

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Review Decision

Review of MTG12: EXOGEN ultrasound bone healing system for long bone fractures with non-union or delayed healing

This guidance was issued in January 2013.

NICE proposes an amendment of published guidance if there are no changes to the technology, clinical environment or evidence base which are likely to result in a change to the recommendations. However the recommendations may need revision to correct any inaccuracies, usually in relation to providing a more accurate estimate of the results of the cost modelling. The decision to consult on an amendment of published guidance depends on the impact of the proposed amendments and on NICE's perception of their likely acceptance with stakeholders. NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance.

1. Review decision

Amend the guidance and do not consult on the review proposal, because the factual changes proposed have no material effect on the recommendations.

A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper.

2. Original objective of guidance

To assess the case for adoption of EXOGEN ultrasound bone healing system for long bone fractures with non-union or delayed healing.

3. Current guidance

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 £1164 per patient compared with current management, through avoiding surgery.

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 and 5.19).

4. Rationale

The 2 versions of the technology considered in the guidance have been replaced by a single updated version which can deliver the same treatments. According to expert advice the care pathway where this technology is used has not changed significantly and so the recommendations remain valid. The new clinical and cost evidence support the current recommendation and so an update is not required however some facts in the original guidance need to be amended.

5. New evidence

The search strategy from the original assessment report was re-run. References from June 2012 onwards were reviewed. Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the care pathways. The company was asked to submit all new literature references relevant to their technology along with updated costs and details of any changes to the technology itself or the CE marked indication for use for their technology. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

5.1 Technology availability and changes

The Exogen express and EXOGEN 4000+ devices assessed in MTG12 are no longer sold in the UK. Both models have been replaced by a single hand-held device, EXOGEN launched in 2013. The new device has the same mechanism of action and ultrasound signal as the previous devices. It can deliver 2 treatment options - EXOGEN 150 and EXOGEN 250, equivalent to EXOGEN express and EXOGEN 4000+ respectively. The new device has a visual treatment-tracking calendar and treatment history log aimed at

improving compliance. EXOGEN controls the number of treatments performed using a Secure Digital (SD) card. The new device operates on a low lithium battery and has a battery door and charger. In addition, the device has a new smart phone 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 CE mark for the device has not changed.

5.2 Clinical practice

The NICE pathway is [Bone and joint conditions](#). The guidance on EXOGEN is referenced in the long bone section of the pathway.

Of the 5 experts contacted, 2 noted that the care pathway and evidence had not changed sufficiently to alter the original recommendation. Another expert who previously used the device in practice, noted that although there is controversy in literature about EXOGEN, some patients who are aware of the device request for it. The main controversy is reflected in the literature due to inconsistent results, however a number of these studies were out of scope for this review.

NICE published low-intensity pulsed ultrasound to promote fracture healing (IPG374) in December 2010. IPG374 stated that the procedure could be considered an option with normal arrangements for clinical governance, consent and audit. New evidence, including 4 systematic reviews, were identified as relevant to this procedure and in July 2018 IPG374 was replaced by low-intensity pulsed ultrasound (LIPUS) to promote healing of delayed-union and non-union fractures ([IPG 623](#)). This recommends that the procedure can be considered providing that special arrangements (such as informed consent and data collection) apply. Whilst this is a more cautious recommendation than the original guidance, the Interventional Procedure Committee’s concerns related to the evidence on clinical efficacy rather than safety. The guidance states that ‘The evidence for low-intensity pulsed ultrasound to promote healing of delayed union and non-union fractures raises no major safety concerns.’

5.3 NICE facilitated research

None.

5.4 New studies

NICE Guidance information services identified 183 studies in its search, 8 of which were considered relevant and included 3 systematic reviews (Leighton et al. 2017, Schandelmaier et al. 2017 and Rutten et al. 2016) and 5 observational studies (Biglari et al. 2016, Roussignol et al. 2012, Rutten et al. 2012, Watanabe et al. 2013 and Zura et al. 2015). The company provided 9 studies (Tajali et al. 2012,) which included those identified by NICE. The company also put forward results of 6 NHS audits of EXOGEN therapy for

delayed and non-union fractures (3 considered within scope) and 2 studies of metatarsal delay and non-unions (Teoh 2018, Nolte 2016) and 2 economic studies (Mehta et al. 2015, Wu et al. 2013). Four of the 5 observational studies were included in at least one of the systematic reviews.

Systematic reviews

The Leighton et al. (2017) study (n=1441) was a systematic review and meta-analysis of 13 observational studies of non-union fractures. The pooled estimate of effect size for long bone heal rates was reported to be 82% (95%CI:77–87%). When non-union fracture were strictly defined as fractures of at least 8 months the pooled effect size was 84%(95%CI:77%–91.6%). Roussignol et al. (2012), Wantabe et al. (2013) and Zura et al. (2015) were among the studies included in the review and reported positive outcomes for the use of EXOGEN. The review included some fractures and LIPUS devices out of scope for this review, however the results did not pool all fractures.

