NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence:

Evaluation title:

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

Sponsor: Smith & Nephew

Date sections A and B submitted: 18th April 2012

Date section C submitted: 15th May 2012

August 2011

Contents

Instructions for sponsors

This is the template for submission of evidence to the National Institute for Health and Clinical Excellence (NICE) as part of the Medical Technologies Evaluation Programme process for developing NICE medical technologies guidance. Use of the submission template is mandatory.

The purpose of the submission is for the sponsor to collate, analyse and present all relevant evidence that supports the case for adoption of the technology into the NHS in England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Medical Technologies Evaluation Programme Methods guide' and the 'Medical Technologies Evaluation Programme Process guide' available at www.nice.org.uk/mt. After submission to, and acceptance by, NICE, the submission will be critically appraised by an External Assessment Centre appointed by NICE.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 11 of this document 'Related procedures for evidence submission'.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level

of detail requested, but that is considered to be relevant to the case for adoption. Appendices will not normally be presented to the Medical Technologies Advisory Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the economic evidence section with 'see appendix X'.

All studies and data included in the submission must be referenced. Identify studies by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126], rather than 'one trial[126]').Please use a recognised referencing style, such as Harvard or Vancouver.

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked 'Response' or in the tables as appropriate. 'Response' text may be deleted.

List of tables and figures

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SECTION C ECONOMIC EVIDENCE

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Quality assessment of health economic studies – SURGERY

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Glossary of terms

Term	Definition
Lone bone	Long bones were specified as humerus, ulna, radius, femur, tibia and fibula for this submission
Bone fracture:	A broken or cracked bone is known as a fracture. This can be a crack or buckle in the structure of the bone or a complete break, producing two or more fragments. A bone fracture can be the result of high force impact or stress, or trivial injury as a result of certain medical conditions that weaken the bones, such as osteoporosis where the fracture is then properly termed a pathologic fracture
Delayed Union	A bone that has failed to show progression to healing over a 3 month period
Osteosynthesis	A surgical procedure that stabilises and joins the ends of fractured (broken) bones by mechanical devices such as metal plates, pins, rods, wires or screws.
Non-union	A bone that has not healed within 9 months from the date of the original injury
Hypertrophic non-union	Callus is formed, but the bone fractures have not joined. This can be due to inadequate fixation of the fracture
Atrophic non-union	No callus is formed. This is often due to impaired bony healing, for example due to vascular causes (e.g. impaired blood supply to the bone fragments) or metabolic causes (e.g. diabetes or smoking). Failure of initial union, for example when bone fragments are separated by soft tissue may also lead to atrophic non-union.
Oligotrophic non-union	The callus is absent and can occur after major displacement of fractures, distraction of fragments, or internal fixation without accurate apposition of fragments. Blood supply is usually good. They demonstrate uptake on radionuclide scans but the healing response is inadequate.
Health Episode Statistics	Hospital Episode Statistics (HES) is the national statistical data warehouse for England of the care provided by NHS hospitals and for NHS hospital patients treated elsewhere
Autogenous bone graft	Bone harvested from the patient's own body, often from the iliac crest
Osteoinduction	Osteoinduction involves the stimulation of cells to differentiate into osteoblasts that then begin new bone formation

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem. Table A1 Statement of the decision problem

Table A1 Statement of the decision problem		
	Scope issued by NICE	**Variation from scope**
Population	Patients with long bone fractures with non-union (failure of healing after 9 months) or delayed healing (no radiological evidence of healing after approximately 3 months)	n/a
Intervention	EXOGEN ultrasound bone healing system	n/a
Comparator(s)	Surgical treatment Internal fixation with or without bone grafting External fixation with or without bone grafting	n/a
Outcomes	The outcome measures to consider include: Bridging on radiograph (3 out of 4 cortices bridged on radiograph) Fracture healing time Return to painless weight bearing Avoidance of further surgery Device-related adverse events	n/a
Cost analysis	Comparator: Surgical treatment (as defined above) Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters. A separate scenario analysis exploring the risk sharing scheme offered by Smith & Nephew should be presented alongside the base case analysis.	n/a
Subgroups to be considered	Non-union fractures Delayed healing fractures Long bone fractures of different location	n/a
Special considerations, including issues related to equality	Because treatment with the EXOGEN ultrasound bone healing system is self-administered, some patients may need assistance in using the technology.	n/a

2 Description of technology under assessment

2.1 Give the brand name, approved name and details of any different versions of the same device.

EXOGEN ultrasound bone healing device

The EXOGEN bone healing system is available in two forms. Both have identical output characteristics and technical specification – only the treatment life varies to accommodate the relevant indication.

EXOGEN 4000+ - designed for treating non-union fractures. Device life is not limited and delivers a minimum of 191 x 20 minute treatments

EXOGEN EXPRESS – designed for treating delayed unions, the device life is limited to 150 x 20 minute treatments

2.2 What is the principal mechanism of action of the technology?

The EXOGEN ultrasound bone healing system delivers low-intensity pulsed ultrasound waves with the aim of stimulating bone healing. It is thought that this is accomplished through stimulating the production of growth factors and proteins (Pounder 2008)[1] that lead to an increase in the removal of old bone, an increase in the production of new bone and an increase in the rate at which fibrous matrix at a fracture site is converted to mineralised bone (Freeman 2009)[2]

3 Clinical context

3.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE.

EXOGEN technology is being considered for the treatment of long bone fractures that have failed to show normal progression to healing.

Long bones were specified as humerus, ulna, radius, femur, tibia and fibula (for the purposes of this submission)

Two categories of abnormal progression to healing were defined:

- Delayed Union, where a fracture has shown no visible progression to healing for 3 months,
- Non-Union, where a fracture has not healed within 9 months from the original date of injury.

For reasons covered in 3.4, the actual prevalence of the delayed unions and non-unions can be very difficult to define precisely.

In order to estimate the patient population size, information was gathered to determine the total number of fractures and then apply the generally accepted rate (from literature) at which a delay in healing is expected. To validate that estimate, data was gathered to determine the current number of surgical interventions in the treatment of non-unions.

What is the total number of fractures per annum in England?

- Published incidence data:

  Donaldson(2008)[3] conducted a community based survey and determined the incidence of all types of fractures (including osteoporosis) in the general population to be 3.6 fractures per 100 people per year in England The incidence of long bone fractures was shown to be 1.2 per 100 for males and 0.8 per hundred for females.

- Health Episode Statistics

  HES data 2009 - 2010 for England show the number of referrals to fracture clinics was 650,522, which implies a lower overall fracture rate of 1.3 fractures per 100 people per year, assuming the population of England estimate of 51,230,227 (NICE) [4]

  This data states the adult (over 18) population as 40,235,268, 78.5% of the total

How many fractures become delayed or non-unions?

Between 5 – 10% of the fracture population will not heal as expected and be classified either as a delayed, or a non-union Rubin (2001)[5] .

Assuming the lower rate of incidence from the HES data, the published rates of delayed / non-union and the adult proportion of 78.5%, the population in England that may benefit from EXOGEN treatment can therefore be estimated to be between 25,536 – 51,072 patients per annum

How many surgical interventions are performed on non-union fractures in 2010?

HES data 2010 -2011 indicates that under diagnosis code M84.1, there were approximately 13,500 finished consultant episodes

3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups and make any recommendations for their treatment. If available, these should be UK based guidelines.

NICE IPG 374[6] identifies delayed union and non-unions as specific subgroups. The guidance states, “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.”

3.3 Describe the clinical pathway of care that includes the proposed use of the technology.

Fractures are described as either closed (skin over the fracture site is intact) or open (involves an open wound).

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

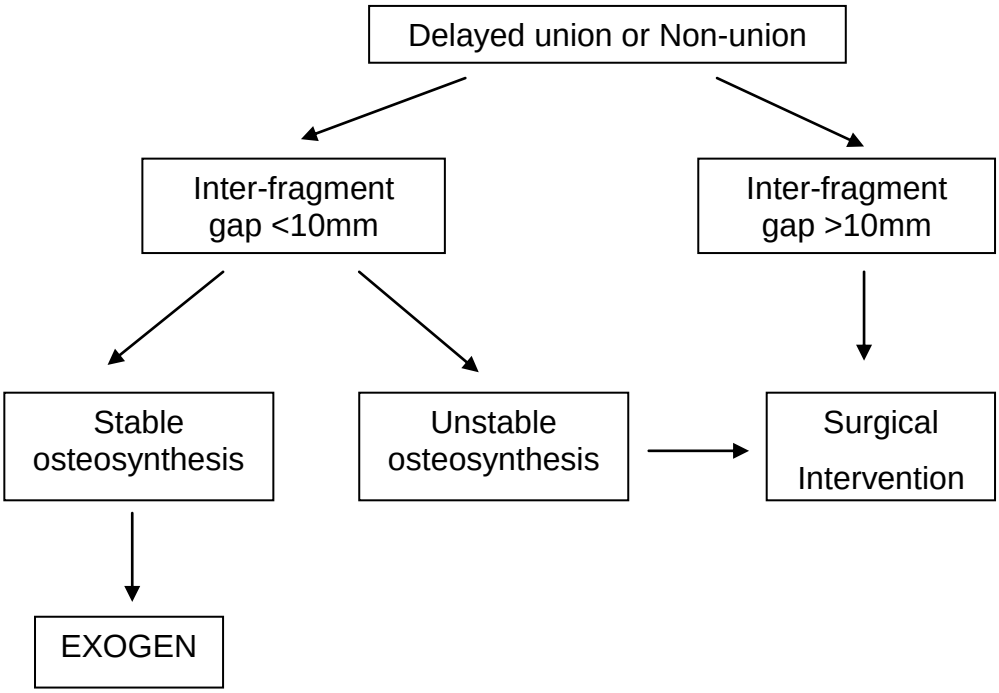
The aim of fracture treatment is to ensure the best possible function of the injured part after healing:

- 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

Failure of the fracture to heal as expected results in a delayed or non-union. This may require complex and prolonged management and has implications for patients' quality of life and functional capacity. Such fractures are treated surgically by open reduction, bone grafting if necessary and internal or external fixation.

The proposal is that patients diagnosed with delayed, or non-union fractures of long bones which are stable and well-aligned should be treated with EXOGEN to attempt to heal the fracture prior to undergoing further surgery as described above.

Figure 1. Treatment flow chart adapted from Roussignol (2012)[7]



NICE has produced a clinical guideline on the management of hip fractures[8], however, as this refers specifically to the hip only this lies outside the scope of this submission.

3.4 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

There is no uniformly accepted method of delayed and non-union diagnosis (and therefore treatment) applicable to all fractures, given variations in the bone tissue and fracture characteristics. Even for fractures in a given bone, there is a range of opinions regarding the time by which a fracture is expected to heal. There are also variations in the specific radiographic and clinical criteria used to diagnose non-union.

Bhandari(2002)[9] found that 79% of surgeons use radiographic evidence of cortical continuity as their primary means of defining non-union fracture healing, but that 42% also used ability to weight-bear and 37% also use pain on palpation of the fracture site. The mean and standard deviation (SD) time from initial fracture of the tibia to diagnosis of non-union was 6 months (SD: 2 months), with a range of 2 to 12 months.

Despite the imaging and clinical methods, determination of the presence of non-union can be very difficult and is often dependent on clinical judgment.

Once diagnosed, various factors affect treatment.

Non-unions are classified as either septic (infected) or aseptic (non-infected), by clinical examination as either stable or mobile, and by radiographic appearance as hypertrophic, atrophic, or oligotrophic (see glossary).

The presence or absence of infection is a key determinant of treatment. In general, implantation of new hardware for stabilisation may need to be delayed until antibiotic therapy and surgical debridement bring the infection under control. In some cases, previously implanted hardware must be removed. An external fixation device is sometimes used for stabilization of

the fracture site in this setting. The fracture site is reassessed when the infection is under control.

Both inadequate stability of the fracture site and impairment of the biological response to fracture play a role in many non-unions.

Inadequate stability is most frequently addressed by use of fixation devices, either external or internal; biologic deficits are currently treated primarily by bone grafts.

Autogenous bone grafts, or other bone graft substitutes provide growth factors and mechanisms for osteoinduction, but depend on adequate vascular supply at the non-union site. In some instances, bone grafts are harvested with an intact vascular supply to overcome inadequate blood supply at the non-union site.

The iliac crest is the most commonly used donor site, although “local bone” may be obtained from a site close to the non-union. Excessive morbidity, primarily related to the harvesting procedure, has led to a demand for alternative means of treatment or the use of bone graft substitutes.

Patient preferences, as well as the assessment of higher levels of risk of complications from surgery, may also lead the orthopaedic surgeon to consider less invasive methods of treatment.[10]

3.5 Describe the new pathway of care incorporating the new technology that would exist if the technology was adopted by the NHS in England.

The new pathway of care if EXOGEN technology is adopted would be as follows:

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

Refer to 3.3, figure 1.

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.

3.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

There would be no changes to the way in which current services are organised or delivered

3.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

No additional test or investigations needed

3.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

No additional facilities, technologies or infrastructure are needed

3.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

Routine use of the EXOGEN device has the potential to reduce the amount of surgical intervention required in the treatment of delayed or non-unions of long bone fractures. Therefore the current tests, investigations (X-ray, MRI, CT, Pathology lab testing for infection) and facilities (plaster room, operating theatre, outpatients clinic), would be in less demand and have less utilisation of those resources within the defined patient groups, Fewer operations also means a reduction in bed stay in the defined patient group.

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in section 3.9 that would no longer be needed with using this technology.

Within the non-union population, the routine introduction of EXOGEN technology could save in excess of 6,500 operative procedures and in excess of 29,000 bed occupancy days per year in England.

There would also be a reduction in out-patient appointments, X-rays and plaster room use, however, this is very difficult to quantify.

Delayed union fractures that may require surgical intervention are not included in the estimate above. Further detail of this will be supplied in section C.

The assumptions made in this calculation are:

- For 2010 – 2011 , initial analysis of HES data indicates that there were approximately 13,500 surgical procedures for non-unions captured under the ICD-10 code M84.1
- 50% of these procedures are carried out on stable, well aligned fractures and under the proposed treatment pathway (flow chart described in figure 1, section 3.3) could be replaced by EXOGEN treatment

- EXOGEN heal rate is 86% in non-unions

4. Regulatory information

4.1 Provide PDF copies of the following documents

- instructions for use
- CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity
- quality systems (ISO 13485) certificate (if required).

All document pdf files are attached

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Yes.

EC Certificate Number**:** CE 512806
First issued: February 20, 2007, Renewed: December 1, 2009

4.3 Does the technology have regulatory approval outside the UK? If so, please provide details..

YES.

EXOGEN has regulatory approval in many other countries, including:
Australia, - ARTG certificate License number 169120, issued 02/2010

Canada – Health Canada Licence number 71087, issued 07/ 2006

Japan – Ninsho PMDA 220ADBZX00062000, issued 02 / 2008

USA – FDA P900009, latest update SO32, issued 03 /2010

4.4 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

Not applicable

4.5 If the technology has been launched in the UK provide information on the use in England.

Many NHS trusts in England have used EXOGEN on a named patient, or special funding request basis.

[redacted]

5 Ongoing studies

5.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

There are no on-going studies relevant to the scope of this submission.

5.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

No other assessments in the UK are planned

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1.1 Describe any equality issues relating to the patient population and condition for which the technology is being used.

None identified

6.1.2 Describe any equality issues relating to the assessment of the technology that may require special attention.

None identified

6.1.3 How will the submission address these issues and any equality issues raised in the scope?

As stated in the scope, because treatment with the EXOGEN ultrasound bone healing system is self-administered, some patients may need assistance in using the technology. It is not felt that this discriminates against any section of the population.

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

7.1 Identification of studies

Published studies

7.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in section 10, appendix 1.

As described 3.4, there is huge variability in the diagnosis and treatment of fractures that are not healing as expected. Such a lack of uniformity makes searching for relevant clinical data difficult.

The quality of data in the identified patient population is also difficult to keep of a high nature. Appropriate surgical intervention by definition cannot be blinded, randomised or well controlled. Placebo controlled studies for the EXOGEN device are possible, but in the case of established non-unions would be considered unethical, as a patient would potentially be denied treatment.

The searches performed intended to minimise the possibility of bias and to produce data described in 7.8 that allows a fair comparison of the findings between EXOGEN and surgical intervention and as much relevance as possible to the scope.

Literature Search Strategy

A systematic approach to identifying clinical and background literature was followed:

- CRD databases returned a number of meta-analyses but they were outside the scope of the submission
- PubMed searches were performed using search terms relevant to the scope
- Identified literature from the PubMed searches was used to source additional clinical literature and background literature relating to surgical treatment of delayed or non-union fractures in long bones.

- Due to the large number of publications identified using the Pubmed search terms, additional selection criteria were identified and used to screen articles.

PubMed covers the vast majority of published clinical studies and was used to identify relevant clinical studies. Searching the cited references in these identified articles for additional supportive studies results in a robust search strategy that identifies, with high reliability, all relevant material.

