant as the patients were self-paired.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Anterior / posterior and lateral radiographs were taken at 1-2 month intervals after the start of EXOGEN. Clinical examination occurred at each follow-up visit. Long term follow up conducted by telephone an average of 402 days after trial completion. Five patients were lost to long term follow-up of the 57 healed patients.	Agree
Statistical tests	One-sided test used to calculate the p-value to assess the superiority of treatment with the EXOGEN device for the per cent of non-unions healed Fisher's exact test used to contrast strata of patient and fracture characteristics	This test is not relevant here as the comparator was the patients themselves.
Primary outcomes (including scoring methods and timings of assessments)	Healed non-union when the fracture was both clinically and radiographically healed. Clinical healing was defined as no pain or motion upon gentle stress, and weight bearing if applicable. Radiographic healing defined as three of four bridged cortices for long bones and bridging callus for flat bones.	Agree
Secondary outcomes (including scoring methods and timings of assessments)		None

Study name Jingushi 2007	**Postoperative delayed union or non-union long bone fractures**	**Comments by the EAC**
Objective	Evaluate the impact of EXOGEN on the above	Agree
Location	Multiple centres in Japan	Agree
Design	Prospective, multi-centre, case series	Agree
Duration of study	Treated until healed (2-7 months)	Not clear in the paper
Patient population	All patients long bone delayed union or non-union following operative treatment	Agree
Sample size	72 fractures	40 non-union and 32 delayed unions
Inclusion criteria	Delayed union or non-union fractures of humerus, radius, ulna, femur or tibia following operative treatment. Closed or open (Gustilo grades 1 to III B)	Agree
Exclusion criteria	Fractures not meeting the above inclusion criteria	Agree
Intervention(s) (n =) and comparator(s) (n =)	EXOGEN (n=72)	Agree
Baseline differences	Not applicable	Mean age 40 yrs. Mean age 40.4. Mean fracture age 18.9 month (3-159)
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Clinical and radiographic evaluation by experienced orthopaedic surgeons on a monthly basis until healed.	Agree
Statistical tests	Not applicable for primary endpoint but statistical analysis for baseline characteristics on union rate	Agree
Primary outcomes (including scoring methods and timings of assessments)	Clinical and radiographic healing as determined by experienced orthopaedic surgeons	Healing rate and average healing time

Secondary outcomes (including scoring methods and timings of assessments)	Assessment of impact of background factors on healing rates.	Include the time from the most recent operation to the beginning of EXOGEN treatment.

Study name Lerner 2004	**Compound High Energy Limb Fractures with Delayed Union**	**EAC comments**
Objective	Evaluate the impact of EXOGEN on the above	Agree
Location	Ramban Medical Center and Faculty of Medicine, Technion, Israel	Agree
Design	Prospective, single centre, case series	Agree
Duration of study	Treated until healed (14 to 52 wks)	EXOGEN was used until the fracture healed with mean duration of 26 weeks (13-52)
Patient population	High energy fractures (war injuries, road traffic and work accidents). All Gustilo open fractures (grades II to III C)	Agree
Sample size	17 patients, 18 fractures	16 patients completed the EXOGEN treatment process
Inclusion criteria	Delayed bone healing (18 to 172 weeks) or impaired bone healing (2 fractures at 4 weeks).	No radiographic evidence of racture callus appearance was noted 4 - 38 (median 6) months after prolonged fixation time.
Exclusion criteria	Low energy fractures	Not mentioned in the paper
Intervention(s) (n =) and comparator(s) (n =)	EXOGEN (n=18)	16 patients were long bone delayed unions
Baseline differences	Not applicable	Age ranged from 19 - 48 yrs.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Usual and customary follow up until healed, and long term follow up out to 6 years. 1 patient lost to follow up	Agree
Statistical tests	Not applicable	Agree.
Primary outcomes (including scoring methods and timings of assessments)	Fracture healing as determined by experienced orthopaedic surgeon	Healing time

Secondary outcomes (including scoring methods and timings of assessments)	Not applicable	Healing rate

Study name Mayr 2000	**Ultrasound – an alternative healing method for non-unions?**	**EAC comments**
Objective	A report on patients suffering from healing problems who use EXOGEN therapy for treatment of delayed or non-unions.	Agree
Location	Augsburg Hospital, Augsburg, Germany	SAFHS worldwide prescription registry for delayed union and non-union patients with a subgroup from the local clinic.
Design	Full prospective patient registry population compared with Ausberg's well controlled trial	Reported SAFHS registry and Ausgerg clinic as whole sample and subgroup and compared between the two.
Duration of study	From October 17,1994, to July 14, 1997,	Agree
Patient population	1,317 patients total; 42 patients-Ausberg	Delayed union and non-union patients treated with EXOGEN.
Sample size	1,317	951 delayed unions and 366 non-unions from SAFHS, 42 from Ausberg.
Inclusion criteria	Non-union (9 months post fracture) or delayed union (3-9 months post fracture)	Agree
Exclusion criteria	Not reported	Agree.
Intervention(s) (n =) and comparator(s) (n =)	Augsburg patients – (n=42) Full registry cohort – (n=1,317) The non-union becomes a perfect example of biological self-pairing since the patient has not healed, and subsequent treatment intervention results in a healing status change. This healed status change is the basis for effectiveness since the patient serves as his or her own control.	The intervention was EXOGEN. There was no comparators in this study but a whole sample and subgroup comparison. It is not clear how the self-pair analysis relevant here.
Baseline differences	N/A	Not reported.

How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Only completers were included in the analysis therefore there are no reported losses to follow-up.	Agree.
Statistical tests	Not stated	Statistical tests were used to examine the difference between the SAFHS registry patients and local clinic patients in terms of healing rate and average healing time, in delayed union and non-union patients.
Primary outcomes (including scoring methods and timings of assessments)	Bony healing, defined as follows: healing criteria: three cortices bridged in two X-ray planes or trabecular bridging of at least 80% of the fracture in the case of cancellous fractures	Agree.
Secondary outcomes (including scoring methods and timings of assessments)	None stated	Agree.

Study name Nolte - 2001	**Low-Intensity Pulsed Ultrasound in the Treatment of Non-unions**	**EAC comments**
Objective	To evaluate the effect of EXOGEN low intensity pulsed ultrasound for the treatment of established non-unions in a consecutively enrolled patient population to see if ultrasound had an effect in the treatment of non-union.	Agree
Location	The Netherlands	Agree
Design	Self-paired study where each patient served as their own control, with the prior failed treatments being the basis for evaluating EXOGEN. Each patient was diagnosed with a non-union, with no expectation of healing. EXOGEN was the only change in the treatment regimen – no additional treatment procedure was allowed at the start of or during the period of EXOGEN low intensity pulsed ultrasound treatment to influence the effect of the ultrasound therapy.	This was a case series non-union study. The way to use non-union patients as their own comparators may be of clinical meaning but the statistical analysis did not provide meaningful information for the decision problem.
Duration of study	18 months	It was not clear but the paper mentioned that 1 year after EXOGEN treatment, the patients were interviewed by telephone. Seem that the patients were followed until fracture healed (maximum 398 days)
Patient population	Patients presented in trauma departments	Agree
Sample size	29 fractures reported 21 long bone fractures (tibia, femur, fibula, humerus, ulna, radius)	22 long bone fractures