Rutten et al. (2016) did a systematic review which pooled evidence from fresh, delayed and non-union fractures and concluded that LIPUS does not directly accelerate recovery or the prevention of delayed union or non-union. The study population included a mix of bone fractures and LIPUS devices, some of which are out of scope, therefore the results may have limited benefit for this review.

Similarly, the Schandelmaier (2017) systematic review and meta-analysis was not considered appropriate because it pooled fresh fractures and distraction osteogenesis alongside non-unions.

Observational studies

Roussignol et al. (2012) reports an observational study with results showing an 88% heal rate for EXOGEN therapy across 59 long bone non-union fractures aged at least six months post-surgery. This study included eight patients with non-unions greater than one year in duration, seven of which healed with EXOGEN (88%).

Rutten et al. (2012) was a non-peer reviewed prospective, observational study of 71 tibial non-unions. The authors reported the mean interval duration after initial fracture was 8.6 months, and patients underwent an average of 1.2 surgical procedures prior to EXOGEN treatment. The overall heal rate of chronic tibial non-unions with EXOGEN was 73%.

Watanabe et al. (2013) was a 1-year observational retrospective cohort study conducted with a consecutive cohort of 101 delayed unions and 50 non-unions after long bone fractures that were treated with EXOGEN. The results

showed 74.3% of delayed unions and 68.0% of non-unions healed without surgical intervention.

Biglari et al. (2016), not reported in any of the systematic reviews was a prospective observational study of 60 patients with non-union fractures treated with EXOGEN. The authors reported that only 32.8% of patients were successfully treated and that overall it delayed time of treatment.

Audit data

Results from 3 audits on a total 87 long bone non-union fractures showed a healing rate ranging from 39-72%. One audit also reported cost savings of £1,215 per patient compared with surgery.

5.5 Cost update

The EAC reviewed and updated the cost parameters in the original cost modelling for both clinical settings. The clinical parameters were not revised.

Non-union healing

A summary of the updated input parameters can be found in Table 1. For a more detailed description please see the EAC's cost update report.

Table 1

Parameter	Original figure	Updated figure	% change
Device cost	£2,562.50	£2,562.50	0%
Surgery	£3,437	£4,311.16	25%
GP visit	£41	£37	-10%
Outpatient visit	£137	£119.19	-13%
Cost of infection (major - staged revision)	£8,932.02	£9,530.12	7%
Drugs (for infection)	£50	£64.90	30%
Cost on non-union surgery	£3,437	£4,311.16	25%
X-ray	£70	£85.32	22%
Wheelchair (month)	£14	£16.25	16%
Crutches (month)	£35	£37.22	6%
Physio (month)	£200	£280.50	40%
Total costs	£18,915.52	£21,355.32	13%

Using the updated costs, the EAC re-ran the model and found EXOGEN ultrasound bone healing system to treat long bone fractures with non-union is associated with an increased cost saving of £2,407 (was £1,164) per patient compared with current management, through avoiding surgery. The increase in savings is primarily due to the increase in length of stay following surgery from 4.9 days to 7 days. Although the same source was used (HES Main procedures & characteristics 2017-2014 W28.1 Application of internal fixation to bone) to establish mean length of stay, the EAC was unable to establish the reason for this increase in bed days.

Delayed healing

A summary of the updated input parameters can be found in Table 2. For a more detailed description please see the EAC's cost update report.

Table 2

Parameter	Original figure	Updated figure	% change
Device cost	£999.00	£1250.00	25%
GP visit	£41	£28	-32%
Outpatient visit	£137	£124.00	-9%
Cost of infection (major - staged revision)	£8,932.02	£9,675.39	8%
Drugs (for infection)	£50	£62.47	25%
Cost on non-union surgery	£3,437	£4,386.13	28%
X-ray	£70	£87.46	25%
Wheelchair (month)	£14	£16.83	20%
Crutches (month)	£35	£43.73	25%
Physio (month)	£200	£297.50	49%
Total costs	£13,915.02	£15,971.51	15%

Using the updated costs, the EAC re-ran the model and found EXOGEN ultrasound bone healing system to treat long bone fractures with delayed union is associated with 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 device.

6. Summary of new information and implications for review

The original guidance included 7 studies (3 non-union, 1 delayed union and 3 both delayed and non-union). The new evidence provided results on both delayed and non-union fractures, with most of the evidence on non-union fractures.

Although there was evidence from 3 systematic reviews, they were of limited benefit for this review as the study populations included a mix of bone fractures, some of which are out of scope and pooled fresh fractures and distraction osteogenesis alongside non-unions. Overall the additional clinical evidence identified since the guidance was published in 2013 supports the current recommendations.

The updated cost model does not change the direction of the recommendations made by the Committee however the magnitude of the savings has changed slightly.

