NICE National Institute for Health and Care Excellence

NICE guidance

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

Medical technologies guidance
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Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties. Providers should ensure that governance structures are in place to review, authorise and monitor the introduction of new devices and procedures.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

NICE medical technologies guidance addresses specific technologies notified to NICE by sponsors. The 'case for adoption' is based on the claimed advantages of introducing the specific technology compared with current management of the condition. This case is reviewed against the evidence submitted and expert advice. If the case for adopting the technology is supported, then the technology has been found to offer advantages to patients and the NHS. The specific recommendations on individual technologies are not intended to limit use of other relevant technologies which may offer similar advantages.

1.1 The case for adopting the EXOGEN ultrasound bone healing system to treat long bone fractures with **non-union** (failure to heal after 9 months) is supported by the clinical evidence, which shows high rates of fracture healing.

1.2 The EXOGEN ultrasound bone healing system to treat long bone fractures with **non-union** is associated with an estimated cost saving of £2,407 per patient compared with current management, through avoiding surgery. **[2019]**

1.3 There is some radiological evidence of improved healing when the EXOGEN ultrasound bone healing system is used for long bone fractures with **delayed healing** (no radiological evidence of healing after approximately 3 months). There are substantial uncertainties about the rate at which bone healing progresses without adjunctive treatment between 3 and 9 months after fracture, and about whether or not surgery would be necessary. These uncertainties result in a range of cost consequences, some cost saving and others that are more costly than current management (see sections 5.12, 5.19 and 5.26).

2 The technology

Description of the technology

2.1 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 or vertebrae, or in children or adolescents because of their skeletal immaturity.

2.2 The EXOGEN system is a single hand-held device with 2 treatment options: EXOGEN 150 and EXOGEN 250. These are equivalent to the former versions EXOGEN Express and EXOGEN 4000+ respectively. The device has a visual treatment-tracking calendar and treatment history log aimed at improving compliance. EXOGEN controls the number of treatments performed using an SD card. The device operates on a low lithium battery and has a battery door and charger. The device also has a smartphone app, EXOGEN Connects, which enables adherence by providing information such as treatment reminders, information on fracture healing and videos on how to use EXOGEN. The phone app has not been assessed as part of the evaluation. **[2019]**

2.3 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. The ultrasound signal emitted by the device is derived from a combination of defined electrical signal parameters and the proprietary transducer design, which generate an acoustic wave pattern specific to EXOGEN. 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.

2.4 The cost of the EXOGEN 4000+ stated in the sponsor's submission was £2,562.50 (excluding VAT) and the cost of the EXOGEN Express device was £999.38 (excluding VAT).

2.5 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
- 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.

Current management

2.6 Long bone fractures are usually treated immediately by closed or open reduction (realignment of the bone ends, which can involve surgery). The affected limb is immobilised using a cast or by internal or external fixation. X-rays are 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.

2.7 Patients 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 may take place between 3 and 9 months after fracture,

but clinical practice varies and decisions about the timing of surgery are made on an individual patient basis. If surgery is considered necessary, it usually involves internal or external fixation and bone grafting (with harvesting from the patient's iliac crest).

3 Clinical evidence

Summary of clinical evidence

3.1 Full details of all clinical outcomes considered by the Committee are available in the assessment report overview. Reference to EXOGEN in the context of non-union should be taken to mean the EXOGEN 4000+ device and in the context of delayed healing to be the EXOGEN Express device, unless otherwise stated.

3.2 The key clinical outcomes for EXOGEN for long bone fractures with non-union or delayed healing presented in the decision problem 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.

3.3 The sponsor presented clinical evidence from 18 studies in its submission. Of these, the External Assessment Centre excluded one because it did not report any outcomes defined in the scope. The clinical evidence for EXOGEN is therefore based on 17 clinical studies (total of 1,710 patients), including 3 randomised controlled trials, 13 case series and 1 prospective comparison. Of these, 13 studies reported on non-union fractures, 2 reported on delayed healing and 2 reported on both types of fracture. There were no controlled or randomised studies in which EXOGEN and surgery were compared directly in the treatment of either non-union or delayed fractures. However, independent estimates of healing rates for EXOGEN and surgery were available from non-comparative case series for non-union fractures. The age of study participants ranged from 13 to 92 years and follow-up across the studies ranged from 2 months to 6 years. None of the studies were carried out in

the UK.

Non-union long bone fracture

3.4 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 (humerus, radius/ulna, femur, tibia-fibula) was 84% (216/256), with a mean healing time of 5.3 months.

