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Norwegian Institute of Public Health

REPORT

2018

SINGLE TECHNOLOGY ASSESSMENT:

EXOGEN™ in the treatment of nonunion fractures

Title	EXOGEN™ in the treatment of nonunion fractures. A single technology assessment
Norwegian title	EXOGEN™ ved behandling av nonunion frakturer. En hurtigmetodevurdering
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Norwegian Institute of Public Health
Oslo, oktober 2018

Executive summary

Title

EXOGEN™ in the treatment of nonunion fractures. A single technology assessment.

Summary

The present report provides a single technology assessment of EXOGEN™ for the treatment of non-union fractures. We did not identify any studies comparing directly EXOGEN™ to other treatment alternatives, foremost surgery, nor sham. Thus, there was not available relevant evidence to assess the clinical effectiveness of this technology compared to alternative treatments which in turn affected the basis for a health economic analysis. In conclusion, there is a need for improved evidence, preferably a randomised controlled clinical trial to assess the clinical effectiveness of EXOGEN™ compared to a relevant alternative.

Background

Most fractures heal within estimated time lines. However, between 5% and 10% of all fractures go on to a delayed (no radiological evidence of healing after approximately three months) or nonunion (failure to heal after nine months) state. The current treatment option in Norway for nonunion fractures is surgical treatment.

EXOGEN™ is a Class IIa Medical Device. It has a CE-certificate and is approved of the Premarket Approval Application (PMA) of the Food and Drug Administration (FDA). It is also approved in UK (NICE), Australia, Canada, Japan and United States of America.

EXOGEN™ is designed to use low-intensity pulsed ultrasound (LIPUS) to help stimulate the body's natural healing of a fracture. The device is portable and self-administered by the patient for 20 minutes per day.

Patient series have suggested that LIPUS might promote healing of nonunion fractures. A recent systematic review of randomised trials for bone healing

concluded that based on moderate to high quality evidence from studies in patients with fresh fracture, LIPUS does not improve outcomes important to patients and probably has no effect on radiographic bone healing. The applicability to other types of fracture such as nonunion fractures is open to debate.

Objective

This single technology assessment was commissioned by the Commissioning Forum in the National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway (ID2015_014). The Forum requested the Norwegian Institute of Public Health to evaluate the efficacy, safety and health economic documentation for EXOGEN™ compared to surgical treatment for the management of patients with nonunion of a fracture. Norwegian Institute of Public Health has evaluated the submitted documentation up towards available published documentation.

Evaluation of the documentation

Efficacy documentation

The submitted documentation for efficacy and safety came from literature identified by searching PubMed using relevant terms. Their search was limited from January 1 1992 to October 31 2015. Articles written in English and available in full text were appraised for inclusion.

Although PubMed is a large medical database, searching only in one database is considered insufficient. Norwegian Institute of Public Health systematically searched for literature related to EXOGEN™ in Embase, MEDLINE, Cochrane Library, PubMed and WHO ICTRP. We conducted an updated search February 2018. Two of the twelve studies included in the submission dossier are excluded from this single assessment report, since these studies did not include patients with nonunion fractures, but only patients affected by delayed union fractures. From these ten publications, we have reviewed the efficacy endpoints described by the submitter: healing rate, healing time and treatment failure related to both treatment arms, and adverse events as infection rate related to surgery treatment. We also presented a propensity-matching study focusing on delayed union factures, four systematic reviews focusing on various fracture sites and different types of fractures, and an article presenting several case series.

The endpoints related to surgery are based on the submitted search in PubMed. The submitter found 19 various studies about surgical treatment of patients affected by nonunion fractures.

We evaluated the quality of the evidence for EXOGEN™ treatment by using The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, and by reading the submitted descriptions of the surgery studies.

Health economic documentation

The submitter performed a cost-effectiveness analysis where the ultrasound bone healing system for the treatment of nonunion fractures – EXOGEN™ – was compared with standard surgery. The analysis adopted a simple Markov approach based on a 1-year time horizon and monthly cycles. The model contained four health states: not healed (nonunion fracture), healed fracture, minor infection and deep infections (osteomyelitis). Patients in the EXOGEN™ pathway have EXOGEN™ as baseline treatment and patients in the surgery pathway have surgery as baseline treatment. In both pathways, if healing has not occurred within six months, it is assumed that further surgery is performed. After the surgical treatment, patients are at risk of infection.

In addition to presenting results calculated by the submitter, we have assessed the submitted documentation by making comments in each section.

Results

The quality of the evidence

Neither Bioventus nor we have identified studies of high quality. Our confidence in the results is therefore very low, and we cannot conclude regarding the effects of EXOGEN™ compared to surgery for patients with nonunion fractures, nor sham. Thus, we are not able to assess the cost-effectiveness of EXOGEN™ compared to alternatives. Here we report the results based on the documentation package from Bioventus, and our own literature searches and evaluations.

Efficacy results

Healing rate and healing time:
Based on the submitted literature in the documentation package, the submitter estimated a healing rate to be about 86% for patients getting treated by EXOGEN™. The mean healing time by getting EXOGEN™ treatment was considered by the same studies used to decide the healing rate. The submitter considered that the healing time would be about six months when the healing rate is 86%. The submitter considered that the mean healing rate and healing time for surgical treatment would be the same as for EXOGEN™ treatment, because the healing rates of the included studies varied between 74% and 100% at six months at six months.

Adverse events: The submitter stated that the EXOGEN™ treatment has no known device related adverse events. However, the individual studies have reported major complications with surgery. The complications includes deep vein thrombosis, deep

and superficial infections (1.2% infection rate), hematoma and poor range of movement. Longer term complications included requirement for further surgery (hardware removal), persistent nonunion 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. Regarding the radiation exposure, the submitter stated that the use of EXOGEN™ represents an opportunity to reduce exposure to radiation.
Treatment failure: Both treatment options are presumed to give the same healing rate at about 86% at the same healing time, six months. That means that 14% of the patients in both treatment options would fail to heal within six months. In both strategies further surgery is required.

Based on the limited documentation and absence of comparative studies nor randomized controlled trial between EXOGEN™ treatment and surgery, we are very uncertain about the effect of LIPUS compared with surgery. Expert opinion suggested that the infection rate at 1.2% was somewhat too low, and that a more reliable rate would be between 1% and 4%. Expert opinion suggested that radiographs are necessary in both treatment options.

Health economic results

The submitted basecase suggested that the technology is dominant for individuals with non-union fracture, i.e. that EXOGEN™ is a cheaper and more effective technology than surgery. The submitter found that the magnitude of the estimated cost-difference declines as surgery becomes more effective than EXOGEN™. This is because EXOGEN™ is a considerably cheaper product than a surgical procedure.

The submitter calculated in their budget impact analysis potential cost savings by introducing EXOGEN™ in Norway. The submitter assumed that the maximum patient share (30% of the patients with nonunion fractures) will be reached within four years, and that it will be cost savings each year by adopting EXOGEN™. They estimated that the total cost savings for year three after adoption of EXOGEN™ in Norway would be about NOK 2,684,753.

We noticed that the budget impact model created by the submitter did not consider the total patient costs. By only using the EXOGEN™ device cost or the one time surgical treatment cost, they did not take into account infections that may occur in both arms if the individuals are “not healed”.

Discussion

Efficacy

Bioventus has submitted documentation supporting the literature search and their presentation of the evidence. However, neither the submitter, nor we, identified any studies that directly compared EXOGEN™ to other treatment alternatives for patients with nonunion fractures, foremost surgery as the standard treatment option today, nor sham treatment. This means that none of the included studies met our PICO requirements. We also missed a critical appraisal from the sponsor of the quality of the evidence for the specific endpoints (GRADE).

There are reported data for efficacy and safety up to six months and 12 months respectively. These time periods are relatively short. We lack evidence on outcomes important to patients. There is no generally accepted definition of fracture healing. Several of the studies only reported radiological criteria, which is insufficient to assess clinical efficacy. Furthermore, all the available evidence came from ten observational studies concerning EXOGEN™ treatment, and 18 observational studies concerning surgical treatment and one RCT comparing surgery with shockwave treatment. This is the main reason why we considered our certainty in the evidence for the specific endpoints to be very low. The present documentation does not give evidence to assess the clinical effectiveness of EXOGEN™ for the treatment of non-union fractures compared to surgery, nor sham.

For new technologies there is a risk of publication bias, since negative studies are less likely to be published than studies showing positive results.

Health economic

The submitter performed economic evaluation by developing a straightforward model with four health states. We do not think that the submitted health economic model captured the outcomes that are clinically relevant to the defined population and intervention, because the model does not take into account that patients who undergo surgery in the EXOGEN™ arm also may be infected or not infected.