EXOGEN data was identified first and then surgical data was matched as closely as possible to the methodologies and design of the relevant papers

Unpublished studies

7.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Searches of internal post-market vigilance and the annual report compiled for the FDA, together with a Google search were conducted

No relevant clinical data was retrieved

7.2 Study selection

Published studies

7.2.1 Complete table B1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B1 Selection criteria used for published studies

Inclusion criteria	
Population	Non-unions and delayed unions in long bones in adults
Interventions	Exogen / Low Intensity Pulsed Ultrasound / Sonic Accelerated Fracture Healing System Surgery, surgical
Outcomes	Healing rates, healing time
Study design	Prospective – 12 or more patients in each series
Language restrictions	English
Search dates	1992 – 2012
Exclusion criteria	
Population	Fresh fractures, fracture healing complications in children
Interventions	Those not in the scope
Outcomes	Lack of healing data
Study design	Retrospective – fewer than 12 patients
Language restrictions	Non-English
Search dates	Pre 1992

7.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Figure 2. **EXOGEN literature search PRISMA flow diagram**

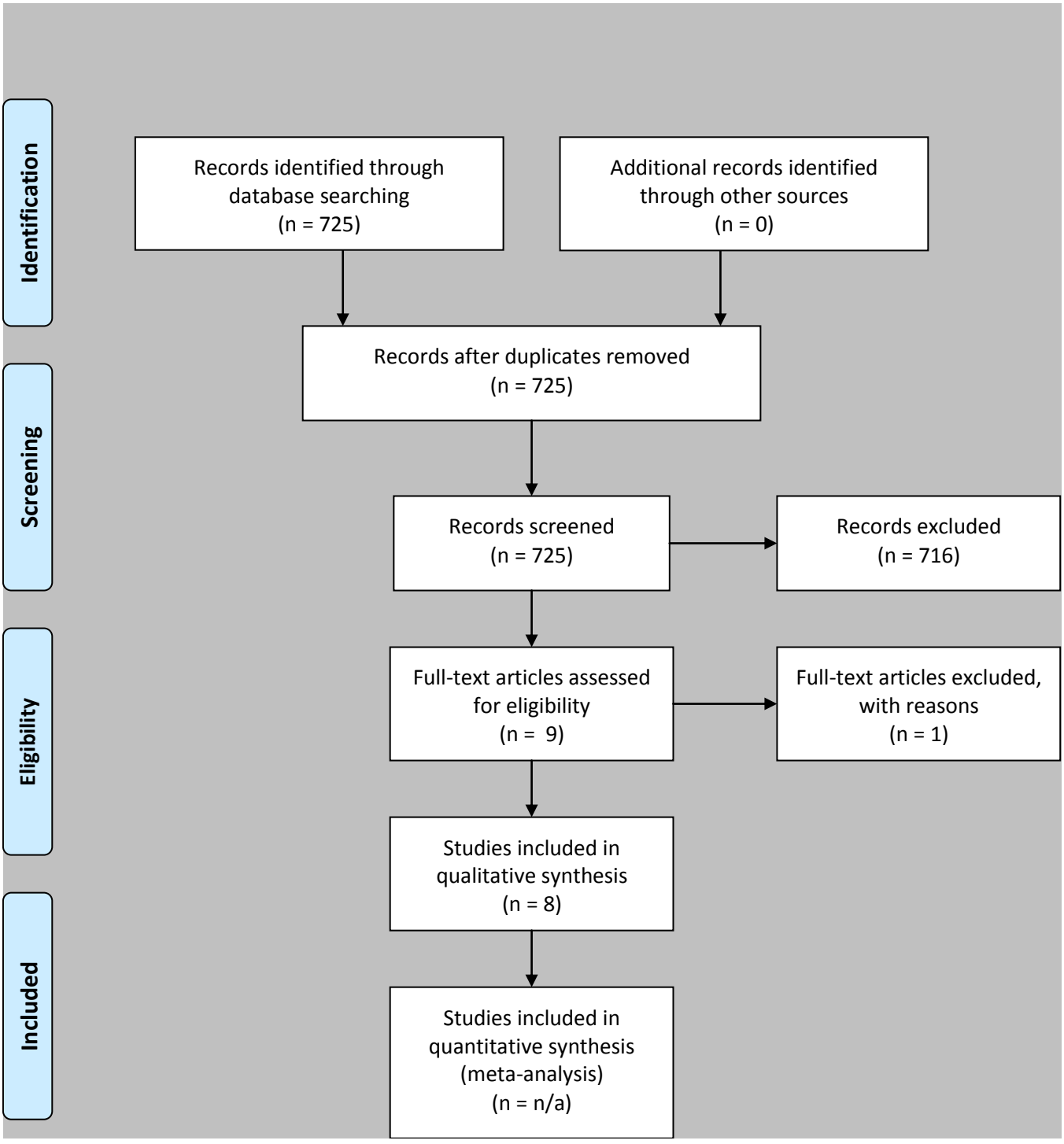
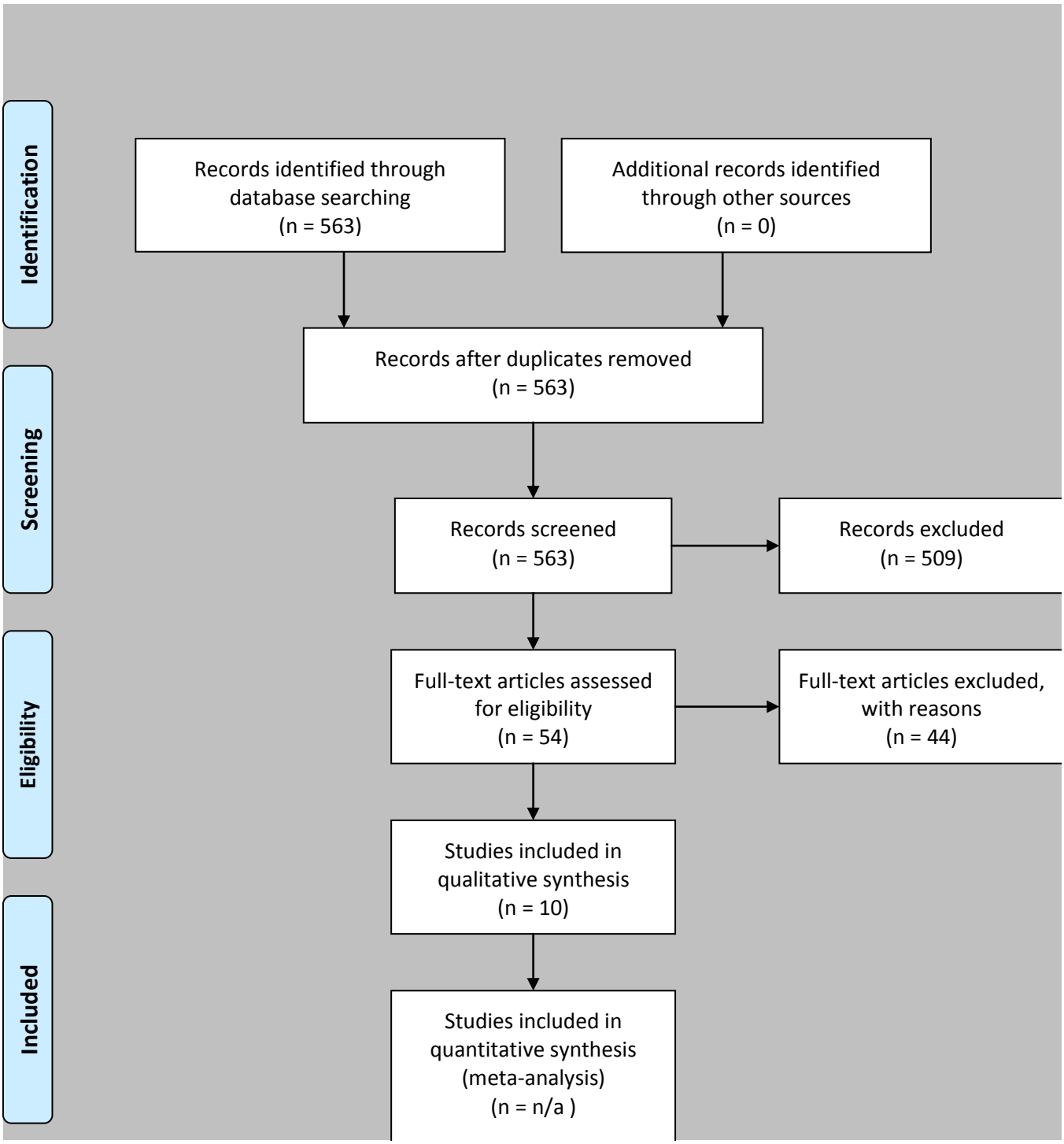


Figure 3. **Surgery literature search PRISMA flow diagram**



Unpublished studies

7.2.3 Complete table B2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B2 Selection criteria used for unpublished studies

Inclusion criteria	
Population	Non-unions and delayed unions in long bones in adults
Interventions	Exogen / Low Intensity Pulsed Ultrasound / Sonic Accelerated Fracture Healing System Surgery, surgical
Outcomes	Healing rates, healing time
Study design	Prospective – 12 or more patients in each series
Language restrictions	English
Search dates	1992 – 2012
Exclusion criteria	
Population	Fresh fractures, fracture healing complications in children
Interventions	Those not in the scope
Outcomes	Lack of healing data
Study design	Retrospective – fewer than 12 patients
Language restrictions	Non-English
Search dates	Pre 1992

7.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

As stated in 7.1.2 no unpublished studies were identified

7.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables B1 and B2.

There were no studies found that directly compare EXOGEN and surgery

Table B3. List of relevant published studies

Primary study reference	Population	Intervention	Comparator
Schofer 2010	Delayed union	EXOGEN	placebo
Rutten 2008	Delayed union	EXOGEN	placebo
Gebauer 2005	Non-union and delayed union	EXOGEN	self-paired
Jingushi 2007	Non-union	EXOGEN	self –paired
Lerner 2004	Delayed union	EXOGEN	none
Mayr 2000	Delayed and Non-union	EXOGEN	none
Nolte 2001	Non-union	EXOGEN	self-paired
Pigozzi 2004	Non-union	EXOGEN	none
Romano 1999	Septic non-union	EXOGEN	self-paired
Bellabarba 2002	Femoral non-union	Plate and screws	None
Birjandinejad 2009	Femoral and Tibial-non-union	Plate and screws augmentation following IM nailing	None
Cacchio 2009	Long-bone non-union	Surgery	Shockwave
Friedlaender 2001	Tibial non-union	rhBMP-7	Autograft
Khalil 2010	Ulna non-union	Contour plate	None
Lin 2010	Humeral non-union	Surgery plus Allograft	Surgery plus autograft
Livani 2010	Humeral non-union	plating	None
Razaq 2010	Femoral non-union	Exchange nailing	None
Ring 1997	Femoral non-unions	Wave plate	None
Wu 2003	Tibial non-union	Reaming bone grafting	None

Table B4 List of relevant unpublished studies – not applicable

7.3.2 State the rationale behind excluding any of the published studies listed in tables B3 and B4.

Pigozzi 2004[11] was excluded as only 2 of the 15 patients had long bone non-unions

7.4 Summary of methodology of relevant studies

7.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables B5 and B6 as appropriate. A separate table should be completed for each study.

Summary of methodology for randomised controlled trials - EXOGEN

Table B5.1 Schofer 2010[12] Summary of methodology

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

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

assessments)	multiple imputation methods (1-sided, p = 0.014). The exponentiated difference in log mean changes was 0.974 (90% CI 0.956 to 0.993) reflecting proportionally smaller average gap area. For untransformed data, the group difference in mean adjusted changes from baseline in bone gap area was -0.457 mm2 (90% CI -0.864 to -0.049) with 1-sided p = 0.03 similarly reflecting a smaller expected gap area in LIPUS-treated subjects compared to controls.

Table B5.2 Rutten 2008[13] Summary of methodology

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

	considered significant.
Primary outcomes (including scoring methods and timings of assessments)	1) area of new bone formation, 2) area of cancellous bone, and 3) area of cortical bone.
Secondary outcomes (including scoring methods and timings of assessments)	None

Summary of methodology for randomised controlled trials - SURGERY

Table B5.a Cacchio 2009[14] Summary of methodology

Study name Cacchio 2009	Extracorporeal Shock-Wave Therapy Compared with Surgery for Hypertrophic Long-Bone Non-unions
Objective	Compare the results of extracorporeal shock-wave therapy produced by two different devices with those of surgical treatment in the management of long-bone non-union.
Location	Multicentre in Italy
Design	Randomised, double-blind, controlled
Duration of study	6 months
Patient population	156
Sample size	126
Inclusion criteria	long-bone non-union and skeletal maturity.
Exclusion criteria	bone tumours, pathologic fractures, infected non-unions, breakage of fixation devices, an implanted pacemaker, blood coagulation disorders, use of anticoagulant drugs, and pregnancy.
Intervention(s) (n =) and comparator(s) (n =)	SWT (1)= 42, SWT (2) = 42 Surgery = 42
Baseline differences	None reported
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Active follow up over 24 months 15 patients were lost to follow up

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

Table B5.b Friedlaender 2001[15] Summary of methodology

Study name Friedlaender 2001	**Osteogenic Protein-1 (Bone Morphogenetic Protein-7) in the Treatment of Tibial Non-unions: A Prospective, Randomized Clinical Trial Comparing rhOP-1 with Fresh Bone Autograft***
Objective	Comparison the clinical and radiographic results with this osteogenic molecule and those achieved with fresh autogenous bone.
Location	Multicentre USA
Design	controlled, prospective, randomized, partially blinded,

Duration of study	24 months, primary endpoint 9 months
Patient population	Adults with non-unions
Sample size	124 fractures
Inclusion criteria	Each patient had a tibial non-union, as based on a 1988 FDA guidance document definition requiring 9 months duration of the non-united fracture with no evidence of progressive healing over the previous 3 months
Exclusion criteria	Patients who, in the judgment of their treating orthopaedic surgeon, were candidates for internal fixation alone (generally reaming and an intramedullary rod), were excluded, as were patients with clinically apparent infection at the fracture site. 1. Patients who do not meet the study inclusion criteria. 2. Patients who are skeletally immature. 3. Patients unable or unwilling to fulfil the follow-up requirements. 4. Patients with severely compromised soft-tissue coverage at the non-union site, sufficient to impair bone healing. 5. Patients with non-unions resulting from pathological fractures (neoplasia, metabolic bone disease). 6. Patients receiving radiation, chemotherapy, immunosuppression, or chronic steroids. 7. Patients who are or could become pregnant during the study or who are breastfeeding. 8. Patients with active infection systemically or at the site of non-union. 9. Patients receiving other investigational treatment. 10. Patients with congenital or synovial pseudarthrosis of the tibia. 11. Patients with complete neuropathy that would interfere with walking or appreciation of pain. 12. Patients with non-unions of multiple bones (other than the tibia). 13. Patients with a known autoimmune disease. 14. Patients with known sensitivity to collagen.
Intervention(s) (n =) and comparator(s) (n =)	Surgery plus rhOP-1 = 63 fractures Surgery plus autograft = 61 fractures
Baseline differences	These two randomly assigned populations were similar in most respects, including age, sex ratio, duration of non-union, and the number of prior surgical interventions. There was, however, a statistically higher prevalence of atrophic non-unions (41 compared with 25%, p = 0.048) and a strong trend toward more smokers (74 compared with 57%, p = 0.057) in the OP-1 group.

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

Summary of methodology, observational studies - EXOGEN

Table B6.1 Gebauer 2005[16] Summary of methodology

Study name Gebauer 2005	**Low-Intensity Pulsed Ultrasound: Effects on Non-unions**
Objective	To study the efficacy of EXOGEN low-intensity pulsed ultrasound on non-union cases with a minimum fracture age of 8 months.
Location	Germany and Austria
Design	Self-paired control study where the control is the patient's own history of failed treatments.