3.5 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, and a minimum of 4 months without surgical intervention before EXOGEN). A healing rate (healing defined as no pain or motion upon gentle stress and weight bearing if applicable, and radiographic healing defined as 3 of 4 cortices bridged) of 90% (46/51) for all long bone fractures (not otherwise described) was reported with a mean healing time of 178 days (range 86 to 375 days).

3.6 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 to 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).

3.7 Nolte et al. (2001) evaluated a case series of 22 patients with non-union fractures (defined as failure of the fracture to unite at a minimum of 6 months from fracture, no progression towards radiographic healing or healing had stopped for a minimum period of 3 months before EXOGEN).

Healing rates (healing 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) for radius-radius/ulna (mean healing time 139 days) and 100% (2/2) for other long bone fractures (mean healing time 153 days) were reported.

3.8 Romano et al. (1999) studied 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).

3.9 Data were identified by the sponsor on the rates of healing 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). 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). These studies reported on fractures of different long bones, including distal femur, femur, tibia and ulna/radius.

Delayed healing long bone fracture

3.10 Schofer et al. (2010) carried out a randomised controlled trial of 101 patients with delayed healing of tibial shaft 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 was reported between the groups in healing rate (judged by clinician, not otherwise described) over a 4-month follow-up period (65% [33/51] for EXOGEN compared with 46% [23/50] for placebo, HR 1.69, p=0.07).

3.11 Mayr et al. (2000) reported on a total of 696 patients from the international register for EXOGEN (see section 3.4) who received treatment for fractures with delayed healing (defined as failure to heal 3 to 9 months after fracture). In this case series, 90% (586/654) of all long bone fractures healed (as defined in section 3.4) in a mean time of

4.4 months. The authors presented healing rates separately for the different types of fracture. Healing rates ranged from 76% (41/54) with a mean healing time of 125 days for fractures of the humerus to 96% (26/27) with a mean healing time of 113 days for fractures of the fibula.

3.12 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). A healing rate (healing defined in section 3.4) for fractures of the femur, tibia, humerus, radius and ulna of 83% (33/40) was reported (follow-up not stated).

3.13 In a case series of 16 patients with delayed healing (defined as no radiological evidence of fracture callus 4 to 38 months after surgical insertion of an intramedullary nail or the Ilizarov procedure [external fixator]), 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 (fractures included femur, tibia, radius/ulna and humerus).

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

Adverse events

3.15 The US Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database reported 3 cases of skin irritation caused by skin sensitivity to the coupling gel (resolved by change of coupling medium) and 1 report of increased chest pain, possibly caused by interference with a cardiac pacemaker, during a 1-year period (the sponsor stated that approximately 55,000 EXOGEN devices were used by patients in the USA over this time period).

3.16 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 its independent search of the literature. In contrast, reports on surgical treatment of non-union and delayed healing fractures documented adverse events including

postoperative wound infection, osteomyelitis and pain.

Committee considerations

3.17 The Committee considered that although the evidence on using EXOGEN for long bone fractures with non-union was from observational studies and related to a limited number of outcomes (healing defined in various ways including weight bearing, and radiographic evidence), it suggested good clinical results after treatment with EXOGEN. The Committee judged that the observed healing rates supported the efficacy of EXOGEN in promoting healing of these fractures and that its use meant that many of these patients avoided surgery.

3.18 For long bone fractures with delayed healing, the Committee found the outcomes after treatment with EXOGEN more difficult to interpret. There were uncertainties, including the rate at which healing progresses between 3 and 9 months after fracture, both with and without EXOGEN. There were also uncertainties about the proportion of patients in whom surgery would be avoided, because some of these fractures heal spontaneously.

3.19 The Committee noted that the clinical evidence comparing the efficacy of EXOGEN with surgery was very limited. The Committee recognised the difficulties in conducting comparative studies (and specifically randomised controlled trials) to collect data on healing rates.

3.20 Clinical experts advised the Committee that the efficacy of EXOGEN may differ depending on which long bone is being treated. The experts stated that non-union most commonly occurs in fractures of the tibia.

3.21 The Committee discussed the applicability of the data from Schofer et al. (2010) in the context of delayed healing. The External Assessment Centre stated that 51 of the 101 patients in this trial had sustained fractures 9 months or more before entry to the study. According to the definition used in the scope, these would be classified as non-union fractures. The Committee was advised by the External Assessment Centre that this trial was not powered to detect differences in healing rates (one of the outcomes defined in the decision problem) and so

considered the other primary clinical outcomes reported; radiographically-measured bone mineral density and gap at the fracture site (assessed by computed tomography scan). The Committee noted that there were significant improvements in these outcomes in the group treated with EXOGEN compared with placebo (sham treatment).

