NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Medical technology guidance

Assessment report overview

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

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the sponsor's submission of evidence and with the EAC's assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: Additional analyses carried out by the External Assessment Centre
- Appendix E: External Assessment Centre correspondence
- Appendix F: Sponsor's factual check of the assessment report and the External Assessment Centre's responses

1 The technology

The EXOGEN ultrasound bone healing system(Smith & Nephew), referred to in this document as EXOGEN, delivers low-intensity pulsed ultrasound waves with the aim of stimulating bone healing. It is thought that healing is promoted by stimulating the production of growth factors and proteins that increase the removal of old bone, increase the production of new bone and increase the rate at which fibrous matrix at a fracture site is converted to mineralised bone. Long bone fractures are suitable for treatment if the fracture is stable and well-aligned. EXOGEN is not indicated for use in fractures of the skull and vertebrae or in people who have skeletal immaturity (children and adolescents).

EXOGEN is available in 2 forms:

- The EXOGEN 4000+ is intended for use in patients with non-union fractures (fractures that have failed to heal after 9 months). The device life is not limited and delivers a minimum of 191 x 20 minute treatments (more than 6 months).

- The EXOGEN Express is intended for use in patients with delayed healing fractures (no radiological evidence of healing after 3 months). The device life is limited up to 150 x 20 minute treatments (less than 5 months).

One device is used per patient and it is non-rechargeable. The EXOGEN device consists of a main operating unit with a permanently connected transducer and a separate fixture strap. The strap is placed around the fractured bone, coupling gel is applied to the transducer head (to aid conduction of ultrasound) and the transducer is secured directly over the fracture site by a fixture on the strap. If the patient’s limb is immobilised in a cast then a hole is cut in the cast to allow access of the transducer to the skin. The device is programmed to deliver ultrasound in 20-minute sessions and

these are self-administered by the patient each day. It is intended to be used in the patient's home.

2 Proposed use of the technology

2.1 Disease or condition

Long bone fractures usually result from traumatic injury and are more likely to occur when there is an underlying reduction in bone mineral density (osteoporosis). It is estimated from Health Survey for England 2002–04 data that the incidence of long bone fractures is approximately 1.2 per 100 person years for men and 0.8 per 100 for women in England (Donaldson et al. 2008).

The conditions relevant to the scope for EXOGEN are long bone fractures with non-union (failure to heal 9 months after fracture) or delayed healing (no radiological evidence of healing after 3 months). For the purposes of this evaluation, long bone fractures are defined as fractures of the humerus, ulna, radius, femur, tibia and fibula.

2.2 Patient group

Non-union and delayed healing are more common in high-energy fractures or open fractures (in which the broken bone is exposed through the skin; source: expert adviser opinion). Some people are at a higher risk of delayed or non-union fractures, for example, those who smoke, older people, or people who have impaired peripheral circulation or who are receiving non-steroidal anti-inflammatory medication.

2.3 Current management

Long bone fractures are usually treated immediately by closed or open reduction (that is, realignment of the bone ends). The affected limb is immobilised using a cast or by internal or external fixation, and X-ray is used to verify alignment of the bone. Progress towards fracture healing is usually

assessed by X-ray demonstration of bridging of the gap between the fractured bone ends with new bone cortex.

Patient's with delayed fracture healing at 3 months do not usually have surgery at this time unless the fracture is complex, for example, an unstable or misaligned fracture or an inter-fragment gap of more than 10 mm. Surgery is usually carried out with internal or external fixing of the bone ends and bone grafting (with harvesting from the patient's iliac crest) as necessary.

Related NICE guidance

'Low-intensity pulsed ultrasound to promote fracture healing' (NICE interventional procedures guidance 374) was issued in 2010 with a recommendation for use with normal arrangements for clinical governance, consent and audit. The recommendation states that 'current evidence on the efficacy of low-intensity pulsed ultrasound to promote fracture healing is adequate to show that this procedure can reduce fracture healing time and gives clinical benefit, particularly in circumstances of delayed healing and fracture non-union. There are no major safety concerns'.

2.4 Proposed management with new technology

Non-union

It is proposed by the sponsor that the EXOGEN 4000+ device is used when non-union is diagnosed in patients with stable, well-aligned fractures, with a gap less than 10 mm. The patient would use the device daily for 20 minutes until their fracture heals or the device expires. The patient should have surgery if their fracture is still unhealed at 6 months from diagnosis of non-union.

Delayed healing

It is proposed by the sponsor that the EXOGEN Express device is used when delayed healing is diagnosed in patients with stable, well-aligned fractures, with a gap less than 10 mm. The patient would use the device daily for

20 minutes until their fracture heals or the device expires. Patients with non-union fractures after use of EXOGEN Express should have surgery.

2.5 Equality issues

It was noted in the scope and by the sponsor that because treatment with EXOGEN is self-administered, some patients may need help in using the technology. However, no equality issues relating to groups with protected characteristics under equalities legislation were identified.

3 Issues for consideration by the Committee

3.1 Claimed benefits

The claimed benefits of EXOGEN for long bone fractures with non-union or delayed healing presented in the case for adoption by the sponsor are:

- reduced healing time compared with surgery
- avoidance of surgery and achievement of comparable clinical outcomes
- quicker return to weight bearing and normal daily living compared with surgery
- improved treatment accessibility with a therapy that can be self-administered in a home environment.

The benefits to the health system claimed by the sponsor are:

- reduced need for high-cost surgical intervention.
- reduced cost because of a reduction in outpatient care, quicker recovery and return to work and normal living.

3.2 Summary of main issues

Clinical evidence

- The EAC noted that the evidence base submitted by the sponsor consisted of data from 1 large register (Mayr et al. 2000), which the EAC considered

to provide quite robust estimates of absolute healing rates with EXOGEN for non-union and delayed healing fractures of different long bones, 1 randomised controlled trial (RCT) comparing EXOGEN with placebo in a mixed population of patients with non-union and delayed healing fractures of the tibia, and several case series.

- There is no direct evidence comparing EXOGEN with surgery in the treatment of either non-union or delayed healing long bone fractures. However, for non-union fractures, independent estimates of healing rates for EXOGEN and surgery were available from non-comparative case series.
- The applicability of the results from the Schofer et al. (2010) trial, which compared EXOGEN with delay in further surgery, was questioned by the EAC because the study included a large proportion of fractures which could be considered to be non-union under the definition of the scope (that is, failure to heal 9 months after fracture).
- The studies were carried out in 12 countries, but not in the UK. The EAC considered that this may limit the applicability of findings to patients treated in the NHS.
- Most of the studies reported healing rates and healing times, but reporting of the other outcomes listed in the scope (return to painless weight bearing, avoiding further surgery and device-related adverse events) was limited.
- The sponsor proposes the use of EXOGEN Express for well-aligned and stable fractures of the long bones with delayed healing (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 to heal 9 months after fracture). The EAC was unsure if this meets the requirements of the scope, which asks for a comparison of EXOGEN with surgery. However, the EAC noted that if current practice was not to offer further surgery for uncomplicated delayed healing fractures, then the comparison presented in the submission might be clinically appropriate. Clinical advice to the EAC suggests that ‘prophylactic’ surgery for fracture

of the long bones does sometimes take place between 3 and 9 months after the fracture, but that this varies according to expectations of individual healing times.

Economic evidence

- The cost models followed patients for a 12-month time horizon, which the EAC considered might not capture all differences in costs and health consequences.
- The EAC considered that there is uncertainty over 2 key drivers in the non-union model; the model is sensitive to changes in assumptions about the relative effectiveness of surgery compared with the EXOGEN 4000+ and the magnitude of the cost saving with the EXOGEN 4000+ is dependent on the estimated cost of surgery.
- The EAC considered that the methods by which healing rates were extracted from the key clinical studies (Mayr et al. 2000 and Schofer et al. 2010) and converted to monthly rates led to an overestimation of the likely relative effectiveness of the EXOGEN Express compared with the control arm in the delayed healing model.
- Both cost analyses only considered fractures of the tibia. The sponsor's submission highlighted the complexity involved in creating a cost model for each fracture site, the lack of good sources of data and the high incidence of healing problems in tibial fractures as reasons for focusing on this group. The EAC noted that although the results from these analyses are not necessarily generalisable to other long bones, analyses of tibial fractures offers a reasonable reflection of likely costs of fractures of other long bones. The EAC considered that the submitted models could potentially be adapted for other long bone fractures.
- The delayed healing model includes an assumption that there is a minimum time to healing of 2 months from baseline in both arms. The EAC received expert advice on this assumption and concluded that it should have applied after surgery (which in this model may occur for patients in either arm whose fracture has not healed by 9 months).

- In the non-union model, patients treated by surgery were assumed to be at risk of infection from when non-union was diagnosed and if they had further revision surgery after 6 months in the non-union state. Patients treated with EXOGEN were assumed to have no risk of infection. The EAC considered that this might be appropriate for the first 6 months (because patients in this arm do not have further surgery during this time) but considered that it is not justified for patients whose fractures do not heal with EXOGEN and who go on to have revision surgery after a further 6 months.

4 The evidence

4.1 Summary of evidence of clinical benefit

The clinical evidence for EXOGEN is based on a total of 17 clinical studies, including 3 RCTs, 13 case series and 1 prospective comparison (table 1).

Of these, 13 studies reported on non-union fractures, 2 reported on delayed healing and 2 reported on both types of fracture. In the studies, there was no direct evidence comparing EXOGEN with surgery in the treatment of either delayed or non-union fractures; however independent estimates of healing rates for EXOGEN and surgery were available from non-comparative case series for non-union fractures.

Key outcomes identified in the scope were:

- evidence of bridging on radiograph (3 out of 4 cortices bridged)
- fracture healing time
- return to painless weight bearing
- avoidance of further surgery
- device-related adverse events

Most of the studies reported fracture healing rate and time but reporting of other outcomes requested in the scope was limited.

The age of study participants ranged from 13 to 92 years old and follow-up across the studies ranged from 2 months to 6 years. None of the studies were carried out in the UK.