7. Implementation

No uptake data was identified for this technology.

8. Equality issues

Treatment with the EXOGEN ultrasound bone healing system is self-administered, therefore some patients may need assistance in using the technology.

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Appendix 1 – explanation of options

If the published Medical Technologies Guidance needs updating NICE must select one of the options in the table below:

Options	Consequences	Selected – ‘Yes/No’
Amend the guidance and consult on the review proposal	The guidance is amended but the factual changes proposed have no material effect on the recommendations.	No
Amend the guidance and do not consult on the review proposal	The guidance is amended but the factual changes proposed have no material effect on the recommendations.	Yes
Standard update of the guidance	A standard update of the Medical Technologies Guidance will be planned into NICE’s work programme.	No
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Medical Technologies Guidance does not need updating NICE must select one of the options in the table below:

Options	Consequences	Selected – ‘Yes/No’
Transfer the guidance to the ‘static guidance list’	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Medical Technologies Guidance on the static list should be flagged for review.	No
Defer the decision to review the guidance	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The Medical Technologies Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Registered and unpublished trials

Trial name and registration number	Details
NCT03382483 Observational, Non-interventional Use of LIPUS to Mitigate Fracture Non-union in Patients at Risk (BONES).	This trial is enrolling by invitation. It is expected to complete in December 2019.
NCT02383160 Scaphoid Non-union and Low-intensity Pulsed Ultrasound.	This trial status is unknown and was expected to complete in December 2018.

Appendix 3 – changes to guidance

Table 3: proposed amendments to original guidance

Section of MTG	Original MTG	Proposed amendment
Costing update		
1.2	The EXOGEN ultrasound bone healing system to treat long bone fractures with non-union is associated with an estimated cost saving of £1164 per patient compared with current management, through avoiding surgery.	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 and 5.19).	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).
Description of technology		
2.2	<p>The EXOGEN system is available as 2 disposable devices, which differ only in the number of treatments they deliver:</p> <ul style="list-style-type: none"> • The EXOGEN 4000+ is intended for use in patients with non-union fractures (fractures that have failed to heal after 9 months). The device delivers a minimum of 191x20 minute treatments (more than 6 months' treatment). • The EXOGEN Express is intended for use in patients with delayed healing fractures (fractures that 	<p>The EXOGEN system is a single hand-held device, EXOGEN. It can deliver 2 treatment options - EXOGEN 150 and EXOGEN 250, 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 SDcard. The device operates on a low lithium battery and has a battery door and charger. The device also has a smart phone app "EXOGEN Connects" which enables adherence by providing</p>

	<p>have no radiological evidence of healing after 3 months). The device delivers a maximum of 150x20 minute treatments (less than 5 months' treatment).</p>	<p>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]</p>
<p>Cost considerations</p>		
<p>5.26</p>		<p>The EAC 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 due to the increase in length of stay following surgery from 4.9 days to 7 days.</p> <p>The EAC 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]</p>

Appendix 4 – References

Biglari B, Yildirim TM et al (2016). Failed treatment of long bone nonunions with low intensity pulsed ultrasound. *Archives of Orthopaedic and Trauma Surgery*; 136, 1121-1134.

Leighton R, Watson JT et al (2017). Healing of fracture nonunions treated with low-intensity pulsed ultrasound (LIPUS): A systematic review and meta-analysis. *Injury*; 48 (7), 1339-1347.

Roussignol X, Currey C et al (2012). Indications and results for the Exogen ultrasound system in the management of non-union: A 59-case pilot study. *Orthopaedics & Traumatology: Surgery & Research*; 98 (2), 206-213.

Rutten S. Low-intensity pulsed ultrasound treatment in delayed bone healing [thesis]. Amsterdam: Vrije Universiteit Amsterdam; 2012.

Rutten S, van den Bekerom MPJ et al (2016). Enhancement of bone-healing by low-intensity pulsed ultrasound: a systematic review. *JBJs Rev*; 4(3), 1-11.

Schandelmaier S, Kaushal A et al (2017). Low intensity pulsed ultrasound for bone healing: systematic review of randomized controlled trials. *BMJ*; 356:j656.

Tajali S, Houghton P et al (2012). Effects of low-intensity pulsed ultrasound therapy on fracture healing: a systematic review and meta-analysis. *American Journal of Physical Medicine & Rehabilitation*; 91 (4), 349-67.

Watanabe Y, Arai Y et al (2013). Three key factors affecting treatment results of low-intensity pulsed ultrasound for delayed unions and nonunions: instability, gap size, and atrophic nonunion. *J Orthop Sci*; 18 (5), 803–810.

Zura R, Della Rocca GJ et al (2015). Treatment of chronic (>1 year) fracture nonunion: Heal rate in a cohort of 767 patients treated with low-intensity pulsed ultrasound (LIPUS). *Injury*; 46, 2036-2041.

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