There were some uncertain points to consider regarding the submission. The Norwegian Institute of Public Health finds it difficult to assume that the submitted considered healing rate of 86% for patients with nonunion fractures using EXOGEN™ is a reasonable estimate, based on the weak evidence. There is also uncertainty whether a one year time horizon is sufficient to catch up all differences in costs and health outcomes.

Conclusion

Efficacy

Studies using patient history as controls suggest that EXOGEN™ induces healing in nonunion fractures. Data from studies examining surgery as the treatment option also indicate that surgery induce healing of nonunion fractures. However, as the interventions has not been compared directly in the same study, using the same kind of patients, it is not possible to estimate or conclude on which treatment option has the highest healing rate or fastest healing. Thus, there is no reason to assume equal efficacy. Heterogeneity within the studies for each of the interventions does not favor pooling data to get more precise estimates of effect and safety. In conclusion, the present documentation does not give evidence to assess the clinical effectiveness of EXOGEN™ for the treatment of non-union fractures compared to surgery, nor sham.

Cost-effectiveness

The submitted model shows that EXOGEN™ is the dominant treatment. The EXOGEN™ device would in this case be considered cheaper and give higher effectiveness in patients having nonunion fractures. However, because of the very low quality of the data on clinical effectiveness, we are unable to assess if EXOGEN™ is cost saving or not, compared to surgical treatment.

Sammendrag (norsk)

Tittel

EXOGEN™ ved behandling av nonunion frakturer. Hurtigmetodevurdering.

Oppsummering

Den foreliggende rapport gir en metodevurdering av teknologien EXOGEN™ for behandling av non-union brudd. Gjennom metodevurderingen er det ikke blitt identifisert studier som direkte sammenlikner EXOGEN™ med andre behandlingsalternativer, i første rekke kirurgi, eller sham. Det er m.a.o. ikke tilgjengelig relevant evidens for å kunne vurdere den kliniske effekten av denne teknologien sammenliknet med andre alternativer, noe som videre influerer på grunnlaget for en helseøkonomisk vurdering.

Dersom en skal kunne vurdere den kliniske effekten av denne teknologien sammenliknet med alternativer, er det behov for bedre dokumentasjon, fortrinnsvis gjennom en randomisert klinisk studie som sammenlikner EXOGEN™ med relevant alternativ.

Bakgrunn

De fleste brudd tilheler i løpet av en viss periode. Likevel er det mellom 5 % og 10 % av alle brudd som går videre til en forsinket tilheling (ingen radiologisk evidens på tilheling etter omkring tre måneder) eller nonunion-tilstand (svikt i tilheling etter ni måneder). Dagens behandlingstilbud i Norge for nonunion-brudd er kirurgisk behandling.

EXOGEN™ er et medisinsk utstyr i klasse IIa. Apparatet er CE-merket og er godkjent av Food and Drug Administration (FDA) for Premarket Approval Application (PMA). Utstyret er også godkjent i UK (NICE), Australia, Canada, Japan og USA.

EXOGEN™ bruker lavintensitet pulset ultralyd (LIPUS) for å få et brudd til å gro. Apparatet kan lett tas med fra ett sted til et annet, og pasienten kan selv håndtere utstyret 20 minutter per dag.

En nylig systematisk oversikt over randomiserte studier på tilheling av brudd, har konkludert med at LIPUS ikke forbedrer utfall som er viktige for pasientene og sannsynligvis ikke har noen effekt på radiografisk tilheling av brudd. Denne konklusjonen baserer seg på evidens med moderat til høy kvalitet fra studier av pasienter med friske brudd. Anvendbarhet av LIPUS ved andre typer brudd, slik som nonunion brudd, er åpen for vurdering.

Problemstilling

Denne hurtigmetodevurderingen ble bestilt av Bestillerforum RHF i Nye metoder (ID2015_014). Målet med denne rapporten er å vurdere klinisk effekt og sikkerhet, samt kostnadseffektivitet av EXOGEN™ sammenlignet med kirurgisk behandling av pasienter med nonunion-brudd.

Vurdering av dokumentasjon

Dokumentasjon for effekt og sikkerhet

Bioventus leverte inn dokumentasjon på effektivitet og sikkerhet basert på litteratur identifisert ved å søke i PubMed databasen. Deres søk var begrenset fra 1.januar 1992 til 31. oktober 2015. Artikler i fulltekst som var skrevet på engelsk ble vurdert for inkludering. Folkehelseinstituttet søkte systematisk etter litteratur relatert til EXOGEN™ i databaser som Embase, MEDLINE, Cochrane Library og WHO ICTRP, i tillegg til PubMed. To av de 12 studiene som var presentert i dokumentasjonspakken er ekskludert fra denne hurtigmetodevurderingen, siden disse to studiene ikke inkluderte rett populasjonsgruppe. Fra de ti inkluderte publikasjonene har vi gjennomgått endepunktene: tilhelingsrate, tilhelingstid og behandlingssvikt relatert til begge behandlingsmetoder, samt bivirkninger som infeksjonsrate relatert til kirurgisk behandling.

Etter forslag fra firmaet og vår kliniske ekspert presenterte vi også en propensity-matchet studie med fokus på forsinket tilheling av brudd, fire systematiske oversikter som fokuserte på ulike bruddsteder og forskjellige bruddtyper, og en artikkel som inneholdt flere kasuistikk-serier.

I denne rapporten presenterer vi de samme endepunktene knyttet til kirurgisk behandling som de vi fant i dokumentasjonspakken. Hele søket er gjort i PubMed.

Dokumentasjonspakken presenterte 19 ulike studier som omfattet kirurgisk behandling av pasienter med nonunion-brudd.

Vi vurderte kvaliteten på dokumentasjonen for EXOGEN™ behandling ved bruk av tilnærmingen til The Grading of Recommendations Assessment, Development and Evaluation (GRADE) og ved å evaluere den innsendte beskrivelsen av studier om kirurgisk behandling.

Helseøkonomisk dokumentasjon

Vi presenterte den innsendte kostnadseffektvitetsanalysen der EXOGEN™ er sammenlignet med standard kirugisk behandling. Kostnadseffektivitetsmodellen ble presentert og gjennomført ved bruk dataprogrammet Microsoft Excel. Modellen var basert på en Markov-tilnærming der sponsor beregnet kostnadseffektiviteten av den nye intervensjonen sammenlignet med standard behandlingsstrategi over et ett-årsperspektiv med månedlige sykluser. Modellen inneholdt fire helsetilstander: ikke tilheling (nonunion-brudd), tilhelet brudd, lett infeksjon og dyp infeksjon (osteomyelitt). Pasienter i EXOGEN™-armen hadde EXOGEN™ som baseline-behandling, mens pasienter i kirurgi-armen hadde kirurgi som baseline-behandling. I begge armene forventes det utført kirurgisk inngrep om ikke bruddet er tilhelet i løpet av seks måneder. Etter et kirurgisk inngrep er pasienten utsatt for en risiko for infeksjon.

I tillegg til å presentere resultater fra dokumentasjonspakken har vi vurdert den innsendte dokumentasjonen. Kommentarer under hvert avsnitt gjenspeiler vår vurdering.

Resultat

Kvaliteten av dokumentasjonen

Verken Bioventus eller FHI har funnet studier av høy kvalitet. Vi har derfor svært liten tillit til resultatene, og vi kan ikke si noe sikkert om den kliniske effekten av EXOGEN™ sammenlignet med kirurgi, sham eller naturlig forløp. Vi kan derfor heller ikke si noe sikkert om kostnadseffektivitet av EXOGEN™ sammenlignet med kirurgi, sham eller naturlig forløp. Vi gjengir her resultatene basert på dokumentasjonspakken fra Bioventus, og våre egne søk og vurderinger.

Effekt og sikkerhetsresultater

Tilhelingsrate og tilhelingstid:
På bakgrunn av firmaets litteratursøk var det estimert en tilhelingsrate på 86 % i dokumentasjonspakken. Gjennomsnittlig tilhelingstid etter behandling med

EXOGEN™ ble vurdert på grunnlag av de samme studiene, og ble antatt å være cirka seks måneder da tilhelingsraten var 86 %.

Bioventus vurderte på bakgrunn av inkluderte studier at gjennomsnittlig tilhelingsrate og tilhelingstid for kirurgisk behandling var lik som ved EXOGEN™ behandling. Tilhelingsraten varierte mellom 74 % og 100 % ved seks måneder.

Uønskede hendelser: Bioventus understreker at det ikke finnes noen uønskede hendelser knyttet til behandling med EXOGEN™. De enkelte studiene har derimot rapportert komplikasjoner knyttet til kirurgi. Komplikasjonene er blant annet dyp venetrombose, dype og overfladiske infeksjoner (1.2 % infeksjonsrate), hematom og dårlig bevegelsesutslag. I følge Bioventus vil EXOGEN™ føre til redusert eksponering for røntgenstråling. Vår kliniske ekspert mente at det er nødvendig med røntgenbilder i begge behandlingsalternativene.