Table 1 Summary of clinical evidence (adapted from tables 1 and 2 in the EAC report)

Study	Country	Study design	Type of long bone fracture	Non-union (NU) or delayed healing (DH)	Mean fracture age (months)	Mean patient age (years)	Intervention	Comparator
EXOGEN studies								
Schofer 2010*****	Germany	RCT	Tibia	DH/NU?	13 >9 (n=51/101)	43 (14–70)	EXOGEN	Sham device
Lerner 2004	Israel	Case series	Femur, tibia, radius/ulna, humerus	DH	6 (range 1–38)	19–48	EXOGEN	
Jingushi 2007	Japan	Case series	Femur, tibia, humerus, radius, ulna	DH/NU	19 (range 3–159)	40 (14–83)	EXOGEN	
Mayr 2000*****	Germany	Case series	Femur, tibia, fibula, radius, ulna, humerus	DH/NU	3–9 (n=951) >9 (n=366)	20–71	EXOGEN	
Gebauer 2005*****	Germany and Austria	Case series	Tibia, fibula, femur, humerus, radius, ulna	NU	>8	23–86	EXOGEN	
Nolte 2001	Netherlands	Case series	Humerus, radius, ulna, femur, tibia, fibula	NU	15 (range 6–34) <9 (n=5/21)	18–90	EXOGEN	
Romano 1999	Italy	Case series	Tibia, humerus, femur	NU (septic)	8–30 <9 (n=1/13)	28–78	EXOGEN	
Surgery studies								
Bellabarba 2002	USA	Case series	Femur	NU	10 (range 3–25)	48 (18–92)	Plate and screws	
Birjandinejad 2009	Iran	Case series	Femur, tibia	NU	-	31 (18–52)	Plate and screws after	

Study	Country	Study design	Type of long bone fracture	Non-union (NU) or delayed healing (DH)	Mean fracture age (months)	Mean patient age (years)	Intervention	Comparator
							intramedullary nailing	
Cacchio 2009	Italy	RCT	Femur, tibia, ulna, radius	NU	11	43	Surgery	Shock Wave
Friedlaender 2001	USA	RCT	Tibia	NU	33	34	Surgery + rhOP-7	Surgery and autograft
Khalil 2010	Egypt	Case series	Ulna	NU		42	Contour plate	
Lin 2010	Taiwan	Prospective comparison	Humerus	NU	>6	42 55	Surgery + allograft	Surgery and autograft
Livani 2010	Brazil	Case series	Humerus	NU	>8	38 (18–74)	Plating	
Razaq 2010	Pakistan	Case series	Femur	NU	-	40	Exchange nailing	
Ring 1997	USA	Case series	Femur	NU	17 (range 6–68)	35 (13–81)	Wave plate	
Wu 2003	Taiwan	Case series	Tibia	NU	22 (range 10–48)	34 (19–58)	Reaming bone grafting	
RCT: randomised controlled trial; rhOP-7:								

*Clinical evidence used in cost model

Non-union long bone fracture

The EAC report summarises the methods and key outcomes of included studies for non-union fractures in table 6 (page 27) and table 8 (page 32) respectively.

Mayr et al. (2000) described 256 patients with non-union fractures (failure to heal 9 months after fracture) from an international register of patients treated with EXOGEN. Healing was defined as 3 cortices bridged in 3 X-ray planes or trabecular bridging of at least 80% of the fracture in the case of cancellous fractures. The mean healing rate across all long bone fractures was 84% (216/256), with a mean healing time of 5.3 months.

Gebauer et al. (2005) described a case series of 51 patients with non-union fractures (defined as minimum fracture age 8 months, radiographic indication that the healing process had stopped for at least 3 months, a minimum of 4 months without surgical intervention before EXOGEN). A healing rate (defined as no pain or motion upon gentle stress and weight bearing if applicable, and radiographic healing defined as 3 of 4 bridged cortices) of 90% (46/51) for all long bone fractures was reported with a mean healing time of 178 days (range 86–375 days).

In a case series of 32 patients with non-union fractures (defined on the basis that surgery was otherwise deemed to be indicated), Jingushi et al. (2007) reported a healing rate (defined as clinical and radiographic healing as determined by experienced orthopaedic surgeons) of 66% (21/32); analyses by individual long bone were not included. A mean healing time of 219 days (range 56–588 days) was reported for a mixed group of 72 patients with non-union and delayed healing fractures. When treatment with EXOGEN was started within 6 months of the most recent operation, the union rate was approximately 90%. When treatment was started after 12 months, the union rate was less than 65% (follow-up not reported).

Nolte et al. (2001) evaluated a case series of 22 patients with non-union fractures (defined as failure of fracture to unite at a minimum of 6 months from fracture, no progression towards radiographic healing or had stopped for a minimum period of 3 months before EXOGEN). They reported healing rates (defined as absence of pain, weight bearing without pain or normal function of the limb, 3 or 4 cortices bridged on radiograph) of 100% (10/10) for tibia-tibia/fibula (mean healing time 144 days), 80% (4/5) for femur (mean healing time 185 days), 80% (4/5) radius-radius/ulna (mean healing time 139 days) and 100% (2/2) for other long bone fractures (mean healing time 153 days).

Romano et al. (1999) reported on 13 patients with non-union fractures of long bones (tibia, humerus and femur) and septic pseudoarthrosis. Healing was reported in 62% (8/13) of patients (no further details reported).

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; full details in table 8 of the EAC report). Across 3 case series and 1 cohort study including a total of 166 patients with non-union fractures treated by surgery, 10 patients needed further surgery (follow-up not reported) (Birjandinejad et al. 2009, Khalil et al. 2010, Lin et al. 2010 and Ring et al. 1997). The EAC commented that these studies differed in population, intervention and outcome, and although some reported on time to weight bearing, the EAC considered that the definition of this outcome was not consistent with the scope.

Delayed healing long bone fracture

The EAC report summarises the methods and key outcomes of included studies for non-union in table 5 (page 26) and table 7 (page 31) respectively.

Schofer et al. (2010) carried out an RCT of 101 patients with delayed healing fractures (defined as lack of clinical and radiologic evidence of union, bony continuity or bone reaction at the fracture site no less than 16 weeks from the index injury or the most recent intervention) treated by EXOGEN (n=51) or

placebo (n=50). No significant difference between the groups in healing rate (judged by clinician, not otherwise described) over a 4 month follow-up period was reported (65% [33/51] versus 46% ([23/50], HR 1.69, p=0.07). However, significant improvements in bone mineral density and bone gap area at the fracture site (both indicators of progression towards healing) were reported. The EAC identified that 51 of the 101 patients in this trial had fractures that had not healed for over 9 months at study entry and would be classified as non-union under the definition in the scope issued by NICE. The EAC therefore questioned the applicability of this trial to the delayed union context. The EAC also noted that the study was not powered to detect differences in healing rates; the primary clinical outcomes were bone mineral density and gap at fracture site (assessed by computed tomography [CT] scan).

Mayr et al. (2000) also reported on a total of 696 patients with delayed healing fractures (defined as 3–9 months after fracture) from the register. In this case series, 90% (586/654) of all long bone fractures healed (as defined previously) in a mean time of 4.4 months.

The case series reported by Jingushi et al. (2007) included 40 patients with delayed healing fractures (defined as union or radiological bone reaction not being observed more than 3 months after the most recent operation) treated with EXOGEN. A healing rate (healing defined previously) of 83% (33/40) was reported (follow-up not stated).

In a case series of 16 patients with delayed healing (defined as no radiological evidence of fracture callus appearance noted 4–38 months after prolonged fixation time) Lerner et al. (2004) reported a healing rate (as determined by an experienced orthopaedic surgeon) of 94% (15/16) over a mean follow-up of 17 months.

No studies that reported healing rates after surgery in patients with delayed healing long bone fractures were presented by the sponsor.

Adverse events

The MAUDE database reported 3 incidences of skin irritation caused by skin sensitivity to the coupling gel and one report of increased chest pain caused by potential interference with a cardiac pacemaker over a 1-year period (approximately 55,000 EXOGEN devices were used by patients in the USA over this time period).

None of the clinical studies reported device-related adverse events and no significant safety concerns were identified by the External Assessment Centre in relation to EXOGEN. In contrast, several surgical papers reported adverse events, including postoperative wound infection, osteomyelitis and pain.

4.2 Summary of economic evidence

The sponsor identified three economic studies, all in UK settings. Taylor et al. (2009) carried out a cost-effectiveness analysis on non-union tibial fractures treated by EXOGEN or surgery (intramedullary nailing). The analysis was based on a Markov model, with monthly cycles over a 1-year time horizon. The authors concluded that for non-union fractures, the dominant strategy is to delay surgery and give a course of ultrasound therapy first, which 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. (2007) carried out a non-comparative analysis to estimate the total cost of treating aseptic non-union long bone fractures by compression plate fixation and grafting over a 6-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. (2006) presented a ‘bottom-up’ costing for 41 complex non-union tibia or femur fractures treated by the Ilizarov surgical procedure (external fixator) with an estimated mean cost per patient of £29,204.

New cost analysis

Two cost models were submitted by the sponsor: one for non-union and one for delayed healing (adapted from the model by Taylor et al. 2009). Markov models, with a 1-year time horizon and monthly cycles were used to carry out the cost analysis.

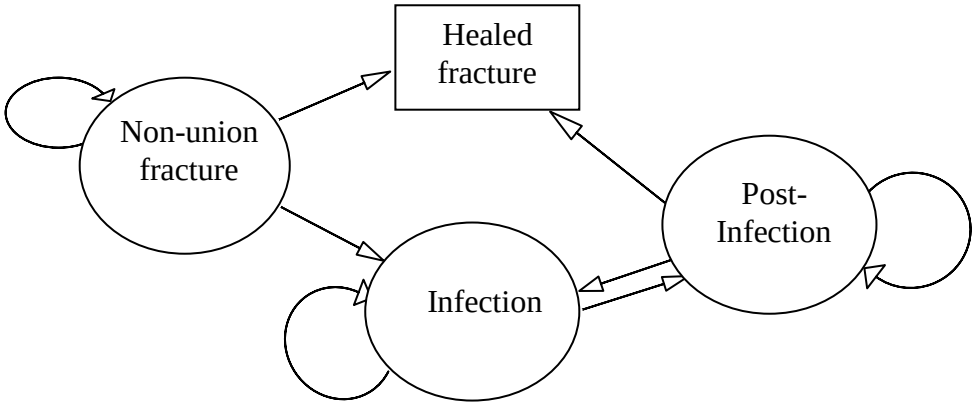
Both analyses were restricted to fractures of the tibia initially treated by surgical insertion of an intramedullary nail. The EAC noted that the sponsor's base-case models were subject to 'internal validation' and the clinical pathways were derived through consultation with expert clinical advisers, but no details were given. The EAC also noted that there was little justification for the 12-month time horizon, but for both models most fractures had healed by the end of the time period.

Non-union model

For non-union fractures, the cost model evaluated the costs and consequences associated with the use of the EXOGEN 4000+ at diagnosis of non-union followed by further surgery if the fracture did not heal within 6 months, compared with surgery at diagnosis followed by repeat surgery if the fracture did not heal within 6 months.