Inclusion criteria	Patients with a non-union fracture as defined by: • A failure of the fracture to unite at a minimum of 6 months from the time of fracture • Radiographic healing had not progressed or had stopped for a minimum period of 3 months before the start of EXOGEN treatment • The fracture line was clearly visible in two orthogonal views • The interval between the last operative procedure and the start of EXOGEN treatment was a minimum of 90 days	Agree
Exclusion criteria	Not reported	Agree
Intervention(s) (n =) and comparator(s) (n =)	EXOGEN (n=21) Non-union (n=21)	Non-union long bone fractures = 22
Baseline differences		Average age 47 yrs (range 18 - 90). Average frature age 61 weeks (range 25 - 137 weeks).
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patients were actively examined in the outpatient department of their respective hospitals at regular intervals of 6 to 8 weeks. No patients were lost to follow-up. Three patients withdrew themselves from the study.	Agree
Statistical tests	Kruskal-Wallis test was used for contrasting heal time and fracture age. The Kruskal-Wallis analysis was a two sided 99% confidence level Monte Carlo estimate of the exact p value computed. Fisher's exact test was used for heal rates.	This was the statistical test for self-paired non-union patients assuming 5% healing rate without any treatments.
Primary outcomes (including scoring methods and timings of assessments)	Clinical healing on the non-union fracture as defined by: • Absence of pain • Weight bearing without pain or normal function of the limb Radiographically healed non-union fracture as defined by: • Three or four cortices bridged	Agree

Secondary outcomes (including scoring methods and timings of assessments)	None	

Study name Romano 1999	**Low-Intensity, Pulsed Ultrasound for the Treatment of Septic Pseudoarthrosis**	**EAC comments**
Objective	To describe the clinical effects of low intensity pulsed ultrasound for the treatment of septic non-unions.	Agree
Location	Istituto Ortopedico Gaetano Pini, Milan, Italy	Agree
Design	Case Report	Agree
Duration of study	Treated until healed (95 to 181 days)	Treated until consolidation was achieved
Patient population	Patients with septic pseudoarthrosis and delayed consolidation	Agree but the delayed consolidation may not be consistent with delayed union in the scope.
Sample size	15 fractures 13 long bones (tibia, humerus femur)	Agree
Inclusion criteria	Patients with septic pseudoarthrosis and delayed consolidation and: • Sufficiently stable fracture • An infection controlled with antibiotics • Sufficient vascularization • Skin covering	Agree
Exclusion criteria	Not reported	Agree
Intervention(s) (n =) and comparator(s) (n =)	EXOGEN (n=15) NA	Agree
Baseline differences	NA	Age ranged from 28 - 78 yrs. Fracture age ranged from 8 - 30 months.

How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patient follow-up information not provided No patients were lost to follow-up.	Agree
Statistical tests	NA	Agree
Primary outcomes (including scoring methods and timings of assessments)	Consolidation (specific definition not provided)	This outcome measure is not included in the scope.
Secondary outcomes	None	Agree

Summary of methodology, observational studies - SURGERY

Study name Bellabarba 2002	Indirect reduction and plating of distal femoral non-unions	EAC comments
Objective	To observe and report the clinical results of indirect reduction and plating in the treatment of distal femoral non-unions	Agree
Location	Single centre, USA	Agree
Design	Prospective consecutive study	Agree
Duration of study	Average follow up 23 months	Agree
Patient population	A consecutive series of patients with non-union of the distal femur, nineteen of whom had undergone operative initial fracture care	Note that the definition of non-union (6 months no progress of healing) was different from the scope
Sample size	20	Agree
Inclusion criteria	Distal femoral non-unions	Agree
Exclusion criteria	Not stated	Agree
Intervention(s) (n =) and comparator(s) (n =)	20 surgical plating	Agree
Baseline differences	N/A	Mean age 48 yrs (ranged 18 - 92). Interval from injury to non-union 10 months (ranged 3 - 25)
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Follow up method not stated No loss to follow up	Agree
Statistical tests	Not stated	None

Primary outcomes (including scoring methods and timings of assessments)	Healing rate and time, (Clinical and radiographical) operative blood loss and time, incidence of complications including instrumentation failure, loss of fixation, infection, and postoperative malalignment. Both the Böstman and Hospital for Special Surgery knee scores were used to quantify postoperative clinical results at an average follow-up of twenty-three months (range 12 to 60 months).	Agree
Secondary outcomes	Not stated	Agree

Study name Birjandinejad 2009	Augmentation plate fixation for the treatment of femoral and tibial non-unions after intramedullary nailing.	EAC comments
Objective	Present authors' experience in plating as an augmentation to primary nailing	Agree
Location	Single centre, Iran	Agree
Design	Prospective case series	Agree
Duration of study	1 year minimum follow up	Agree
Patient population	Femoral and tibial non-unions	Agree
Sample size	25	Agree
Inclusion criteria	Not stated	Agree
Exclusion criteria	Infection	Agree
Intervention(s) (n =) and comparator(s) (n =)	25 surgical intervention	Agree
Baseline differences	N/A	Mean age 31.4 yrs (ranged 18 - 53).
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Clinic attendance	Agree
Statistical tests	Not stated	Agree
Primary outcomes (including scoring methods and timings of assessments)	Clinical and radiographical healing. Disappearance of lucencies on X-ray and ability to weight bear	No information of ability to weight bearing.
Secondary outcomes (including scoring methods and timings of assessments)	Not stated	Agree

Study name Khalil 2010	**Contoured plating for proximal ulna non-union: an improved technique**	**EAC comments**
Objective	Present results of an improved plating technique	Agree
Location	Single centre, Faculty of medicine, Tanta University, Egypt	Agree
Design	Prospective case series	Agree
Duration of study	22 months average follow up	Agree
Patient population	Patients with proximal ulna non-union	Agree but no clear definition of non-union was reported
Sample size	21	Agree
Inclusion criteria	Ununited proximal ulnar fractures	Agree
Exclusion criteria	Cases with painless stiff non-union with a stable elbow having a range of movement greater than 90° were excluded	Agree
Intervention(s) (n =) and comparator(s) (n =)	21 surgical plating	Agree
Baseline differences	N /A	Mean age 41.7 yrs.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Every 2 weeks	Agree
Statistical tests	Not stated	Agree
Primary outcomes (including scoring methods and timings of assessments)	Clinical and radiographic healing was assessed every 2 weeks Functional outcomes were calculated using the Broberg-Morrey scoring system. Radiographs were evaluated for union, articular congruity and alignment. Radiographic signs of arthritis were graded according to the system of Broberg and Morrey	Agree
Secondary outcomes (including scoring methods and timings of assessments)	None stated	Agree

Study name Lin 2010	**Allografting in Locked Nailing and Interfragmentary Wiring for Humeral Non-unions**	**EAC comments**
Objective	Compare outcomes after repair of humeral non-unions when morsellized fresh-frozen allograft or autograft was used to augment repair by intramedullary nailing	Agree
Location	Single centre, Taiwan	Agree
Design	Prospective, non-blinded, comparative study	Agree
Duration of study	+ 2 years	Agree
Patient population	Patients with humeral non-union	Agree but definition of non-union was different from the scope (6 months no progress)
Sample size	65	Agree
Inclusion criteria	Humeral shaft (3 cm below the lesser tuberosity and 5 cm above the olecranon fossa) non-union of more than 6 months' duration with gross instability at the non-union site	Agree
Exclusion criteria	Exclusion criteria were non-unions with intra-articular extension, active deep infection, or bone defect greater than 3 cm	Agree
Intervention(s) (n =) and comparator(s) (n =)	Surgery plus allograft = 36 Surgery plus autograft = 28	Agree
Baseline differences	No significant differences	Agree
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Follow up though regular clinic attendance. The follow up was defined as the duration between the operation and the last regular follow up before the article was written.	Agree