3.22 The Committee discussed the variation in fracture healing time among patients. It was advised that there is a considerable natural inter-patient variation in healing rates and that this could explain differences in healing rates reported across the studies. In addition, variation in healing time is more pronounced in the early stage of the healing process and that contributes to the greater complexity of interpreting outcomes for fractures with delayed healing compared against those with non-union.

3.23 The Committee recognised that there may be subgroups of patients in whom healing takes place at a slower rate than the general population. However, it considered that neither current evidence nor expert opinions provided sufficient information to model the potential impact of EXOGEN in these groups of patients.

4 NHS considerations

System impact

4.1 No studies were identified that included avoiding surgery as a result of treatment with EXOGEN as an outcome measure. In addition, no studies presented data on return to weight bearing and normal daily living after EXOGEN treatment, compared with surgery.

Committee considerations

4.2 The Committee considered that any effective treatment that avoids or reduces the need for surgery is of significant benefit to patients and also has potential advantages to the NHS in terms of resource use. Such advantages might include reducing the duration of NHS care, the number of outpatient visits or the number of X-rays that patients need.

4.3 The Committee considered that the healing rates reported across the clinical studies indicate that surgery can be avoided and that healing time can be reduced by treatment with EXOGEN. The Committee heard persuasive comments from a patient expert about the benefits EXOGEN treatment can provide in terms of return to activity and quality of life.

4.4 The Committee discussed the proportion of patients who might avoid surgery as a result of treatment with EXOGEN. The Committee was advised by clinical experts that approximately one third of non-union tibial fractures might be suitable for treatment with EXOGEN, although estimates of the total number of non-union long bone fractures varied.

4.5 The Committee noted that treatment with EXOGEN is self-administered, and therefore some patients may need help when using the device. The Committee was told by the patient expert and clinical experts that the device is easy to use and can be administered by a carer instead of the patient.

5 Cost considerations

Cost evidence

5.1 The sponsor identified 3 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 by surgery (intramedullary nailing). The model developed for this study was adapted for use in the sponsor's submission. Kanakaris et al. (2007) presented a non-comparative analysis of the cost of compression plate fixation and bone grafting to treat aseptic non-union long bone fractures, and Patil et al. (2006) reported a similar analysis for the Ilizarov surgical procedure to treat complex non-union tibia or femur fractures.

5.2 The sponsor submitted a de novo cost analysis for EXOGEN. Full details of all cost evidence and modelling considered by the Committee are available in the assessment report overview.

5.3 Two cost models were submitted by the sponsor – 1 for non-union and 1 for delayed healing (both 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 each cost analysis. The patient population included patients with fractures of the tibia initially treated by surgical insertion of an intramedullary nail.

5.4 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.

5.5 The non-union model had 4 health states: 'non-union fracture', 'healed fracture', 'infection' and 'post infection'. All patients began in the 'non-union fracture' health state. Patients in the EXOGEN arm had treatment with EXOGEN 4000+ from baseline, whereas patients in the control 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 was needed. In the surgery arm, patients were at risk of infection as a complication of surgery from the time of diagnosis of non-union, and also if they had further revision surgery after 6 months in the non-union state. The model assumed that no infection would occur in the EXOGEN arm.

5.6 In the sponsor's base case for non-union fracture, the key assumptions were cited as follows:

- Healing rates and healing times are equivalent for both the 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 online 2010/11).
- Average theatre time for non-union surgery is 3 hours.
- All initial non-union surgical management includes autologous iliac crest bone graft.
- In the EXOGEN 4000+ group, in most cases, only 1 additional operation 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, 2011) respectively.
- Infection lasts for a maximum of 2 months, but all costs associated with its treatment are incurred in the first month.
- In the case of osteomyelitis, staged revision surgery is carried out.
- Patients with osteomyelitis are given intravenous antibiotics in hospital over a minimum of 3 weeks.

5.7 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 intervention at diagnosis followed by

surgery if the fracture did not heal within 6 months.