The model had four health states: non-union fracture, healed fracture, infection and post infection, as shown in figure 1. All patients begin in the non-union fracture health state. Patients in the EXOGEN arm had treatment with EXOGEN from baseline, while patients in the comparator arm had surgery at baseline. In both arms, if healing had not occurred after 6 months in the non-union fracture health state, it was assumed that further surgery is needed. In the surgery arm, patients are at risk of infection from diagnosis of non-union and also if they have further revision surgery after 6 months in the non-union state. However, the model assumes that no infection can occur in the EXOGEN arm.

Figure 1 Model structure for non-union (extracted from EAC report, page 49)



Key assumptions for non-union model

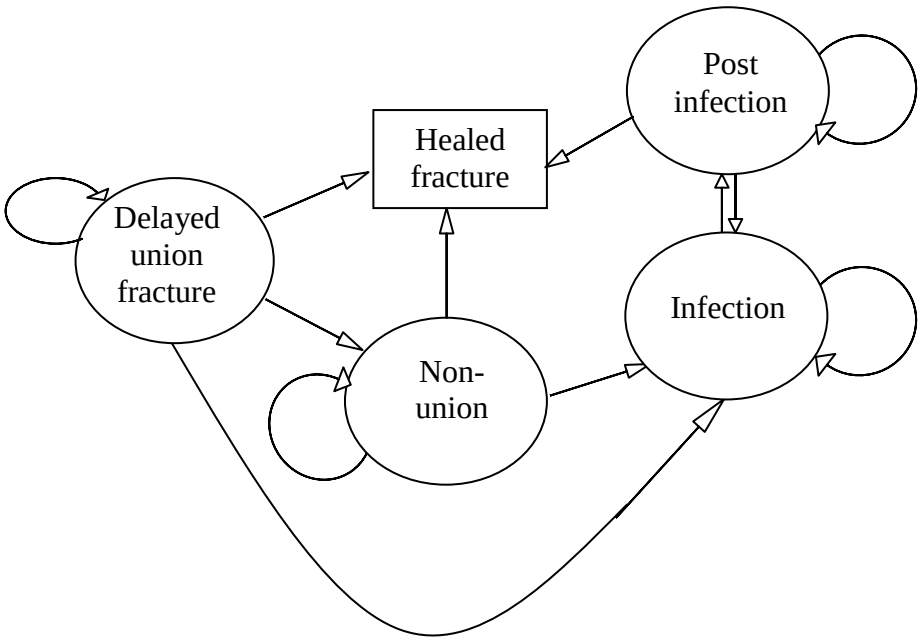
- Healing rates and healing times are equivalent for both EXOGEN 4000+ and surgery in the case of stable, well-aligned fractures.
- Average length of bed stay for surgery is 4.9 days (Hospital episode statistics [HES] online 2010/11)
- Average theatre time for non-union surgery is 3 hours.
- All initial non-union surgical management includes the use of autologous iliac crest bone graft.
- In the EXOGEN 4000+ group only 1 additional surgery will be offered over 1 year if the fracture has not healed.
- Non-procedure-related costs (for example, physiotherapy, X-ray) are the same in both treatment arms.
- Infection rates in the EXOGEN 4000+ and control groups are assumed to be 0% and 1.4% per month (Health Protection Agency [HPA], 2011) respectively.
- Infection lasts for a maximum of 2 months, but all costs associated with the treatment are incurred in the first month.
- In the case of osteomyelitis, staged revision surgery is carried out.
- Patients with osteomyelitis are administered intravenous antibiotics in hospital over a minimum of 3 weeks.

Delayed healing model

For delayed healing, the costs and consequences associated with the use of the EXOGEN Express at diagnosis of delayed healing followed by surgery if the fracture did not heal within 6 months (9 months after fracture) were compared with no further intervention at diagnosis followed by surgery if the fracture did not heal within 6 months (at non-union).

The model had five health states, as shown in figure 2. All patients begin in the delayed union state. It is assumed that surgical intervention (intramedullary nailing) had been carried out before delayed healing was diagnosed, shortly after the fracture.

Figure 2 Model structure for delayed healing (extracted from EAC report, page 47)



The model for delayed union is run twice: once for the EXOGEN arm, when patients start using the EXOGEN Express device at the beginning of the modelling period; and once for the control arm, when patients are assumed to have no further treatment (observation only) until non-union is diagnosed. In subsequent cycles, patients can move to healed (an absorbing state),

infection, or after 6 months in the model, to non-union. After infection a staged revision surgery process begins, with the administration of intravenous antibiotics and removal of metalwork. It is considered that the infection will take 2 months to clear up, at which point revision surgery will take place. Patients can become re-infected having previously moved into the post-infection state.

After 6 months of delayed healing, and no infection occurring, the patient progresses to non-union fracture, when further surgery takes place. In subsequent cycles, non-union fractures may heal or become infected.

Key assumptions for delayed healing model

- For both arms in the model, patient treatment pathways start with a surgical intervention to treat a fresh fracture.
- On diagnosis of delayed union the patient will either have treatment with EXOGEN Express or will receive no further treatment (observation only) until either bony union is achieved or non-union is diagnosed.
- Healing rates for delayed healing at 6 months are a linear progression with those reported at 4 months in the Schofer et al. (2010) study and in the absence of any comparative data on healing rate from other RCTs.

Clinical parameters

Monthly healing rates, converted from 6-month rates, are used to determine transition from delayed healing and non-union health states to the healed state. In the delayed healing model, the healing rate in the EXOGEN arm is based on 65% healing at 16 weeks from Schofer (2010) and in the surgery arm it is based on 92% healing (tibia/tibia-fibula) at approximately 4 months in Mayr (2000). These rates were extended over a 6-month period. In the non-union model, healing rates for both the EXOGEN and surgery arms were based on Gebauer et al. (2005), estimated to be 86% for 6 months.

The models used an infection rate of 1.4% based on a 2011 Health Protection Agency report to inform transition from delayed union and non-union states to the infection state.

Costs and benefits

The cost analyses included the costs associated with surgery (including the surgical intervention, theatre time, drugs, bed stay), GP visit, outpatient visit, cost of treatment of infection (including surgery), drugs for infection, X-ray, wheelchair, crutches and physiotherapy. The unit costs and their sources are described on pages 51 and 52 of the EAC report. 'Hip fracture' (NICE clinical guideline 124) was used to inform the components of theatre time, bed stay and physiotherapy. The EAC questioned whether these estimates reflect usual care for patients with long bone fractures because of the different demographic characteristics of patients with hip and long bone fractures and their different clinical needs. The cost of a GP visit and wheelchair were taken from Curtis et al. (2010). Estimates of resource use for surgical interventions, and the cost of X-ray and crutches were informed by clinical opinion. The cost of an outpatient visit was taken from NHS reference costs and the EAC considered that reference cost data might be a more suitable source for an estimate of the cost of surgery (the sponsor applied a cost higher than the relevant healthcare resource group (HRG)-based reference cost).

The cost of the EXOGEN 4000+ device used in the cost model was £2562.50 and the cost of the EXOGEN Express device used in the cost model was £999.38. The sponsor did not apply VAT to devices and consumables in the cost model.

The cost models only included NHS costs. The sponsor justified this approach as conservative and explained that inclusion of personal social services costs would only increase the estimated cost savings with EXOGEN. The EAC considered this to be a fair point.

The sponsor included a deterministic sensitivity analysis to explore parameter uncertainty and the effect of this on the cost of EXOGEN. One- and two-way analyses were carried out, varying the healing rates for EXOGEN and surgery. The rate of infection was also varied.

The scope issued by NICE requested that a separate scenario analysis should be presented exploring the risk sharing scheme currently offered to the NHS by the sponsor. The sponsor's submission did not contain this analysis and no information was available to the EAC to assess this scenario.

Results

Non-union

In the sponsor's base case for non-union fractures, the average cost per patient for the EXOGEN 4000+ device was £4647 and the average cost per patient for surgery was £6957. The EXOGEN 4000+ was therefore associated with a cost saving of £2310 compared with surgery.

The sponsor carried out a deterministic sensitivity analysis to vary the rates of healing and infection. The analysis showed that the model was insensitive to changes in rates of healing and infection and the EXOGEN 4000+ remained cost saving for non-union fractures in all scenarios tested (see page 147 of sponsor's submission). The EAC confirmed these results.

The EAC considered that a number of assumptions used in the model were not justified:

- There was a small error in the price of the EXOGEN 4000+ applied in the sponsor's base case. The EAC clarified this with the sponsor and confirmed that the correct price for the EXOGEN 4000+ is £2562.50 + VAT.
- The sponsor's submission indicated a health state cost of £255 for patients who are 'not healed-not infected' and that costs do not differ between arms (page 137 of the sponsor's submission). However, the models have different costs for delayed union and non-union patients in this state, based

on resource estimates in the model. In the non-union model these health state costs also differ between arms and the EAC identified that these differences were not intended, so corrected them (assuming 1 day per month physiotherapy for both EXOGEN and surgery arms).

- Healing rates for EXOGEN and surgery were based on Gebauer et al. (2005), estimated to be 86% for 6 months. The EAC used the healing rate for EXOGEN from Mayr et al. (2000; 88% for tibia/tibia-fibula fractures over approximately 6 months).
- The EAC noted that the non-union model contains an error in months 7, 8 and 9, when the total number of patients in the cohort increases above the initial 1000.
- In the non-union model, patients treated with surgery were assumed to be at risk of infection from diagnosis of non-union and also if they had further revision surgery after 6 months in the non-union state. Patients treated with EXOGEN were assumed to have no risk of infection. The EAC considered that this might be appropriate for the first 6 months (because patients in this arm do not have further surgery during this time) but that it is not justified for patients whose fractures do not heal with EXOGEN and who go on to have revision surgery after a further 6 months. The EAC therefore allowed infection in the EXOGEN arm after surgery at 6 months.
- The model uses an infection rate of 1.4%, based on a 2011 HPA report, to inform transition from delayed and non-union states to the infection state. This rate was calculated from 7580 cases of reduction of long bone fracture of which 104 led to readmission. This rate was applied as a monthly rate in the submitted models and the EAC questioned the validity of this approach. The EAC considered that it would be more appropriate to have applied this as a one-off probability in the first month after surgery. The EAC therefore applied a one-off rate of infection after any surgery and used an estimated post-surgical infection rate of 2.6%.
- The sponsor's model used 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 that needs intravenous antibiotics, incurring a 3-week inpatient stay in addition to the costs of revision surgery. The EAC considered this to be at odds with estimates from the HPA report, which indicates that 48.7% of infections after 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 antibiotic treatment on an outpatient basis (estimated at £3210 in 2006 prices). The EAC considered this to be a more realistic estimate, at least for those patients with superficial infections. The EAC therefore estimated a cost of infection comprising £14,527 for the 51% of patients with deep infections, and an updated reference cost value (£3109) for the remaining 49% with superficial infections.