Duration of study	22 months
Patient population	Consecutively entered German and Austrian population of fractures, of all fracture ages, who were prescribed the use of EXOGEN as an alternative to surgery, based on the patient's decision. All the non-union fractures were consecutively entered into the study, provided the patient did not decide on a surgical revision of the non-union.
Sample size	85 treated non-union cases. 67 cases met the study inclusion criteria
Inclusion criteria	• Established non-union defined as a fracture with a minimum age of 8 months from the fracture date • Radiographic assessments displaying a clearly visible fracture line, before and at the start of EXOGEN treatment indicating that the fracture healing process had not progressed or had stopped for at least 3 months before the start of EXOGEN treatment • A minimum period of 4 months without surgical intervention before EXOGEN.
Exclusion criteria	• Patients who were not skeletally mature • Women who were pregnant or nursing • Patients who could not comply with their physicians' instructions • Fractures that were malaligned, grossly unstable, actively infected or had extensive bone loss
Intervention(s) (n =) and comparator(s) (n =)	EXOGEN (n=67) Non-union (n=67)
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Anterior / posterior and lateral radiographs were taken at 1-2 month intervals after the start of EXOGEN. Clinical examination occurred at each follow-up visit. Long term follow up conducted by telephone an average of 402 days after trial completion. Five patients were lost to long term follow-up of the 57 healed patients.
Statistical tests	One-sided test used to calculate the p-value to assess the superiority of treatment with the EXOGEN device for the per cent of non-unions

	healed Fisher's exact test used to contrast strata of patient and fracture characteristics
Primary outcomes (including scoring methods and timings of assessments)	Healed non-union when the fracture was both clinically and radiographically healed. Clinical healing was defined as no pain or motion upon gentle stress, and weight bearing if applicable. Radiographic healing defined as three of four bridged cortices for long bones and bridging callus for flat bones.
Secondary outcomes (including scoring methods and timings of assessments)	

Table B6.2 Jingushi 2007[17] Summary of methodology

Study name Jingushi 2007	**Postoperative delayed union or nonunion long bone fractures**
Objective	Evaluate the impact of Exogen on the above
Location	Multiple centres in Japan
Design	Prospective, multi-centre, case series
Duration of study	Treated until healed (2-7 months)
Patient population	All patients long bone delayed union or non-union following operative treatment
Sample size	72 fractures
Inclusion criteria	Delayed union or non-union fractures of humerus, radius, ulna, femur or tibia following operative treatment. Closed or open (Gustilo grades 1 to III B)
Exclusion criteria	Fractures not meeting the above inclusion criteria
Intervention(s) (n =) and comparator(s) (n =)	Exogen (n=72)
Baseline differences	Not applicable
How were participants followed-up (for example, through pro-	Clinical and radiographic evaluation by experienced orthopaedic surgeons on a monthly basis until healed.

active follow-up or passively). Duration of follow-up, participants lost to follow-up	
Statistical tests	Not applicable for primary endpoint but statistical analysis for baseline characteristics on union rate
Primary outcomes (including scoring methods and timings of assessments)	Clinical and radiographic healing as determined by experienced orthopaedic surgeons
Secondary outcomes (including scoring methods and timings of assessments)	Assessment of impact of background factors on healing rates.

Table B6.3 Lerner 2004[18] Summary of methodology

Study name Lerner 2004	**Compound High Energy Limb Fractures with Delayed Union**
Objective	Evaluate the impact of Exogen on the above
Location	Ramban Medical Center and Faculty of Medicine, Technion, Israel
Design	Prospective, single centre, case series
Duration of study	Treated until healed (14 to 52 wks)
Patient population	High energy fractures (war injuries, road traffic and work accidents). All Gustilo open fractures (grades II to III C)
Sample size	17 patients, 18 fractures
Inclusion criteria	Delayed bone healing (18 to 172 weeks) or impaired bone healing (2 fractures at 4 weeks).
Exclusion criteria	Low energy fractures
Intervention(s) (n =) and comparator(s) (n =)	Exogen (n=18)
Baseline differences	Not applicable
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of	Usual and customary follow up until healed, and long term follow up out to 6 years. 1 patient lost to follow up

follow-up, participants lost to follow-up	
Statistical tests	Not applicable
Primary outcomes (including scoring methods and timings of assessments)	Fracture healing as determined by experienced orthopaedic surgeon
Secondary outcomes (including scoring methods and timings of assessments)	Not applicable

Table B6.4 Mayr 2000[19] Summary of methodology

Study name Mayr 2000	Ultrasound – an alternative healing method for nonunions?
Objective	A report on patients suffering from healing problems who use EXOGEN therapy for treatment of delayed or nonunions.
Location	Augsburg Hospital, Augsburg, Germany
Design	Full prospective patient registry population compared with Ausberg's well controlled trial
Duration of study	From October 17,1994, to July 14, 1997,
Patient population	1,317 patients total; 42 patients-Ausberg
Sample size	1,317
Inclusion criteria	Nonunion (9 months post fracture) or delayed union (3-9 months post fracture)
Exclusion criteria	Not reported
Intervention(s) (n =) and comparator(s) (n =)	Augsburg patients – (n=42) Full registry cohort – (n=1,317) The non-union becomes a perfect example of biological self-pairing since the patient has not healed, and subsequent treatment intervention results in a healing status change. This healed status change is the basis for effectiveness since the patient serves as his or her own control.
Baseline differences	N/A
How were participants followed-up (for example, through pro-	Only completers were included in the analysis therefore there are no reported losses to follow-up.

active follow-up or passively). Duration of follow-up, participants lost to follow-up	
Statistical tests	Not stated
Primary outcomes (including scoring methods and timings of assessments)	Bony healing, defined as follows: healing criteria: three cortices bridged in two X-ray planes or trabecular bridging of at least 80% of the fracture in the case of cancellous fractures
Secondary outcomes (including scoring methods and timings of assessments)	None stated

Table B6.5 Nolte 2001[20] Summary of methodology

Study name Nolte - 2001	**Low-Intensity Pulsed Ultrasound in the Treatment of Nonunions**
Objective	To evaluate the effect of EXOGEN low intensity pulsed ultrasound for the treatment of established non-unions in a consecutively enrolled patient population to see if ultrasound had an effect in the treatment of non-union.
Location	The Netherlands
Design	Self-paired study where each patient served as their own control, with the prior failed treatments being the basis for evaluating EXOGEN. Each patient was diagnosed with a non-union, with no expectation of healing. EXOGEN was the only change in the treatment regimen – no additional treatment procedure was allowed at the start of or during the period of EXOGEN low intensity pulsed ultrasound treatment to influence the effect of the ultrasound therapy.
Duration of study	18 months
Patient population	Patients presented in trauma departments
Sample size	29 fractures reported 21 long bone fractures (tibia, femur, fibula, humerus, ulna, radius)
Inclusion criteria	Patients with a non-union fracture as defined by: • A failure of the fracture to unite at a minimum of 6 months from the time of fracture • Radiographic healing had not progressed or

	had stopped for a minimum period of 3 months before the start of EXOGEN treatment • The fracture line was clearly visible in two orthogonal views • The interval between the last operative procedure and the start of EXOGEN treatment was a minimum of 90 days
Exclusion criteria	Not reported
Intervention(s) (n =) and comparator(s) (n =)	EXOGEN (n=21) Non-union (n=21)
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patients were actively examined in the outpatient department of their respective hospitals at regular intervals of 6 to 8 weeks. No patients were lost to follow-up. Three patients withdrew themselves from the study.
Statistical tests	Kruskal-Wallis test was used for contrasting heal time and fracture age. The Kruskal-Wallis analysis was a two sided 99% confidence level Monte Carlo estimate of the exact p value computed. Fisher's exact test was used for heal rates.
Primary outcomes (including scoring methods and timings of assessments)	Clinical healing on the non-union fracture as defined by: • Absence of pain • Weight bearing without pain or normal function of the limb Radiographically healed non-union fracture as defined by: • Three or four cortices bridged
Secondary outcomes (including scoring methods and timings of assessments)	None

Table B6.6 Romano 1999[21] Summary of methodology

Study name Romano 1999	**Low-Intensity, Pulsed Ultrasound for the Treatment of Septic Pseudoarthrosis**
Objective	To describe the clinical effects of low intensity pulsed ultrasound for the treatment of septic non-unions.
Location	Istituto Ortopedico Gaetano Pini, Milan, Italy
Design	Case Report
Duration of study	Treated until healed (95 to 181 days)
Patient population	Patients with septic pseudoarthrosis and delayed consolidation
Sample size	15 fractures 13 long bones (tibia, humerus femur)
Inclusion criteria	Patients with septic pseudoarthrosis and delayed consolidation and: • Sufficiently stable fracture • An infection controlled with antibiotics • Sufficient vascularization • Skin covering
Exclusion criteria	Not reported
Intervention(s) (n =) and comparator(s) (n =)	EXOGEN (n=15) NA
Baseline differences	NA
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patient follow-up information not provided No patients were lost to follow-up.
Statistical tests	NA
Primary outcomes (including scoring methods and timings of assessments)	Consolidation (specific definition not provided)
Secondary outcomes	None

Summary of methodology, observational studies - SURGERY

Table B6.a Bellabarba 2002[22] Summary of methodology

Study name Bellabarba 2002	Indirect reduction and plating of distal femoral nonunions
Objective	To observe and report the clinical results of indirect reduction and plating in the treatment of distal femoral nonunions
Location	Single centre, USA
Design	Prospective consecutive study
Duration of study	Average follow up 23 months
Patient population	A consecutive series of patients with non-union of the distal femur, nineteen of whom had undergone operative initial fracture care
Sample size	20
Inclusion criteria	Distal femoral non-unions
Exclusion criteria	Not stated
Intervention(s) (n =) and comparator(s) (n =)	20 surgical plating
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Follow up method not stated No loss to follow up
Statistical tests	Not stated
Primary outcomes (including scoring methods and timings of assessments)	Healing rate and time, (Clinical and radiographical) operative blood loss and time, incidence of complications including instrumentation failure, loss of fixation, infection, and postoperative malalignment. Both the Böstman and Hospital for Special Surgery knee scores were used to quantify postoperative clinical results at an average follow-up of twenty-three months (range 12 to 60 months).
Secondary outcomes	Not stated

Table B6.b Birjandinejad 2009 [23] Summary of methodology

Study name Birjandinejad 2009	Augmentation plate fixation for the treatment of femoral and tibial non- unions after intramedullary nailing.
Objective	Present authors' experience in plating as an augmentation to primary nailing
Location	Single centre, Iran
Design	Prospective case series
Duration of study	1 year minimum follow up
Patient population	Femoral and tibial non-unions
Sample size	25
Inclusion criteria	Not stated
Exclusion criteria	Infection
Intervention(s) (n =) and comparator(s) (n =)	25 surgical intervention
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Clinic attendance
Statistical tests	Not stated
Primary outcomes (including scoring methods and timings of assessments)	Clinical and radiographical healing. Disappearance of lucencies on X-ray and ability to weight bear
Secondary outcomes (including scoring methods and timings of assessments)	Not stated

Table B6.c Khalil 2010[24] Summary of methodology

Study name Khalil 2010	Contoured plating for proximal ulna non-union: an improved technique
Objective	Present results of an improved plating technique
Location	Single centre, Faculty of medicine, Tanta University, Egypt
Design	Prospective case series
Duration of study	22 months average follow up
Patient population	Patients with proximal ulna non-union
Sample size	21
Inclusion criteria	Ununited proximal ulnar fractures
Exclusion criteria	Cases with painless stiff non-union with a stable elbow having a range of movement greater than 90° were excluded
Intervention(s) (n =) and comparator(s) (n =)	21 surgical plating
Baseline differences	N /A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Every 2 weeks
Statistical tests	Not stated
Primary outcomes (including scoring methods and timings of assessments)	Clinical and radiographic healing was assessed every 2 weeks Functional outcomes were calculated using the Broberg-Morrey scoring system. Radiographs were evaluated for union, articular congruity and alignment. Radiographic signs of arthritis were graded according to the system of Broberg and Morrey
Secondary outcomes (including scoring methods and timings of assessments)	None stated

Table B6.d Lin 2010[25] Summary of methodology

Study name Lin 2010	Allografting in Locked Nailing and Interfragmentary Wiring for Humeral Nonunions
Objective	Compare outcomes after repair of humeral nonunions when morsellized fresh-frozen allograft or autograft was used to augment repair by intramedullary nailing
Location	Single centre, Taiwan
Design	Prospective, non-blinded, comparative study
Duration of study	+ 2 years
Patient population	Patients with humeral non-union
Sample size	65
Inclusion criteria	Humeral shaft (3 cm below the lesser tuberosity and 5 cm above the olecranon fossa) non-union of more than 6 months' duration with gross instability at the non-union site
Exclusion criteria	Exclusion criteria were nonunions with intra-articular extension, active deep infection, or bone defect greater than 3 cm
Intervention(s) (n =) and comparator(s) (n =)	Surgery plus allograft = 36 Surgery plus autograft = 28
Baseline differences	No significant differences
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Follow up though regular clinic attendance. The follow up was defined as the duration between the operation and the last regular follow up before the article was written.
Statistical tests	Statistical analysis was performed using SPSS software, Version 16 (SPSS Inc, Chicago, IL). Continuous variables were compared with Student's t tests. Binary variables were compared with chi square tests (comparing two proportions) or Fisher's exact tests if cell counts were less than five. For power analysis, with a usual level of statistical significance ($\alpha = 0.05$ for a two-sided test) and a given power of 0.8 ($\beta = 0.2$), the present sample size could detect a minimal difference of 3.0 weeks for time to union and 4.8 points for Neer score.

Primary outcomes (including scoring methods and timings of assessments)	Primary end points were union rate and functional recovery. The follow up was defined as the duration between the operation and the last regular follow up before this article was written. Clinical union was defined as visible callus bridging the fracture in at least three cortices on radiographs and the patients could use their arms without considerable pain or weakness. Although this was an open-label study, the investigators had no special preference regarding the graft type. The end points were measured by two blinded, fellowship-trained orthopaedic trauma surgeons (SMH, XYH). The two evaluators had pre-study consensus on examination methods. Functional assessment included Neer functional score] and Constant and Murley score for shoulders, Mayo performance score for elbows, and shortened Disabilities of the Arm, Shoulder, and Hand (QuickDASH) score for the upper extremity function. Postoperatively, the Constant and Murley score was compared between the injured and uninjured arms
Secondary outcomes (including scoring methods and timings of assessments)	Secondary end points included operative blood loss, operation time, hospital stay, time to fracture healing, and complications.

Table B6.e Livani 2010[26] Summary of methodology

Study name Livani 2010	Anterior plating as a surgical alternative in the treatment of humeral shaft non-union
Objective	Report the results of anterior plating procedure
Location	Single centre, Brazil
Design	Prospective case series
Duration of study	36 months
Patient population	Patients with humeral non-union
Sample size	15
Inclusion criteria	Not stated
Exclusion criteria	Not stated
Intervention(s) (n =) and comparator(s) (n =)	15 treated with anterior plate
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Clinic attendance
Statistical tests	No loss to follow up
Primary outcomes (including scoring methods and timings of assessments)	Clinical (method not stated)and radiographic healing callus formation and cortical continuity)
Secondary outcomes (including scoring methods and timings of assessments)	Not stated

Table B6.f Razaq 2010[27] Summary of methodology

Study name Razaq 2010	EXCHANGE NAILING FOR NON-UNION OF FEMORAL SHAFT FRACTURES
Objective	Analyse the role of exchange nailing for aseptic non-union of femoral shaft fractures.
Location	Single centre, Pakistan
Design	Prospective, consecutive case series
Duration of study	18 months
Patient population	Patients with aseptic femoral non-unions
Sample size	41 patients, 43 fractures
Inclusion criteria	Inclusion criteria 1. All male and female patients who were aged 13 years and above 2. All patients who had initially closed post traumatic fractures of the shaft femur 3. All patients who had one or more times previous surgical treatment done for the fracture 4. All patients had last surgery for the fracture in the preceding 9–12 months in the form of IM nailing. (either K-nail or interlocking nail) 5.All patients had aseptic hypertrophic or atrophic non-union on clinical and radiological assessment performed at 9 months or later after the last surgery 6. All patients had less than 1cm shortening and no bone comminution or bone loss at the time of study
Exclusion criteria	1. Patients with infected non-unions 2. Patients who had segmental bone defects greater than one cm 3. Patients with bent or broken IM nail/Interlocking nail which had required open removal.
Intervention(s) (n =) and comparator(s) (n =)	Exchange nailing = 43
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants	All operated patients were followed-up in the outpatient department at 2 weeks for suture removal and wounds examination. Patients were followed up subsequently for clinical and/or radiological check-up at one month intervals for minimum period of one year after the surgery or till

lost to follow-up	time when bone healing at non-union site has occurred. The fracture showing radiological evidence of healing, as confirmed by independent radiologist, was considered healed.
Statistical tests	Not stated
Primary outcomes (including scoring methods and timings of assessments)	Radiographic healing (exact method not stated)
Secondary outcomes (including scoring methods and timings of assessments)	Not stated

Table B6.g Ring 1997[28] Summary of methodology

Study name Ring et al	COMPLEX NONUNION OF FRACTURES OF THE FEMORAL SHAFT TREATED BY WAVE-PLATE OSTEOSYNTHESIS
Objective	Report results of wave plate versus conventional plate techniques
Location	5 centres, USA
Design	Prospective case series
Duration of study	33 months follow up
Patient population	Complex ununited fractures of the femoral shaft
Sample size	42 fractures
Inclusion criteria	Patients treated with a wave plate
Exclusion criteria	Patients treated with conventional plate and bone grafting
Intervention(s) (n =) and comparator(s) (n =)	Wave plate and bone graft
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	All patients were reviewed at regular intervals with serial radiographs and clinical examination. At final follow-up, the capacity to bear weight, any leg-length discrepancy, alignment and the range of movement in the joints of the leg were noted. 33 months follow up, no losses to follow up
Statistical tests	Not stated

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

Table B6.h Wu 2003[29] Summary of methodology

Study name Wu 2003	Reaming bone grafting to treat tibial shaft aseptic non-union after plating
Objective	To investigate the effects of using intramedullary reaming to provide cancellous bone graft, and reamed intramedullary nail stabilisation to provide fragment stability on treating tibial shaft aseptic nonunions after plating.
Location	Single centre, Taiwan
Design	Prospective case series
Duration of study	Follow up median 2.2 years
Patient population	Tibial shaft aseptic non-unions after plating
Sample size	31
Inclusion criteria	Indications for this technique included a tibial shaft non-union with an inserted plate, a fracture level fit for traditional or locked nail stabilisation, absence of suspected infection and segmental bony defect at the time, and shortening of less than 2 cm.
Exclusion criteria	Patients with suspicious latent deep infection were excluded from the study,
Intervention(s) (n =) and comparator(s) (n =)	Reaming and nail insertion = 31
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patients were followed up via the hospital's Outpatients Department at 4 to 6 week intervals 3 were lost to follow up

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

7.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Not applicable

7.4.3 Highlight any differences between patient populations and methodology in all included studies.

The search criteria and exclusion parameters were applied to ensure, as far as possible, that the included studies have similar patient populations and methodology

7.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 7.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

Not applicable

7.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Not applicable

7.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

Only one paper in the EXOGEN studies – Lerner 2004[18] – cites a loss to follow-up and no explanation is given

7.5 Critical appraisal of relevant studies

7.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables B7 and B8.