Statistical tests	Statistical analysis was performed using SPSS software, Version 16 (SPSS Inc, Chicago, IL). Continuous variables were compared with Student's t tests. Binary variables were compared with chi square tests (comparing two proportions) or Fisher's exact tests if cell counts were less than five. For power analysis, with a usual level of statistical significance ($\alpha = 0.05$ for a two-sided test) and a given power of 0.8 ($\beta = 0.2$), the present sample size could detect a minimal difference of 3.0 weeks for time to union and 4.8 points for Neer score.	Since both treatments were surgical process, the statistical analyses don't provide extra information to address the decision question.
Primary outcomes (including scoring methods and timings of assessments)	Primary end points were union rate and functional recovery. The follow up was defined as the duration between the operation and the last regular follow up before this article was written. Clinical union was defined as visible callus bridging the fracture in at least three cortices on radiographs and the patients could use their arms without considerable pain or weakness. Although this was an open-label study, the investigators had no special preference regarding the graft type. The end points were measured by two blinded, fellowship-trained orthopaedic trauma surgeons (SMH, XYH). The two evaluators had pre-study consensus on examination methods. Functional assessment included Neer functional score] and Constant and Murley score for shoulders, Mayo performance score for elbows, and shortened Disabilities of the Arm, Shoulder, and Hand (QuickDASH) score for the upper extremity function. Postoperatively, the Constant and Murley score was compared between the injured and uninjured arms	Agree
Secondary outcomes (including scoring methods and timings of assessments)	Secondary end points included operative blood loss, operation time, hospital stay, time to fracture healing, and complications.	Agree

Study name Livani 2010	Anterior plating as a surgical alternative in the treatment of humeral shaft non-union	EAC comments
Objective	Report the results of anterior plating procedure	Agree
Location	Single centre, Brazil	Agree
Design	Prospective case series	Agree
Duration of study	36 months	Agree
Patient population	Patients with humeral non-union	Agree but non-union was defined as no clinical, radioological or bone scan signs of healing after 8 months
Sample size	15	Agree
Inclusion criteria	Not stated	Patients with humeral shaft fracture who had no clinical, radioological or bone scan signs of healing after 8 months
Exclusion criteria	Not stated	Agree
Intervention(s) (n =) and comparator(s) (n =)	15 treated with anterior plate	Agree
Baseline differences	N/A	Mean age 37.53 yrs (range 18 - 74).
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Clinic attendance	Agree
Statistical tests	No loss to follow up	None
Primary outcomes (including scoring methods and timings of assessments)	Clinical (method not stated)and radiographic healing callus formation and cortical continuity)	Callus formation and cortical continuity as evidence of radiological union. Clinical assessment included functional outcomes for patients who returned to work with no limitation on daily activities.
Secondary outcomes (including scoring methods and timings of assessments)	Not stated	Agree

Study name Razaq 2010	EXCHANGE NAILING FOR NON-UNION OF FEMORAL SHAFT FRACTURES	EAC comment
Objective	Analyse the role of exchange nailing for aseptic non-union of femoral shaft fractures.	Agree
Location	Single centre, Pakistan	Agree
Design	Prospective, consecutive case series	Agree
Duration of study	18 months	Not clear in the paper
Patient population	Patients with aseptic femoral non-unions	Agree
Sample size	41 patients, 43 fractures	Agree
Inclusion criteria	Inclusion criteria 1. All male and female patients who were aged 13 years and above 2. All patients who had initially closed post traumatic fractures of the shaft femur 3. All patients who had one or more times previous surgical treatment done for the fracture 4. All patients had last surgery for the fracture in the preceding 9–12 months in the form of IM nailing. (either K-nail or interlocking nail) 5.All patients had aseptic hypertrophic or atrophic non-union on clinical and radiological assessment performed at 9 months or later after the last surgery 6. All patients had less than 1cm shortening and no bone comminution or bone loss at the time of study	Agree
Exclusion criteria	1. Patients with infected non-unions 2. Patients who had segmental bone defects greater than one cm 3. Patients with bent or broken IM nail/Interlocking nail which had required open removal.	Agree
Intervention(s) (n =) and comparator(s) (n =)	Exchange nailing = 43	Agree
Baseline differences	N/A	Mean age 38.8 yrs (SD 13.8)

How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	All operated patients were followed-up in the outpatient department at 2 weeks for suture removal and wounds examination. Patients were followed up subsequently for clinical and/or radiological check-up at one month intervals for minimum period of one year after the surgery or till time when bone healing at non-union site has occurred. The fracture showing radiological evidence of healing, as confirmed by independent radiologist, was considered healed.	Agree
Statistical tests	Not stated	Agree
Primary outcomes (including scoring methods and timings of assessments)	Radiographic healing (exact method not stated)	Agree
Secondary outcomes (including scoring methods and timings of assessments)	Not stated	Agree

Study name Ring et al	COMPLEX NON-UNION OF FRACTURES OF THE FEMORAL SHAFT TREATED BY WAVE-PLATE OSTEOSYNTHESIS	**EAC comments**
Objective	Report results of wave plate versus conventional plate techniques	Agree
Location	5 centres, USA	Agree
Design	Prospective case series	Agree although the author mentioned their study as retrospective.
Duration of study	33 months follow up	Mean 33 months follow up (12 – 66)
Patient population	Complex ununited fractures of the femoral shaft	Agree
Sample size	42 fractures	Agree
Inclusion criteria	Patients treated with a wave plate	Agree
Exclusion criteria		
Intervention(s) (n =) and comparator(s) (n =)	Wave plate and bone graft	Wave plate combined with bone grafting
Baseline differences	N/A	Mean age 35 yrs (13 - 81), mean duration of non-union before the surgery was 17 months (6 - 68).
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	All patients were reviewed at regular intervals with serial radiographs and clinical examination. At final follow-up, the capacity to bear weight, any leg-length discrepancy, alignment and the range of movement in the joints of the leg were noted. 33 months follow up, no losses to follow up	Agree
Statistical tests	Not stated	Agree
Primary outcomes (including scoring methods and timings of assessments)	Radiographic and clinical healing	Agree

Secondary outcomes (including scoring methods and timings of assessments)	At final follow-up, the capacity to bear weight, any leg-length discrepancy, alignment and the range of movement in the joints of the leg were noted.	Agree

Study name **Wu 2003**	Reaming bone grafting to treat tibial shaft aseptic non-union after plating	EAC comments
Objective	To investigate the effects of using intramedullary reaming to provide cancellous bone graft, and reamed intramedullary nail stabilisation to provide fragment stability on treating tibial shaft aseptic non-unions after plating.	Agree
Location	Single centre, Taiwan	Agree
Design	Prospective case series	Agree
Duration of study	Follow up median 2.2 years	Agree, range 1 – 5.2 years.
Patient population	Tibial shaft aseptic non-unions after plating	Agree
Sample size	31	Agree
Inclusion criteria	Indications for this technique included a tibial shaft non-union with an inserted plate, a fracture level fit for traditional or locked nail stabilisation, absence of suspected infection and segmental bony defect at the time, and shortening of less than 2 cm.	Agree.
Exclusion criteria	Patients with suspicious latent deep infection were excluded from the study,	Agree
Intervention(s) (n =) and comparator(s) (n =)	Reaming and nail insertion = 31	Agree
Baseline differences	N/A	Median age 34 (19-58). Median of time from injury to current treatment was 1.8 yrs (0.8 - 4.2)
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patients were followed up via the hospital's Outpatients Department at 4 to 6 week intervals 3 were lost to follow up	Agree
Statistical tests	Not stated	Agree

Primary outcomes (including scoring methods and timings of assessments)	Clinical and radiographical healing processes were recorded. Bony union was clinically defined as the absence of pain and tenderness, and the ability of the patient to walk without aids. It was radiographically defined as abridgement of solid callus with cortical density for both segments	Agree. Not totally consistent with scope.
Secondary outcomes (including scoring methods and timings of assessments)	Not stated	Agree

Appendix B. Critical appraisal of clinical studies

	Schofer – 2010		
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Comments by the EAC**
Was randomisation carried out appropriately?	Yes	Treatment was assigned randomly to each subject on a 1:1 basis in blocks of six and randomization was stratified within each clinical site. The randomization code was developed using a computer random number generator.	Agree
Was the concealment of treatment allocation adequate?	Yes	The investigators, subjects and sponsor were blinded to the random allocation sequence prior to initiation of treatment and throughout the entire duration of this study.	Agree
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Inspection of background characteristics between study groups showed generally good balance achieved through randomization	Agr4ee
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	The investigators, subjects and sponsor were blinded to the random allocation sequence prior to initiation of treatment and throughout the entire duration of this study. Once the study was complete and the last subject reached 16 weeks of follow-up, the randomization code was broken and treatment assignments revealed to the study statistician. Quantitative radiographic assessments of BMD and gap area also were undertaken without knowledge of treatment group assignment.	Agree