Full details of the changes the EAC made to the sponsor’s model are reported in the EAC report on pages 56–59. Having made these changes, the EAC’s analysis showed average costs per patient for the EXOGEN 4000+ and for surgery of £5688 and £6852 respectively. The EXOGEN 4000+ was therefore associated with a cost saving of £1164 compared with immediate surgery for non-union.

The EAC carried out further sensitivity analysis and these results are reported in full on pages 59–60 of the EAC report. Sensitivity analysis showed 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. The EAC considered that this is because EXOGEN is significantly cheaper than surgery. In a two-way sensitivity analysis, varying the baseline healing rate with EXOGEN and the relative risk of healing with surgery compared with EXOGEN, showed stable results. Only if the healing rate with EXOGEN was reduced to its lower limit and the relative risk of healing with surgery increased to its upper limit does EXOGEN become more expensive than surgery. The

EAC also carried out sensitivity analyses to apply no delay to the onset of healing, add VAT on devices and consumables and use HRG costs for infection and surgery. The EXOGEN 4000+ remained cost saving for all scenarios tested.

Delayed healing

For delayed healing, the sponsor's base case presented an average per patient cost of £4290 for the EXOGEN Express and £4974 for routine observation. The EXOGEN Express was therefore associated with a cost saving of £684 per patient compared with routine observation.

The sponsors varied the rates of healing and infection in a sensitivity analysis and showed that EXOGEN was no longer cost saving when the difference in healing rates between EXOGEN and the control arm was reduced (see page 147 of sponsor's submission). The EAC confirmed these results.

The EAC considered that a number of assumptions used in the model were not justified:

- The price of the EXOGEN Express applied in the sponsor's base case was incorrect. The EAC clarified this with the sponsor and confirmed that the correct price for the EXOGEN Express is £999.38 + VAT.
- The EAC considered that the methods used to calculate healing rates from the clinical data were not clearly explained in the submission. In the sponsor's delayed healing model, the 6-month healing rate for the control arm was taken from the control arm of the Schofer trial and multiplied by 6/4 to adjust it from 4 to 6 months. The EAC considered that 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 was 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 6 months.

- The EAC also adjusted the model to allow for infection in the EXOGEN arm after further surgery for patients who have not healed after 6 months (9 months post-fracture) and changed costs to apply to delayed union resource use (as per model) at baseline, not fresh fracture. The infection rate and associated costs were also adjusted as for non-union.

The EAC estimated results for 8 scenarios reflecting different sources of healing rates and different assumptions about the minimum time to healing after surgery and EXOGEN, and the persistence of relative benefits of the EXOGEN Express. All results for these scenario analyses are presented in section 4.6 of the EAC report. In the EAC's preferred scenario, the best estimate of healing rate with EXOGEN is taken from register data (Mayr et al. 2000) and the best estimate of relative healing rates with EXOGEN compared with no further treatment until non-union, is taken from Schofer et al. (2011). This scenario also assumes that healing after surgery or starting treatment with EXOGEN will not usually be observed within 2 months and also assumes that EXOGEN does not continue to enhance the background healing rate once ultrasound has finished after 4 months (the duration of follow-up in Schofer et al. 2011). The EAC's preferred scenario resulted in a total cost for the EXOGEN Express of £3033 and a total cost for routine observation of £2529. The EXOGEN Express was therefore associated with a cost increase of £504 per patient compared with routine observation.

The EAC carried out a two-way sensitivity analysis to vary the baseline healing rate with the EXOGEN Express and the relative risk of healing compared with control using the preferred scenario. They found that the results were not sensitive to varying these estimates and the EXOGEN Express remained more costly than waiting to see if the patient heals without further intervention. The EAC carried out further sensitivity analyses to vary the risk of infection, applying VAT on devices and consumables, and the use of HRG costs for infection and surgery. EXOGEN remained more expensive

than the comparator for delayed healing under all of the scenarios tested (results detailed in full on pages 64 and 65 of the EAC report).

5 Ongoing research

The sponsor and the EAC have not identified any ongoing research relevant to the scope on EXOGEN for long bone fractures with non-union or delayed healing.

6 Authors

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Sally Doss, Technical Adviser

NICE Medical Technologies Evaluation Programme

July 2012

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- Lord J, Glover M, Yang Y et al. External Assessment Centre report: EXOGEN ultrasound bone healing system for long bone fractures with non-union or delayed healing. June 2012

B Submissions from the following sponsors:

- Smith & Nephew

C Related NICE guidance

- Low-intensity pulsed ultrasound to promote fracture healing. NICE interventional procedures guidance IPG374 (2010). Available from http://guidance.nice.org.uk/IPG374.

D References

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NICE (2011) Hip fracture costing template (CG124)

NICE clinical guideline 124 (2011) Hip fracture: the management of hip fracture in adults. Available from http://guidance.nice.org.uk/CG124

Health Protection Agency Surveillance of Surgical Site Infections in NHS hospitals in England 2010/2011

Schofer M, Block J, Aigner J et al. (2010) Improved healing response in delayed unions of the tibia with low-intensity pulsed ultrasound: results of a randomized sham-controlled trial. BMC Musculoskeletal Disorders 11: 229

Mayr E, Frankel V, Ruter A et al. (2000) Ultrasound – an alternative healing method for nonunions? Archives of Orthopaedic Trauma Surgery 120: 1–8

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Cacchio A, Giordano L, Colafarina O, et al. (2009) Extracorporeal shock-wave therapy compared with surgery for hypertrophic long bone nonunions. Journal of Bone and Joint Surgery 91: 2589–97

Friedlaender GE, Perry CR, Cole JD, et al. (2001) Osteogenic protein-1 (Bone Morphogenetic Protein-7) in the treatment of tibial nonunions: a prospective, randomised clinical trial comparing rhOP-1 with fresh bone autograft. Journal of Bone and Joint Surgery 83-A Supplement 1(Pt 2): S151–S158

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Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Mr Roger Atkins
Consultant Orthopaedic Surgeon, British Orthopaedic Association and British Limb Reconstruction Society

Mr Mark Jackson
Consultant Orthopaedic Surgeon, British Orthopaedic Association and British Limb Reconstruction Society

Mr Angus MacLean
Consultant Orthopaedic Surgeon, British Orthopaedic Association

Mr Mark Phillips
Consultant Orthopaedic Surgeon, British Orthopaedic Association

- Four expert advisers had direct involvement with the use of EXOGEN. One expert adviser considered this technology to be a significant modification of an existing technology with real potential for different outcomes and impact. Three experts considered the technology to be thoroughly novel.
- The expert advisers generally considered this to be of most use in the management of non-union or delayed healing fractures to accelerate fracture repair and bone regeneration. One of the advisers stated that patients with high energy tibial fractures with failure to progress to union over more than 3 months would benefit significantly from the use of this technology while they are on the NHS waiting list for surgery (typically 3 months).
- The expert advisers considered the likely additional benefits for patients of using this technology to be accelerated and/or more reliable fracture

healing, painless symptom-free treatment, non-invasive treatment, and avoiding surgery and associated risks including infection, nerve injury (especially at bone graft harvest site), persistent non-union (20%), scarring and cardiorespiratory risks.

- The expert advisers considered the likely additional benefits for the healthcare system of using this technology to be reduced need for surgery so the technology could ease pressure on NHS waiting lists, reduce complications and associated costs and accelerate recovery, which may reduce overall costs.
- Regarding the cost consequences of introducing this technology, one expert commented that although the initial cost of the device is high, if it prevents non-union then it will result in significant savings to the NHS. The advisers commented that social costs are also likely to be reduced if recovery is accelerated and the patient returns to work sooner. One adviser considered that avoiding more invasive therapies could be cost effective.
- The expert advisers considered that NICE guidance on this technology would be very useful.

Appendix C: Comments from patient organisations

The following patient organisations were contacted and no response was received.

- Arthritis and Musculoskeletal Alliance (ARMA)
- BRAKE
- British Orthopaedic Association Patient Liaison Group
- Brittle Bone Society
- CritPaL
- ICU Steps
- National Osteoporosis Society
- Paget's Association
- Roadpeace

Appendix D: Additional analyses carried out by the External Assessment Centre

All additional work carried out is incorporated into the final EAC report. No separate reports are presented in this appendix.

Appendix E: External Assessment Centre correspondence

Submission document section/sub-section number	Question/request Please indicate who was contacted. If an expert adviser, only include significant correspondence and include clinical area of expertise	Response Attach additional documents provided in response as appendices and reference in relevant cells below	Action/impact/other comments
9	Email from Joanne Lord to Jeff Stonadge (Smith & Nephew) 25/05/12 to ask if the company intended to submit information regarding the risk sharing scheme (Exogen guarantee)	Response from Jeff Stonadge 25/05/12. Reported that the company did not intend to submit this information.	No further action
9	Email from Joanne Lord to Jeff Stonadge 6/6/12 to clarify a number of points relating to the de novo cost analysis.	Response from JS 07/06/12.See email below.	Informed EAC decisions over choice of model assumptions and parameters for sensitivity analysis.
Various	Email from Joanne Lord to clinical experts (Mark Phillips, Mark Jackson, Roger Atkins and Angus MacLean) 07/06/12.	Response from AM 07/06/12. See email below.	Added comments to report regarding usual clinical practice. Informed EAC decisions over costing.
Various	Phone call from Joanne Lord to Mark Phillips 22/06/12 to request advice on three key clinical questions: 1) usual practice in surgical intervention for patients between	1) MP noted that the timing of surgery for delayed union fractures would vary, depending on the bone type (one would not expect tibia	Comments added to report regarding usual practice.

Submission document section/sub-section number	Question/request Please indicate who was contacted. If an expert adviser, only include significant correspondence and include clinical area of expertise	Response Attach additional documents provided in response as appendices and reference in relevant cells below	Action/impact/other comments
	3 and 9 months 2) minimum time to healing following surgery or treatment with EXOGEN and 3) persistence of enhanced healing rate with EXOGEN after termination of treatment.	fractures to heal until 6 months anyway) and individual risk factors for impaired healing (e.g. smokers might take longer to heal). Many surgeons would consider surgery in this period. But the current waiting time for treatment is 2–3 months. 2) One would normally expect a delay of 6 weeks to 2 months before healing would be observed following surgery or start of treatment with EXOGEN. 3) Healing curves take a sigmoid shape. Curves for surgery and EXOGEN are likely to be most different at 4 month, relative	

Submission document section/sub-section number	Question/request Please indicate who was contacted. If an expert adviser, only include significant correspondence and include clinical area of expertise	Response Attach additional documents provided in response as appendices and reference in relevant cells below	Action/impact/other comments
		risk difference would be unlikely to persist beyond this point.	