Critical appraisal, randomised control trials - EXOGEN

Table B7.1 Schofer 2010[12] Critical appraisal

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

unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	treatment outcomes, consequently 84 subjects were included in descriptive analyses of 'completers'. There was notable differential drop-out between groups with 24% (12 of 50) of sham-treated subjects and 9.8% (5 of 51) of active-treated subjects missing post-treatment BMD values. The ITT cohort was preserved by imputing missing clinical endpoints using a multiple imputation procedure that minimizes bias from differential drop-outs and properly accounts for uncertainty in imputed values when performing statistical inference.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The ITT cohort was preserved by imputing missing clinical endpoints using a multiple imputation procedure that minimizes bias from differential drop-outs and properly accounts for uncertainty in imputed values when performing statistical inference.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table B7.2 Rutten - 2008[13] Critical appraisal

Study name	**Rutten – 2008**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Randomisation of treatment was computerised
Was the concealment of treatment allocation adequate?	Yes	Neither patient nor investigator knew whether the patient had received an active Exogen device
Were the groups similar at the outset of the study in terms of prognostic factors, for example,	Yes	Patients in both treatment groups had similar ages, gender distribution, fracture type and duration of treatment

severity of disease?		
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Unblinding of the trial was performed after completion of the histomorphometric and histologic analysis, and after all patients included in the trial completed their 5 month clinical treatment phase
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	N/A	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	N/A	
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Critical appraisal, randomised control trials – SURGERY

Table B7.a Cacchio - 2008[14] Critical appraisal

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

Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	All outcome analyses were performed according to the intention-to-treat principle. The intention-to-treat analysis was carried out according to a ‘‘worst case scenario’’ analysis: subjects who did not complete the treatment or did not undergo the post-treatment or final follow-up assessments were assigned a poor outcome, with the final follow-up evaluation considered to be the last observation performed.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD’s guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table B7.b Friedlaender 2001[15] Critical appraisal

Study name	**Friedlaender 2001**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Not clear	Treatment was randomly assigned, but method is not made clear
Was the concealment of treatment allocation adequate?	Yes	
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	These two randomly assigned populations were similar in most respects, including age, sex ratio, duration of non-union, and the number of prior surgical interventions. There was, however, a statistically higher prevalence of atrophic nonunions (41 compared with 25%, p = 0.048) and a strong trend toward more smokers (74 compared with 57%, p = 0.057) in the OP-1 group. There were also trends toward higher percentages of comminuted fractures at injury, prior failures of bone autografts, and prior use of intramedullary rods in the individuals in the OP-1 treated group.
Were the care providers, participants and	Not clear	Surgeons were aware of treatment after randomisation, radiographers assessing the cases were blinded throughout. Low risk of

outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		bias
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Critical appraisal, observational studies – EXOGEN

Table B8.1 Gebauer 2005[16] Critical Appraisal

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

		long bones versus other bones. These were all as a result of failed scaphoid cases which were atrophic, each having a fracture age and last surgical procedure interval of over 10 years previously.
Was the follow-up of patients complete?	Yes	Long term healed status of all patients was verified in a telephone follow up conducted approximately one year post study completion. Long term follow up was obtained for 52 of the 57 healed patients.
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	p=0.0001 Confidence interval not reported
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B8.2 Jingushi 2007[17] Critical appraisal

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

How precise (for example, in terms of confidence interval and p values) are the results?	N/A	75% of fractures healed plus analysis of factors contributing to higher or lower success rates.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B8.3 Lerner 2004[18] Critical appraisal

Study name	**Lerner 2004**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Sought to recruit high energy fractures with delayed or impaired healing and did so by clinical evaluation using standard definitions
Was the exposure accurately measured to minimise bias?	Yes	Followed the recommended 20 minutes per day until healed treatment.
Was the outcome accurately measured to minimise bias?	Yes	Solid bone union as determined by X-ray evaluation
Have the authors identified all important confounding factors?	Yes	Age, type of injury, location of injury, cause of injury, Gustilo score, MESS score, presence of vascular injury, fixation method and flap.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	16/17 fractures for which outcomes were determined exhibited positive outcomes, so no meaningful contribution from confounding factors was evidenced.
Was the follow-up of patients complete?	Yes	For 17 out of 18 fractures
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	16/17 fractures healed equates to 94%.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B8.4 Mayr 2000[19] Critical appraisal

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

Table B8.5 Nolte 2001[20] Critical appraisal

Study name:	**Nolte - 2001**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	All patients who met the inclusion criteria were included
Was the exposure accurately measured to minimise bias?	Yes	Patients followed the recommended 20 minutes per day until healed treatment. The EXOGEN device automatically provides 20 minute treatments.
Was the outcome accurately measured to minimise bias?	Yes	Fracture union as determined by clinical and radiographic assessment.
Have the authors identified all important confounding factors?	Yes	Potential variables identified as gender, age, fracture age, prior interval without surgery, bone, smoking habit, non-union type, fixation type present before, at the start of, and during ultrasound treatment.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Data stratified by the patient and fracture characteristics. All the stratification variables were non significant except for the comparison of smoking strata.
Was the follow-up of patients complete?	Yes	All healed fractures were followed up for an average of 62 weeks (range 30-110 weeks)
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	p=0.0001 Confidence interval not reported
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B8.6 Romano 1999[21] Critical appraisal

Study name:	**Romano 1999**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	All patients who met the inclusion criteria were included
Was the exposure accurately measured to minimise bias?	Yes	Patients followed the recommended 20 minutes per day until healed treatment.
Was the outcome accurately measured to minimise bias?	Not clear	Information not provided
Have the authors identified all important confounding factors?	Yes	We did not conduct a controlled double-blind since this study design would not be acceptable. It denies treatment to one study arm and it may be impossible to carry out in patients suffering with infected pseudoarthrosis. In all of the treated cases in this study, the course of fracture healing showed over a period of time that there was no change in the healing process in the presence of an infection and, therefore, the patient was his own control. The only new event that was introduced at the start of treatment was the use of low intensity pulsed ultrasound.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	
Was the follow-up of patients complete?	Yes	
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Critical appraisal, observational studies - SURGERY

Table B8.a Bellabarba 2002[22] Critical appraisal

Study name	Bellabarba 2002	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Prospective consecutive series
Was the exposure accurately measured to minimise bias?	Yes	
Was the outcome accurately measured to minimise bias?	Yes	Extensive measurements in many parameters were taken using two scoring systems
Have the authors identified all important confounding factors?	Yes	Extensive discussion of all potential confounding factors on p.267
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Confounding factors are well measured and reported in the analysis
Was the follow-up of patients complete?	Yes	There was no loss to follow up
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B8.b Birjandinejad 2009[23] Critical appraisal

Study name	**Birjandinejad 2009**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Clear definition is given as to how and why patients were treated with this modality. Not clear whether there was informed consent
Was the exposure accurately measured to minimise bias?	N/A	
Was the outcome accurately measured to minimise bias?	Not clear	Clear definitions of whether the fracture had healed radiographically and clinically. It is not clear if the assessors were independent
Have the authors identified all important confounding factors?	Not clear	Infection is identified and is an exclusion factor, but little discussion concerns other confounding issues
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	There is no discussion of this in the text
Was the follow-up of patients complete?	Yes	
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B8.c Khalil 2010[24] Critical appraisal

Study name	**Khalil 2010**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Clear definitions of how and why patients were recruited. All patients gave informed consent.
Was the exposure accurately measured to minimise bias?	N/A	
Was the outcome accurately measured to minimise bias?	Yes	Recognised scoring systems were used
Have the authors identified all important confounding factors?	Yes	There is extensive discussion of potential confounding factors on p.441
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Clinical and radiographic outcomes were measured with an appropriate scoring system
Was the follow-up of patients complete?	Yes	No loss to follow up
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B8.d Lin 2010[25] Critical appraisal

Study name	**Lin 2010**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Clear definition of how and why patients were recruited. Patients entered the study with full knowledge, treatment choice and consent
Was the exposure accurately measured to minimise bias?	N/A	
Was the outcome accurately measured to minimise bias?	Yes	Extensive measurements of primary and secondary outcomes
Have the authors identified all important confounding factors?	Yes	Yes, extensive discussion of all confounding factors is noted on p.853
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Confounding factors are clearly identified in the analysis
Was the follow-up of patients complete?	Yes	One patient died 4 months post-op, all other patients completed
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	95% confidence interval
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B8.e Livani 2010[26] Critical appraisal

Study name	**Livani 2010**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Clear definition of how and why patients were recruited. All patients gave informed consent
Was the exposure accurately measured to minimise bias?	N/A	
Was the outcome accurately measured to minimise bias?	Not clear	Clinical and radiological outcomes are clearly defined, but no recognised scoring system is noted
Have the authors identified all important confounding factors?	Yes	Table 1. P1026 discusses potential confounding pre-op factors
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	Pre-op confounding factors are identified and other factors are identified in the results presentation
Was the follow-up of patients complete?	Yes	No loss to follow up
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B8.f Razaq 2010[27] Critical appraisal

Study name	**Razaq 2010**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Clear definition of how and why patients were recruited. All patients gave informed consent. Extensive inclusion and exclusion criteria noted
Was the exposure accurately measured to minimise bias?	N/A	
Was the outcome accurately measured to minimise bias?	Yes	Regular assessments were made by independent assessors
Have the authors identified all important confounding factors?	Yes	Data regarding patients' age and gender and other characteristics like femur fracture location, type of non-union as to whether hypertrophic or atrophic and injured side as to left or right, duration of fracture healing after exchange interlocking nailing, period of postoperative follow up period and complication were recorded and analysed using SPSS-10.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Major confounding factors detailed in tables on p.108
Was the follow-up of patients complete?	Yes	No loss to follow up
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B6.g Ring 1997[28] Critical appraisal

Study name	**Ring - 1997**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Clear explanation of how and why patients were included. No details as to whether this was with informed consent
Was the exposure accurately measured to minimise bias?	N/A	
Was the outcome accurately measured to minimise bias?	Not clear	All patients were reviewed at regular intervals with serial radiographs and clinical examination. At final follow-up, the capacity to bear weight, any leg-length discrepancy, alignment and the range of movement in the joints of the leg were noted.
Have the authors identified all important confounding factors?	Yes	Age, duration of Non-union, previous operations, previous infection are noted
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Analysis of patients including potential confounding factors reported on p. 291
Was the follow-up of patients complete?	Yes	No loss to follow up
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B6.h Wu 2003[29] Critical appraisal

Study name	**Wu - 2003**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Clear description of how and why patients were included. No details given of informed consent
Was the exposure accurately measured to minimise bias?	N/A	
Was the outcome accurately measured to minimise bias?	Yes	Clinical and radiographical healing processes were recorded. Bony union was clinically defined as the absence of pain and tenderness, and the ability of the patient to walk without aids. It was radiographically defined as abridgement of solid callus with cortical density for both segments.
Have the authors identified all important confounding factors?	Yes	Age, gender, initial fracture type, Initial treatment, fracture location, non-union period, No. of previous operations, Type of nail used
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	Reporting of patient outcomes is not shown
Was the follow-up of patients complete?	No	Three patients were lost to follow up
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

7.6 Results of the relevant studies

Outcomes included in the scope are:

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

7.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table B9.

Outcomes from published and unpublished studies – EXOGEN

Table B9.1 Schofer 2010[12] Outcomes

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

Table B9.2 Rutten 2008[13] Outcomes

Study name		**Rutten 2008**
Size of study groups	**Treatment**	7
	Control	6
Study duration	**Time unit**	6 months
Type of analysis	**Intention-to-treat/per protocol**	Intention to treat
Outcome	**Name**	Bone volume increase
	Unit	%
Effect size	**Value**	33% greater than placebo
	95% CI	
Statistical test	**Type**	Student's independent t-test (two-tail).
	p value	0.02
Other outcome	**Name**	Mineral apposition rate
	Unit	µm/ day
Effect size	**Value**	27% greater than placebo
	95% CI	
Statistical test	**Type**	Student's independent t-test (two-tail).
	p value	0.04
Comments		Although fewer than 15 patients, In this randomised, double-blind, placebo controlled study histomorphometric and histologic analysis was performed to determine bone formation and resorption parameters in delayed unions of the osteotomized fibula. This the first time the influence of Exogen treatment on clinical fracture healing at the tissue level could be reported.

Table B9.3 Gebauer 2005[16] Outcomes

Study name		Gebauer 2005
Size of study groups	**Treatment**	67 fractures reported 46 long bone fractures (tibia, femur, fibula, humerus, ulna, radius)
	Control	46
Study duration	**Time unit**	Average healing time was 168 days. Patients followed up at an average of 402 days.
Type of analysis	**Intention-to-treat/per protocol**	Per Protocol and Intent to Treat
Outcome	**Name**	Fracture Clinically and Radiographically Healed; time to healing
	Unit	Yes / No
Effect size	**Value**	Per Protocol: • All fractures: 85% (57/67) healed in an average treatment time of 168 days • Long bone fractures: 89% (41/46) healed in an average time of 185 days Intent to Treat: • All fractures: 85% (70/85) healed
	95% CI	
Statistical test	**Type**	Fishers exact test
	p value	0.00001
Comments		Mean fracture age of the 67 patients was 39 ± 6.2 months. Average number of prior failed surgeries = 2.0 Long bone non-union fractures: 89% (41/46) (p=0.05) healed in an average time of 185 days The study did not include any cases that were malaligned, grossly instable, actively infected or that had extensive bone loss.

Figure 4. Statistical analysis chart from Gebauer 2005[16]

Table 4. Effectiveness summary for the study group and its subsets A and B and for the intention-to-treat analysis

	Total	Healed	Failed	% Healed	*p* value*
Study group:	67	57	10	85	0.00001
Subset A (completely validated by PIs from radiographs)	48	41	7	85	0.00001
Subset B (documented by PIs with clinical records, fracture age, and long-term follow-up)	19	16	3	84	0.00001
Intention-to-treat analysis (all cases including excluded cases)	85	70	15†	82	0.00001

* *p* value for comparison against prior orthopedic treatment results of 100% failed cases;
† Combines 10 failed and 5 incomplete cases into "Not healed" outcome for intention-to-treat analysis.