Behandlingssvikt: Bioventus antar basert på tilgjengelig svak dokumentasjon at begge behandlinger gir samme tilhelingsrate på 86 % ved samme tilhelingstid på seks måneder. Dette betyr at 14 % av pasientene i begge behandlingsalternativer ikke vil oppnå tilheling av brudd i løpet av seks måneder. I begge alternativer er ytterlig kirurgi nødvendig om bruddet ikke tilheler.

Basert på begrenset dokumentasjon og mangel på studier med kontrollgruppe, inkludert randomiserte kontrollerte studier som sammenlikner EXOGEN™ behandling og kirurgisk behandling, antar Bioventus at effekten vil være omtrent den samme i begge behandlingsstrategier.

Helseøkonomiske resultater

Den innsendte modellen tyder på at EXOGEN™ er dominant for pasienter med nonunion-brudd, det vil si at basert på firmaets kalkulasjoner er EXOGEN™ både kostnadsbesparende og mer effektiv enn kirurgisk behandling. Ved bruk av denne modellen fant vi at størrelsen på de estimerte kostnadsbesparelsene avtar dersom kirugisk behandling er mer effektiv enn behandling med EXOGEN™.

Bioventus beregnet potensielle kostnadsbesparelser ved å introdusere EXOGEN™ i Norge. Firmaet anslår at den totale kostnadsbesparelsene for år tre vil være om lag 2,684,753 NOK. Vi la merke til at den innsendte budsjettkonsekvensanalysen ikke tok de totale pasientkostnadene med i betraktning. Ved kun å analysere enheteskostnaden knyttet til EXOGEN™ og prosedyrekostnaden knyttet til en kirurgisk behandling vil ikke infeksjonskostnadene for de fortsatt syke pasientene utover seks måneder bli inkludert med i analysen.

Diskusjon

Effekt og sikkerhet

Bioventus har sendt inn dokumentasjon basert på sitt litteratursøk og en presentasjon av de ulike observasjonsstudiene. Imidlertid identifiserte verken Bioventus eller FHI noen studier som direkte sammenligner EXOGEN™ med andre behandlingsalternativer, eller med sham eller naturlig forløp. Dette betyr at ingen av de inkluderte studiene oppfylte våre krav til PICO. Dokumentasjonspakken inneholdt heller ingen kritisk vurdering av kvaliteten på evidensen for de spesifikke endepunktene (GRADE).

Det er rapportert data for effekt og sikkerhet opp til henholdsvis seks og tolv måneder. Disse tidsperiodene er begge relativt korte. All tilgjengelig evidens knyttet til EXOGEN™ var basert på ti observasjonsstudier, og evidensen knyttet til kirurgisk behandling var basert på 18 observasjonsstudier og en RCT som sammenlignet kirurgi med sjokkbølgebehandling. Dette er hovedgrunnen til at vi har vurdert vår tillit til dokumentasjonen for de spesifikke endepunktene til å være svært lav. Den foreliggende dokumentasjon gir ikke grunnlag for å kunne vurdere den eventuelle effekt EXOGEN™ har eller ikke har på tilheling av nonunion brudd sammenlignet med kirurgi, sham eller naturlig forløp.

Det finnes ingen god eller allment akseptert definisjon av tilheling. I følge klinisk ekspert er det sannsynligvis nødvendig å komme frem til forskjellige kriterier for forskjellige brudd eller grupper av brudd. Det er også nødvendig å bruke pasientens kliniske tilstand som en del av vurderingen, og ikke bare røntgenkriterier. Flere av studiene det refereres til har tilheling på røntgen som eneste endepunkt. De vanlige tidskriteriene som brukes er arbitrære og passer i beste fall bare noen typer brudd, ifølge klinisk ekspert.

Helseøkonomi

Bioventus utførte en økonomisk evaluering basert på en enkel modell som inkluderte fire helsetilstander. Vi tror ikke at den helseøkonomiske modellen fanger opp de relevante utfallene for den definerte populasjonen og intervensjonen, i og med at den innsendte modellen ikke tar hensyn til at pasienter som får kirurgisk behandling i EXOGEN-armen også kan få infeksjoner.

Vi vurderte noen usikre aspekter av dokumentasjonspakken. Den innsendte, antatte tilhelingsraten på 86 % for pasienter med nonunion brudd i EXOGEN™-armen er basert på svak evidens. Folkehelseinstituttet synes derfor det er for usikkert å benytte seg av denne antakelsen. Det er også usikkerhet knyttet tid modellens tidshorisont som kun går over ett år. Vi er ikke sikre på at denne tidshorisonten er tilstrekkelig for å fange opp alle forskjeller i kostnader og helseutfall.

Konklusjon

Effekt og sikkerhet

Studier som bruker pasienthistorie som kontroll (der pasienter med nonunion brudd har blitt behandlet ved kirurgisk operasjon) kan tyde på at EXOGEN™ kan fremkalle en tilheling i brudd med ulik brudd-alder. Tilsvarende viser data fra studier som omfatter kirurgisk behandling at kirurgi induserer tilheling av nonunion- brudd. I og med at intervensjonene ikke er sammenlignet med hverandre i samme studie, med samme type pasienter, er det ikke mulig å sammenligne de med hverandre. Heterogenitet i studiene for hver av intervensjonene gjør at det ikke er hensiktsmessig å slå sammen data for å få mer presise estimater av effekt og sikkerhet. På denne bakgrunn er det ikke grunnlag for å kunne vurdere den eventuelle effekt EXOGEN™ har eller ikke har sammenliknet med kirurgi , sham eller naturlig forløp.

Kostnadseffektivitet

Modellen til Bioventus indikerer at EXOGEN™ er dominerende, i og med at de har kalkulert både høyere effekt og lavere kostnader ved bruk av EXOGEN™ sammenlignet med kirurgi. Det er imidlertid stor usikkerhet knyttet til evidensen av den kliniske effekten. Derfor er det umulig for oss å si om EXOGEN™ er kostnadsbesparende eller ikke.

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Preface

What is a single technology assessment

A single-technology assessment is one of a series of health technology assessment (HTA) products that can be mandated in Nye Metoder (previously denoted "The National System for Introduction of New Health Technologies" within the Specialist Health Service in Norway).

Within the system "Nye metoder", the Commissioning Forum RHA ("Bestillerforum RHF"), where the four Regional Health Authorities are represented, evaluates submitted suggestions and decides on which technologies should be assessed and the type of assessment needed. In a single-technology assessment (STA), the technology (a pharmaceutical or a medical device) is assessed based on documentation submitted by the company owning the technology, or their representatives ("the submitter").

The HTA unit of the Norwegian Institute of Public Health (NIPH) receives and evaluates the submitted documentation, but is not the decision-making authority. Single-technology assessments conducted at NIPH are published on our website (www.fhi.no) and on https://nyemetoder.no/

Objective

The Commissioning Forum RHA reviewed the proposal regarding use of EXOGEN™, id2015_014, on 1 June 2015. The objective is to assess the clinical effectiveness, cost-effectiveness and safety of EXOGEN™ in treating nonunion fractures.

Log

27.04.2015: Proposal submitted
01.06.2015: Commissioning Forum RHA commissioned a single technology assessment (STA) from the Knowledge Centre (later included in the Norwegian Institute of Public Health), ID2015_014.
June-August 2015: Dialogue and meeting with company
18.08.2015: Company confirmed intent to submit documentation

22.01.2016: Valid submission received, start of evaluation
02.09.2016: End of 180 days evaluation period
August - September 2017: Peer review conducted by additional clinical expert
22.09.2017: Follow-up meeting with company
04.10.2017: Additional documentations from company received
06.02.2018: Update of literature search and subsequent evaluation
April-May 2018: Internal review
31.05.2018: Draft report communicated to Bioventus
June 2018: External review
10.09.2018: Report clarified by the Commisioning Forum RHA for forwarding to the regional health authorities

Project group

The project group consisted of:
Project coordinator: Beate C. Fagerlund
Health economist: Beate C. Fagerlund and Ulrikke H. Lund
Research librarian: Ingrid Harboe
Department director: Øyvind Melien

In addition, we received help and feedback from the following persons:
Clinical expert: Wender Figved

Peer reviews: Frede Frihagen

The peer review was selected on the basis of a proposal by the Commissioning Forum RHA (Bestillerforum RHF)

External review: Vidar Halsteinli

Kåre Birger Hagen *Research director*	Øyvind Melien *Department director*	Beate Charlotte Fagerlund *Project coordinator*

Background

Name of the device and the manufacturer who prepared the submission

Name of device: EXOGEN™ ultrasound bone healing system.
Name of the manufacturer which submitted the application: Bioventus LLC.