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	Seventeen subjects had missing post-treatment outcomes, consequently 84 subjects were included in descriptive analyses of 'completers'. There was notable differential drop-out between groups with 24% (12 of 50) of sham-treated subjects and 9.8% (5 of 51) of active-treated subjects missing post-treatment BMD values. The ITT cohort was preserved by imputing missing clinical endpoints using a multiple imputation procedure that minimizes bias from differential drop-outs and properly accounts for uncertainty in imputed values when performing statistical inference.	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No		Agree
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The ITT cohort was preserved by imputing missing clinical endpoints using a multiple imputation procedure that minimizes bias from differential drop-outs and properly accounts for uncertainty in imputed values when performing statistical inference.	Agree

Study name	Rutten – 2008		
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Comments by the EAC**
Was randomisation carried out appropriately?	Yes	Randomisation of treatment was computerised	Agree
Was the concealment of treatment allocation adequate?	Yes	Neither patient nor investigator knew whether the patient had received an active EXOGEN device	Agree
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Patients in both treatment groups had similar ages, gender distribution, fracture type and duration of treatment	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Unblinding of the trial was performed after completion of the histomorphometric and histologic analysis, and after all patients included in the trial completed their 5 month clinical treatment phase	Agree
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	N/A		Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No		Agree
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	N/A		Agree

Critical appraisal, randomised control trials – SURGERY

Study name	**Cacchio – 2009**		
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	
Was randomisation carried out appropriately?	Yes	Randomization of the patients and monitoring of the data were performed in a university hospital (Department of Physical Medicine and Rehabilitation, School of Medicine, ''La Sapienza'' University, Rome) not involved in the treatment procedures, according to the CPMP/ ICH (Committee for Proprietary Medicinal Products/International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Guideline for Good Clinical Practice12 and Guideline for Statistical Principles for Clinical Trials1	
Was the concealment of treatment allocation adequate?	Yes	IN comparison of the shockwave treatments, yes. However, it is impossible to conceal surgical intervention	
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	There were no significant differences in baseline characteristics	
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	The study states that it is double blind, however, only the independent assessors were blind to the treatment for the shockwave treatment group	

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes	There was a high rate of drop out in the atrophic non-union group. A requirement for separate analysis was noted, but not carried out due to low numbers	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	All outcome analyses were performed according to the intention-to-treat principle. The intention-to-treat analysis was carried out according to a ''worst case scenario'' analysis: subjects who did not complete the treatment or did not undergo the post-treatment or final follow-up assessments were assigned a poor outcome, with the final follow-up evaluation considered to be the last observation performed.	

Study name	Friedlaender 2001		
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Comments by the EAC**
Was randomisation carried out appropriately?	Not clear	Treatment was randomly assigned, but method is not made clear	Agree
Was the concealment of treatment allocation adequate?	Yes		Agree
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	These two randomly assigned populations were similar in most respects, including age, sex ratio, duration of non-union, and the number of prior surgical interventions. There was, however, a statistically higher prevalence of atrophic non-unions (41 compared with 25%, p = 0.048) and a strong trend toward more smokers (74 compared with 57%, p = 0.057) in the OP-1 group. There were also trends toward higher percentages of comminuted fractures at injury, prior failures of bone autografts, and prior use of intramedullary rods in the individuals in the OP-1 treated group.	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Not clear	Surgeons were aware of treatment after randomisation, radiographers assessing the cases were blinded throughout. Low risk of bias	Agree
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No		Agree. No loss of follow-up.

Is there any evidence to suggest that the authors measured more outcomes than they reported?	No		Agree
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No		Agree.

Critical appraisal, observational studies – EXOGEN

Study name: Gebauer 2005			
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Comments by the EAC**
Was the cohort recruited in an acceptable way?	Yes	All consecutive patients who met the inclusion criteria were included. The initial injury or fracture management was not a consideration in the study inclusion criteria.	Agree
Was the exposure accurately measured to minimise bias?	Yes	Patients followed the recommended 20 minutes per day until healed treatment. The EXOGEN device automatically provides 20 minute treatments. A patient compliance monitor stored the compliance data in the EXOGEN device. Output of daily use was downloaded when the devices were returned upon completion of the treatment. Additionally, the inclusion criterion to minimize the possible bias of the effects of surgery on the resulting heal rate was no surgical procedure during the 4 months before the start of EXOGEN treatment.	Agree
Was the outcome accurately measured to minimise bias?	Yes	Fracture union as determined by clinical and radiographic assessment.	This is consistent with the scope.
Have the authors identified all important confounding factors?	Yes	Potential variables identified as initial fracture treatment, subsequent surgical or other interventions during the prior period, demographics including gender and age, prior orthopaedic and surgical history including the initial injury type, involved bone and location within the bone, smoking status, non-union type, the interval in days from the last failed surgery to the start of EXOGEN treatment, and the overall fracture age.	Agree

Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Data stratified by the patient and fracture characteristics. All the stratification variables were non-significant apart from overall fracture age, the time from the last surgical procedure to the start of EXOGEN treatment, bone type and long bones versus other bones. These were all as a result of failed scaphoid cases which were atrophic, each having a fracture age and last surgical procedure interval of over 10 years previously.	Not relevant here as this is a case series study.
Was the follow-up of patients complete?	Yes	Long term healed status of all patients was verified in a telephone follow up conducted approximately one year post study completion. Long term follow up was obtained for 52 of the 57 healed patients.	Agree
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	p=0.0001 Confidence interval not reported	This is not relevant to the decision question as the test was between EXOGEN treated and no treatment non-union patients themselves.

tudy name Jingushi - 2007			
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Comments by the EAC**
Was the cohort recruited in an acceptable way?	Yes	Recruitment was from a larger more inclusive study reported separately. Identification of cases that met these prospectively defined criteria was performed as defined	Agree
Was the exposure accurately measured to minimise bias?	Yes	Followed the recommended 20 minutes per day until healed treatment.	Agree
Was the outcome accurately measured to minimise bias?	Yes	Solid bone union as determined by X-ray evaluation plus usual and customary clinical healing determination	Agree
Have the authors identified all important confounding factors?	Yes	Gender, age, location of injury, Gustilo score, presence of operative fixation, fracture age, time since recent operation, number of prior surgeries, treatment time.	Agree
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Full odds ratio analysis of background factors	Agree
Was the follow-up of patients complete?	Yes	All patients	Agree
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	75% of fractures healed plus analysis of factors contributing to higher or lower success rates.	Agree

Study name Lerner 2004			
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Comments by the EAC**
Was the cohort recruited in an acceptable way?	Yes	Sought to recruit high energy fractures with delayed or impaired healing and did so by clinical evaluation using standard definitions	Agree.
Was the exposure accurately measured to minimise bias?	Yes	Followed the recommended 20 minutes per day until healed treatment.	Agree.
Was the outcome accurately measured to minimise bias?	Yes	Solid bone union as determined by X-ray evaluation	Agree. This definition of healing is different from what defined in the scope.
Have the authors identified all important confounding factors?	Yes	Age, type of injury, location of injury, cause of injury, Gustilo score, MESS score, presence of vascular injury, fixation method and flap.	Provided description of characteristics of the patient population as a case series study.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	16/17 fractures for which outcomes were determined exhibited positive outcomes, so no meaningful contribution from confounding factors was evidenced.	Agree.
Was the follow-up of patients complete?	Yes	For 17 out of 18 fractures	Agree.
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	16/17 fractures healed equates to 94%.	Confidence interval and P value were not reported and applicable for this case series study.