Table B9.4 Jingushi 2007[17] Outcomes

Study name		**Jingushi 2007**
Size of study groups	**Treatment**	72 fractures
	Control	N/A
Study duration	**Time unit**	2-7 months treatment time
Type of analysis	**Intention-to-treat/per protocol**	Probably best described as PP
Outcome	**Name**	Fracture healing
	Unit	Yes/No
Effect size	**Value**	75% healed
	95% CI	
Statistical test	**Type**	N/A
	p value	
Other outcome	**Name**	Analysis of impact of background factors on healing rate
	Unit	Odds ratio
Effect size	**Value**	There was a significant relationship between the union rate and the time from the most recent operation to the beginning of LIPUS treatment ($P < 0.01$), the time from the fracture to the beginning of treatment ($P < 0.04$), and the time after the beginning of treatment that radiological improvement was first observed ($P < 0.02$)
	95% CI	
Statistical test	**Type**	Log regression analysis
	p value	See above
Comments		When LIPUS treatment was started within 6 months of the most recent operation, the union rate was approximately 90%. In contrast, when it was started after 12 months, the union rate was less than 65%

Table B9.5 Lerner 2004[18] Outcomes

Study name		**Lerner 2004**
Size of study groups	**Treatment**	18 fractures
	Control	N/A
Study duration	**Time unit**	14 to 52 weeks treatment time and up to 6 years follow up
Type of analysis	**Intention-to-treat/per protocol**	ITT and PP
Outcome	**Name**	Fracture healing; time to healing
	Unit	Yes/No; weeks
Effect size	**Value**	94% healed (PP), 89% (ITT) in a mean of 26 weeks.
	95% CI	
Statistical test	**Type**	Not known
	p value	
Comments		

Table B9.6 Mayr 2000[19] Outcomes

Study name		**Mayr 2000**
Size of study groups	**Treatment**	42 fractures in prospective study
	Control	Prospective registry 1317
Study duration	**Time unit**	Follow up was seen up to 755 days
Type of analysis	**Intention-to-treat/per protocol**	ITT
Outcome	**Name**	Fracture healing / time to healing
	Unit	% healed / days
Effect size	**Value**	See figure 5 for healing rates and times
	95% CI	Not known
Statistical test	**Type**	Not known
	p value	No significant differences seen between healing times and rates between study and registry patient groups
Comments		In the prospective study, delayed unions had an average fracture age of 150 days and healed in an average of 129 ± 2.7 days, with a healing rate of 91%. Nonunions had an average fracture age of more than 2 years and healed in an average time of 152 ± 5.3 days with a healing rate of 86%. None of these results were significantly different to those seen in the prospective registry of 1317 patients

Figure 5. Mayr 2000[19] (source NICE IPG374)

Abbreviations used: CI, confidence interval; NR, not reported; NS, not significant; RCT, randomised controlled trial; SD, standard deviation

Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Mayr E (2000)[7] **Case series (registry data)** Germany Recruitment period: 1994–1997 Study population: patients with delayed unions and non-unions n = **1317** Age: not reported Sex: not reported Patient selection criteria: patients with delayed unions, defined as healing 91–269 days after the fracture date and non-union, defined as failure of the healing process after 270 days. Technique: low-intensity pulsed ultrasound (daily 20 minute session, width 200µs, 1.5MHz sine waves, repetition rate 1 kHz and intensity 30 mW/cm^2). Follow-up (fracture age): **up to 755 days** Conflict of interest/source of funding: not reported	Number of patients analysed: **1317** **Type of fracture** / **Outcome** All types: Healing rate 89% (117/1317); Average healing time 131 ± 2.4 days; Average fracture age 312 ± 18.5 days Delayed unions: Healing rate 91% (862/951); Average healing time 124 ± 2.6 days; Average fracture age 151 ± 1.6 days Non-unions: Healing rate 86% (314/366); Average healing time 152 ± 5.3 days; Average fracture age 755 ± 62.8 days	None reported	**Follow-up issues** Loss to follow-up was not reported. **Study design issues** Method used to confirm healing was not reported.

Table B9.7 Nolte 2001[20] Outcomes

Study name		**Nolte 2001**
Size of study groups	**Treatment**	29 fractures reported 21 long bone fractures (tibia, femur, fibula, humerus, ulna, radius)
	Control	21
Study duration	**Time unit**	Average healing time was 152 days. Patients followed up at an average of 62 weeks from the healed date (range 30-110 weeks)
Type of analysis	**Intention-to-treat/per protocol**	Per Protocol and Intent to Treat
Outcome	**Name**	Fracture Clinically and Radiologically Healed; time to healing
	Unit	Yes / No ; weeks
Effect size	**Value**	Per Protocol: • All fractures: 86% (25/29) healed in an average treatment time of 22 weeks • Long bone fractures: 86% (18/21) healed in an average time of 22 weeks Intent to Treat: • All fractures: 80% (33/41) healed in an average treatment time of 20 weeks • Long bone fractures: 86% (25/29) in an average treatment time of 20 weeks
	95% CI	
Statistical test	**Type**	One sided test, not specified
	p value	Healed rate, significantly better ($p < 0.0001$) when compared with the assumed rate of 5% for the prior failed treatment period
Other outcome	**Name**	Healing rates and times were stratified by age, gender, concomitant disease, bone location, fracture age, prior last surgery interval, non-union type, smoking habits, and fixation before and during treatment
	Unit	
Statistical test	**Type**	For stratification analyses, the Kruskal-Wallis test was used for contrasting heal time and fracture age and the Fisher's exact test was used for healed rates. The Kruskal- Wallis analysis was a two-sided 99% confidence level Monte Carlo estimate of the

		exact p value computed
	p value	Not significant except in smokers
Comments		Average age of the non-unions treated was 1.2 years, average number of prior surgeries = 1.4. Stratification of the healed and failed outcome for age, gender, concomitant disease, bone location, fracture age, prior last surgery interval, non-union type, smoking habits, and fixation before and during treatment showed a significant difference only in the smoking habit strata.

Table B9.8 Romano 1999[21] Outcomes

Study name		**Romano 1999**
Size of study groups	**Treatment**	15 fractures reported 13 long bone fractures (tibia, femur, humerus)
	Control	NA
Study duration	**Time unit**	Average healing time was 152 days. Patients followed up at an average of 62 weeks from the healed date (range 30-110 weeks)
Type of analysis	**Intention-to-treat/per protocol**	NA
Outcome	**Name**	Consolidation
	Unit	Consolidation, Non-consolidation, progression of callus but necessity of new surgery, still in treatment
Effect size	**Value**	Of the 13 long bone fractures, 8 consolidated, 1 had progression of callus but required a new surgery, 1 non-consolidation, and 3 patients are still in treatment
	95% CI	NA
Statistical test	**Type**	NA
	p value	NA
Comments		"our experience demonstrates that this simple and non-invasive treatment, requiring only 20 minutes a day of therapy at home, must be taken under consideration before performing surgical interventions that are both more complex and expensive for the patient and associated heath care organizations."

Outcomes from published and unpublished studies – SURGERY

Table B9.a Cacchio 2009[14] Outcomes

Study name		**Cacchio 2009**
Size of study groups	**Treatment**	42 (Shockwave group 1) + 42 (shockwave group 2)
	Control	42 surgery (group 3)
Study duration	**Time unit**	24 months
Type of analysis	**Intention-to-treat/per protocol**	Intention to treat
Outcome	**Name**	Healed / not healed
	Unit	Yes / no
Effect size	**Value**	Healing rates at 6 months: 70% of the thirty-seven patients in Group 1, 71% of the thirty-eight in Group 2 , 74% of the thirty-eight in Group 3. There was no significant difference in the rate of successful treatment among the three groups (chi square = 0.08, p = 0.95).
	95% CI	
Statistical test	**Type**	A two-sided chi-square test was carried out to compare the success rate at six months in the extracorporeal shock-wave therapy groups with that in the surgery group; the level of significance was 5%.
	p value	
Other outcome	**Name**	DASH and LEFS questionnaires and visual analogue pain scale
	Unit	
Effect size	**Value**	At three and six months, the pain, DASH, and LEFS scores were significantly better in Groups 1 and 2 than in Group 3
	95% CI	
Statistical test	**Type**	A two-way analysis of variance, with the group as the between-subjects factor and time as the within-subjects factor, was used to assess whether there were significant differences in the DASH, LEFS, and visual analogue scale scores among the three groups and between the preoperative and scheduled follow-up time points within each group. A Tukey post hoc comparison was used to assess significant differences between mean values when a significant main effect and interaction were found. The model for all of the analyses included the main effects of treatment, time, and the treatment · time interaction. Significance levels for multiple comparisons were adjusted with the Bonferroni

		procedure. The level of significance was set at $p < 0.05$. It was determined that, in order to detect a difference of 30% in the success rates with a power of 80%, the necessary sample size was thirty-five subjects in each group. Success rates were assumed to be 65% and 95% in the extracorporeal shockwave therapy groups and surgery group, respectively.
	p value	
Comments		

Table B9.b Friedlaender 2001[15] **Outcomes – see next page**

Study name		Friedlaender 2001
Size of study groups	**Treatment**	61 – surgery + rhOP-1
	Control	61 - surgery
Study duration	**Time unit**	24 month follow up. Primary end point at 9 months
Type of analysis	**Intention-to - treat/per protocol**	Intention to treat
Outcome	**Name**	Healed / not healed at 9 months
	Unit	Yes / No
Effect size	**Value**	Bridging in at least three of four views—resulted in radiographic healing rates in both groups: 62% of the OP-1 recipients and 74% of the autograft-treated group Clinical success in this study required a patient to be fully weight-bearing with less than severe pain at the fracture site. By these criteria, at 9 months following surgery, 81% (51 of 63) of the OP-1-treated group and 85% (52 of 61) of the autograft-treated group were considered to have successful outcomes
	95% CI	
Statistical test	**Type**	Chi-square test and a p value of ≤ 0.05 was considered statistically different.
	p value	p = 0.158, or radiographic healing p = 0.524 for clinical healing
Other outcome	**Name**	Length of stay, operative time, and operative blood loss
	Unit	Days, hours, ml
Effect size	**Value**	The trend toward longer operative and hospitalization times and the statistically significant increased blood loss (p = 0.049) in the autograft-treated group were imposed by the nature of a bone donor recovery site.
	95% CI	
Statistical test	**Type**	Differences in the frequency of adverse events were evaluated by a two-tailed chi-square or Fisher's exact test, as appropriate. Comparison of the means of operative blood loss was performed with a Student t test. For the length of stay and operative time, Wilcoxon rank sum tests were performed, which are appropriate for variables that are not normally distributed. A p value of ≤ 0.05 for analysis of safety variable was considered significant.
	p value	See effect size
Comments		

Table B9.c Bellabarba 2002[22] Outcomes

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

Table B9.d Birjandinejad 2009[23] Outcomes

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

Table B9.e Khalil 2010[24] Outcomes

Study name		**Khalil 2010**
Size of study groups	**Treatment**	21
	Control	N/A
Study duration	**Time unit**	12 -36 months - average follow up 22 months
Type of analysis	**Intention-to-treat/per protocol**	ITT
Outcome	**Name**	Healed /not healed; Time to healing
	Unit	Yes / no
Effect size	**Value**	90.5% healed at an average of 9.6 weeks (range 8 – 24)
	95% CI	N/A
Statistical	**Type**	Not known

test	**p value**	N/A
Other outcome	**Name**	Functional outcome
	Unit	Broberg – Morrey scoring system
Effect size	**Value**	20 / 21 patients had good to excellent results
	95% CI	N/A
Statistical test	**Type**	Not known
	p value	N/A
Comments		All cases included had implant failure associated with the non-union. 4 patients considered to have achieved union required further surgical intervention

Table B9.f Lin 2010[25] Outcomes

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

Table B9.g Livani 2010[26] Outcomes

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

Table B9.h Razaq 2010[27] Outcomes

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

Table B9.i Ring 1997[28] Outcomes

Study name		**Ring 1997**
Size of study groups	**Treatment**	42
	Control	N/A
Study duration	**Time unit**	Maximum follow-up 66 months, mean 33
Type of analysis	**Intention-to-treat/per protocol**	ITT
Outcome	**Name**	Healed / not healed – time to healing
	Unit	Yes / no – months
Effect size	**Value**	97% healed – average time to healing = 6 months. However, three of these patients required secondary surgical intervention
	95% CI	N/A
Statistical test	**Type**	Not known
	p value	N/A
Other outcome	**Name**	Range of movement
	Unit	
Effect size	**Value**	All patients had full mobility at the hip and ankle, and 31 (72%) regained full movement at the knee. Seven had residual limitation of knee flexion and two lacked 10° of extension. One patient with severe limitation of knee flexion required quadriceps lengthening, which gave a range of 1° to 60° at the latest follow-up. One patient had residual knee instability.
	95% CI	N/A
Statistical test	**Type**	Not known
	p value	N/A
Comments		Patients with previous infection were treated. Two patients with previous infection had recurrence. One of the fractures failed to unite; the other healed, but developed a draining fistula. Another patient with persistent non-union had a second bone-grafting procedure 12 months after the insertion of a wave plate and the fracture had united by 18 months. Two of the four patients in whom a large bony defect had been treated with a vascularised fibular graft required an additional grafting procedure before union.

Table B9.j Wu 2003[29] Outcomes

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

7.6.2 Justify the inclusion of outcomes in table B9 from any analyses other than intention-to-treat.

Not applicable

7.7 Adverse events

In section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

7.7.1 Using the previous instructions in sections 7.1 to 7.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

Please see 7.7.2, plus appendices 10.1 and 10.2

7.7.2 Provide details of all important adverse events reported for each study.

No device related adverse events were reported in the EXOGEN studies

Adverse events across patient groups in surgery studies

Cacchio 2009[14]

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

Friedlaender 2001[15]

All patients in the autograft group had pain at the donor site following the operative procedure, and more than 80% judged their postoperative pain as moderate or severe. Furthermore, more than 20% of patients had persistent pain, mild or

moderate in nature, at their 6-month visit, and approximately 13% had persistent pain at the donor site 12 months following the operative procedure.

Forty-four percent of both groups had serious adverse events, none of which were considered related to the OP-1 implant or the bone autograft. Osteomyelitis was reported at the fracture site in 21% of patients following treatment with bone autograft but in only 3% of those receiving OP-1 (p = 0.002).

Bellabarba 2002[22]

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

Birjandinejad 2009[23]

No serious adverse events were reported

Khalil 2010[24]

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

Lin 2010[25]

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

Livani 2010[26]

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

Razaq 2010[27]

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

Ring 1997[28]

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

Wu 2003[29]

No deep infections or other complications were reported

7.7.3 Describe all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude).

A 1 year search (April 2011 – April 2012) of the MAUDE database report four (4) recorded instances of EXOGEN adverse event reporting. In the same period approximately 55,000 EXOGEN devices have been used by patients in the USA.

There were three (3) instances of skin complaints:

The EXOGEN IFU states: “Some patients have experienced mild skin irritation caused by skin sensitivity to the coupling gel. Resolution can be obtained by a change of coupling medium to mineral oil or glycerin.”

There was one (1) report of increased chest pain due to potential interference with cardiac pacemaker, which is also a stated precaution in the IFU

The EXOGEN IFU states “The operation of active, implantable devices, such as cardiac pacemakers may be adversely affected by close exposure to the EXOGEN device. The physician should advise the patient or other person in

close proximity during treatment to be evaluated by the attending cardiologist or physician before starting treatment with the EXOGEN device."

7.7.4 Provide a brief overview of the safety of the technology in relation to the scope.

The EXOGEN IFU states, "No device related adverse reactions or medical complications related to the use of this device were reported during the clinical studies."

There are no safety concerns regarding EXOGEN in relation to the scope

7.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

7.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Evidence synthesis and meta-analysis was not considered suitable for the studies identified in the scope of this submission

7.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

Evidence synthesis is not considered appropriate for the following reasons:

- Controls are either absent or too varied
- Outcome measurements are too varied
- Patient cohorts and fracture types are too varied
- Type of surgical intervention is too varied
- Assumed healing rates in non-unions are unsafe and vary from study to study
- The studies vary widely with regard to the type of fracture treated
- Baseline characteristics of patients are too varied

Qualitative Review

Overall, within the limitations of the patient population and controls that can be applied the outcomes for the studies for EXOGEN show a consistent heal rate and time to healing with no adverse events related to the device.

Surgical intervention shows consistent heal rates and time to healing across a variety of diagnoses and interventions. Major complications are reported. Potential for bias in the surgical clinical studies is much higher. The studies are often case series by experts in that field and may not be reproducible by other surgeons. There is less statistical rigour applied.

7.9 Interpretation of clinical evidence

7.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology.

Principal findings:

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

Roussignol (2012)[7] retrospective case series of 58 non-unions demonstrated a heal rate of 88% and corroborates that the EXOGEN device is most effective when the fracture is stable and well aligned.

EXOGEN treatment has no known device related adverse events

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

from the searches performed. Brinker (2007)[30] corroborates these findings in a review of exchange nailing studies.

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

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

7.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

Delayed unions

Strengths – Level 1 evidence showing significant evidence that EXOGEN treated patients had greater progression to healing

Limitations - For ethical reasons, patients could not be followed to full healing and treatment was limited

Non-unions

Strengths – high rates of healing in patients who had undergone multiple previous surgical interventions, across a variety of bones and a variety of diagnoses

Limitations – no control group, no blinding, no randomisation of treatment. Large variety of fracture types and locations

7.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and system-benefits described in the scope.

The evidence base offers clear evidence that EXOGEN, when used in the correct patient type is highly relevant to the claimed benefits in the scope, namely:

- A reduced time to healing compared with surgery, particularly with reference to delayed union.
- The avoidance of surgical intervention to achieve comparable clinical outcomes. Similar healing rates and time to healing are reported.
- Use of the EXOGEN ultrasound bone healing system may reduce the need for high cost surgical intervention. Assuming the heal rates reported, EXOGEN has the potential to reduce 86% of the operations that are currently performed on stable, well-aligned delayed or non-union fractures
- There is less clarity regarding the impact of EXOGEN on a quicker return to weight bearing and normal daily living as compared with surgery.

Section C will address:

- Improved treatment accessibility with a therapy that can be self-administered in a home environment, and; A reduction in costs due of a reduction in out-patient care, enhanced recovery and speedier return to work and normal living.

7.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

Patients were all adults. No patients with fresh fractures were included in the study populations. All types of non-unions were treated.

7.9.5 Based on external validity factors identified in 7.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

EXOGEN would be suitable for

- Patients who are skeletally mature
- Patients with delayed unions which are stable and well aligned
- Patients with all types of non-union which are stable and well aligned
- Patients who have, or have not undergone previous surgical procedures

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

8 Existing economic evaluations

8.1 Identification of studies

8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

A systematic approach to identifying clinical and background literature was followed:

- PubMed searches were performed using search terms relevant to the scope, please refer to Section 10, Appendix 3

- The publications were identified using the Pubmed search terms, then additional selection criteria were identified and used to screen articles.