Present approval

EXOGEN™ is a Class IIa Medical Device. It has a CE-certificate, CE 587463, first issued November 2012 and expiration date November 2017. In Australia the device was also approved for Australian Register of Therapeutic Goods (ARTG) in November 2013. In Canada it was given a Health Canada Licence in February 2014, a British Standards Institution (BSI) Certificate in Japan and it was given a Premarket Approval Application (PMA) in United States of America in May 2014.

Approval of the PMA by the Food and Drug Administration (FDA) was based on pivotal clinical papers by Heckman and Kristiansen in 1994 and 1997 (1;2). In 1999, EXOGEN™ 2000 was approved by the FDA, and the following year EXOGEN™ 3000 was approved. FDA approved EXOGEN™ for treatment of nonunion fractures in 2001 based on pivotal work (3). This was an early version of the device. The same year EXOGEN™ 2000+ was approved by the FDA. In 2006, EXOGEN™ 4000+ was approved by FDA. This version included a large LCD screen, one button operation and a 5 cell battery pack. In 2013, the newest EXOGEN™ version was launched with compliance calendar in EU. The current version was launched in EU in 2013 alongside a compliance calendar. EXOGEN™ was recommended for patients with non-union fractures by NICE in 2013 (4).

Description of the technology

The device

The manufacturer of EXOGEN™ describes the technology in the following way:

“EXOGEN™ device is portable and self-administered by the patient for 20 minutes per day. The strap is placed around the fractured bone, coupling gel is applied to the transducer head (to aid conduction of ultrasound) and the transducer is secured directly over the fracture site by a fixture on the strap (figure 1). If the fracture is in a cast, a hole must be cut to allow access of the transducer to the skin.

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

Figure 1. The device (pictures taken from the submission file)

EXOGEN™ device sends low intensity, pulsed ultrasound waves through the skin and soft tissue to reach the fracture. The ultrasound waves activate cell surface mechanoreceptors called integrin, initiating an intracellular cascade leading to upregulation of genes and expression of proteins and growth factors critical to bone healing. Low intensity pulsed ultrasound has been demonstrated in vivo to accelerate all stages of the fracture repair process (inflammation, soft callus formation, hard callus formation). In addition to this, accelerated mineralization has been demonstrated in vitro with increases in osteocalcin, alkaline phosphatase, VEGF and MMP-13 expression. These pathways have been directly linked to the production of COX-2 and prostaglandin, which are key to the processes of mineralisation and endochondral ossification in fracture healing. Within the fracture callus, healing requires the creation of woven bone and the removal of cortical bone. Micro-computed tomography shows that EXOGEN™ treatment benefits both processes by activating the bone healing cascade, increasing the removal of original cortical bone and enhancing endochondral ossification.”

Intended use

The submission dossier describes the intended use as:
"EXOGEN™ Ultrasound Bone Healing System is indicated for the non-invasive treatment of osseous defects (excluding vertebra and skull) that include:

- Treatment of delayed unions and nonunions
- Accelerating the time to heal of fresh fractures
- Treatment of stress fractures
- Accelerating repair following osteotomy
- Accelerating repair in "bone transport" procedures
- Accelerating repair in distraction osteogenesis procedures
- Treatment of joint fusion"

However, this single technology assessment only deals with the intended use related to treatment of nonunion fractures.

Description, incidence and current treatment for nonunion fractures

The patient handbook in Norsk Helseinformatikk states that there are several types of bone fractures. The medical treatment depends on the severity of the fracture, if the fracture is open or closed, and which bone is broken. The most common treatment for a bone fracture includes closed or open reduction (alignment of bone) and immobilisation using a cast or internal fixation" (5).

Generally, the time to bone healing is six weeks in the lower extremities/part of the body and eight weeks in the upper extremities/part of the body.

Description and incidence of patients with nonunion fractures

Most fractures heal within estimated time lines. However, some fractures go on to delayed or nonunion.

A recent overview of bone stimulators by Cook and colleagues refers to different definition of nonunion (6). They give the following examples: "A nonunion is considered to be established when a minimum of nine months has elapsed since injury and the fracture site shows no visibly progressive signs of healing for minimum of three months" (The US Food and Drug Administration) and "The designation of a delayed union or nonunion is currently made when the surgeon believes the fracture has little or no potential to heal" (Dr. Wiss and Dr. Stetson). Expert opinion suggests that a common term for nonunion fractures is fractures that do not heal within nine months.

Based on clinical suggestions between 5% and 10% of all fractures go on to a delayed or nonunion state, but there are little available data for this assumption. However, in a systematic review of 13 randomized controlled trials (7) examining the effects of low-intensity pulsed ultrasound and pulsed electromagnetic fields on bone growth stimulation in acute fractures, the rate was 35 out of 382 patients (9%) showing nonunion in the placebo groups. In the 13 included trials, the definition of union varied. It may be that this is a somewhat biased group as it was patients willing to participate in trials; they may have risk factors that render them more susceptible for delayed or nonunion fractures. Such risk factors include advanced age, smoking status and comorbid illnesses (8).

Current treatment

Current treatment options in Norway for nonunion fractures correspond to the pathway summarized by Higgins and colleagues in their review of development of National Institute for Health and Care Excellence (NICE) guideline on EXOGEN™ use (4).

Bones are realigned as soon as possible after the fracture. They are immobilised with or without operative fixation. X-rays are used to track progress towards healing through bridging the gap between the fractured bone ends with new bone cortex. Failure of the fracture to heal as expected by nine months after the original injury results in a nonunion fracture. 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 main research questions

Based on the original proposal and subsequent commission from The Ordering Forum ("Bestillerforum RHF"), we developed the main research questions shown in Table 1 below: The main research questions are organised according to the relevant PICO's (P= Population, I= Intervention, C= Comparator, O= Outcomes (Endpoints)).

Table 1. The main research questions in the single technology assessment

Patient group:	Skeletally mature patients with stable and corrected/well-aligned fractures, but no sign of healing (excluding skull and vertebrae fractures)
Intervention:	EXOGEN™ ultrasound bone healing system
Comparator:	Surgical treatment (with and without bone graft, +/- bone morphogenetic proteins (BMPs)
Outcomes:	Healing rate Time to healing Need for surgery

	Adverse events Change in radiation dose
Exclusion criteria:	Patients that did not have nonunion fractures Study design Abstracts were full text articles are not available Studies with less than 12 patients Pre 1992

Previous evidence

There are several systematic reviews on the effects of LIPUS for patients with different types of fractures. Schandelmaier et al (9) conducted a systematic review of randomised trials comparing LIPUS with sham device or no device for different types of fractures, and they identified ten previous systematic reviews (7;10-18). These previous reviews provided no definite conclusions about the effect of LIPUS on outcomes important to patients and radiographic healing, due to studies with high risk of bias, small sample sizes and failure to cover outcomes important to patients. The TRUST trial was the largest trial on LIPUS treatment for bone healing presented in the systematic review by Schandelmaier et al (9). TRUST was a concealed, randomized, blinded, sham controlled clinical trial with a parallel group design of 501 patients, enrolled between October 2008 and September 2012 in USA. The participants were men or women with an open or closed tibial fractures. The TRUST trial assessed time to return to work and time to full weight bearing with a time to event analysis and found no significant effect in both outcomes (hazard ratio 1.11 favoring control, 95% confidence interval 0.82 to 1.50; 343 patients; hazard ratio 0.87 favoring LIPUS, 95% confidence interval 0.70 to 1.08; 451 patients). There was also no difference in time to radiographic healing (hazard ratio 1.07, 95% confidence interval 0.86 to 1.34; P=0.55).

Based on moderate to high quality evidence from studies in patients with fresh fracture, Schandelmaier et al (9) concluded that LIPUS does not improve outcomes important to patients and probably has no effect on radiographic bone healing.

In a linked BMJ paper based on this systematic review, a guideline panel unanimously agreed to issue a strong recommendation against LIPUS for patients with any bone fractures, including nonunion fractures (19). A particular challenge for the guideline panel was to determine to what extent the most trustworthy evidence—coming from trials of patients with fresh tibial and clavicle fractures managed operatively—could be applied to different types of fracture. The panel found no compelling anatomical or physiological reasons why LIPUS

would be beneficial in other patient populations. According to the guideline authors, if LIPUS on patients with fresh fractures does not decrease the incidence of nonunions, it is unlikely to exert a beneficial effect in the conversion of nonunions into healed bones (19).