Study name Mayr 2000			
	Response yes/no/not clear/N/A)	**How is the question addressed in the study?**	**Comments by the EAC**
Was the cohort recruited in an acceptable way?	Yes	The study included all patients who met the inclusion criteria and who were completers	Agree
Was the exposure accurately measured to minimise bias?	Yes	The treatment method was provided for one daily 20-min treatment period which the patient self-administers at home.	Agree
Was the outcome accurately measured to minimise bias?	Yes	Healing criteria: three cortices bridged in two X-ray planes or trabecular bridging of at least 80%.	Agree
Have the authors identified all important confounding factors?	Yes	Age, fracture type, use of certain drugs and smoking are variable factors.	Agree
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Results were stratified to these populations as well as averaged overall.	Agree
Was the follow-up of patients complete?	Yes	Only completers were measured.	Agree
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	N/A	Agree
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study			

Study name: Nolte - 2001			Comments by the EAC
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**	
Was the cohort recruited in an acceptable way?	Yes	All patients who met the inclusion criteria were included	
Was the exposure accurately measured to minimise bias?	Yes	Patients followed the recommended 20 minutes per day until healed treatment. The EXOGEN device automatically provides 20 minute treatments.	
Was the outcome accurately measured to minimise bias?	Yes	Fracture union as determined by clinical and radiographic assessment.	
Have the authors identified all important confounding factors?	Yes	Potential variables identified as gender, age, fracture age, prior interval without surgery, bone, smoking habit, non-union type, fixation type present before, at the start of, and during ultrasound treatment.	
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Data stratified by the patient and fracture characteristics. All the stratification variables were non significant except for the comparison of smoking strata.	
Was the follow-up of patients complete?	Yes	All healed fractures were followed up for an average of 62 weeks (range 30-110 weeks)	
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	p=0.0001 Confidence interval not reported	

Study name: Romano 1999			
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Comments by the EAC**
Was the cohort recruited in an acceptable way?	Yes	All patients who met the inclusion criteria were included	Agree
Was the exposure accurately measured to minimise bias?	Yes	Patients followed the recommended 20 minutes per day until healed treatment.	Agree
Was the outcome accurately measured to minimise bias?	Not clear	Information not provided	Yes.
Have the authors identified all important confounding factors?	Yes	We did not conduct a controlled double-blind since this study design would not be acceptable. It denies treatment to one study arm and it may be impossible to carry out in patients suffering with infected pseudoarthrosis. In all of the treated cases in this study, the course of fracture healing showed over a period of time that there was no change in the healing process in the presence of an infection and, therefore, the patient was his own control. The only new event that was introduced at the start of treatment was the use of low intensity pulsed ultrasound.	This is a case report study.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes		Not relevant.
Was the follow-up of patients complete?	Yes		Agree
How precise (for example, in terms of confidence interval and p values) are the results?	N/A		Agree

Critical appraisal, observational studies - SURGERY

Study name **Bellabarba 2002**			
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Comments by the EAC**
Was the cohort recruited in an acceptable way?	Yes	Prospective consecutive series	Agree. Case series study.
Was the exposure accurately measured to minimise bias?	Yes		Yes. Very detailed description of the surgery.
Was the outcome accurately measured to minimise bias?	Yes	Extensive measurements in many parameters were taken using two scoring systems	Yes for those which are relevant to the scope and other outcome measures.
Have the authors identified all important confounding factors?	Yes	Extensive discussion of all potential confounding factors on p.267	Not relevant here.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Confounding factors are well measured and reported in the analysis	Not relevant here.
Was the follow-up of patients complete?	Yes	There was no loss to follow up	Agree.
How precise (for example, in terms of confidence interval and p values) are the results?	N/A		Not applicable.

Study name Birjandinejad 2009			
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Comments by the EAC**
Was the cohort recruited in an acceptable way?	Not clear	Clear definition is given as to how and why patients were treated with this modality. Not clear whether there was informed consent	Clear
Was the exposure accurately measured to minimise bias?	N/A		Yes. Had detailed description of the surgery process.
Was the outcome accurately measured to minimise bias?	Not clear	Clear definitions of whether the fracture had healed radiographically and clinically. It is not clear if the assessors were independent	Yes.
Have the authors identified all important confounding factors?	Not clear	Infection is identified and is an exclusion factor, but little discussion concerns other confounding issues	N/A
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	There is no discussion of this in the text	N/A
Was the follow-up of patients complete?	Yes		Agree
How precise (for example, in terms of confidence interval and p values) are the results?	N/A		N/A

Study name Khalil 2010			
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Comments by the EAC**
Was the cohort recruited in an acceptable way?	Yes	Clear definitions of how and why patients were recruited. All patients gave informed consent.	Agree
Was the exposure accurately measured to minimise bias?	N/A		Yes
Was the outcome accurately measured to minimise bias?	Yes	Recognised scoring systems were used	Healing rate and healing time were reported
Have the authors identified all important confounding factors?	Yes	There is extensive discussion of potential confounding factors on p.441	Not relevant to the decision question
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Clinical and radiographic outcomes were measured with an appropriate scoring system	Not relevant to the decision question
Was the follow-up of patients complete?	Yes	No loss to follow up	Agree
How precise (for example, in terms of confidence interval and p values) are the results?	N/A		Agree

Study name Lin 2010			
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Comments by EAC**
Was the cohort recruited in an acceptable way?	Yes	Clear definition of how and why patients were recruited. Patients entered the study with full knowledge, treatment choice and consent	Agree
Was the exposure accurately measured to minimise bias?	N/A		Yes. Two surgical processes were clearly described and reported.
Was the outcome accurately measured to minimise bias?	Yes	Extensive measurements of primary and secondary outcomes	Agree
Have the authors identified all important confounding factors?	Yes	Yes, extensive discussion of all confounding factors is noted on p.853	Since the comparison was between two surgical interventions so this did not address the decision question. Nevertheless, the baseline demographic characteristics provided useful information for the study population in order to facilitate comparison between intervention (EXOGEN) and comparator (surgery) in the scope.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Confounding factors are clearly identified in the analysis	Not relevant.
Was the follow-up of patients complete?	Yes	One patient died 4 months post-op, all other patients completed	Agree
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	95% confidence interval	Agree

Study name Livani 2010			Comments by the EAC
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**	
Was the cohort recruited in an acceptable way?	Yes	Clear definition of how and why patients were recruited. All patients gave informed consent	Agree
Was the exposure accurately measured to minimise bias?	N/A		Yes
Was the outcome accurately measured to minimise bias?	Not clear	Clinical and radiological outcomes are clearly defined, but no recognised scoring system is noted	Agree
Have the authors identified all important confounding factors?	Yes	Table 1. P1026 discusses potential confounding pre-op factors	Agree
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	Pre-op confounding factors are identified and other factors are identified in the results presentation	Agree
Was the follow-up of patients complete?	Yes	No loss to follow up	Agree
How precise (for example, in terms of confidence interval and p values) are the results?	N/A		Agree

Study name Razaq 2010			
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Comments from the EAC**
Was the cohort recruited in an acceptable way?	Yes	Clear definition of how and why patients were recruited. All patients gave informed consent. Extensive inclusion and exclusion criteria noted	Agree
Was the exposure accurately measured to minimise bias?	N/A		Yes.
Was the outcome accurately measured to minimise bias?	Yes	Regular assessments were made by independent assessors	Agree
Have the authors identified all important confounding factors?	Yes	Data regarding patients' age and gender and other characteristics like femur fracture location, type of non-union as to whether hypertrophic or atrophic and injured side as to left or right, duration of fracture healing after exchange interlocking nailing, period of postoperative follow up period and complication were recorded and analysed using SPSS-10.	Agree
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Major confounding factors detailed in tables on p.108	Not relevant
Was the follow-up of patients complete?	Yes	No loss to follow up	Agree
How precise (for example, in terms of confidence interval and p values) are the results?	N/A		Agree