- Identified literature from the PubMed searches was used to source additional references and background literature relating to the economics of treatment of delayed or non-union fractures in long bones.

PubMed covers the vast majority of published clinical studies and was used to identify relevant studies. Searching the cited references in these identified articles for additional supportive studies results in a robust search strategy that identifies, with high reliability, all material relevant to the scope.

Internal Smith & Nephew databases were also searched, together with a Google search to identify any unpublished material, not previously cited in the published references determined from the initial search.

The results of all search methods derived very similar results to those presented by Button (2009)[31]

Final publication selections were made with reference to the scope and relevance to UK clinical practice and costs.

The difficulties in producing high quality data for the indications within the scope have been previously discussed in section 7.1.1.

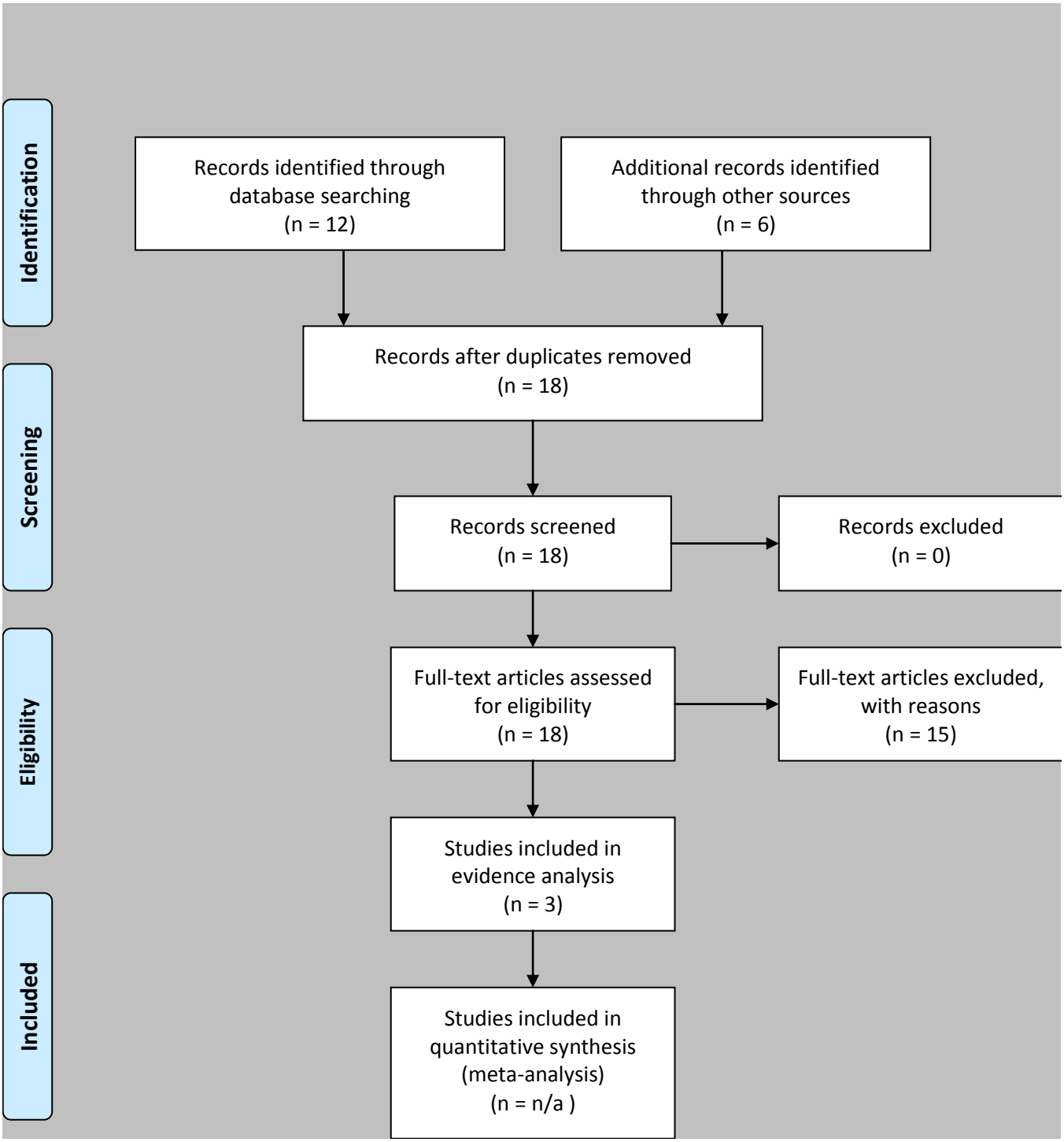
8.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C1 Selection criteria used for health economic studies

Inclusion criteria	
Population	Adults with delayed or non-union fractures of long bones
Interventions	EXOGEN / Surgery
Outcomes	Healing
Study design	Any
Language restrictions	English
Search dates	1992 - 2012
Exclusion criteria	
Population	Under 16 years old
Interventions	All outside scope technology and comparator
Outcomes	N/A
Study design	N/A
Language restrictions	Non-English
Search dates	Pre 1992

8.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Figure 6 Economics literature search PRISMA flow diagram



8.2 Description of identified studies

8.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table C2.

. Table C2.1 Summary list of all evaluations involving costs- EXOGEN

Study name (year)	Location of study	Summary of model and comparators	Patient population	Costs	Patient outcomes	Results
Taylor (2009)[32]	UK cost modelling applied to data review	A Markov model, with monthly cycle length, was constructed in Excel. In each month the fracture is in one of a number of discrete health states: unhealed (not infected), unhealed (osteomyelitis), non-union, healed. Monthly probabilities of healing (for fresh fractures and non-unions) and osteomyelitis were derived from estimates of non-union rates, time to healing and incidence of	Studies of tibial fractures in adults which were classified as fresh fractures, fractures at risk (i.e. those unlikely to heal within 10 -13 weeks) and non-unions were included in the review	Costs included in the model comprise interventions costs (surgery or Exogen), theatre time, hospital stay and post-operative costs, such as O/P consultations, GP visits and the need for assistive devices. **Fractures at risk:** The cost per patient with EXOGEN is £3494 to heal 95.4% of patients in 12-months (including non-unions subsequently healed). This compares with	The primary outcome of the analysis was fracture healing. Infections were also reported. **Fractures at risk:** EXOGEN - 95.4% of patients healed in 12-months IM nailing 91.5% healed in 12 months **Non-unions** EXOGEN 86% heal rate Surgery 86% heal rate	For patients at particular risk of non-union the combination of ultrasound and casting is a dominant option compared with IM nailing or casting alone, assuming that the addition of ultrasound improves healing by more than 25% compared with casting alone. The literature is consistent with an improvement of around 60%. Non-unions where the nature of the fracture allows, the most cost-effective strategy for non-unions is to postpone surgery and try a course of ultrasound first. Expected cost with

		complications reported in original research or systematic reviews of published evidence. Comparators were casting, casting plus EXOGEN and IM nailing for fractures at risk. Surgery versus EXOGEN for non-union		the cost of IM nailing (£6264 to heal 91.5%) **Non-unions** Expected costs per patient are £6718 (surgery) and £3926 (EXOGEN).		surgery is £6718 compared with £3926 for ultrasound.

Table C2.2 Summary list of all evaluations involving costs- Surgery

Study name (year)	**Location of study**	**Summary of model and comparators**	**Patient population**	**Costs**	***Patient outcomes***	***Results***
Kanakaris (2007)[33]	Leeds, England	Review of literature applied to UK costs to deal with Humeral,(HN) Tibial(TN) and Femoral Non-union(FN) No comparator	Patients with long bone non-unions	Best case scenario costs, with indirect costs removed are as follows: For a HN the cost is estimated around the sum of £3,111 for FN around	The study assumes best case outcomes, that is surgery is 100% successful at 6 months, and has zero complications, therefore requiring no further resource utilisation	N/A There is no comparative group and so there is no annual cost saving, or cost per QALY stated

				£3,440 and for TN around £3,266.		
Study name (year)	**Location of study**	**Summary of model and comparators**	**Patient population**	**Costs**	***Patient outcomes***	***Results***
Patil (2006)[34]	Middlesbrough, England	Review of 41 complex non-unions managed surgically. No comparator	Patients with femoral and tibial non-unions	Mean cost of managing these fractures was £29,204	Patient outcomes measured were by the ASAMI (Association for the Study and Application of the Methods of Ilizarov) scoring system: **Bone results** 14 Excellent Union, no infection, deformity < 7°, limb-length discrepancy < 2.5 cm 17 Good Union + any two of the following: absence of infection, < 7° deformity and limb-length inequality of < 2.5 cm 4 Fair Union + only one of the following: absence of infection, deformity < 7° and limb-length inequality < 2.5 cm 6 Poor Nonunion/re-fracture/union + infection + deformity > 7° + limb-	N/A There is no comparative group and so there is no annual cost saving, or cost per QALY stated

					length inequality > 2.5 cm **Functional results** 14 Excellent Active, no limp, minimum stiffness (loss of < 15° knee extension/< 15° dorsiflexion of ankle), no reflex sympathetic dystrophy (RSD), insignificant pain 14 Good Active, with one or two of the following: limp, stiffness, RSD, significant pain 2 Fair Active, with three or all of the following: limp, stiffness, RSD, significant pain 2 Poor Inactive (unemployment or inability to return to daily activities because of injury) 2 Failures Amputation	

8.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table C3.

Quality assessment of health economic studies – EXOGEN
Table C3.1 Taylor (2009)[32]

Study name	**Taylor 2009**	
Study design		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	In terms of cost to the NHS and bed days.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	NHS perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Not clear	States clinical pathways are based on literature review and interviews with surgeons
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Systematic reviews and published literature
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Reference to previously published systematic review
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	NA	Cost effectiveness analysis, no attempt to attribute utility values to health states.

13. Were the details of the subjects from whom valuations were obtained given?	NA	
14. Were productivity changes (if included) reported separately?	NA	
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	Yes	Note: limited space in manuscript restricted reporting. Full details in model.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	See above
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	NA	
20. Were details of any model used given?	Yes	Markov model
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Patients can be categorised into discrete health states (healed, unhealed) and have a risk of developing adverse outcomes (osteomyelitis)
22. Was the time horizon of cost and benefits stated?	Yes	12 Months.
23. Was the discount rate stated?	NA	
24. Was the choice of rate justified?	NA	
25. Was an explanation given if cost or benefits were not discounted?	Yes	Model adopted a one-year time horizon
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	Confidence intervals for some parameters not available (e.g. costs based on HRGs). Effectiveness varied using a threshold analysis that identified cost neutrality.
27. Was the approach to sensitivity analysis described?	Yes	One way and two way conducted. Limited reporting in the manuscript.
28. Was the choice of variables for sensitivity analysis justified?	Yes	Effectiveness and costs
29. Were the ranges over which the parameters were	Yes	% change in effectiveness as part of the threshold analyses

varied stated?		
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	Incremental cost per healed fracture. No cost utility analyses presented.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Quality assessment of health economic studies – surgery

Table C3.2 Kanakaris (2007)[33]

Study name	**Kanakaris 2007**	
Study design	**Literature review**	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	The aim of this study is to review the existing evidence of the average economic cost of treatment of tong-bone fracture non-unions, and also to provide clear guidelines as to which parameters an economic analysis of the treatment schemes for non-unions should incorporate.
2. Was the economic importance of the research question stated?	Yes	As above
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	The viewpoints were from both the hospital and a societal perspective

4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	N/A	
5. Were the alternatives being compared clearly described?	N/A	
6. Was the form of economic evaluation stated?	Yes	Direct medical costs and indirect costs to the healthcare system.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Babhulkar S, Pande K. Nonunion of the diaphysis of long bones. Clin Orthop Relat Res 2005; 431:50-6.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Total cost per procedure
12. Were the methods used to value health states and other benefits stated?	No	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	As a "best-case scenario" for each of the different fracture sites - HN, FN, TN we consider the aseptic case where by utilising the gold standard method of treatment, according to the literature, the minimal antibiotic

		prophylaxis of 3 doses, a standard period of thromboprophylaxis, a standard number (5) of outpatient visits and investigations, a minimum number of physiotherapy sessions (10), clinical, radiological heating and return to work occurs at an average time of 6 months post non-union operative intervention. No additional complications or interventions are included, and the functional outcome is assumed to be optimal.
18. Were currency and price data recorded?	Yes	Pounds sterling
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	No	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
22. Was the time horizon of cost and benefits stated?	Yes	6 months from the surgical intervention
23. Was the discount rate stated?	N/A	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	
28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	

31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	For a humeral fracture non-union, treated with compression plate fixation and grafting (gold standard) with a length of in-hospital stay of 4 days, outpatient clinic visits and when the union is achieved at the mean reported time of 4 months, the best-case scenario cost is approximately £15,566. In a best-case scenario of femoral or tibial fracture non-union with exchange nailing the cost is estimated at £17,200 and £16,330 respectively.
34. Did conclusions follow from the data reported?	Yes	The authors have confirmed that the actual economic burden of a treatment method is a complex entity and should not be judged from implant costs alone.
35. Were conclusions accompanied by the appropriate caveats?	Yes	Patients treated for a long-bone fracture non-union are submitted to frequent hospital admissions and a number of interventions. The lengthier the treatment of a non-union, the higher is also the risk of developing additional complications, and of course the greater the financial burden to the healthcare system.
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table C3.3 Patil (2006)[34]

Study name	**Patil 2006**	
Study design	**Retrospective case series**	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	The aim of this study was to assess the functional and radiological outcome in patients with complex femoral and tibial non-union treated by the Ilizarov technique, as well as the costs involved.

2. Was the economic importance of the research question stated?	Yes	It is important to evaluate the outcome and cost of this treatment in view of the considerable investment in time and resources by both the patient and the health service.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	The viewpoint was from direct costs to the treating hospital
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	N/A	
5. Were the alternatives being compared clearly described?	N/A	
6. Was the form of economic evaluation stated?	Yes	The cost of treatment was calculated for each patient using the estimate for the year 2004-2005 provided by the Finance Department at the treating hospital.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	N/A	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	The results were from the treating clinician's own data using the ASAMI criteria for outcome of non-union
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Please refer to the study, table III p.930
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	
12. Were the methods used to value health states and other benefits stated?	N/A	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported	Yes	Return to work was recorded

separately?		
15. Was the relevance of productivity changes to the study question discussed?	Yes	**Social benefits and compensation**. All 18 patients who lost employment were on disability or incapacity benefits. Some received large compensation awards. Two patients commented that they 'did not bother to look for work'. Therefore using employment as a benchmark for assessing functional outcome may not necessarily reflect the true outcome, particularly in countries where people receive substantial unemployment and incapacity benefits.
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Please refer to the study, table V, p.930
18. Were currency and price data recorded?	Yes	Pounds sterling
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
22. Was the time horizon of cost and benefits stated?	Yes	14.1 months
23. Was the discount rate stated?	N/A	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	N/A	
28. Was the choice of	N/A	

variables for sensitivity analysis justified?		
29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	N/A	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	Most complex nonunions end up in large centres. At present, in the United Kingdom there is no system of reimbursement to adequately support limb reconstruction in these centres. We hope that our cost data will help clinicians and managers resolve this. The results in our view justify the costs of this treatment.
34. Did conclusions follow from the data reported?	Yes	The average cost of treatment for limb reconstruction of tibial non-unions using the Ilizarov method has been reported to be $59 213 (approx. £33 752), which is similar to our costs. Despite this, the results are satisfying both for the patient and for the surgeon.
35. Were conclusions accompanied by the appropriate caveats?	Yes	Several factors were identified that may confound results **Delay in referral**. We recommend that all patients with complex non-union of femoral and tibial fractures should be referred to a limb reconstruction centre by six months after injury. **Social benefits and compensation.** Using employment as a benchmark for assessing functional outcome may not necessarily reflect the true outcome, particularly in countries where people receive substantial unemployment and incapacity benefits. **Severity of injury or associated injury**
36. Were generalisability	No	

issues addressed?		
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1 Description of the de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

A de novo analysis was developed, building on the published economic evaluation by Taylor (2009)[32]. Further cost analysis is required because:

- Costs in the published models are outdated and there is recently published relevant clinical data that was not included.
- There is only published data for highly complex surgical cases and the de novo cost analysis of the relevant interventions is more consistent with the scope and shows the costs associated with current clinical pathways.
- The de novo cost analysis aligns with existing NICE guidance CG124[8]

In updating the parameter values to reflect recently published evidence every attempt was made to adopt a conservative approach and the changes made in the de novo cost analysis are not believed to introduce any systematical bias in favour of EXOGEN compared to the published evidence.

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

The scope concerns skeletally mature patients with delayed or non-unions of long bones.