5.8 The delayed healing model had 5 health states: 'delayed union', 'healed fracture', 'non-union', 'infection' and 'post infection'. All patients begin in the delayed union state. It was assumed that surgical intervention (intramedullary nailing) had been carried out before delayed healing was diagnosed, shortly after the fracture occurred. The model for delayed union was run twice; once for the EXOGEN arm, when patients started using the EXOGEN Express device at the beginning of the modelling period; and once for the control arm, when patients were assumed to have no further treatment (observation only) until non-union was diagnosed. In subsequent cycles, patients could move to 'healed fracture' (an absorbing state), 'infection', or after 6 months in the model, to 'non-union'. After infection, a staged revision surgery process began, with the administration of intravenous antibiotics and removal of metalwork. It was considered that the infection would take 2 months to clear, at which point revision surgery would take place. Patients could become re-infected having previously moved into the post-infection state. After 6 months of delayed healing, and no infection occurring, the patient could progress to 'non-union fracture', when further surgery would take place. In subsequent cycles, non-union fractures may have healed or become infected.

5.9 In the sponsor's base case for delayed healing the key assumptions were as follows:

- For both arms in the model, patient treatment pathways start with a surgical intervention (insertion of an intramedullary nail) to treat a fresh fracture.
- On diagnosis of delayed union, the patient will either have treatment with the 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 of those reported at 4 months in the Schofer et al. (2010) study in the absence of any comparative data on healing rate from other randomised controlled trials.

5.10 The cost models were from an NHS cost perspective. The cost analyses included costs associated with surgery (including surgical intervention,

theatre time, drugs, bed stay) and costs associated with GP visits, outpatient visits, treating infection (including surgery and medication), X-rays, wheelchair, crutches and physiotherapy.

5.11 In the sponsor's base case for non-union fractures, the average cost per patient for the EXOGEN 4000+ device was £4,647 and the average cost per patient for surgery was £6,957. The EXOGEN 4000+ was therefore associated with a cost saving of £2,310 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 is not sensitive to changes in rates of healing and infection, and the EXOGEN 4000+ remained cost saving for non-union fractures in all scenarios tested.

5.12 For delayed healing, the sponsor's base case presented an average cost per patient of £4,290 for the EXOGEN Express and £4,974 for current management (observation followed by surgery at non-union if needed). The EXOGEN Express was therefore associated with a cost saving of £684 per patient on early use compared with current management. The sponsor varied the rates of healing and infection in a sensitivity analysis and showed that the model is sensitive to changes in these parameters.

5.13 For the non-union model, the External Assessment Centre considered that a number of the assumptions were not justified and it made several changes to the sponsor's base-case model. These were as follows:

- applying the healing rate for EXOGEN from Mayr et al. (2000)
- allowing for infection in the EXOGEN arm following surgery at 6 months
- applying a one-off rate of infection following any surgery
- adjusting the post-surgical infection rate
- correcting minor errors in the model.

5.14 For the non-union model, the External Assessment Centre's additional analysis showed average costs per patient for the EXOGEN 4000+ of £5,688 and for surgery of £6,852. The EXOGEN 4000+ was therefore associated with a cost saving of £1,164 compared with immediate

surgery for non-union. Sensitivity analysis showed that the model is relatively insensitive to changes in assumptions about the relative effectiveness of surgery compared with EXOGEN. The External Assessment Centre considered that the EXOGEN 4000+ is significantly cheaper than surgery.

5.15 In a 2-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 did EXOGEN become more expensive than surgery. The External Assessment Centre also carried out sensitivity analyses to apply no delay to the onset of healing, add VAT on devices and consumables, and use healthcare resource group costs for infection and surgery. The EXOGEN 4000+ remained cost saving for all scenarios tested.

5.16 For the delayed healing model, the External Assessment Centre considered that several of the sponsor's assumptions were not justified and made a number of changes to the base-case model. These changes included:

- allowing for infection in the EXOGEN arm following further surgery for patients who have not healed after 6 months (9 months after fracture)
- changing costs to apply to delayed healing resource use (as per model) at baseline, not fresh fracture
- adjusting the infection rate and associated costs as for non-union.

5.17 After applying these changes, the External Assessment Centre estimated results for 8 scenarios that reflected different sources of healing rates (Mayr et al. 2000 for the EXOGEN Express arm and relative risk from Schofer et al. 2010 compared with Schofer et al. 2010 alone), different assumptions about the minimum time to healing following surgery and EXOGEN (no delay compared with 2-month delay before healing is observed), and the persistence of relative benefits of EXOGEN (persistence of enhanced healing rate compared with no persistence between the end of EXOGEN treatment at 4 months and further surgery

if needed at 6 months).