Previous single technology assessments

We identified three assessments on EXOGEN™ compared with surgery (20-22). One assessment was performed by the Medical Services Advisory Committee (MSAC), Australia from 2001 (20), the second by the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS), Québec, Canada from 2004 (21), and a third assessment was performed by the Health Economics Research Group (HERG), United Kingdom from 2012 (22). The latter assessment report was requested by the National Institute of Health and Care Excellence (NICE).

Each of the assessments concluded that the clinical evidence were generally weak. Furthermore, they concluded that there were no direct comparative evidence for effectiveness between EXOGEN™ and surgery.

MSAC stated in the end of their STA report: "With respect to non-unions, the cost-effectiveness of LIPUS relative to current Australian practice was unable to be investigated due to the lack of comparative efficacy data" (20). Furthermore, they recommended that on the basis of the evidence available on low intensity ultrasound treatment for acceleration of bone fracture healing, public funding should not be supported for this procedure (20). The Australian Minister for Health and Ageing accepted this recommendation on 5th of February 2002.

AETMIS considered in 2004 that low-intensity ultrasound might be an exceptional treatment option for a very limited number of patients. As for patients with tibial fracture nonunion (21).

The National Institute of Health and Care Excellence (NICE) in United Kingdom stated in their guidance of 2013 (23) that EXOGEN can be used to treat non-union fractures of long bones, but NICE has announced that they will review this guidance from August 2018.

Evaluation of the clinical documentation

Literature searches and identification of relevant published literature

Literature searches

Bioventus' literature search to identify clinical documentation

Bioventus based their clinical documentation on literature identified by searching PubMed using relevant terms. The search was limited from January 1 1992 to October 31 2015. Articles written in English and available in full text were appraised for inclusion. Bioventus obtained information about relevant, currently supported studies from the Bioventus external studies committee. In addition, the submitter searched for ongoing studies in adequate sources for planned and ongoing studies. They identified one ongoing EXOGEN™ study that may become available for assessment in subsequent years.

We show Bioventus' search strategy, their inclusion and exclusion criteria and finally the flow charts for selection of studies in Appendix 1.

The Norwegian Institute of Public Health's literature searches to identify clinical documentation

Bioventus searched for published literature in PubMed. Although PubMed is a large medical database, searching only in one database is considered insufficient. Thus, we have searched for literature in other databases as well in order to see if additional research is available. We did not limit the search to a specific study design.

We systematically searched for literature in the following databases:

- Ovid Embase 1974 to 2016 March 03
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

- Cochrane Library: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect, Central Register of Controlled Trials, Health Technology Assessment Database, NHS Economic Evaluation Database
- PubMed articles ahead of print

We searched for ongoing clinical trials in WHO ICTRP (Clinical Trials Search Portal) and ClinicalTrials.gov.

The research librarian Ingrid Harboe planned and executed all the searches. The searches are limited to EXOGEN™ treatment. The complete search strategy was carried out 2016.03.04 and is presented in appendix 2.

We conducted an updated search on 2018.02.06 for studies with a control group. The updated search is presented in appendix 3.

The Norwegian Institute of Public Health's identification of relevant published literature

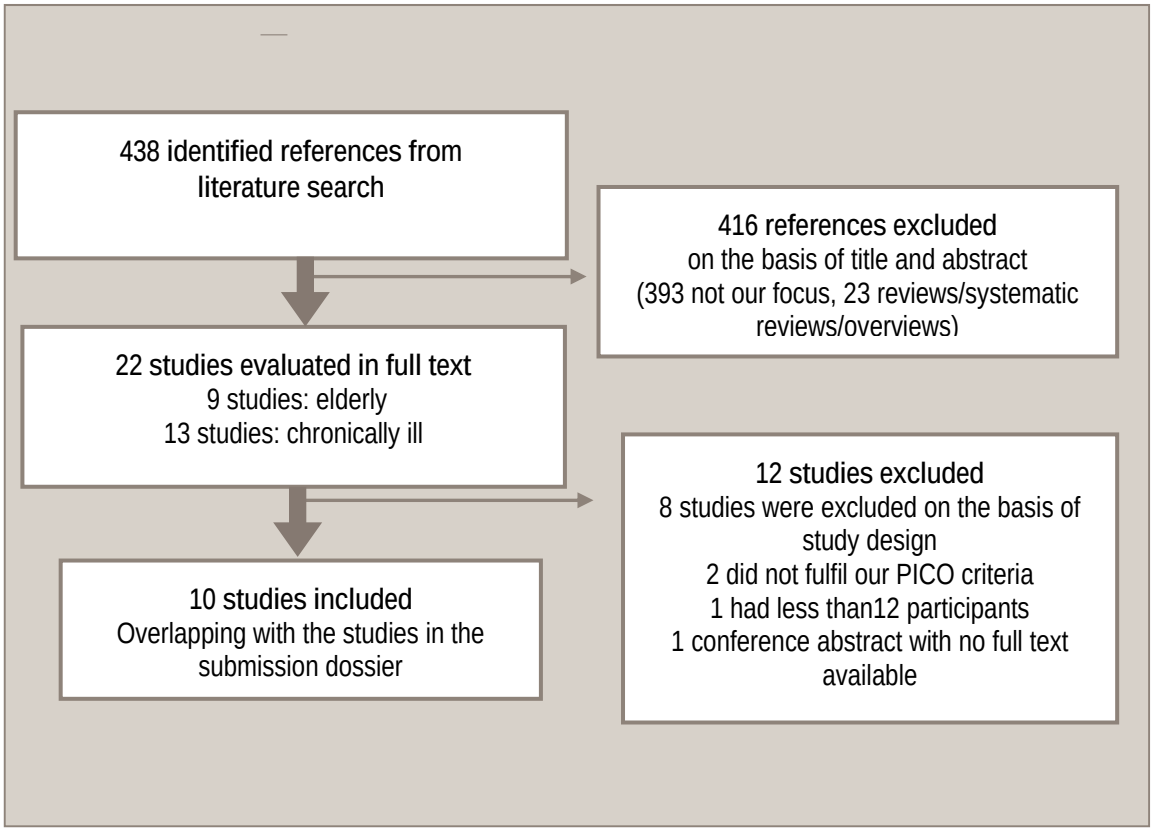


Figure 2. *A flow chart of our selection of literature*

Two of the twelve studies included in the submission dossier are excluded from this single technology assessment report, since these studies did not include patients with nonunion fractures, but only patients affected by delayed union fractures (24;25). In our search we found ten of the studies reported in the submission and two additional studies which were not mentioned in the submitted documentation package. However, these studies were excluded because one of the studies included less than 12 patients and one study only contained a conference abstract. We did not identify any relevant primary studies in the updated search in February 2018.

Identification of ongoing trials

We identified only one ongoing EXOGEN™ study that may become available for assessment in subsequent years. This study is a prospective, double-blind randomized controlled trial to determine the effectiveness of EXOGEN™ in decreasing the time to union of scaphoid nonunions after operative fixation as measured by serial CT scanning. Multiple centres

within the Calgary zone will be involved in the study in order to recruit enough patients to power the study. Blinding will include patients, surgeons, research assistants, as well as all data handlers and analysts until trial completion or mid-term analysis. The study started in October 2014 and the expected end date is in December 2018. Publications available for assessment relating to this study are unlikely to be available before 2019 (26).

Description of included studies

Neither Bioventus, nor we, identified any studies that directly compared EXOGEN™ to other treatment alternatives, foremost surgery as the standard treatment option today. This means that none of the included studies met our PICO requirements, as they did not include a comparator group.

Description of the included EXOGEN™ publications

We assessed ten of the twelve studies that Bioventus had included. All the included studies are single arm observational studies, and they are not appropriate for evaluation of efficacy. Patients in the different studies followed the recommended 20 minutes EXOGEN™ treatment per day until healed fracture. The studies are shown in table 2 and described in more detail below.

Description of the included publications of EXOGEN™

Gebauer, 2005 (27):

This publication is a self-paired control study from Germany and Austria, where the control is the patient's own history of failed treatments. The study period lasted from July 1995 to April 1997. This study contained 67 participants with nonunion fractures (defined as minimum fracture age 8 months, radiographic indication that the healing process had stopped for at least 3 months, and a minimum of 4 months without intervention before EXOGEN™). A healing rate (defined as no pain or motion upon gentle stress and weight bearing if applicable, and radiographic healing defined as 3 of 4 bridged cortices) of 85% for all long bone fractures (not otherwise described) was reported with a mean healing time of 168 days (SE +/- 10.2 days).

Jingushi, 2007 (28):

This study is based on prospective, multi-center, case series from Japan. The data was collected in 2003. The study contained 32 patients with nonunion fractures (defined on the basis that surgery was otherwise deemed to be indicated). The reported healing rate (defined

as clinical and radiographic healing as determined by experienced orthopaedic surgeons) was 66% (21/32); analyses by individual long bone were not included. A mean healing time of 219 days (range 56–588 days) was reported for a mixed group of 72 patients with nonunion and delayed healing fractures. When treatment with EXOGEN™ was started within 6 months of the most recent operation, the union rate was approximately 90%. When treatment was started after 12 months, the union rate was less than 65% (follow-up not reported).