Questions for clinical experts about EXOGEN submission

Health Economics Research Group, Brunel University, Birmingham and Brunel EAC

Email from Joanne Lord (Brunel EAC) to clinical experts 7 June 2012
Response from Mr A D MacLean (Consultant Orthopaedic and Trauma Surgeon, Glasgow Royal Infirmary 7 June 2012

Clinical pathway

1. JL - Is the clinical pathway proposed in the submission (see box below) realistic and appropriate?

   AM - I believe pathways are both realistic and appropriate

2. JL - Is it reasonable to assume that no fracture healing will occur until at least two months post surgery?

   AM - Healing occurs before 2 months but is frequently not clinically measurable – ie on x-ray no sign of healing at 8 weeks is normal.

3. JL - Is it reasonable to assume a similar (2 month) minimum time to healing after patients start to use the EXOGEN bone healing system?

   AM - Yes, broadly speaking.

4. JL - How many surgeries might it be reasonable to assume a patient with an unhealed fracture would receive in a 12 month period?

AM - Usually conservative treatment would be 3-6 months then surgery if not healing. Surgery would normally be given 3-6 months to be effective before revision contemplated.

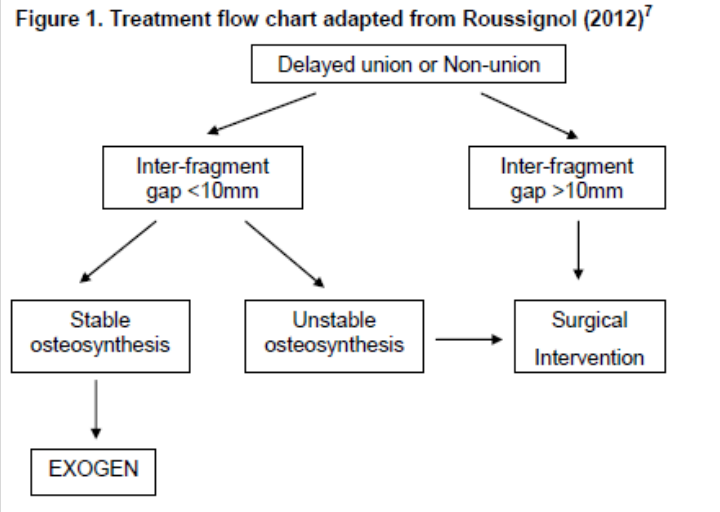
5. JL - Is it reasonable to assume that an infection will take a minimum of two months to heal?

AM - Sorry I don't understand this question. Infections in bone generally require 6-8 weeks of antibiotic therapy in addition to surgery to treat.

Box 1 Clinical pathway from EXOGEN submission

"Treatment for a bone fracture includes closed or open reduction (alignment of bone) and immobilisation using a cast or internal fixation.

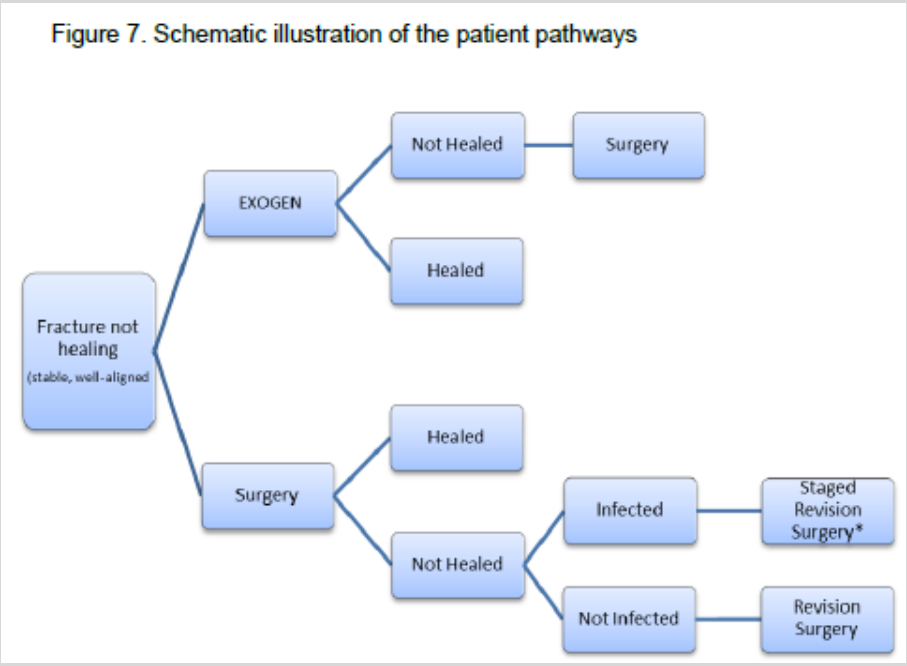
- The fractured pieces of bone are placed in their natural positions
- X-rays can be taken to verify the alignment
- The fractured limb can be immobilised with a plaster or splint
- Surgery may be required to insert surgical nails/screws/plates/wires



"If the fracture is stable and well aligned, yet there has been no progression to healing over a 3 month period, the EXOGEN EXPRESS device should be used daily for 20 minutes by the patient at home, until the fracture has healed or until the unit expires.

If the fracture is stable, well aligned and has not healed within 9 months from the date of the original injury, the EXOGEN 4000+ device should be used for 20 minutes daily by the patient at home, until the fracture has healed.

Failure of the treatment with the EXOGEN device (i.e. the fracture remains ununited) would then predicate further surgical intervention."



Resource use and costs

6. JL - The costs estimates in the manufacturer's submission are based on delayed or non-union tibia fractures, assumed to have been treated at the time of the fracture with an IM nail.

   Do the following estimates of healthcare use appear reasonable for this patient group?

   a) ***Patients with delayed healing of tibia fractures*** (no radiological evidence of healing after approximately 3 months) are assumed to require one outpatient visit, one X-ray, and 8.5 hours of physiotherapy per month. They all have a pair of crutches, and 10% have use of a wheelchair.

      AM - Sounds reasonable

   b) ***Surgery for patients with non-union tibia fractures*** (failure of healing after 9 months) is assumed to take 3 hours, and involve use of autologous iliac crest bone graft and IM nail.

      AM - Yes about right.

   c) ***Following surgery, patients with unhealed non-union tibia fractures*** have one outpatient visit, one X-ray, and 8.5 hours of physiotherapy per month. They all have a pair of crutches, and 20% have use of a wheelchair.

      AM - Sounds reasonable

   d) ***While using EXOGEN prior to surgery, patients with unhealed non-union tibia fractures*** as above (c), but only 4.25 hours of physiotherapy on average per month.

      AM - Not sure why physio would be less.

   e) ***Patients who get an infection***

      i) Initial surgery to remove metalwork, debridement, and temporary fixator - procedure takes 3 hours.

         AM - Agree

      ii) Antibiotics administered for 3 weeks as a minimum. It is assumed that all patients with osteomyelitis are administered IV antibiotics (6 hourly) and are not switched to an oral administration route. Following fitting of temporary fixator and during IV administration of antibiotics, the patient is in hospital for 21 days. This is common practice in many hospitals. I have a well funded set up which provides an outpatient antibiotic service which is well published in Glasgow. This entails a 5 day stay in hospital and then a minimum of 6-8 weeks of IV antibiotics which is recommended by infectious disease teams in Glasgow with special

focus on osteomyelitis. Oral antibiotics in osteomyelitis being treated actively is generally ineffective. Usually dual therapy with 2 separate antibiotics is given, occasionally one of these is oral.

iii) External fixation procedure (3 hours theatre time), with synthetic bone graft and antibiotic prophylaxis, incurs an additional hospital stay of 11.1 days.

AM - My average length of stay for this procedure is closer to 7 days.

iv) In the first month of infection, patients also have one GP visit, one outpatient visit, 2 X-rays and 8.25 hours of physiotherapy. All have crutches and 50% have use of a wheelchair.

AM - Underestimates need to attend GP and clinic – usually weekly or more in the initial month

v) In the second month of infection, patients also have one GP visit, one outpatient visit, 1 X-ray and 8.25 hours of physiotherapy. All have crutches and 20% have use of a wheelchair.

AM - Probably reasonable but likely an underestimate.

vi) Post infection (month 3 onwards), patients have one outpatient visit, one X-ray, and 8.25 hours of physiotherapy per month until the fracture is healed. 50% have crutches, and 10% use of a wheelchair.

AM - Probably reasonable or slight underestimate

7. JL - Is health care use by patients with delayed/ non-union fractures of other long bones likely to be similar to that for patients with delayed and non-union fractures of the tibia?

AM - On the whole yes, femoral non unions are more disabled and demanding of resource, upper limb non unions less so.

8. JL - Will the resource use involved with surgical procedures for patients with hip fracture be similar to that for patients with long bone fractures?

AM - No long bone fractures require greater input.

Questions for Smith & Nephew about EXOGEN submission

Health Economics Research Group, Brunel University, Birmingham and Brunel EAC

Email from Joanne Lord (Brunel EAC) to Jeff Stonadge (Smith & Nephew) 6 June 2012.
Responses from Jeff Stonadge 12 June 2012.

Costs

1. JL - Please can you clarify the ***cost of the technology***? The prices differ between the submission (£2,562.50 + VAT for EXOGEN 4000+ and £999.38 + VAT for EXOGEN Express, p134) and the figures used in the model (£2667 and £998 respectively).

   JS - The correct prices are £2,562.50 + VAT for EXOGEN 4000+ and £999.38 + VAT for EXOGEN Express.

2. JL - I understand that ***VAT*** is chargeable on top of these prices, and NICE have advised us that VAT should be included in the cost calculations. Please let us know if you think this is incorrect.

   JS - VAT was left off all quoted prices for several reasons:

   a. The instructions in the submission template state to quote list price. List prices are customarily quoted ex-VAT

   b. NICE did not include VAT in their hip fracture costing template – "Drug prices. These are based on either the BNF or Drug Tariff prices – the source and edition will be noted in the footnotes; national prices exclude VAT. These can be updated to the latest prices, which could reflect local discounts or incorporate VAT."

   c. Our reference for previous technologies undergoing this process did not include VAT. Please see attached document for the Deltex CardioQ-ODM - Oesophageal Doppler Monitor. Table A1 on page 15 states the price without VAT and this value is confirmed in table 2 on page 77.

   d. VAT is also chargeable on many other items in the cost calculation such as drugs, implants, theatre disposables and it the costs listed for those do not include VAT.

   Should you include VAT on the EXOGEN devices for the purposes of the cost analysis, then this should also be applied to all other VAT –able items.