5.18 For delayed healing the External Assessment Centre's preferred scenario from among the 8 in its report applied the following key assumptions:

- The best estimate of the healing rate with EXOGEN is from the register data reported by Mayr et al. (2000).
- The best estimate of relative healing rates with the EXOGEN Express compared with no further treatment until non-union is provided by Schofer et al. (2010).
- It is reasonable to assume that healing following either surgery or the start of treatment with the EXOGEN Express will not usually be observed within 2 months (expert opinion).
- It is conservative to assume that EXOGEN does not continue to enhance the background healing rate once ultrasound treatment has finished after 4 months (the duration of follow-up in Schofer et al. 2010).

5.19 The External Assessment Centre's preferred scenario for the treatment of long bone fractures with delayed healing showed a total cost for the EXOGEN Express of £3,033 and a total cost for current management of £2,529. The EXOGEN Express was therefore associated with a cost increase of £504 per patient compared with observation followed by surgery at non-union if necessary.

5.20 The External Assessment Centre carried out a 2-way sensitivity analysis in which the baseline healing rate was varied 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: the EXOGEN Express remained more costly than waiting to see if fractures healed without further intervention. The External Assessment Centre carried out further sensitivity analyses to vary the risk of infection, applying VAT on devices and consumables, using healthcare resource group costs for surgery and for the treatment of infection. The EXOGEN Express remained more expensive than the comparator for delayed healing under all of the scenarios tested.

Committee considerations

5.21 For long bone fractures with non-union the Committee accepted that treatment with the EXOGEN 4000+ results in cost savings. It was advised by clinical experts that the costs associated with surgery in the cost models might well be underestimates and so the cost savings could be even greater in practice.

5.22 The Committee discussed the healing rates applied in the sponsor's base case for delayed healing. It was advised by the External Assessment Centre that the methods by which healing rates were extracted from the clinical studies (Mayr et al. 2000 and Schofer et al. 2010) and converted to monthly rates were likely to represent an overestimate of the relative effectiveness of EXOGEN Express compared with the control arms. Clinical experts stated that the patient group suitable for treatment with EXOGEN is heterogeneous and treatment strategies are made on an individual patient basis. On the basis of all this information, the Committee considered that the External Assessment Centre's approach to scenario analyses was reasonable.

5.23 For long bone fractures with delayed healing, the Committee discussed the scenarios presented by the External Assessment Centre and accepted the External Assessment Centre's preferred scenario as the most likely. However, as for non-union fractures, it considered that the costs associated with surgery might have been underestimated.

5.24 The Committee considered that it was acceptable for the cost models to be limited to tibial fractures (as opposed to fractures of other long bones) because the tibia is the most common long bone for which treatment of non-union is needed.

5.25 The Committee questioned whether the 12-month time horizon used in the cost models might be too short. However, it was advised by the External Assessment Centre that it is likely that extending the time horizon would have little impact on the results, because most fractures would have healed by the end of the 12 months, regardless of the intervention.

5.26 The External Assessment Centre applied the updated cost of the device and other costs to the cost model for non-union healing and reported net savings increased from £1,164 to £2,407 per patient compared with current management, through avoiding surgery. The increase in savings is primarily because length of hospital stay if a patient has surgery has increased from 4.9 days to 7 days. The External Assessment Centre also applied updated costs to delayed healing. It reported an estimated cost increase of £628 (was £504) per patient compared with current management. The increase in incremental costs is primarily due to the increase in the cost of the EXOGEN 150 device. **[2019]**

6 Conclusions

6.1 The Committee recognised that the available clinical data on the effectiveness of EXOGEN for treating long bone fractures with **non-union** show high rates of fracture healing and it judged them sufficient to support the efficacy and utility of EXOGEN treatment. Despite the absence of direct evidence on avoiding surgery, the Committee considered that the assumptions in the cost model were plausible and that EXOGEN is cost saving compared with current management for the treatment of non-union. Overall, therefore, the case for adoption of EXOGEN in the treatment of long bone fractures with non-union was found to be supported by the evidence.

6.2 For long bone fractures with **delayed healing** the Committee considered that the clinical evidence was more limited. In addition there were significant uncertainties about the rate at which healing progresses between 3 and 9 months after fracture, both with and without EXOGEN, and about whether or not surgery would be required if EXOGEN was not used. These and other considerations influenced the Committee's views about the most appropriate assumptions for cost modelling: the model considered to be most appropriate estimated that EXOGEN treatment would be more costly than current management. The Committee therefore judged that the case for adoption of EXOGEN to treat long bone fractures with delayed healing was not supported by the current evidence.