Study name Ring - 1997			
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Comments by the EAC**
Was the cohort recruited in an acceptable way?	Not clear	Clear explanation of how and why patients were included. No details as to whether this was with informed consent	Agree
Was the exposure accurately measured to minimise bias?	N/A		Yes, the surgical process was described in details.
Was the outcome accurately measured to minimise bias?	Not clear	All patients were reviewed at regular intervals with serial radiographs and clinical examination. At final follow-up, the capacity to bear weight, any leg-length discrepancy, alignment and the range of movement in the joints of the leg were noted.	Agree
Have the authors identified all important confounding factors?	Yes	Age, duration of Non-union, previous operations, previous infection are noted	Agree.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Analysis of patients including potential confounding factors reported on p. 291	Agree
Was the follow-up of patients complete?	Yes	No loss to follow up	Agree
How precise (for example, in terms of confidence interval and p values) are the results?	N/A		Agree

Study name Wu - 2003			
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Comments by the EAC**
Was the cohort recruited in an acceptable way?	Not clear	Clear description of how and why patients were included. No details given of informed consent	Case reports so no informed consent was obtained.
Was the exposure accurately measured to minimise bias?	N/A		Yes, the process of surgical was described in details.
Was the outcome accurately measured to minimise bias?	Yes	Clinical and radiographical healing processes were recorded. Bony union was clinically defined as the absence of pain and tenderness, and the ability of the patient to walk without aids. It was radiographically defined as abridgement of solid callus with cortical density for both segments.	Agree
Have the authors identified all important confounding factors?	Yes	Age, gender, initial fracture type, Initial treatment, fracture location, non-union period, No. of previous operations, Type of nail used	Agree
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	Reporting of patient outcomes is not shown	Not relevant.
Was the follow-up of patients complete?	No	Three patients were lost to follow up	Agree
How precise (for example, in terms of confidence interval and p values) are the results?	N/A		Agree

Appendix C: Results of individual studies

Study name		Schofer 2010	EAC comments
Size of study groups	**Treatment**	EXOGEN: n=51	Agree
	Control	Sham: n=50	Agree
Study duration	**Time unit**	16 weeks	Agree
Type of analysis	**Intention-to - treat/per protocol**	The primary analysis was intention-to-treat (ITT) and involved all subjects who received random treatment assignments and initiated device usage.	Agree
Outcome	**Name**	Increase in bone mineral density	Agree
	Unit	Hounsfield units	Agree
Effect size	**Value**	0.53	Agree
	95% CI	0.09 to 0.97	Agree
Statistical test	**Type**	1-sided ANCOVA after multiple imputation.	Agree
	p value	0.007	Agree
Other outcome	**Name**	Reduction in fracture gap size	Agree
	Unit	mm2	Agree
Effect size	**Value**	-0.47	Agree
	95% CI	-0.91 to -0.03	Agree
Statistical test	**Type**	Multiple imputation methods (1-sided)	Agree
	p value	p = 0.014	Agree
Comments		*"These findings demonstrate significantly greater progress toward bone healing after LIPUS treatment compared to no LIPUS treatment in subjects with established delayed unions of the tibia."*	Healing rate data were also reported in the paper.

Study name		Rutten 2008	EAC comments
Size of study groups	Treatment	7	Agree
	Control	6	Agree
Study duration	Time unit	6 months	2 – 4 months
Type of analysis	Intention-to-treat/per protocol	Intention to treat	Agree
Outcome	Name	Bone volume increase	Agree
	Unit	%	Agree
Effect size	Value	33% greater than placebo	Agree
	95% CI		
Statistical test	Type	Student's independent t-test (two-tail).	Agree
	p value	0.02	
Other outcome	Name	Mineral apposition rate	Agree
	Unit	µm/ day	
Effect size	Value	27% greater than placebo	Agree
	95% CI		
Statistical test	Type	Student's independent t-test (two-tail).	Agree
	p value	0.04	
Comments		Although fewer than 15 patients, In this randomised, double-blind, placebo controlled study histomorphometric and histologic analysis was performed to determine bone formation and resorption parameters in delayed unions of the osteotomized fibula. This the first time the influence of EXOGEN treatment on clinical fracture healing at the tissue level could be reported.	Due to the small sample size, the fact that the comparator was not surgical treatment, and outcome measures were not those suggested in the scope, this study did not provide useful information to address the decision problem of interests.

Study name		Gebauer 2005	EAC comments
Size of study groups	**Treatment**	67 fractures reported 46 long bone fractures (tibia, femur, fibula, humerus, ulna, radius)	51 long bone fractures.
	Control	46	51 non-union patient served as their own control
Study duration	**Time unit**	Average healing time was 168 days. Patients followed up at an average of 402 days.	Agree
Type of analysis	**Intention-to - treat/per protocol**	Per Protocol and Intent to Treat	Agree
Outcome	**Name**	Fracture Clinically and Radiographically Healed; time to healing	Agree
	Unit	Yes / No	Plus days to heal.
Effect size	**Value**	Per Protocol: • All fractures: 85% (57/67) healed in an average treatment time of 168 days • Long bone fractures: 89% (41/46) healed in an average time of 185 days Intent to Treat: • All fractures: 85% (70/85) healed	In a maximum of 375 days follow-up, 90% healed. Average healing time for long bone fractures was 178 days.
	95% CI		
Statistical test	**Type**	Fishers exact test	This test is between EXOGEN and no treatment (assuming 5% healing rate of non-union without treatment).
	p value	0.00001	
Comments		Mean fracture age of the 67 patients was 39 ± 6.2 months. Average number of prior failed surgeries = 2.0 Long bone non-union fractures: 89% (41/46) (p=0.05) healed in an average time of 185 days The study did not include any cases that were malaligned, grossly instable, actively infected or that had extensive bone loss.	EXOGEN produced 90% healing rate at 1 year for non-union.

Study name		Jingushi 2007	EAC comments
Size of study groups	**Treatment**	72 fractures	Agree
	Control	N/A	Agree
Study duration	**Time unit**	2-7 months treatment time	Not clear from the paper
Type of analysis	**Intention-to-treat/per protocol**	Probably best described as PP	Agree
Outcome	**Name**	Fracture healing	Fracture healing rate, Mean fracture healing time
	Unit	Yes/No	Days to heal
Effect size	**Value**	75% healed	75% for all non-union and delayed unions. 66% for non-union and 82.5% for delayed union. 219days (56-588 for all delayed and non-union fractures)
	95% CI		
Statistical test	**Type**	N/A	Chi-squared test to examine relationship between healing rate and background factors, such as age, gender, type of fractures, time from the most recent operation to the EXOGEN treatment, number of prior surgical operations.
	p value		
Other outcome	**Name**	Analysis of impact of background factors on healing rate	Agree
	Unit	Odds ratio	Plus Chi-squared test.
Effect size	**Value**	There was a significant relationship between the union rate and the time from the most recent operation to the beginning of LIPUS treatment ($P < 0.01$), the time from the fracture to the beginning of treatment ($P< 0.04$), and the time after the beginning of treatment that radiological improvement was first observed ($P < 0.02$)	Agree
	95% CI		
Statistical test	**Type**	Log regression analysis	Not clear what this is.
	p value	See above	

Study name	Jingushi 2007	EAC comments
Comments	When LIPUS treatment was started within 6 months of the most recent operation, the union rate was approximately 90%. In contrast, when it was started after 12 months, the union rate was less than 65%	Agree

Study name		Lerner 2004	EAC comments
Size of study groups	**Treatment**	18 fractures	16 delayed long bone fractures
	Control	N/A	Agree.
Study duration	**Time unit**	14 to 52 weeks treatment time and up to 6 years follow up	Median 26 weeks (13 -52) and up to 6 years followup
Type of analysis	**Intention-to - treat/per protocol**	ITT and PP	??
Outcome	**Name**	Fracture healing; time to healing	Agree
	Unit	Yes/No; weeks	Agree
Effect size	**Value**	94% healed (PP), 89% (ITT) in a mean of 26 weeks.	94% healed. Mean healing time was 74 weeks (34 – 224)
	95% CI		
Statistical test	**Type**	Not known	None
	p value		
Comments			The healing rate reported in text and table were not consistent with each other. Seems that the quality of the study and report is poor.