3. JL - Please can you clarify the assumptions regarding the ***2 month minimum time to healing*** in the models – when and why is this meant to apply? In the delayed

union model, no healing occurs in month 1, although all patients enter the model having had surgery three months previously (ie at the time of the fracture), and only have further surgery if they have not healed after 6 months in the model (ie 9 months after fracture) (p129) – so why can't they heal in the 4th month after surgery? The minimum time to healing is applied to both arms in the non-union model (implying that both EXOGEN and surgery take a minimum time to work). But this assumption does not seem to apply following non-union surgery after six-months.

JS - The healing time assumptions were informed by input from clinicians. Exogen may well lead to healing within 4 weeks although typically this will not be clearly identifiable by x-ray until week 8. It is a fair comment to suggest that healing from surgery could well occur at month 4, 5 or 6 after surgery (which equate to month 1,2 and 3 in the model) in the delayed union model.

The delayed union model was an adaptation of the original fresh fracture model and given the time restrictions for the submission, correcting the calculation to allow for healing in month one was not done. However, in fairness this oversight was applicable to the surgery + EXOGEN and the surgery only (observation) groups.

The effect of this has not been modelled to date, although it is not expected to be a significant impact on the resulting outcomes.

4. JL - 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. In the non union model these health state cost also differ between arms. Are these differences intended?

JS - No, these differences are not intended, Any differences would seem to arise from input errors on the number of resources used in each health state. This can be easily rectified by changing the resources allocated to each health state in the sheet entitled 'Resource use'. Any differences are expected to relate to the use of physiotherapy or wheel-chairs, both of which are very low priced and ultimately, will have only a marginal effect on the resulting outcomes.

Calculation of healing rates

JL - The ***methods used to calculate healing rates from the clinical data*** are not explained in the submission. We have attempted to work them out from the model, and would be grateful for any clarifications or comments that you might have.

Delayed Union Model

5. JL - In the delayed union model, it appears that the 6-month healing rate with surgery alone is taken from the control arm of the Schofer trial, simply multiplied

by 6/4 to adjust it from 4 to 6 months (0.46*6/4=0.69). This method of linear extrapolation is not justified; a more conventional assumption would be of constant hazard (leading to an estimated 6-month rate of 0.6) or to assume no change beyond the observed follow-up (6-month rate 0.46).

JS - This is the only reference we could find for the spontaneous (i.e. without further intervention – observation only) healing rate of delayed unions which had been initially treated by methods reflective of current practice in the UK.

Linear extrapolation was used without accurate knowledge of other conventional assumptions. This was felt to be reasonable at the time due to the fact that it was over a two-month time period which is relatively short in the case of the progression of fracture healing.

The model allows for variation of the healing rate and can be easily amended.

6. JL - The healing rate for the surgery + EXOGEN arm appears to be taken from the Mayr registry paper (92% for tibia/tibia-fibula delayed union fractures at a mean follow up of 138 days). This figure has not been adjusted from the average 4.5 months to six-months. Under a constant hazard assumption, this rate would rise to 96% over six months.

   JS - The lower figure was used to minimise any bias that may favour of EXOGEN.

7. JL - No justification is given for using these two separate data sources, rather than the comparative evidence that is available from the Schofer trial. A direct comparison of healing rates from the trial arms would give 0.46 vs 0.65 healing rates at 4 months (or 0.60 vs. 0.79 at 6 months assuming constant hazard). This does appear to be applicable to the comparison in the delayed union model, although approximately half of the patients in the Schofer trial had unhealed fractures for 9 months or more at baseline assessment (and therefore might be classed as 'non-union' cases).

   JS - As in point 5, the same linear extrapolation of 4 month healing rate for EXOGEN was conducted (which we now know is unjustified) from Schofer, which gave a 6 month heal rate for EXOGEN of 97.5%. This was felt to favourably bias the EXOGEN arm of the analysis and that is why two different sources were used.

   You correctly note that in the patient population in Schofer, there are a substantial number of patients with fractures that could be considered non-unions, with the largest number of those being in the EXOGEN treatment arm. Using this data would be reasonable as this again helps to minimise any bias in the models that may favour EXOGEN.

8. JL - An alternative approach would be to take the baseline healing rate with EXOGEN from the Mayr paper (0.96 at 6 months), dividing by the relative risk for EXOGEN vs no further treatment from Schofer (1.69 hazard ratio) to yield an

indirect estimate of the 6-month healing rate without EXOGEN (0.86). This might be more appropriate if the population in the registry is more generalisable than that in the Schofer trial, and if the relative hazard is constant across populations.

JS - The options given in point 7, taking both EXOGEN and surgery + EXOGEN healing rates from Schofer, is probably the fairest (as all fractures are similar in nature and treated in the same manner) and is the most representative of today's clinical practice in the UK.

Although the data in Mayr is generalisable, the main concern is that the surgically treated group is not further stratified by bone type. That is, it is unknown how many long bones were treated surgically or non-surgically prior to EXOGEN treatment and it is unknown how many other bone types are included in the surgical or non-surgical analysis.

The uncertainties in Mayr may introduce unfavourable bias, so the recommendation in point 7 is the best option in our opinion, using either method.

9. JL - The method of adjusting from 6-month to 1-month rates for use in the Markov model is also unclear. It assumes constant hazard, but applying the assumption of no healing over the first 2 months, spreads the six-month rate over five months (6 months – 2 months + 1). Why is this five rather than six months?

   JS - This is an attempt to model the effectiveness over 6 months using the available data whilst incorporating a pragmatic decision regarding the inability to detect healing at month 1. In practice, this results from building the model and deriving the input values and then 'retro-fitting' the model to reflect clinical opinion, such as the assumption of no detection of healing rates at month 1.

10. JL - From 6 to 12 months, the delayed union model applies an 86% healing rate following further surgery for non-union fractures, which is consistent with the non-union model and gives a monthly rate of 0.279.

    JS - It is not clear whether this was a question, or required comment. Please clarify.

Non Union Model

11. JL - The non-union model assumes equal healing rates for surgery and EXOGEN based on the Gebauer paper (0.86% over ~ 6 months). As in the delayed union model, this rate is adjusted to a one-month rate by assuming constant hazard over 5 months (why not 6?).

    JS - Please see comment relating to point 9

12. JL - It is also unclear how the 12-month healing rate is calculated in the non-union model. Assuming that 86% of cases not healed by 6 months would be healed by 12 months, yields a cumulative 12-month rate of 98% (86% + (1-86%)*86%), rather than the 93% in the model. Why is this?

    JS - Unfortunately, due to availability it has not been possible to get an answer to this question directly as to why the particular calculation was used.

    However, taking the healing rates from literature and expert opinion, the figure of 93% would appear to be higher, but more in line with the real situation. (Also, in reality if there had been no progression to healing at 6 months post-intervention there would likely be a further intervention) Again, this rate is applied equally to both arms in the model and does not favour EXOGEN and changing this heal rate to 98%, or keeping it at 86% in the model makes minimal difference to the outcome.

13. JL - As an aside, there appears to be an error on the Markov sheets of the non-union model. In months 7, 8 and 9, the total number of people in the cohort increases above the initial 1,000. This is due to double counting of unhealed cases, caused by an ambiguity in the 'time until further surgery' on the parameter sheet: cell J7 sets this at 9 months, whereas the hidden cell J8 sets it at 6 months. Could you please confirm whether this is a programming error (presumably caused by adapting the model from Taylor et al?).

    JS - With apologies, it is not possible comment on this as the version we have adds up to 1,000 throughout.

Infection rates and costs

JL - The model appears to inflate the frequency and costs of surgery-related infections.

JS - We respectfully disagree with this statement and will answer each point in turn.

14. JL - The 1.4% infection rate from the Health Protection Agency (HPA Surgical Site Infection report 2010/11) is used as a recurring monthly probability. This figure relates to 104 cases of infection reported over 7,580 operations (reduction of long bone fracture), and includes 62 cases occurring during the inpatient stay, and 42 cases identified after discharge due to readmission (over a three month period); clinical review of day visits (A&E or outpatient); reported following a visit by a community based health professional; or 30-day patient wound healing questionnaires. Though unlikely to capture all surgical site infections, it is also very unlikely that this rate would persist for every month post surgery.

    JS - The HPA data was used to give as current data from England, within the scope, as possible. Its weaknesses are that the rate for infection is taken from the general long bone fracture population and is not stratified by fracture type, type of surgery, smoking history, patient age or co-morbidities to

identify the rate at which patients who are at high risk of having healing difficulties and develop osteomyelitis.

With regards to the assumption that this rate of infection is a recurring monthly rate, osteomyelitis is a complex disease with many potential causes both acutely and longer term. These factors, along with data on the relative rates and time of onset of acute versus late infection are described in a retrospective study by Hadidi http://www.sid.ir/en/VEWSSID/J_pdf/88120110220.pdf studying 330 patients controlled patients reported early deep infections (within 2 – 4 weeks) versus late (1 month – 12 months). 110 patients presented with infection. 55% of the infections were considered early and 45% considered late. Among the limitations of this study is the very high overall rate and that osteomyelitis is not specified, however, the patients all underwent further surgery to treat their infection which shows the degree of seriousness and it gives an indication of when patients can present.

Given the extreme complexity of causes and potential patient factors in long bone non-union surgery, it was felt reasonable to assume that the osteomyelitis rate can remain constant throughout the time frame of the scope as it can present at any time.

However, having sought expert opinion and understanding your concerns about the model, it would also be reasonable to have a higher rate initially followed by a lower monthly incidence. That initial rate would be higher than 1.4% as will be considered in point 16.

15. JL - The non-union model assumes that there is no risk of infection in patients treated with EXOGEN, despite the fact that many (most/all?) of these patients will have already received surgery at some time in the preceding 9 months. Furthermore, the model assumes no risk of infection for the portion of the cohort who do not heal after six months and go on to receive surgery. This assumption is justified in the submission by referring to the summary of clinical data (section 7.91.). However, although no device-related adverse events were reported in the EXOGEN studies, no evidence was presented to suggest that the device is protective against infections from surgery prior to or after use, and this does seem unlikely.

    JS - As the same assumptions are made are made for both groups, i.e. at the time of treatment either with EXOGEN or surgery the fracture is not infected in the first instance, this assumption does not bias the model.

    Not only the data used in the submission, but all other EXOGEN clinical and post-marketing registry data, including the FDA MAUDE adverse event database, show that using the EXOGEN device has not resulted in a single reported event of deep infection.

In relation to the point about protection against infection, this comment is surprising given the evidence presented in the submission by Romano, particularly the editorial comment and case study examples. Also, Ayan *Acta Orthop Traumatol Turc* 2008;42(4):272-277 shows that a protective effect has been observed. This particular pre-clinical evidence was not presented in the submission as it was not within the scope.