Lerner, 2004 (29):

This study is based in a prospective, single-centre, case series from Israel. The data was collected in the time period 1997-2001. EXOGEN™ was used to treat high energy complex fractures which were delayed in healing or had become nonunion. Seventeen patients with 18 high energy fractures caused by war injuries, road traffic accidents and accidents at work were included. Fractures were treated until healed, this time ranged from 13-52 weeks. No side effects of treatment were seen. In this paper 16/18 fractures healed (88.9%). One patient was lost to follow-up and a second required further surgery.

Mayr, 2000 (30):

This publication is based on an international patient registry, from the time period October 1994 to July 1997. The study was located in Germany and described 366 registered patients, where 256 patients were affected by nonunion fractures (failure to heal 9 months after fracture). The mean healing rate across all long bone fractures (humerus, radius/ ulna, femur, and tibia-fibula) was 84% (216/256), with a mean healing time of 5.3 months.

Nolte, 2001 (3):

This publication is based on a self-paired study where each patient served as their own control. The patients were collected from 19 centres in the Netherlands during the time period November 1995 to May 1997. The study contained 22 patients with nonunion fractures (defined as failure of fracture to unite at a minimum of 6 months from fracture, no progression towards radiographic healing or healing had stopped for a minimum period of 3 months before EXOGEN™). They reported healing rates (defined as absence of pain, weight bearing without pain or normal function of the limb, 3 or 4 cortices bridged on radiograph) of 100% (10/10) for tibia-tibia/fibula (mean healing time 144 days), 80% (4/5) for femur (mean healing time 185 days), 80% (4/5) radius-radius/ulna (mean healing time 139 days) and 100% (2/2) for other long bone fractures (mean healing time 153 days).

Pigozzi, 2004 (31):

This publication is based on a prospective longitudinal study from Italy. Patients were followed up to 24 weeks in the time period September 2000 to April 2002. Pigozzi et al. 2004 investigated the use of EXOGEN™ to treat nonunion fractures. Fifteen nonunion fractures were included in a variety of locations including the clavicle, scaphoid, femur, tibia, wrist and ankle. Patients were followed up every 4 weeks, all fractures went on to heal in an average time of 94.7 days ± 43.8 days.

Romano, 1999 (32):

This study is based on a case series report from Italy. The patient follow-up period was not reported. The study conducted on 15 patients with septic nonunion of long bones (tibia, humerus and femur). Of the 15 fractures, 9 were healed, 4 was still ongoing, and 1 required additional surgery before the end of treatment and 1 showed no signs of healing. Of the 9 that healed, healing time ranged from 95 – 181 days, with the time from fracture varying from 8 – 30 months.

Roussignol, 2012 (33):

This is a publication based on a continuous retrospective analysis, case series from France. The study period lasted from 2004 to 2009. The study analysed 59 nonunion patients treated with EXOGEN™, and investigated the effect of fracture gap and stability on the heal rate. Mean fracture-to-surgery interval was 271 days. The 6-month consolidation rate was 88%. There was no loss to follow-up. Mean ultrasound treatment duration was 151 days (range, 90-240 days). Bone healing correlated significantly with stability of the internal fixation assembly (P=0.01). They concluded that a fracture needs to be stable to be treated with EXOGEN™ and that a fracture gap up to 10 mm does not affect healing.

Watanabe, 2013 (34):

The publication is based on a retrospective analysis of a consecutive population at one centre. The study consisted of 101 delayed unions and 50 nonunions. The data was collected between May 1998 and April 2007 in Japan. Patients were followed up at least every 4 weeks, and had x-rays to assess healing at each visit. The heal rate in the nonunion fracture group was 68.0%, failure of low-intensity pulsed ultrasound (LIPUS) therapy in this group was associated with method of fixation, instability at fracture site and maximum fracture gap size more than 8 mm. Fractures were classified as failed to heal if they had not healed after 12 months of LIPUS therapy.

Zura et al. 2015 (8):

This publication is an American study based on a retrospective analysis of prospectively collected registry data as part of a post market approval study required by the FDA as a condition for approval of P900009. The data were collected between 1994 and 1998. Patients were analysed in this study if they had a nonunion fracture that was greater than one year old and if they had four data points (fracture date, date EXOGEN™ treatment started, date EXOGEN™ treatment ended and fracture healing outcome). This data was used to calculate the number of days the patients was on treatment (DOT) and the days to treatment (DTT). Data from 767 patients was analysed in total. Results showed that there was an 86.2% healing rate in all fractures over 1 year old and 82.7% in fractures greater than 5 years old. The mean time to fracture healing was 168 days. The only factor that was significantly (p=0.004) associated with a decreased heal rate was patient age; this decrease was, however, modest and only a 12% decrease between the ages of 20 and 80.

Table 2. Overview of studies using EXOGEN™

Study information	**Patient group**	**Outcomes**	
		Healing rate *Mean*	Healing time in days *Mean +/- SE (range)*
Gebauer 2005* (27) Period:07.1995-04.1997 EXOGEN™ (n=67)	Nonunion fracture: Humerus, ulna, femur, tibia, fibula	85%	168 +/- 10.2
Jingushi 2007 (28) Japan Period: 2003 EXOGEN™ (n=32)	Nonunion and delayed union - long bones fractures: Humerus, radius, ulna, femur and tibia.	66%	219 (56-588)
Lerner 2004* (29) Period: 1997-2001 EXOGEN™ (n=16)	Nonunion fractures: Femur, tibia, forearm, humerus	88.9%	182 (91-364)
Mayr 2001* (30) Patient registry: 10.1994-07.1997 EXOGEN™ (N=366) registered, (n=256) for long-bones	Nonunion fractures: Humerus, radius/radius-ulna, femur, tibia/tibia-fibula, others	86%	162 +/- 5.3
Nolte 2001* (3) Period: 11.1995-05.1997 EXOGEN™ (n=29)	Nonunion fractures: Humerus, radius, ulna, femur, tibia/fibula, scaphoid, metatarsal, clavicle	86%	152 +/- 15.2 119
Pigozzi 2005* (31) Period: 09.2000-04.2002 EXOGEN™ (n=15)	Nonunion fractures: Wrist, scaphoid, clavicle, malleolar, talus, femur, tibia	100%	94.7 +/- 46.8
Romano 2011* (32) Period not reported EXOGEN™ (n=15)	Nonunion fractures: Tibia, humerus and femur, cubitus, ancle	63%	152

Roussignol 2012* (33) Period: 2004-2009) EXOGEN™ (n=59)	Nonunion fractures: Humerus, ulna, femur, tibia, fibula and other	88%	151 (90-240)
Watanabe 2013 (34) Japan Period: 05.1998-04.2007 EXOGEN™ (n=50)	Nonunion fractures: Humerus, radius/ulna, femur, tibia/fibula	68%	365
Zura 2015 (8) USA Period: 1994 – 1998 EXOGEN™ (n=767)	Nonunion fractures: Tibia, femur, radius/ulna, humerus, tibia/fibula, scaphoid, ankle, metatarsal, foot, others	86,2%	168 +/1 113.6

*If not otherwise stated, the study population is European

All the 10 studies using EXOGEN™ are observational studies, and one of them is based on patient registry (30). The study populations varied between 15 patients and 767 patients. None of the studies mentioned above (table 2) included a control group. The population groups differed in kind of fracture sites. The healing rates varied between 63% and 100%, and the healing time varied between 94 and 365 days.

Description of other included literature

We were in contact with both the submitter and a clinical expert. Both parts presented additional literature they wanted us to include in this report.

The submitter presented a propensity-matching study based on delayed union, where patients treated by LIPUS was the intervention group and patients treated by surgery was the comparator (35). Registry data were collected over a 5-year period, and a total of 594 metatarsal fractures were treated with LIPUS, including 161 Jones fractures. The heal rate with LIPUS treatment was 97.3%, comparable to the heal rate of 95.3% among claims patients in 2011 who did not receive LIPUS (P = 0.0654).