Study name		Mayr 2000	EAC comments
Size of study groups	**Treatment**	42 fractures in prospective study	All registry patients and local patients were treated by EXGEN
	Control	Prospective registry 1317	
Study duration	**Time unit**	Follow up was seen up to 755 days	This paper reported findings from patient's registry. It is not clear how long those patients were followed up. The longest fracture was 871 (instead of 755) days.
Type of analysis	**Intention-to - treat/per protocol**	ITT	??
Outcome	**Name**	Fracture healing / time to healing	Agree
	Unit	% healed / days	Agree
Effect size	**Value**	See figure 5 for healing rates and times	Healing rate for non-union: 69% (Humerus, 33/48); 95% (21/22, radius/ulna); 86%(57/66, femur); 88%(105/120, tibia/tibia-fibula) Healing time for non-union: 174 days (Humerus, SD 19.5); 117 days (radius/ulna, SD 16.1); 157 days (femur, SD 10.3); 166 days (tibia/tibia-fibula, SD 10.6) Healing rate for delayed union: 76% (Humerus 41/54), 94%(Radius-ulna), 87%(femur (85/98), 92%(tibia 350/380), 96% (fibula, 26/27) Healing time for delayed union: 125 days (humerus, SD 11.7), 115 (Radius-ulna, SD 9.3), 130 (Ulna, SD 15.3), 140 (femur (SD 8.3), 138 (tibia SD 4.5), 113(fibula, 9.6). The author's clinic reported an average healing time of 130 days (SD 9.8), which is not significantly different with the registry data for delayed union of the tibia.
	95% CI	Not known	Agree
Statistical test	**Type**	Not known	Not clear from the paper
	p value	No significant differences seen between healing times and rates between study and registry patient groups	Agree

Study name	**Mayr 2000**	**EAC comments**
Comments	In the prospective tudy, delayed unions had n average fracture age of 50 days and healed in an verage of 129 ± 2.7 days, ith a healing rate of 91%. lon-unions had an verage fracture age of nore than 2 years and ealed in an average time f 152 ± 5.3 days with a ealing rate of 86%. None of these results were significantly different to those seen in the prospective registry of 1317 patients	The registry included other bone fractures so it is important to select relevant information within the scope. See above for detailed outcome from long bone fracture non-union and delayed union.

Study name		Nolte 2001	EAC Comments
Size of study groups	**Treatment**	29 fractures reported 21 long bone fractures (tibia, femur, fibula, humerus, ulna, radius)	Essentially case series study.
	Control	21	Self-paired
Study duration	**Time unit**	Average healing time was 152 days. Patients followed up at an average of 62 weeks from the healed date (range 30-110 weeks)	Agree
Type of analysis	**Intention-to - treat/per protocol**	Per Protocol and Intent to Treat	???
Outcome	**Name**	Fracture Clinically and Radiologically Healed; time to healing	Agree
	Unit	Yes / No ; weeks	Days
Effect size	**Value**	Per Protocol: • All fractures: 86% (25/29) healed in an average treatment time of 22 weeks • Long bone fractures: 86% (18/21) healed in an average time of 22 weeks Intent to Treat: • All fractures: 80% (33/41) healed in an average treatment time of 20 weeks • Long bone fractures: 86% (25/29) in an average treatment time of 20 weeks	Not sure where the sponsor 's outcome data came from. The EAC found the below healing rate within 2 years: 100% (10/10,Tibia-tibia/fibula), 80% (femur, 4/5), 80% (radius-radius/ulna, 4/5), 100 (other long bones, 2/2). Healing time: 144 days(Tibia-tibia/fibula), 185(femur), 139 (radius-radius/ulna, 4/5), 153 (other long bones, 2/2)
	95% CI		
Statistical test	**Type**	One sided test, not specified	Not very meaningful for the decision question.
	p value	Healed rate, significantly better ($p< 0.0001$) when compared with the assumed rate of 5% for the prior failed treatment period	
Other outcome	**Name**	Healing rates and times were stratified by age, gender, concomitant disease, bone location, fracture age, prior last surgery interval, non-union type, smoking habits, and fixation before and during treatment	Agree but beyond the scope.
	Unit		

Study name		Nolte 2001	EAC Comments
Statistical test	**Type**	For stratification analyses, the Kruskal-Wallis test was used for contrasting heal time and fracture age and the Fisher's exact test was used for healed rates. The Kruskal- Wallis analysis was a two-sided 99% confidence level Monte Carlo estimate of the exact p value computed	Agree but beyond the scope.
	p value	Not significant except in smokers	
Comments		Average age of the non-unions treated was 1.2 years, average number of prior surgeries = 1.4. Stratification of the healed and failed outcome for age, gender, concomitant disease, bone location, fracture age, prior last surgery interval, non-union type, smoking habits, and fixation before and during treatment showed a significant difference only in the smoking habit strata.	Agree

Study name		Romano 1999	Comments by the EAC
Size of study groups	**Treatment**	15 fractures reported 13 long bone fractures (tibia, femur, humerus)	Agree
	Control	NA	Agree
Study duration	**Time unit**	Average healing time was 152 days. Patients followed up at an average of 62 weeks from the healed date (range 30-110 weeks)	Agree
Type of analysis	**Intention-to - treat/per protocol**	NA	Agree
Outcome	**Name**	Consolidation	Agree but note that consolidation is not included as outcome measure in the scope
	Unit	Consolidation, Non-consolidation, progression of callus but necessity of new surgery, still in treatment	Agree
Effect size	**Value**	Of the 13 long bone fractures, 8 consolidated, 1 had progression of callus but required a new surgery, 1 non-consolidation, and 3 patients are still in treatment	Agree
	95% CI	NA	Agree
Statistical test	**Type**	NA	Agree
	p value	NA	Agree
Comments		"our experience demonstrates that this simple and non-invasive treatment, requiring only 20 minutes a day of therapy at home, must be taken under consideration before performing surgical interventions that are both more complex and expensive for the patient and associated heath care organizations."	EAC suggests exclude this study from submission

Study name		Friedlaender 2001	Comments by the EAC
Size of study groups	**Treatment**	61 – surgery + rhOP-1	Agree
	Control	61 - surgery	61 FOR autograft surgery treatment
Study duration	**Time unit**	24 month follow up. Primary end point at 9 months	Agree
Type of analysis	**Intention-to-treat/per protocol**	Intention to treat	Agree
Outcome	**Name**	Healed / not healed at 9 months	Agree. Healing was defined as bridging in at least three of four views. Fully weight bearing with less than severe pain was also used as outcome measure.
	Unit	Yes / No	Agree
Effect size	**Value**	Bridging in at least three of four views—resulted in radiographic healing rates in both groups: 62% of the OP-1 recipients and 74% of the autograft-treated group Clinical success in this study required a patient to be fully weight-bearing with less than severe pain at the fracture site. By these criteria, at 9 months following surgery, 81% (51 of 63) of the OP-1-treated group and 85% (52 of 61) of the autograft-treated group were considered to have successful outcomes	Agree
	95% CI		
Statistical test	**Type**	Chi-square test and a p value of ≤ 0.05 was considered statistically different.	Agree
	p value	p = 0.158, or radiographic healing p = 0.524 for clinical healing	There was no statistically significant difference of radiographic and clinical healing outcomes between the two treatment groups. 5-10% patients need surgical re-treatment.