Given the level of complexity in creating a cost model for each potential fracture site and surgical management option, for the purposes of this submission, the de novo models are based on the following scenarios:

Tibial non-union - assuming that the fracture is stable and well aligned, the economic comparison is between further surgical intervention or treatment with EXOGEN 4000+. The model and the results are reported as either EXOGEN or Surgery

Tibial delayed union – the original fracture has been treated with an IM nail. The nail remains in situ with no immediate further surgical intervention. The economic comparison is made between treatment with EXOGEN Express, or no further surgical intervention (i.e. routine observation over time). The model and results are reported as surgery plus EXOGEN, or surgery alone.

The tibia is a commonly fractured long bone and is associated with a high incidence of healing problems. This has been extensively reported and consequently there is a robust data set upon which an analysis can be based.

Technology and comparator

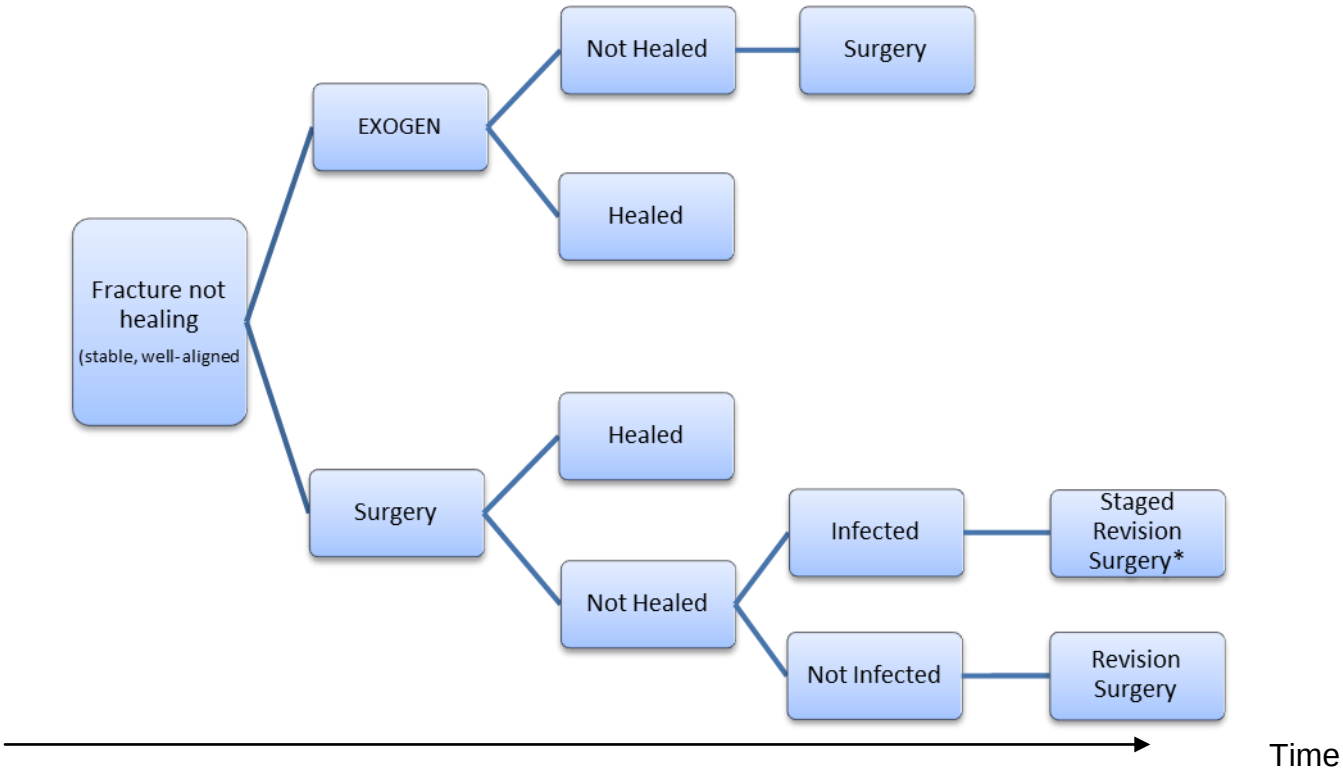
9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

Not applicable

Model structure

9.1.4 Provide a diagram of the model structure you have chosen.

Figure 7. Schematic illustration of the patient pathways



Model description

The model adopts a simple Markov approach, based on a monthly cycle with a time horizon of 1 year. The model assumes that patients who do not respond to their initial treatment may undergo a maximum of one additional surgical procedure per patient per year. The schematic above provides an illustration of the possible pathways that patients may follow in the model.

*Staged revision involves treatment with IV antibiotics, removal of metalwork, debridement of affected tissues and stabilisation. Once the infection has been eradicated, revision surgery is undertaken. Cierney (2003)[37] Cost details are outlined in table C8

9.1.5 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

The chosen model aligns exactly with the proposed and existing pathways of clinical care in 3.3. A Markov approach was considered appropriate as patients can be categorised into distinct health states. The one year time horizon is adopted as a pragmatic assumption, as required in the scope.

9.1.6 Provide a list of all assumptions in the cost model and a justification for each assumption.

In both models, all assumptions made are considered to be conservative and validated by expert opinion. None of the assumptions made are intended to introduce bias in favour of EXOGEN.

Non-union

- In the case of stable, well-aligned fractures, healing rates and healing times are assumed to be equivalent for both EXOGEN and surgery in the base case, as demonstrated in the clinical evidence section 7.9.1.

- Infection rates in the EXOGEN group are assumed to be zero, as shown in the clinical evidence 7.9.1; in the surgical group infection rates are assumed to be 1.4% in the base case, ref Health Protection Agency[38], however, this rate has been shown to be 5.18% (3.7 times higher) in high risk patients such as smokers, Castillo (2001)[39] and 4.95% in the over 65 age group, Taylor (2009)[32].

- Average length of bed stay for surgery is assumed to be 4.9 days, ref HES online 2010/11 data for W28.1 (Application of internal fixation to bone, NEC)

- In the EXOGEN group, it is assumed that only one additional surgery will be offered in a 1 year time frame if the treatment has not achieved healing of the fracture.

- In the case of long bone deep infection (osteomyelitis), it is assumed that a staged revision procedure is performed, based on expert opinion. See table C.8 for cost breakdown and assumptions.

- It is assumed that patients with osteomyelitis are administered intra-venous (I.V.) antibiotics and are not switched to an oral administration route. (ref Trust antibiotic protocols)[43,44], I.V. antibiotic treatment regime involves dosing every 6 hours and close monitoring which is difficult to manage in a community setting. Therefore it is assumed that patients are kept in hospital for the duration of this treatment.

- It is very difficult to determine the average length of time that a patient will require I.V. antibiotics. Based on product prescribing information and expert opinion, 3 weeks is assumed as the minimum length of time that this treatment is required.

- Average theatre time for non-union surgery is assumed to be 3 hours – expert opinion.

- Heal rates for EXOGEN assume that it is only those patients who have stable, well - aligned fractures undergo EXOGEN treatment.

- It is assumed that all initial non-union surgical management includes the use of autologous iliac crest bone graft.

- The model assumes that infection lasts for a maximum of 2 months, but all costs associated with the treatment are incurred in the first month. In subsequent months, some monitoring costs may be incurred although this assumption can be changed in the model.

- Non procedure related costs (e.g. Physiotherapy, X-ray) are assumed to be the same in both treatment arms.

Delayed Union

- It is assumed that for both arms in the model, patient treatment pathways start with a surgical intervention to treat a fresh fracture.
- On diagnosis of delayed union it is assumed that the patient will either have an EXOGEN Express applied, or will receive no further treatment (observation only) until either a) bony union is achieved or b) non-union is established.
- Healing rates for delayed unions at 6 months are assumed to be a linear progression with those seen at 4 months. EXOGEN at 4 months = 66%, no further surgical intervention = 45%, reference Schofer (2010)[12]. This assumption is made in the absence of any other level 1 comparative healing rate data.

9.1.7 Define what the model's health states are intended to capture.

For both delayed union and non-union treatments, the health states captured are:

Healed

Not healed – not infected

Not healed – newly infected

(Cost of treating infection is captured at this point. The patient may remain infected for up to 2 months but costs assumed to be incurred only in month 1. This assumption can be changed in the model.)

9.1.8 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Table C4 Key features of model not previously reported

Factor	Chosen values	Justification
Time horizon of model	1 year	Consistent with scope and clinical data
Discount of 3.5% for costs	N/A	
Perspective (NHS/PSS)	NHS	Current NHS costs and data are readily identifiable and fully referenced. PSS costs are not captured within the data identified
Cycle length	Monthly	This is pragmatic as the patient is typically reviewed monthly and is unlikely to change health states in a shorter time period
NHS, National Health Service; PSS, Personal Social Services		

9.2 Clinical parameters and variables

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

Similar healing rates and similar time to healing of non-unions –derived from the following references clinical data identified in section 7- for surgical treatment [14, 15, 22 - 30] , and for EXOGEN [7,11,12 16 -21] were used in the de novo cost analysis. Healing rates of delayed unions treated with EXOGEN and sham control[12] were also used. The clinical data reported in section 7.7 also showed potential adverse events and complications associated with surgery, such as infection and the requirement for further surgical intervention. These have been quantified and costed using current UK data to make them relevant to the scope.

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

No

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

No

9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Yes, infection.

Infection rates were taken from table 1, p.7 of the HPA 2011 report.[38] Management of deep infection was taken from established practice, as described in Cierny(2003).[37]

Removal of metalwork after the fracture has healed was also considered as this is widely reported. However, as this is not routine practice with the vast majority of UK surgeons, Jamil (2008)[41] it was discounted from the analysis.

Other complications of surgery reported in 7.7 were deep and superficial DVT, poor range of movement and donor site pain (from harvesting bone graft). These were difficult to quantify and allocate cost, so have not been included in the analysis.

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Clinical advice was sought to validate some of the model inputs, such as estimates of resource use associated with the standard of care. However, no formal elicitation techniques were used and any assumptions derived from clinical advice were subject to sensitivity analyses.

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission.

Healing rate at 6 months for both EXOGEN and surgery was included from the clinical data reported in section 7.

For non-unions this was considered to be 86% in both arms, for delayed unions this was considered to be 69% for surgery and 92.8% for EXOGEN.

These absolute values were tested in the sensitivity analysis.

Infection rate for surgical intervention was included at 1.4%. Infection rates were taken from table 1, p.7 of the HPA 2011 report.[38] This rate has been shown to be 5.18% (3.7 times higher) in high risk patients such as smokers, Castillo 2001[39] and 4.95% in the over 65 age group, Taylor(2009)[32].

These ranges were also tested in the sensitivity analysis.

Infection rates from studies included in section 7 were not included. The HPA report[38] was felt to be a better source as it contains current data from UK hospitals.

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

The management of delayed unions and non-union in long bones covers a large range of fracture sites, as set out under the ICD-10 guidance. Each fracture may be managed from a range of surgical options detailed in the OPCS codes. Each combination will map to an individual tariff as set out in Appendix 5.

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

Codes for surgery are shown in Appendix 5.

At the time of submission there is no OPCS code for EXOGEN treatment. There is an outstanding request for a code, UID 1245 which was submitted in February 2011.

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

In addition to the search performed and detailed in 8.1.1, further searches of the following databases were performed to identify resources, measurement and costs:

ICD -10 database, OPCS database, DoH PbR road test tariff 2012-13, HES online, National Schedule of reference costs 2009 -10 for NHS Trusts, NICE guidelines CG124[8], BNF (cost of antibiotics), Internal company databases (costs of implants / devices)

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model

Please see 9.2.5

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

EXOGEN 4000+ (non-union)	= £2,562.50	+ VAT
EXOGEN Express (delayed union)	= £999.38	+ VAT

Both of the EXOGEN devices are regulated as single patient use. There are no additional costs for maintenance, training, consumables or others associated with their use. There is no additional resource needed for the application of the EXOGEN device as this takes place during routine out-patient follow-up.

There are no hidden costs with regard to the widespread adoption of EXOGEN treatment in the NHS. Minimal changes in clinical pathways are required and minimal implementation costs are likely to be incurred. .

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

Not applicable

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model.

Costs are derived from the de novo analyses and include the price /cost plus associated treatment costs. They are expressed as cost per patient, per year. Maintenance, consumables, training and other costs are either not applicable, or are captured in the price of the technology or comparator.

Table C5.1 Costs per treatment/patient associated with EXOGEN in the cost model – Non-Unions

Items	Value	Source
Total cost per treatment/patient /year	£4,647	Taylor(2009)[32] updated to reflect current costs

Table C5.2 Costs per treatment/patient associated with surgery in the cost model – Non-Unions

Items	Value	Source
Total cost per treatment/patient/year	£6,957	Taylor(2009)[32] updated to reflect current costs

Table C6.1 Costs per treatment/patient associated with EXOGEN + surgery in the cost model – Delayed Unions

Items	Value	Source
Total cost per treatment/patient/year	£4,290	Taylor(2009)[32] updated to reflect current costs

Table C6.2 Costs per treatment/patient associated with surgery alone in the cost model – Delayed-Unions

Items	Value	Source
Total cost per treatment/patient/year	£4,974	Taylor(2009)[32] et al updated to reflect current costs

Health-state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented in table C7. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

Note: the model adopts a bottom-up approach to deriving health state costs. For each health state, an estimate of the number of resources consumed is multiplied by the expected cost of each resource. As a result, a combination of sources are used, comprising PSSRU Unit Costs, NHS Reference Costs and expert opinion.

Healed – once a patient is healed, apart from one confirmatory X-ray, no further costs should be incurred.

Not healed – not infected. The value is the monthly average of the cost to perform routine investigations and post-operative treatment. If additional surgery takes place, this is costed as an event, rather than a health state, or monthly occurrence

Not healed – newly infected. The value reflects the cost of performing a staged revision surgical procedure which is incurred in the first month plus further routine resources, such as physiotherapy.

Table C7 List of health states and associated monthly costs in the economic models

Health states	Items	Value	Reference
Healed	**X-ray**	£70	Expert opinion
Not healed – not infected	O/P visit, wheelchair use, crutches, x-ray, physio	£255	Expert opinion, PSSRU, NHS Reference Costs
Not healed – newly infected	Cost of treating major infection, O/P visits, wheelchair use, crutches, x-ray, physio	£15037	Expert opinion, PSSRU, NHS Reference costs

Adverse-event costs

9.3.9 Complete table C8 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Table C8 List of adverse events and summary of costs included in the cost models

Adverse events	Items	Value	Reference
Deep Infection treatment by staged revision procedure, Cierny 2003	Removal of metalwork and debridement	£ 957 theatre costs	Assumed average 3 hours total operating theatre time £319 per hour - NICE CG124 costing template
	Stabilising temporary fixator	£1050	4 pin longitudinal fixator, Smith & Nephew UK price - personal communication
	Bed stay	£7,758	Total average 32.1 days, 21 days for IV antibiotic, plus 11.1 days post external fixation (W30.4) procedure £241.69 per day – NICE CG124[8]
	Antibiotics	£823	I/V Flucloxycillin 0.5g 1.63/vial (3 weeks) –source BNF
	External fixation procedure	£957 £14.50 £448 £2520	Assumed average 3 hours total theatre time Antibiotic prophylaxis Synthetic bone graft, average price from iDATA market report[42] Simple circular external fixation frame Smith & Nephew UK - personal communication
	Total	**£14,527**	

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Long term fracture management can involve multiple additional costs involved in the patient care, such as dealing with ongoing pain management, psychological issues, appropriate social care, occupational therapy,

physiotherapy and others. These are very difficult to quantify and vary greatly from patient to patient. These can be included or excluded in the model.

9.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Other complications of surgery reported in 7.7 were deep and superficial DVT, poor range of movement and, donor site pain (from harvesting bone graft). These were difficult to quantify and allocate cost, so have not been included in the analysis, but could present an opportunity to save resources if initial surgery had been avoided.

Long-term bed stay could also result in development of pressure sores and the avoidance of these is another area for cost saving.

Results of staged revision shows that in 94% of infected fractures the limb will be successfully salvaged – reference Salvana (2006).[40] Therefore there is also potential saving of costs associated with palliative care, or amputation in the patients whose limbs are not salvaged.

9.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

The model structure is assumed to be a fair representation of current clinical practice and there was limited benefit to varying any structural assumptions (e.g. time horizon etc.). One-way and two-way sensitivity analyses were conducted to explore parameter uncertainty around the effectiveness of the interventions (EXOGEN) and the comparator (surgery / observation), with additional analyses conducted around infection rates. Furthermore, sub-group analyses were performed to explore the cost effectiveness of treating populations at elevated risk of healing complications (such as smokers).

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Deterministic analyses were undertaken examining changes in the effectiveness of the intervention and the comparator. These analyses explored the incremental cost of EXOGEN compared to surgery when the

effectiveness of the intervention was reduced from the base-case, which was derived from a systematic review.

The values chosen were designed to investigate EXOGEN being 10% or 20% less effective than base case, thus providing ‘best case’ and ‘worst case’ type scenarios in the two-way analyses. Surgery was tested to investigate 5% or 10% greater effectiveness than base case. In the non-union analysis, a further variable of a higher infection rate was tested as this was seen to be a key driver in the initial investigation.