Both the submitter and the clinical expert presented several meta-analyses focusing on fractures treated either by LIPUS or surgery that we included in our report (Table 3):

Table 3. Overview of meta-analyses comparing fractures treated either with LIPUS or surgery

Systematic review	Fracture site and type of fracture	Number of references	Patients (N)	Outcomes	
				Healing rate *Mean*	Healing time in months
Leighton 2017 (36)	Tibia Femur Scaphoid Humerus Radius+Ulna	10 9 6 6 5	354 110 61 44 18	86% 80.4% 78% 74% 77.5%	2.3 – 7.9 months

Seger 2017 (37)	Scaphoid	5	166	78.6%	4.2 months
Schandelmaier 2017 (9)	Long bone and other bones	26 RCTs	Median sample size of 30 (range 8-501)	Fails to accelerate radiographic healing.	
Bashardoust 2012 (10)	All type of bones	23 human clinical trials		There is weak evidence that LIPUS also supports radiographic healing in delayed unions and nonunions.	

In addition to these systematic reviews, our clinical expert presented an article showing a lower healing rate in 61 case series, where patient with nonunion fractures treated with EXOGEN™ LIPUS therapy were analyzed. 32% patients showed bone consolidations with an average time of healing of 5.3 (2-7) months (38). These publications were not included in our literature search because they included delayed union fractures.

Description of the included surgery publications

The submitter did not identify any studies that directly compared EXOGEN™ to other treatment alternatives, foremost surgery as our preferred comparator. The submitter solved this by performing a separate search for published surgery literature considering treatment of nonunion fractures.

We used Bioventus' search for published literature on surgical treatment of nonunion fracture to compare EXOGEN™ with surgery. We did not carry out any additional search for published literature on surgery, since our initial search did not identify any published studies with EXOGEN™ as a control group compared to surgery. Based on the submitted documentation and our search, none of the EXOGEN™ studies met our PICO requirements (surgery as the comparator).

Most of the submitted surgery studies related to nonunion fractures had no comparator, and none of the surgery studies which included a comparator are directly compared to EXOGEN™ treatment. Table 4 shows the included studies on surgery.
We noticed that one of the surgery studies is a randomized double blind controlled study from 2009 (39). This trial compared two treatment options for nonunion fractures of long bones, and included three groups: Groups 1 and 2 were treated 4 times with shockwave therapy (0.4 or 0.7mJ/mm2), group 3 were treated surgically. Six months after treatment, 70% of the nonunions in group 1 had healed, 71% of group 2 had healed and 73% of group 3 had healed.

Table 4. Bioventus' included studies on surgery

Study information	Patient group	Outcomes	
		Healing rate *Mean*	Healing time in days *Mean*
Bellabarba, 2002 (40) USA Intervention (n=20) **	Nonunion fractures: Femoral	100%	98 (84-140)
Birjandinejad, 2009 (41) Iran Intervention (n=38) **	Nonunion fractures: Femoral and tibia	Femur: 100% Tibia: 84.6%	143.4 (30-180)
Cacchio, 2009 (39) Italy Randomised controlled trial* Intervention (n=38) Control group: Shock-wave therapy (n=84)	Nonunion fractures: Long-bone	74%	180
Faraud, 2014 (42) France Intervention (n=21) **	Nonunion fractures: Clavicle nonunion	90,5%	-
Farsetti, 2015 (43) Italy Period: 1991-2007 Intervention (n=29) **	Nonunion fractures: Scaphoid	93.1%	114
Ferreira, 2015 (44) South Africa Period: 01.2010 – 12.2014 Intervention (N=122) **	Nonunion fractures: Tibia	92.6%	114
Henry, 2010 (45) USA Period: 01.2010-12.2014 Intervention (n=15) **	Nonunion fractures: Open fractures. Thumbs, fingers, long, ring and small	92,6%	63
Khalil, 2010 (46) Egypt Intervention (n=15) **	Nonunion fractures: Ulna	90%	67.2
Khurana, 2013 (47) USA Intervention group: distal fubula nonunion (1A) and medial malleolar nonunion (1B) (n=15) Comparison: Non-operative patients and operation of acute fractures (n=69)	Nonunion fractures: Fibula, tibia, ankle	-	1A = 132 1B = 195
Lin, 2010 (48) Taiwan Intervention: Surgery plus allograft (n=36) Comparison_ Surgery plus autograft (n=28)	Nonunion fractures: Humeral shaft	Intervention: 93% Comparison: 95%	Intervention: 131 Comparison: 140.7
Livani, 2010 (49) Brazil Intervention (n=15) **	Nonunion fractures: Humeral shaft	100%	63 (42-126)
Niu, 2010 (50) China Intervention (n=19) **	Nonunion fractures: (Lower limb long bone) Femoral shaft and tibial shaft	100%	Femoral shaft: 185 (112-420) Tibia shaft: 165.2 (84-280)
Park, 2013 (51) Korea Intervention (N=67)**	Nonunion fractures: Group A: Unstable scaphoid factures	Group A: 88.2% Group B: 87.1%	101,5

	Group B: Stable scaphoid fractures		
Razag, 2010 (52) Pakistan Intervention (n=41) **	Nonunion fractures: Femoral shaft	90%	149,1 (+/- 45.9)
Ring, 1997 (53) USA Intervention (n=42) **	Nonunion fractures: Femoral shaft	97%	180
Singh, 2014 (54) India Intervention: nonunion (N=40) Group A: Humerus interlocking nail (n=20) Group B: Locking compression plate (n=20)	Nonunion fractures: Humeral diaphyseal fracture nonunions managed with humerus interlocking nail	Group A: 95% Group B: 100%	Group A: 110.6 (+/- 29.4) Group B: 120.4 (+/- 26.6)
Tall, 2014 (55) Burkina Faso Intervention (n=50) **	Nonunion fractures: Humerus, ulna, radius, tibia, femur	100%	Upper limb:90 Lower limb: 120
Vilaca , 2012 (56) Brazil Intervention (n=15) **	Nonunion fractures: Diaphyseal nonunion of humerus	100%	Postoperatively in 11 patients: 45 in 3 patients: 60 in 1 patient: 90
Wu, 2003 (57) Taiwan Intervention (n=31) **	Nonunion fractures: Tibia shaft	100%	135 (90-225)

*One randomized double blind controlled study. ** Only intervention group. No control group.

All studies were observational studies, except one randomized trial from Italy, where patients who were treated by surgery were compared to patients who went through shockwave therapy (39). This trial showed a somewhat lower healing rate (74%) than most of the observational studies (84.6% - 100%). The randomized controlled study also showed a quite long healing time of 180 days (6 months). Based on the surgery observational studies, the healing time ranged from 51 to 180 days.

The study populations varied between 14 and 122 patients in the intervention groups. Only 2 of the 19 studies mentioned above (table 3) included control groups. In the study by Cacchio et al. (39) the control group patients underwent shockwave therapy, and in the study by Khurana et al. (47) the control group patients were non-operative patients or underwent operative fixation.

The population groups differed regarding fracture sites. Fifteen of the 19 studies analyzed the number of long bone nonunion fractures as tibia, femur, ulna, radius and/or humerus, and 4 of the 19 studies analyzed the number of shorter bones as scaphoid, clavicle, thumbs and fingers. The healing rates vary between 74% and 100%, and the healing time ranged from 63 to 180 days.

Critical appraisal of included studies

According to the submission template, the company has critically appraised all the ten included studies (3;8;27-34). We present their appraisal in Appendix 4. According to the submitter, in all the ten included studies the cohorts were recruited in an acceptable way, the exposures were accurately measured to minimise bias, the authors had identified all important confounding factors and the follow-ups of patients were complete. In two of the ten included studies (31;32) it was not clear if the outcomes were accurately measured to minimise bias. In two of the ten studies (31;33) it was unclear and not applicable if the authors had identified all important confounding factors. Further, in five of the ten included studies (28;29;31-33) it was not applicable how precise (in terms of confidence intervals and p values) the results were.

Clinical results

Bioventus' description of the clinical results of EXOGEN™ treatment

Healing rate, healing time and adverse events
The submitter claimed that:

According to the largest data collection on the use of EXOGEN™ to heal nonunion fractures (8) a healing rate (HR) of 86.2% is reported. The publication states: "*Nine previous studies of LIPUS for nonunion have reported HRs ranging from 73% to 100% with a median HR of 86%. Our results are also consistent with a systematic review of LIPUS for nonunions, which reported an HR of 87% in 594 nonunions from 8 studies, with a mean fracture age of 22.2 months and mean heal time of 4.8 months.*"

The mean healing rate for nonunion long bone fractures reported in Mayr et al. 2000 (30), based on EXOGEN™ registry data, was 84% over a mean of 5.3 months. Other estimates ranged from 66% for a mixture of long bone fractures (28) to 95% for radius and ulna fractures and 100% for tibia and tibia/fibula fractures (30). EXOGEN™ shows healing rates of approximately 86% in nonunions with faster progression to healing than placebo and a healing time similar to surgery (from 152-192 days) in the case of nonunions. Roussignol et al. 2012 (33) retrospective case series of 58 nonunions demonstrated a healing rate of 88% which corroborates that the EXOGEN™ device is most effective when the fractures are stable and well aligned.