It is understandable that the zero rate of infection for EXOGEN used in the model has been considered to "seem unlikely", although this is contrary to all available clinical evidence. Developing an infection following the initiation of EXOGEN treatment such as in the case described above is a hypothetical possibility, so a very low infection rate compared with surgery could be modelled.

16. JL - The model uses 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 assumption appears at odds with the rate of infection from the HPA SSI report (1.4% per month), which includes both 'superficial' and 'deep/organ space' infections. Figure 4 in the HPA report (p15) indicates that approximately 60% 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.

JS - The answers to this question are broken down into several categories:

The stated deep infection rate of 1.4%

The HPA data has already been discussed (in point 14) in the context of the general long bone fracture population versus the rate of osteomyelitis in patients who have difficulty healing bone.

Reports not included in the submission support the assumed 1.4% rate of deep infection in the general hip fracture population:

- From the Cochrane library, Gillespie 2009, shows the deep infection rate in closed long bone fractures in the general population to range from 1.14 – 1.96% dependent on type of antibiotic prophylaxis used.
- A recent publication by Duckworth (http://dx.doi.org/10.1016/j.injury.2012.03.029) prospectively followed 2718 hip fracture surgery patients, finding the deep infection rate to be 1.6% after.

Other publications included in the submission consider the osteomyelitis rate to be considerably higher in the scope population

- The osteomyelitis rate quoted in Taylor is 4.95%, based on an analysis of US Medicare claims in the over 65's. Taylor also cites the increasing likelihood of osteomyelitis where there has been a history of smoking. Both the elderly and the smoking population are highly susceptible to problems with fracture healing.
- Castillo reports an average rate of osteomyelitis of 12.5% in 268 open tibial fractures (again with a high susceptibility to healing difficulties), with a rate of 16.7% in 158 patients who underwent surgery to stimulate the fracture to heal. The osteomyelitis rate in non-smokers (n=81) was 4.9%, whereas the rate smokers (n=105) was 17.1%.

Given published data on the rates of osteomyelitis in patient groups that are of known risk for problems in healing 1.4% is a very conservative estimate.

Infection management costs quoted in Taylor

The cost of treating infection in Taylor (£3210) is tariff based, not cost based, so this needs to be taken into consideration and also to be updated.

Administration of antibiotic treatment

As stated in the submission (p.128), patients requiring IV antibiotics need to be administered and monitored every 6 hours, which makes the possibility of being managed at home very difficult. The data published by Duckworth looking at deep infection following hip fracture, states a course of 6 weeks of antibiotic therapy with 2 – 6 weeks administered IV, depending on clinical response. Expert opinion from infection control leads tells us that the overwhelming majority of these patients are in-patients.

The costs of treating superficial infection in the model are assumed to be negligible.

Cost of treating infected non-union

The cost of £14,527 used in the model to treat an infection is a very conservative estimate compared with the figures quoted from data in the submission – for example, Patil 2006 describes limb salvage procedure costs to be approximately £30,000 and Thakar 2010 reported the mean cost of treating deep infection as £22,846.

In summary, it is felt that the figures for both the deep infection (osteomyelitis) rate and the associated cost of management used in the model are robust, conservative and probably understate rather than inflate the true situation.

Should there be a requirement to change the rate of infection from a constant, as this may be a more accurate expression of the presentation in clinical practice then an initial rate of 4.9% , refs Taylor and Castillo, with a subsequent monthly rate of 0.1% (approximately half the rate derived from Hadidi) would seem reasonable .

Appendix F: Sponsor's factual check of the assessment report and the External Assessment Centre's responses

	Sponsor's description of factual inaccuracy	Sponsor's description of proposed amendment	Sponsor's justification for amendment	EAC response
1	Page 3. Evidence for delayed union, paragraph 4. "Other outcomes requested in the scope were not reported."	Please change this statement to "No device related adverse events were reported"	Schofer 2010, p4 states "There were no device-related adverse events in this study group."	We have added a note to say that no device-related adverse events were observed in the Schofer trial.
2	Page 3. Evidence for non-union, paragraph 2 "No reports for other outcomes requested in the scope"	Please change this statement to: "Although not separately expressly stated, the rate of avoidance of further surgery is assumed to be the same as healing rate"	Patients that healed with EXOGEN treatment would not require surgical intervention for the fracture in question, therefore it is a reasonable conclusion that healing the fracture with a non-invasive therapy has avoided further surgery.	We have replaced this sentence with: "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 avoid the need for surgery."
3	Page 4. Summary critique of clinical evidence submitted by the sponsor,	Please change this statement to – "and it did report statistically significant improvements in	With reference to Schofer 2010, p.1, results and p.5, discussion. The summary is slightly	We have changed this to: "and it did report statistically significant improvements in

	Sponsor's description of factual inaccuracy	Sponsor's description of proposed amendment	Sponsor's justification for amendment	EAC response
	paragraph 3 with reference to Schofer, the report states "and it did report improvements in indicators of progression towards healing (bone mineral density and bone gap area.)"	indicators of progression towards healing (bone mineral density and bone gap area, which are strongly associated with several indices of biomechanical and structural integrity indicative of the repair and healing processes."	imbalanced as it highlights where significant differences were not seen, but does not apply equal weight to where significant differences in important results were seen.	indicators of progression towards healing (bone mineral density and bone gap area)." The EAC has not commented on the strength of the indicators of bone healing, as these were not included as outcomes in the scope, and we have not reviewed evidence or sought clinical advice on this point.
4	Page 4, Summary critique of submitted evidence, delayed union, paragraph 3 states: "The applicability of these results to delayed union fractures is questionable, as the study included a large proportion of non-union patients."	Please amend this statement to: "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 have non-unions. However, in clinical practice, certain tibial fractures may not be considered to be delayed unions until 6 months and confirmed (no progression seen on X-ray) at 9 months."	Expert opinion	We have changed this to: "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)." The EAC has not sought evidence or advice on the appropriateness of the scope definition of non-union.
5	Page 6 EAC comment on robustness of evidence, submitted by sponsor,:	Remove this statement please	From the EAC report page 60, table 14, for EXOGEN to be no longer cost – saving EXOGEN heal rates needed to be at the	We have changed this statement to: "Under a 'worst case scenario' of

	Sponsor's description of factual inaccuracy	Sponsor's description of proposed amendment	Sponsor's justification for amendment	EAC response
	paragraph 2 states "Under plausible variations to these parameters, EXOGEN was no longer a cost-saving alternative to surgery for non-union."		lowest CI limit and have a relative risk compared to surgery of 2.5. None of the evidence presented suggests that this is a plausible scenario. Also, it is believed that the infection costs and rate are understated and repeat analysis would potentially change this. Please see issues 18 and 19.	the healing rate with EXOGEN (82%) and the relative risk of healing with surgery (2.5), EXOGEN was no longer a cost-saving alternative to surgery for non-union." The results were not sensitive to the infection rate or cost, as shown in table 15 (p60) of our report, and noted in the final paragraph of the summary on p6.
6	Page 7 Section 2.1 paragraph 5 "The sponsor notes that the scope is limited to delayed and non-union fractures of the long bones: which they define as the humerus, ulna, radius, femur, tibia and fibula for the purposes of this evaluation."	Please change this statement to "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."	The specific bones were defined by NICE. In discussions prior to the scope being issued, Smith & Nephew presented the case for metatarsal bones to be included, as they are long bones, but this was not accepted.	Thank you, we have corrected this statement.
7	Page12, paragraph 1 states "The Schofer trial is an important study, as it is the only sizeable randomised controlled trial	Please amend to "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	Expert opinion Please see issue 4	We have changed this statement to: "…However, its applicability to this context is unclear, because under the definition of the scope it

	Sponsor's description of factual inaccuracy	Sponsor's description of proposed amendment	Sponsor's justification for amendment	EAC response
	of EXOGEN, and it is a key input to the costing model for delayed union. However, its applicability to this context is unclear, because it included a large proportion of non-union patients."	the costing model for delayed union. Under the definition of the scope it included a large proportion of non-union patients, however, in clinical practice many tibial fractures would not be considered to be potential delayed unions until 6 months post operation."		included a large proportion of patients with non-union fractures (failure of healing after 9 months)." As noted above, the EAC has not sought evidence or advice on the appropriateness of the scope definition of non-union.
8	Page .12, paragraph 4, states: "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."	Please amend to "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 directly include any outcomes specified in the scope. There were significant increases in markers of bone healing over control.	The evidence from Rutten is an important piece of supportive evidence from a randomised trial, because it supports the data from Schofer which in turn indicates an acceleration of progress to healing over control. These factors will influence bridging on radiograph and time to healing which are outcomes included in the scope. From Rutten 2008 – "LIPUS significantly increased osteoid thickness by 47%, mineral apposition rate by 27%, and bone volume by 33%. Our results suggest that LIPUS accelerates clinical fracture healing of delayed unions of the	We disagree that Rutten provides important supportive evidence of effectiveness. It is clearly out of scope, as it did not report any of the outcomes specified in the scope. We also do not believe that it proves strong supportive evidence, as it is a very small study (only 13 patients entered the trial, and results are reported for 11; 7 EXOGEN and 6 control).

	Sponsor's description of factual inaccuracy	Sponsor's description of proposed amendment	Sponsor's justification for amendment	EAC response
			fibula by increasing osteoid thickness, mineral apposition rate, and bone volume, indicating increased osteoblast activity, at the front of new bony callus formation."	
9	Page 16, paragraph 1 States," 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."	Please remove this statement.	Extreme values would be required for the model to show that this is the case. Page 59, Results of the EAC sensitivity analysis states "There is uncertainty over the relative healing rate for surgery compared with EXOGEN. We therefore tested this in sensitivity analysis (Table 13, page 60). 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." None of the clinical evidence presented indicates that this is a	This statement was intended to explain our motivation for testing the relative effectiveness of surgery vs EXOGEN in our sensitivity analysis, given the weakness of the available evidence on this point. We have added a reference to this effect: "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."

	Sponsor's description of factual inaccuracy	Sponsor's description of proposed amendment	Sponsor's justification for amendment	EAC response
			plausible scenario	
10	Page16, Table 3 Jingushi 2007 and Gebauer 2005 are stated to not report painless weight bearing Page 16, Table 3 All studies apart from Romano are shown to not report avoidance of further surgery Page 16, table 3 Schofer is stated as not reporting adverse events	1. Change Jingushi 2007 and Gebauer 2005 to "YES" to indicate that painless weight bearing is reported. 2. Change all EXOGEN studies to YES for avoidance of further surgery. 3. Change Schofer to YES for adverse events	Jingushi 2007 p.36 and Gebauer p.1396 state that if there was painful weight bearing, the patients would not have been considered to have healed, therefore it can be concluded that although not expressly stated, return to painless weight bearing is reported. As the patients had healed with EXOGEN, that fracture would not require further surgery, therefore it can be concluded that although not expressly stated, avoidance of surgery is reported. Please see issue 1	We have added a footnote to Table 16 to specify that the definition of healing in Jingushi 2007 and Gebauer included painless weight bearing, although these papers did not report time to painless weight bearing (which might have occurred at a different time to other criteria for healing).' It cannot be concluded that healing following use of EXOGEN necessarily implies the avoidance of surgery for patients with delayed union fractures, since their fractures might have healed without the use of EXOGEN. However, we agree that for the non-union studies healing following use of EXOGEN does imply a likely avoidance of surgery. We have added a footnote to this effect. We agree and have made the change requested.
11	Page 23, paragraph 2 states "The EAC excluded	These studies should be included, Rutten for the	Please see issue 8. Closer examination of Romano	We disagree about the inclusion of Rutten 2008, as noted above.