Appendix A: Committee members and NICE lead team

Medical Technologies Advisory Committee members

The Medical Technologies Advisory Committee is a standing advisory committee of NICE. A list of the Committee members who took part in the discussions for this guidance appears below.

Committee members are asked to declare any interests in the technology to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each Medical Technologies Advisory Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Bruce Campbell (Chair)
Consultant Vascular Surgeon, Exeter

Dr Peter Groves (Vice Chair)
Consultant Cardiologist, Cardiff and Vale NHS Trust

Professor Dilly Anumba
Chair of Obstetrics and Gynaecology/Honorary Consultant Obstetrician and Gynaecologist, University of Sheffield

Ms Susan Bennett
Lay member

Professor Bipin Bhakta
Charterhouse Professor in Rehabilitation Medicine and NHS Consultant Physician, University of Leeds

Dr Keith Blanshard
Consultant Radiologist, Leicester Royal Infirmary

Dr Martyn Bracewell
Senior Lecturer in Neurology and Neuroscience, Bangor University

Professor Daniel Clark
Head of Clinical Engineering, Nottingham University Hospitals NHS Trust

Professor Karl Claxton
Professor of Economics, University of York

Mrs Gail Coster
Radiography Manager, Strategy, Planning and Governance, Yorkshire NHS Trust

Dr Alex Faulkner
Senior Research Fellow, Centre for Biomedicine and Society, King's College London

Professor Tony Freemont
Professor of Osteoarticular Pathology, University of Manchester

Professor Peter Gaines
Consultant Interventional Radiologist, Sheffield, Vascular Institute and Sheffield Hallam University

Mr Harry Golby
Head of Commissioning, Acute, Access and Diagnostics, Salford NHS

Mr Matthew Hill
Lay member

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General Practitioner, Department of Health Services Research, University of Liverpool

Dr Paul Knox
Reader in Vision Science, University of Liverpool

Ms Catherine Leonard

Reimbursement Manager, Medtronic UK

Dr Susanne Ludgate
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Mrs Jacqui Nettleton
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Dr Allan Swift
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Dr Allan Wailoo
Reader in Health Economics, School of Health and Related Research (ScHARR), University of Sheffield

Professor Stephen Westaby
Consultant Cardiac Surgeon, John Radcliffe Hospital, Oxford

Dr Janelle Yorke
Lecturer and Researcher in Nursing, University of Manchester

NICE lead team

Each medical technology assessment is assigned a lead team of a NICE technical analyst and technical adviser, an expert adviser, a technical expert, a patient expert, a non-expert member of the Medical Technologies Advisory Committee and a representative of the External Assessment Centre.

Suzi Peden
Technical Analyst

Rebecca Albrow
Technical Analyst

Sally Doss
Technical Adviser

Mark Jackson
Lead Expert Adviser

Mark Phillips
Lead Expert Adviser

Paul Flintoff
Patient Expert

Dr Janelle Yorke
Non-expert MTAC Member

Dr Joanne Lord
External Assessment Centre Representative

Appendix B: Sources of evidence considered by the Committee

A The External Assessment Centre report was prepared by the Health Economics Research Group (HERG), Brunel University, as part of the Birmingham and Brunel External Assessment Centre:

- 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 sponsor:

- Smith & Nephew

C The following individuals gave their expert personal view on EXOGEN for long bone fractures with non-union or delayed healing by providing their expert comments on the draft scope and assessment report.

- 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.

D The following individuals gave their expert personal view on EXOGEN for long bone fractures with non-union or delayed healing in writing by completing an expert adviser questionnaire or patient questionnaire provided to the Committee.

- Mr Roger Atkins, Consultant Orthopaedic Surgeon, British Orthopaedic Association and British Limb Reconstruction Society (expert adviser).
- Mr Mark Jackson, Consultant Orthopaedic Surgeon, British Orthopaedic Association and British Limb Reconstruction Society (expert adviser).

- Mr Angus MacLean, Consultant Orthopaedic Surgeon, British Orthopaedic Association (expert adviser).
- Mr Mark Phillips, Consultant Orthopaedic Surgeon, British Orthopaedic Association (expert adviser).
- Mr Paul Flintoff (patient expert), nominated by Mr Mark Phillips.

Update information

October 2019: We updated this guidance to reflect 2019 costs. Details of the modifications are explained in the review decision. The update also includes revised cost-saving estimates. New evidence and updated costs identified during the guidance review are denoted as **[2019]**.

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Accreditation