Study name		Friedlaender 2001	Comments by the EAC
Other outcome	**Name**	Length of stay, operative time, and operative blood loss	Furthermore, all patients in each group had at least one mile or moderate adverse event. 40% of patients in each treatment group had serious adverse events.
	Unit	Days, hours, ml	Agree
Effect size	**Value**	The trend toward longer operative and hospitalization times and the statistically significant increased blood loss (p = 0.049) in the autograft-treated group were imposed by the nature of a bone donor recovery site.	Agree
	95% CI		
Statistical test	**Type**	Differences in the frequency of adverse events were evaluated by a two-tailed chi-square or Fisher's exact test, as appropriate. Comparison of the means of operative blood loss was performed with a Student t test. For the length of stay and operative time, Wilcoxon rank sum tests were performed, which are appropriate for variables that are not normally distributed. A p value of ≤ 0.05 for analysis of safety variable was considered significant.	Agree
	p value	See effect size	
Comments			Both treatments are surgical intervention. Similar outcomes and high chance of adverse events were observed.

Study name		**Bellabarba 2002**	**Comments by the EAC**
Size of study groups	**Treatment**	20	Agree
	Control	N/A	Agree
Study duration	**Time unit**	Maximum follow up 60 months, average 23	Agree
Type of analysis	**Intention-to - treat/per protocol**	ITT	?
Outcome	**Name**	Healed / not healed	Agree
	Unit	Radiographic healing + full weight bearing	Agree
Effect size	**Value**	100% union at an average of 14 weeks	Agree
	95% CI	N/A	Agree
Statistical test	**Type**	N/A	Agree
	p value	N/A	Agree
Other outcome	**Name**	Böstman and HSS scores for post-operative assessment	Agree but this outcome is beyond the scope
	Unit	Good to excellent results in 19 patients	See above
Effect size	**Value**	Not known	
	95% CI	N/A	
Statistical test	**Type**	Not known	
	p value	N/A	
Comments			

Study name		**Birjandinejad 2009**	EAC Comments
Size of study groups	**Treatment**	25 femoral non-unions , 13 tibial non-unions	Agree
	Control	N/A	Agree
Study duration	**Time unit**	1 year follow up	Agree
Type of analysis	**Intention-to - treat/per protocol**	ITT	??
Outcome	**Name**	Healed / not healed	Agree
	Unit	Radiographic + clinical observation	Agree
Effect size	**Value**	100% femur healed, Tibia 84.6 healed – average time to union was 4.78 months	Agree
	95% CI	N/A	Agree
Statistical test	**Type**	Not known	Agree
	p value	N/A	Agree
Comments		No non-unions were infected	Non-union was not clearly defined in the paper.

Study name		**Lin 2010**	EAC Comments
Size of study groups	**Treatment**	Autograft – 28	Agree but both treatment and control were surgery.
	Control	Allograft - 37	Agree
Study duration	**Time unit**	2 years	Agree
Type of analysis	**Intention-to - treat/per protocol**	ITT	??
Outcome	**Name**	Healed / not healed; time to healing	Agree
	Unit	Yes / No; weeks	Agree
Effect size	**Value**	95% v 93%; 18.8 v 20.1 weeks	Agree
	95% CI	(-0.1 to 0.14) ; (-3..7 to 0.77)	Agree
Statistical test	**Type**	Continuous variables – student's t test, binary variables chi squared or Fisher's exact	Agree
	p value	0.85 ; 0.22	Agree
Other outcome	**Name**	Post-op Neer score ; Post-op DASH score	Agree
	Unit		
Effect size	**Value**	90.8±6.6 v 88.5 ±6.9 ; 20.5 ±5.2 v 17.6 ± 7.5	Agree
	95% CI	(-1.11 to 5.71) ; (-0.62 to 6.02)	Agree
Statistical test	**Type**	Continuous variables – student's t test, binary variables chi squared or Fisher's exact	Agree
	p value	6.18 ; 0.11	Agree
Comments		At patients request 11 in the autograft and 16 in the allograft had their nail removed, involving a further surgical procedure.	Agree

Study name		**Livani 2010**	EAC Comments
Size of study groups	**Treatment**	15	Agree
	Control	N/A	Agree
Study duration	**Time unit**	Average follow up 35.8 months	Agree
Type of analysis	**Intention-to - treat/per protocol**	ITT	???
Outcome	**Name**	Healed / not healed; time to healing	Agree
	Unit	Yes / no; weeks	Agree
Effect size	**Value**	100% healed - average time to healing was nine weeks	Agree
	95% CI	N/A	Agree
Statistical test	**Type**	Not known	N/A
	p value	N/A	Agree
Comments			

Study name		**Razaq 2010**	EAC Comments
Size of study groups	**Treatment**	43 fractures in 41 patients	Agree
	Control	N/A	Agree
Study duration	**Time unit**	Follow up maximum 18 months	Agree
Type of analysis	**Intention-to - treat/per protocol**	ITT	????
Outcome	**Name**	Healed / not healed; time to healing	Agree
	Unit	Yes / no	
Effect size	**Value**	90% healed – 4.97± 1.53 months	Agree
	95% CI	N/A	
Statistical test	**Type**	Not known	Agree
	p value	N/A	
Comments		No infected fractures were treated in this study	Adverse events were reported.

Study name		**Ring 1997**	EAC Comments
Size of study groups	**Treatment**	42	Agree
	Control	N/A	Agree
Study duration	**Time unit**	Maximum follow-up 66 months, mean 33	Agree
Type of analysis	**Intention-to - treat/per protocol**	ITT	???
Outcome	**Name**	Healed / not healed – time to healing	Union was judged clinically by the absence of pain on weight bearing and on radiographs by evidence of incorporation of bone graft at the site of non-union and cortical changes.
	Unit	Yes / no – months	Agree
Effect size	**Value**	97% healed – average time to healing = 6 months. However, three of these patients required secondary surgical intervention	Agree
	95% CI	N/A	Agree
Statistical test	**Type**	Not known	N/A
	p value	N/A	N/A
Other outcome	**Name**	Range of movement	Agree
	Unit		
Effect size	**Value**	All patients had full mobility at the hip and ankle, and 31 (72%) regained full movement at the knee. Seven had residual limitation of knee flexion and two lacked 10° of extension. One patient with severe limitation of knee flexion required quadriceps lengthening, which gave a range of 1° to 60° at the latest follow-up. One patient had residual knee instability.	Agree but this is not the outcome measure relevant to the scope
	95% CI	N/A	Agree
Statistical test	**Type**	Not known	Agree
	p value	N/A	Agree

Study name	**Ring 1997**	EAC Comments
Comments	Patients with previous infection were treated. Two patients with previous infection had recurrence. One of the fractures failed to unite; the other healed, but developed a draining fistula. Another patient with persistent non-union had a second bone-grafting procedure 12 months after the insertion of a wave plate and the fracture had united by 18 months. Two of the four patients in whom a large bony defect had been treated with a vascularised fibular graft required an additional grafting procedure before union.	These were process related adverse events, which are relevant to the scope.

Study name		**Wu 2003**	EAC Comments
Size of study groups	*Treatment*	31 – 28 were followed up	Agree
	Control	N/A	Agree
Study duration	*Time unit*	Mean follow up 2.2 years ,maximum 5.2 years	Median 2.2 years
Type of analysis	*Intention-to - treat/per protocol*	Per protocol as the losses to follow up were discounted	???
Outcome	*Name*	Healed / not healed ; time to healing	Agree
	Unit	Yes / no / months	Agree
Effect size	*Value*	100% union,(excluding 3 losses to follow up) mean 4.5 months (range 3 – 7.5)	All fractures healed eventually but it was not clear when was the cut-off assessment point.
	95% CI	N/A	Agree
Statistical test	*Type*	Not known	Agree
	p value	N/A	Agree
Comments		No infected fractures were included	Agree