	Sponsor's description of factual inaccuracy	Sponsor's description of proposed amendment	Sponsor's justification for amendment	EAC response
	two studies from the sponsor's submission (Rutten 2008, and Romano), because they did not report outcome measures defined in the scope. These examined the clinical effectiveness of EXOGEN or surgery in terms of bone mineral density, osteoid thickness or consolidation."	relevance and support of the findings in Schofer. Romano as we believe that there is a misunderstanding of the choice of words used in translation.	1999 shows outcomes within the scope. The misunderstanding comes from the translated term "consolidation" which is used instead of "healed". Romano also expressly reports whether further surgery was required.	Regarding Romano 1999, it is difficult to confirm the mistranslation. However, the paper does state that 9 out of 15 patients had 'recovered', and it is reasonable to suppose that this is equivalent to 'healed'. We have therefore replaced this study in the results tables.
12	Page 38 Evidence for delayed union, paragraph 3. In discussing limitations of the Schofer paper, the EAC reports: "Firstly, the trial included patients with non-union 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	Please change these statements to: "o Firstly, the trial included patients with fractures that under the scope could potentially be described as non-unions as well as delayed union fractures – as 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 first comment is based on the timing of diagnosis of tibial delayed union in complex fractures, which, as referenced in issues 4 and 7 can often be later than the 3 month time point defined in the scope. With regard to the second statement, the EAC report on p. 64, Conclusions, Delayed union states "This comparison relies on evidence from the Schofer sham-controlled randomised trial, and it should be noted that this study did not find a	We have changed the first bullet point to: "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. …" As noted above, the EAC has not sought evidence or advice on the appropriateness of the scope definition of non-union. Regarding the second bullet point,

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	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. o Secondly, it is not clear whether the Schofer trial was powered to detect differences in healing rates. The primary outcomes of this trial were BMD and gap at fracture site (assessed by CT scan).	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, although expert opinion suggests that this may be a reasonable definition of delayed union in these types of fractures, particularly in patients who have co-morbidities. o 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) which showed significant improvement over control."	significant difference in healing rates, although it was not powered for this outcome"	the results for the indirect indicators of healing are not relevant to the point being made here.
13	Page 40, paragraph 1 "If EXOGEN were to be less effective than surgery at non-union, then it could not	Please remove or qualify this statement	See issue 9	Our motivation for noting this possibility here is to explain the importance of testing this in sensitivity analysis. We have

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	be dominant in this context.			added another reference to this at this point.
14	Page 41, Discussion of sponsor interpretation of clinical evidence, paragraph 4 states "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 non-union patients, and although intermediate measures of bone healing (BMD and bone gap) were better in the EXOGEN-treated group, differences in healing rates were not significant."	Please change to: "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 that may be considered to be non-union patients, 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 (although the study was not powered for this). Rutten 2008, does add supportive evidence as there was significantly greater progression to healing in many markers.	See issues 4,7,8,11 and 12	We have changed this statement to: "…(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." We have not added a reference to Rutten 2008, as we believe this should have been excluded due to the lack of outcomes relevant to the scope.
15	Page..49, Resource identification, measurement and valuation, paragraph 3 states: "The EAC would question	Please amend this statement to: "The NICE guideline (CG124) was used to inform the components of theatre time and bed stay. Although this relates to hip fracture, the costs are standard for orthopaedic theatre	These are standard costs for an orthopaedic operating theatre and an orthopaedic ward. The differences in these costs between hip fracture cases and long bone cases should be	We have changed this statement to: "Information from the NICE hip fracture guideline (CG124) is used to inform the components of theatre time and bed stay. The

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	the validity of using information from the NICE guideline (CG124) to inform the components of theatre time and bed stay as this relates to hip fracture."	time and orthopaedic ward bed occupancy and it is reasonable to assume the same for long bone trauma cases."	minimal or zero.	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."
16	Page 52, Resource identification, measurement and valuation, cost of treatment of infection. With regards to Patil 2006 and Thakar 2010, the EAC states, "However, these relate to particularly complex cases are not reflective of mean costs across the all cases.	Please remove this statement.	Patil defines complex cases as follows: "Of these, we classified 41 in 40 patients as complex cases because of infection (22), bone loss (6) or failed previous surgery (13)." These are exactly the types of patients included in the model. Thakar also describes complications as those found within the model (with the exception of dislocation) and that the most expensive to deal with are deep infections. It is therefore reasonable to assume that these costs are reflective across the cases modelled for deep infections	We disagree that the costs estimates from these studies are representative of costs likely to be incurred for patients with infections following surgery for non-union tibial fractures (which include superficial as well as deep infections). 19 of the 41 patients in the Patil study did not have an infection. Patients had undergone a mean of 3 operations prior to referral to this tertiary treatment centre, with a mean time from fracture to referral of 16 months for the patients with infection. The quoted figure from Thakar et al related specifically to deep infections of femoral fractures.
17	Page 56 Section 4.5, Additional work undertaken	The reference cost value used in the test should be more	We understand that HD24A and HD24B refer to 'Non-	HB23B relates to "Intermediate Knee Procedures for non Trauma

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	by the External Assessment Centre in relation to economic evidence, Costs, paragraph 4 states: "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. We test the effect of changing this to a Reference Cost value: cost of surgery £2,349 (weighted mean of HD24A, HD24B elective with CC/with major CC)."	applicable to the scope.	inflammatory bone or joint disorders' and do not believe that these are the most appropriate to apply to the cost model as they do not include a surgical procedure. HB23B or HB23C would be more appropriate, if reference costs are to be used in this test.	with CC". We assume that the sponsor intended to refer to HD23B and HD23C. The definitions for these codes are: HD23B= "Inflammatory Spine, Joint or Connective Tissue Disorders with CC" HD23C= "Inflammatory Spine, Joint or Connective Tissue Disorders without CC" These are not appropriate codes for surgery for (non-infected) non-union fractures. For our sensitivity analysis, we used HD24A and HD24B HD24A= "Non-Inflammatory Bone or Joint Disorders with Major CC" HD24B= "Non-Inflammatory Bone or Joint Disorders with CC" These map to ICD codes including 'nonunion of fracture' (M841) and 'Delayed union of fracture (M842). However, after further investigation, we found that HRG code HA99Z "Other Procedures for

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				Trauma" includes the OPCS procedure W191 to W269. We therefore used two HRG-based estimates of the cost of surgery in our sensitivity analysis: HB24A/B (£2,349) and HA99Z (£4,126). In our other analyses we used the sponsor's estimate for the cost of surgery of £3,437.
18	Page 58, Infection rates and costs, paragraph 4, the EAC report states "Figure 4 in the HPA report (p15) indicates that approximately 60% of infections following reduction of long bone fracture are superficial."	We request that the rates of superficial infection which were applied to the model by the EAC are changed to 49% and the models re-run and re-reported	Table 4, page 15 of the HPA report shows the superficial infection rate for inpatients and re-admissions, (re-admission being the case in delayed and non-union surgery), is 48.7% of the total infections. From table 1, page 7 and table 4, page 15, it can be deduced that the rate of superficial infection in re-admission patients is 17%. The patients included in both models are, by definition, re-admissions and so a lower rate of superficial infection should be used.	We agree that the correct figure to use for the breakdown of superficial to deep/organ-space infections following reduction of long bone fractures is 48.7% to 51.3%, based on Table 4 (p15) of the HPA SSI report. This figure relates to infections detected during the patients' hospital stays and subsequently through readmissions. We have therefore used this figure to weight the costs of treatment for superficial/deep infections in the EAC versions of the models.
19	Page 59 section 4.6,	The change to a one off infection	Taylor 2009 shows an analysis	As noted by the sponsor the HPA

	Sponsor's description of factual inaccuracy	Sponsor's description of proposed amendment	Sponsor's justification for amendment	EAC response
	results of the EAC sensitivity analysis, changes are made to the Non-union model, including: "Infection rate 1.4% in first month following surgery and 0% up until repeat surgery"	rate occurring in the first month is acceptable, but the rate of 1.4% is too low, based on the submitted evidence. We request that the rate of infection which was applied to the model by the EAC are changed to a minimum of 2.6% (a weighted average of infection rates reported in high risk cases in HPA report, table 2 page 9) and the models re-run and re-reported	of Medicare claims demonstrating a rate of deep infection of 4.95%. Castillo 2001 shows a deep infection rate in the general population of open tibial fractures of 4.9%, raising to 17.1% in smokers. The HPA data for long bone fractures also states that in higher risk patients there is an increased rate of infection, category 1 = 2.3% infection and category 2 = 4.5%. By definition, patients requiring repeat surgery cannot be classified as category 0 Therefore recalculation applying a weighted average of the infection rates and risk factors will give a more accurate picture of the infection rate.	SSI report includes a breakdown of infection rates using the National Nosocomial Infections Surveillance (NNIS) risk index. This adds one point for each of three risk factors if present at the time of surgery: a) ASA pre-operative assessment score of 3, 4 or 5 (patient with severe systemic disease, incapacitating systemic disease or moribund); b) an operation classified as contaminated or dirty; c) an operation lasting for more than a specific period of time (2 hours for reduction of long bones). We agree that it is likely that patients undergoing surgery for non-union fractures of the long bones are likely to fall into NNIS risk category 1-3. We therefore changed the risk of infection in the EAC basecase analyses to 2.6% (a weighted sum of risk categories 1-3). We have already included a

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				sensitivity analysis assuming an infection rate of 4.9%, based on the Medicare claims data used in Taylor 2009.
20	Page 61, changes made to the delayed union model "Infection rate 1.4% in first month following surgery and then 0% in subsequent cycles until repeat surgery "Cost of infection weighted using for £14,527 40% deep and HRG £3,108 for 60% superficial."	Please change both of these values and re-report as requested in issues 18 and 19	Please see issues 18 and 19	We have changed the statements of model assumptions throughout the report to match the changes specified in points 17, 18 and 19 above.