Further two-way sensitivity analyses were conducted which explored the incremental cost of EXOGEN, as the effectiveness of both the intervention and the comparator were varied, using the values above. This allowed for exploration of threshold values, at which point EXOGEN shows cost neutrality /saving, as well as extreme values. Full details of the sensitivity analyses are available in the models, although only limited analyses could be reported in the manuscript.

Rationale: Further sensitivity analyses of all parameter values showed effectiveness of EXOGEN and the comparator, together with infection rate to be the greatest drivers. The model was relatively insensitive to variation in all other parameter values. Costs of key events were reviewed, including extreme values, but these had a comparatively low impact.

9.4.3 Complete tables as appropriate to summarise the variables used in the sensitivity analysis.

Table C9.1.1 Variables used in one-way scenario-based deterministic sensitivity analysis – Non-Union

Variable	Base-case value	Range of values
Exogen heal rate	86%	77.4 – 86%
Surgery heal rate	86%	86 – 94.6%
Infection rate	1.4%	1.4 – 5.1%

Table C9.1.2 Variables used in one-way scenario-based deterministic sensitivity analysis – Delayed-unions

Variable	Base-case value	Range of values
Exogen + surgery heal rate	92%	73.6 – 92%
Surgery heal rate	69%	69 – 76%
Infection rate	1.4%	1.4 – 5.1%

Variables used in multi-way scenario-based sensitivity analysis – Non-union

In the multi-way scenario-based sensitivity analysis, EXOGEN heal rate, with values from 68% to 86%, versus surgery heal rates from 86% to 94.6% were analysed at infection rates of either 1.4% or 5.1%.

This gave 18 different scenarios

Variables used in multi-way scenario-based sensitivity analysis – Delayed union

In the multi-way scenario based sensitivity analysis, EXOGEN plus surgery heal rates from 92% to 73.6% and surgery alone heal rates from 69% to 76% were analysed, giving nine different scenarios. There is only one infection rate considered as the one-way sensitivity analysis showed little difference in impact of infection. This was as expected, due to both groups undergoing the same number of surgical procedures

9.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

Not applicable

9.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base-case analysis

9.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis..

Table C10.1 Base-case results, non- union

	Total per patient cost (£)
EXOGEN 4000+	£4,647
Surgery	£6,957

Table C10.2 Base-case results, delayed union

	Total per patient cost (£)
Surgery + EXOGEN Express	£4,290
Surgery + observation	£4,974

9.5.2

Report the total difference in costs between the technology and comparator(s).

Non-Union base case – if a fracture is stable and well – aligned, treating patients with EXOGEN 4000+ will save £2,310 per patient compared to surgery.

Delayed Union base case – treating patients with EXOGEN Express on diagnosis of delayed union will save £684 per patient compared with observation,

9.5.3 Provide details of the costs for the technology and its comparator by category of cost. .

The costs reported above include all costs incurred, covering the device/surgery costs and any other health service resources. The vast majority of the cost is derived from the intervention. As the interventions are one-off events – surgery or single use of the Exogen device – there are no further maintenance costs etc. Costs incurred in each health state can easily be identified from the model.

9.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state.

Not appropriate in this case. The total costs over the course of one year of treatment are presented.

If appropriate, provide details of the costs for the technology and its comparator by adverse event. Not appropriate in this case

Sensitivity analysis results

9.5.5 Present results of deterministic one-way sensitivity analysis of the variables described in table C9.1.1 and C9.1.2

Table C11.1 one-way scenario-based deterministic sensitivity analysis – Non-Union

Variable	Cost EXOGEN versus Surgery
Exogen heal rate – 86%	-£2,310
Exogen heal rate – 77.4%	- £1,879
Exogen heal rate – 68.8%	- £1,416
Surgery heal rate – 86%	-£2,310
Surgery heal rate - 90.3%	- £1,986
Surgery heal rate – 94.6%	- £1,654
Infection rate – 1.4%	- £2,310
Infection rate – 5.1%	-£3,076

Table C.11.2 one-way scenario-based deterministic sensitivity analysis – Delayed union

Variable	Cost of EXOGEN + surgery versus surgery alone
Exogen + surgery heal rate – 92%	-£684
Exogen + surgery heal rate – 82.8%	+£7
Exogen +surgery heal rate – 73.6 %	+£669
Surgery heal rate – 69%	-£684
Surgery heal rate – 72.5%	-£434
Surgery heal rate – 76%	-£183
Infection rate – 1.4%	-£684
Infection rate – 5.1%	-£617

9.5.6 Present results of deterministic multi-way scenario sensitivity analysis.

Table C.12.1multi-way scenario-based sensitivity analysis – Non-union, infection rate 1.4%

Variable	*EXOGEN – 86%*	*EXOGEN – 77.4%*	*EXOGEN - 68.8%*
Surgery 86%	-£2,310	-£1,879	-£1,416
Surgery 90.3%	-£1,986	-£1,555	-£1,092
Surgery 94.6%	-£1,654	-£1,223	-£761

Table C12.2 multi-way scenario-based sensitivity analysis – Non-union, infection rate 5.1%

Variable	*EXOGEN – 86%*	*EXOGEN -77.4%*	*EXOGEN – 68.8%*
Base case Surgery 86%	-£3,076	-£2,645	-£2,182
Surgery 90.3%	-£2,765	-£2,334	-£1,871
Surgery 94.6%	-£2,448	-£2,017	-£1,554

Table C.12.3 multi-way scenario-based sensitivity analysis – Delayed union

Variable	*EXOGEN – 92%*	*EXOGEN -82.8%*	*EXOGEN – 73.6%*
Base case Surgery 69%	-£684	+£7	+£669
Surgery 72.5 %	-£434	+£257	+£919
Surgery 76%	-£183	+£508	+£1,170

9.5.7 Present results of the probabilistic sensitivity analysis.

Not Applicable

9.5.8 What were the main findings of each of the sensitivity analyses?

The sensitivity analyses show that in the all of the scenarios for non-union, EXOGEN remains the dominant option.

In the case of delayed union, unless there are improved healing rates from the surgical intervention and observation (although this has not been seen in the clinical data see 7.9.1) EXOGEN is the dominant option provided the device performs as shown in the literature presented in 7.9.1.

EXOGEN remains cost saving wherever the scenario shows that normal healing may be compromised for both non-unions and delayed unions. EXOGEN only becomes cost additive under ‘worst-case’ sensitivity analyses in delayed unions, where the effectiveness of EXOGEN is decreased and the effectiveness of surgery is increased above that observed in trials. This suggests that the findings are relatively insensitive to changes in key parameter values and that EXOGEN appears to be a cost effective intervention.

9.5.9 What are the key drivers of the cost results?

The key drivers are:

- Time to healing (healing rate) – which is linked to co-morbidities and or risk factors
- In the case of non-unions, infection rate

Miscellaneous results

9.5.10 Describe any additional results that have not been specifically requested in this template. If none, please state.

None

9.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

9.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1 and sections 3.2 and 7.4.4.

Further subgroup analysis was not undertaken separately for this submission.

Taylor (2009)[32] reports sub-groups at risk of delayed healing and increased infection and conducts sensitivity analyses in these scenarios. In these cases the cost effectiveness of EXOGEN increased.

In the situation of fresh fractures, it would be relevant to stratify by risk factor, however, this is not within the scope of this document.

9.6.2 Define the characteristics of patients in the subgroup(s).

Not applicable in this analysis. Taylor (2009)[32] shows smokers and the elderly at particular risk of delayed healing and of developing infection.

9.6.3 Describe how the subgroups were included in the cost analysis.

Not applicable

9.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

Not applicable

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Yes, fresh fractures were not included as this is outside the scope

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The model was subject to internal validation and the methods were also reviewed as part of the peer-review process during publication. Clinical pathways used in the model were derived through consultation with expert clinical advisors. However, no formal validation techniques were used.

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Yes. The current, cost-based analysis results are consistent with the literature. Taylor (2009)[32] concludes," From an NHS perspective, adjunctive ultrasound offers a cost-effective choice for patients at particular risk of non-union, and for non-union fractures which are stable and well-aligned." The de novo analysis, based on updated treatment costs and revised infection rates supports this conclusion. Any assumptions adopted in the analysis are believed to be conservative, suggesting that the potential savings presented may be underestimated.

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

Yes, the analysis applies to all relevant groups and settings. It is important to note that widespread adoption of EXOGEN would involve minimal change in current practice and incur minimal cost to implement. Savings could be realised very quickly in the NHS

Even assuming the base-case scenarios and the lower end estimates of potential patient populations identified in section 3.1 and 3.10, wider adoption of EXOGEN into the NHS would lead to significant cost savings and further efficiencies.

Taking the Rubin (2001)[5] estimate of 5-10% of fractures having difficulty in healing and noting the likelihood of these becoming non-unions, the estimate from the very conservative base case models is between £25 and £50m in

direct cost savings per year to the NHS. The removal of the requirement for further surgical intervention in certain indications will also lead to other efficiencies in patient flow and bed occupancy.

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

Strengths:

The cost model was built by acknowledged experts in Health Economics; it is transparent and has been published in a peer-reviewed journal. Any assumptions concerning clinical practice have been validated by expert opinion. The data for the key drivers has been derived from systematic review and by current UK reports of clinical practice. The costs are current, UK referenced and, compared with the literature, are very conservative.

Weaknesses:

The model is based on the tibia and is assumed to be applicable to all long bones. The analysis did not test for poorer outcomes for surgery, although this was reported in 7.9.1. Although accurately referenced, costs are assumed and not based on rigorous audit. Other complications of surgery, such as deep and superficial DVT, poor range of movement, donor site pain (from harvesting bone graft), were difficult to both quantify and allocate cost. Therefore they were not included in the analysis.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Full audit of cases and a clearer understanding of clinical coding practices would enhance the robustness of the results.

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10 Appendices

10.1 Appendix 1: Search strategy for clinical evidence (section 7.1.1)

The following information should be provided:

10.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Pubmed was the primary database searched

10.1.2 The date on which the search was conducted.

Last database update search was conducted on 12th Apr 2012

10.1.3 The date span of the search.

1st Jan 1992 to 12th Apr 2012

10.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

EXOGEN search

(((ultrasound[All Fields] AND bone[All Fields] AND stimulation[All Fields]) OR LIPUS[All Fields] OR PLIUS[All Fields] OR EXOGEN[All Fields] OR SAFHS[All Fields]) OR (Low[All Fields] AND Intensity[All Fields] AND pulsed[All Fields] AND ("ultrasonography"[Subheading] OR "ultrasonography"[All Fields] OR "ultrasound"[All Fields] OR

"ultrasonography"[MeSH Terms] OR "ultrasound"[All Fields] OR "ultrasonics"[MeSH Terms] OR "ultrasonics"[All Fields])))

SURGERY search

(non-union*[Title] OR nonunion*[Title]) AND (surgical[Title] OR surgery[Title] OR treatment*[Title])

10.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

PubMed covers the vast majority of published clinical studies and was used to identify relevant clinical studies. Searching the cited references in these identified articles for additional supportive studies results in a robust search strategy that identifies, with high reliably, all relevant material.

10.1.6 The inclusion and exclusion criteria.

EXOGEN Inclusion/exclusion criteria

- EXOGEN device
- Non-union or delayed union
- Long bones
- Skeletally mature
- Prospective
- 12 or more subjects
- English language

SURGERY Inclusion/exclusion criteria

- Surgical intervention
- Non-union or delayed union

- Long bones
- Skeletally mature
- Prospective
- 12 or more subjects
- English language

10.1.7 The data abstraction strategy.

Tables were created with defined headings corresponding to relevant data to be extracted. Articles were manually searched for the information under each heading and this data was abstracted accordingly.

10.2 Appendix 2: Search strategy for adverse events (section 7.7.1)

The following information should be provided.

The search strategy for adverse events is as described in section 10.1. Additions to this strategy are noted below.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

10.2.2 As 10.1.1The date on which the search was conducted.

EXOGEN data was last updated on 12th Apr 2012

10.2.3 The date span of the search.

Since EXOGEN product was launched in 1999

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

As in 10.1.4

10.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Internal EXOGEN complaint databases were searched

10.2.6 The inclusion and exclusion criteria.

Include all EXOGEN adverse events reported, do not exclude any reported adverse events

10.2.7 The data abstraction strategy.

Report all adverse event data found

10.3 Appendix 3: Search strategy for economic evidence (section 8.1.1)

The following information should be provided.

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT

- NHS EED.

The search strategy for economic evidence is as described in section 10.1, specific modified search terms are noted in section 10.3.4.

10.3.2 The date on which the search was conducted.

April 12th 2012

10.3.3 The date span of the search.

January 1st 1992 – April 1st 2012

10.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

EXOGEN ECONOMIC search

(economic OR cost) AND (((ultrasound[All Fields] AND bone[All Fields] AND stimulation[All Fields]) OR LIPUS[All Fields] OR PLIUS[All Fields] OR EXOGEN[All Fields] OR SAFHS[All Fields]) OR (Low[All Fields] AND Intensity[All Fields] AND pulsed[All Fields] AND ("ultrasonography"[Subheading] OR "ultrasonography"[All Fields] OR "ultrasound"[All Fields] OR "ultrasonography"[MeSH Terms] OR "ultrasound"[All Fields] OR "ultrasonics"[MeSH Terms] OR "ultrasonics"[All Fields]))))

SURGERY ECONOMIC search

(cost* OR economic*) AND (non-union* OR nonunion* OR (delayed AND fracture*))

10.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

10.4 Appendix 4: Resource identification, measurement and valuation (section 9.3.2)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

The search conducted as described in 10.3.1 and 10.3.4

10.4.2 The date on which the search was conducted.

See 10.3.2

10.4.3 The date span of the search.

See 10.3.3

10.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See 10.3.4

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Resources that were identified through the literature search were measured using the HES online database and or existing NICE guidelines. Treatment protocols were identified using further cross-references from the screened and eligible papers and a Google search.

Other resources were valued using standard NHS reference costs

10.4.6 The inclusion and exclusion criteria.

See 8.1.2

10.4.7 The data abstraction strategy.

See 10.1.7

10.5 APPENDIX 5: Diagnosis and treatment codes, associated tariffs

OPCS – procedural codes

W19 Primary open reduction of fracture of bone and intramedullary fixation

W20 Primary open reduction of fracture of bone and extramedullary fixation

W21 Primary open reduction of intra-articular fracture of bone

W22 Other primary reduction of fracture of bone

W23 Secondary open reduction of fracture of bone

W24 Closed reduction of fracture of bone and internal fixation

W25 Closed reduction of fracture of bone and external fixation

W26 Other closed reduction of fracture of bone

W28 Other internal fixation of bone

W30 Other external fixation of bone

ICD – 10 diagnosis codes

M84.1 Nonunion of fracture [pseudarthrosis]

M84.2 Delayed union of fracture

Tariff generated

HRG code	HRG name	Combined day case / elective tariff (£)
HB13Z	Intermediate Hip Procedures for non Trauma Category 2	5,194
HB14B	Intermediate Hip Procedures for non Trauma Category 1 with CC	3,509
HB14C	Intermediate Hip Procedures for non Trauma Category 1 without CC	2,152
HB15D	Minor Hip Procedures for non Trauma Category 2 19 years and over with CC	1,718
HB15E	Minor Hip Procedures for non Trauma Category 2 19 years and over without CC	1,463
HB22B	Major Knee Procedures for non Trauma Category 1 with CC	3,387
HB22C	Major Knee Procedures for non Trauma Category 1 without CC	2,414
HB23B	Intermediate Knee Procedures for non Trauma with CC	2,342
HB23C	Intermediate Knee Procedures for non Trauma without CC	1,896
HB24B	Minor Knee Procedures for non Trauma Category 2 with CC	1,798
HB24C	Minor Knee Procedures for non Trauma Category 2 without CC	1,159
HB32B	Intermediate Foot Procedures for non -Trauma Category 2 18 years and under	2,606
HB34D	Minor Foot Procedures for Non -Trauma Category 2 19 years and over with CC	2,126
HB34E	Minor Foot Procedures for Non -Trauma Category 2 19 years and over without CC	1,372
HB53Z	Intermediate Hand Procedures for non Trauma Category 2	2,498
HB55B	Minor Hand Procedures for non Trauma Category 2 with CC	1,032
HB55C	Minor Hand Procedures for non Trauma Category 2 without CC	948
HB56B	Minor Hand Procedures for non Trauma Category 1 with CC	843
HB56C	Minor Hand Procedures for non Trauma Category 1 without CC	825
HB62B	Intermediate Shoulder and Upper Arm Procedures for non Trauma with CC	3,196

HB62C	Intermediate Shoulder and Upper Arm Procedures for non Trauma without CC	2,415
HB63Z	Minor Shoulder and Upper Arm Procedures for non Trauma	1,401
HB71B	Major Elbow and Lower Arm Procedures for non Trauma with CC	5,396
HB71C	Major Elbow and Lower Arm Procedures for non Trauma without CC	5,068
HB72Z	Intermediate Elbow and Lower Arm Procedures for non Trauma	2,466
HB73Z	Minor Elbow and Lower Arm Procedures for non Trauma	1,283

11 Related procedures for evidence submission

11.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

11.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted

correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

11.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).