The submitter pointed out that the EXOGEN™ treatment has no known device related adverse events.

Bioventus' description of the clinical results of surgical treatment

Healing rate and healing time:
The submitter expresses that: The surgical management of nonunions in long bones produces good results and is an appropriate management option. The healing rates of 74% - 100% seen at six months in the individual trials are supported by other literature excluded from the searches performed. Brinker et al. 2013 (58) corroborates these findings in a review of exchange nailing studies.

Adverse events: Bioventus claims that surgery has reported major complications – within the individual studies the immediate complications are reported as deep vein thrombosis (DVT), infection (deep and superficial), haematoma and poor range of movement (ROM). Longer term complications included requirement for further surgery (hardware removal), persistent nonunion 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.

The sponsor also assumes that the infection rate related to surgery treatment is 1.2% (CI 1.0% – 1.4%) – and out of the 1.2% infections, the probability for deep infection is 54% and bases this assumption on estimations by UK Health Protection Agency (59).

Radiation protection aspects for EXOGEN™ and surgery treatment

The submission dossier state:
"The use of EXOGEN™ represents an opportunity to reduce exposure to radiation.
A central principle in radiation protection is "as low as reasonably achievable." (The European Council Directive 2013/59/Euratom).
The gold standard for confirmation of fracture healing is radiographic evidence of 3 bridged cortices on plain X - Ray from 3 views. In nonunion fractures repeat exposure to radiation to qualify if the fracture has healed places the patients at a higher level of exposure. For each consultation and surgery avoided, there is a reduced exposure to X-ray."

If the patient undergoes surgery, expert opinion suggests that there should be a minimum of six X-ray exposures to confirm placement of fixation devices, plus pre- and post–operative views.

The Norwegian Institute of Public Health's description the clinical results from the included studies

Comments on the included EXOGEN™ studies

The data for all the endpoints are taken from the ten studies about EXOGEN™ treatment of patients affected by nonunion fractures. The endpoints "healing rate" and "healing time" are

the approximate medians based on the outcome by the included EXOGEN™ studies. The healing rate of 86 % and healing time of 165 days are also close to the mentioned healing rates and healing time in the largest studies (8;27;30;33). The study by Watanabe et al. 2013 (34) did only report the healing rate at 12 months, that's why this study is excluded from the endpoint "treatment failure" (Table 5).

Table 5: Summary of findings

Endpoints		Nr. of studies	Quality of evidence (GRADE)	
Healing rate	86 % (63 % - 100 %)	10 1 register study, 9 observational studies	⊕◯◯◯ VERY LOW	1,3,4
Healing time	165 days (94.7-360 days)	10 1 register study, 9 observational studies	⊕◯◯◯ VERY LOW	1,2,3,4,5
Treatment failure (need for surgery)	The patients who did not achieve health state «healed» in 6 months went through surgery.	9 1 register study, 8 observational studies	⊕◯◯◯ VERY LOW	1,3,4
Adverse events	None of the included studies reported any adverse events			

1. Few patients to follow-up
2. Mixture of delayed union fracture and nonunion fracture
3. Different fracture sites
4. Lack of events / patients
5. Different definitions / outcome

GRADE Working Group grades of evidence (60)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect .

The patients who failed to heal within 6 months needed surgical operation. Based on the included studies this rate should be 14% in both treatment strategies. All the included studies stated that they had not observed any adverse events by the use of the EXOGEN™ device only. Regarding the radiation dose, we did not find any dose changes between the two strategies.

Comments on the included surgery studies

The data for all the endpoints are based on the 19 studies about surgical treatment of patients affected by nonunion fractures. One exception is the infection rate which is taken from UK Health Protection Agency (59). Based on the included surgery studies, the healing rate at 86 % seems to be a reasonable assumption, since the randomized double blinded control trial (39) shows a somewhat lower healing rate (74%) compared with the healing rates taken from the observational studies (84.6% - 100 %).

A 6 months healing time may also sound as a reasonable assumption, because the total range of healing time varied from 63 to 180 days in the observational studies, and the randomized double blinded trial (39) presented a healing time at 180 days. However, since none of the surgery studies, including the one RCT, are specifically compared to the EXOGEN™ treatment, it is impossible to compare the values of these endpoints to the endpoint values related to the EXOGEN™ treatment. We did not GRADE the findings. A summary of findings table would in this case show very low quality of evidence of the endpoint values.

Expert opinion suggests the infection rate to be higher than 1.2% according to Norwegian conditions. They think an infection rate between 1% and 4% seems like a more reasonable assumption.

Comments from the Norwegian Institute of Public Health and the Norwegian Radiation Protection Agency on the radiation aspects in both treatment strategies

Expert opinion suggests that x-ray is necessary in both treatment options. A patient has to undergo radiographic examination to confirm the need of any of the treatment options.

An X-ray of the extremities (arms and legs) is related to very low effective doses (range: 0.0002-0.12 mSv) and hence the risk for radiation induced cancer is negligible (less than 1 in a million). There is no risk for deterministic effects related to X-rays of extrimities. Occupational risk is also negligible as long as the X-ray examinations are carried out according to the national radiation protection regulation.

The introduction of EXOGEN™ may have the potential to reduce the need for surgery and associated X-rays, according to the submitter. Even though the radiation doses and risks associated with these X-rays are low, the introduction of EXOGEN™ may be favorable from a

radiation protection point of view. However, the radiation detriment has to be implemented in the total risk-benefit evaluation of the method.

No direct comparative study of EXOGEN™ to other treatment alternatives exist for nonunion fractures, but we acknowledge the concept that it may possibly lead to reduced exposure to X-ray. However, the submission file does not include any measured data to visualize potential differences between EXOGEN™ and treatment alternatives. Hence, this aspect cannot be included in the evidence base regarding benefits or disadvantages of the new technology.

Cost-effectiveness

General

The submitter, Bioventus LLC, has submitted a cost-effectiveness analysis where the ultrasound bone healing system for the treatment of nonunion fractures – EXOGEN™ – is compared with standard surgery. Delayed fractures are fractures which have shown no radiographic progression to healing over a three month period. Nonunion fractures are fractures that are not healed after nine months.

The submitter identified four published economic studies, three from UK and one from USA, including one single technology assessment. Incremental effectiveness was not stated in any of their listed economic studies.

Table 6: The economic studies

Study information	Mode analysis	Population	Costs	Comparison
Taylor et al. 2009 (61) UK	Cost-minimisation analysis	Fresh and nonunion tibia fractures	Equivalent healing rate to immediate surgery. EXOGEN™ shows a lower cost (£3,926) compared with surgery (£6,718).	EXOGEN™ vs. surgery
Kanakaris et al. 2007 (62) UK	Non-comparative analysis (Cost study)	Nonunion fractures of humerus, tibia and femur	Costs: Humerus – £15,566 Tibia – £17,200 Femur – £16,330	Surgery
Patil et al. 2006 (63) UK	Non-comparative analysis (Cost study)	Nonunion fractures of femoral and tibial nonunions.	Mean cost: £29,204 per patient	Surgery

Mehta et al. 2015 (64) Data: 2007-2010 USA	Retrospective cohort study by pairwise demographic matching among patients who received "surgery only" of "LIPUS only"	Nonunion fractures mainly of foot and leg	"Surgery group": $6,289 higher costs than patients in "LIPUS group". Outpatient costs: significantly higher (+$3,484) among the "surgery group" cohort. Total inpatient costs: significanly higher among the "surgery group" (+$2,921).	LIPUS vs. surgery

*Low-intensity pulsed ultrasound (LIPUS)

Costs per QALY have been estimated, based on Norwegian health care costs, healing rates from Zura et al. (2015) (8) which is the largest registry study conducted in nonunion treatment with EXOGEN™ and the comparative efficacy paper by Taylor et al. (2009) (61).

In addition to include several health economic studies comparing LIPUS and surgery we present the conclution from another health technology assessment by a Health Economics Reasearch Group from an External Assessment Center (EAC), Brunel University (22):

The EAC report concluded that the clinical evidence generally is weak. Further, the report stated that in non-union fractures of long bones there is no direct comparative evidence for outcomes of interest for surgery versus EXOGEN. There is a fair estimate of the absolute healing rate with EXOGEN from a large registry study, and supportive evidence from smaller non-comparative case series. There are also estimates of the healing rate with surgery from case series. However, these non-controlled studies provide reasonable evidence of effectiveness for each intervention and it is difficult to measure the size of their relative effect. For delayed union there is no evidence comparing healing rates with surgery and EXOGEN in the treatment of delayed union fractures of long bones. This means that it is not possible to evaluate the comparison requested in the scope.

According to the EAC report, the costing model for delayed union presented by the sponsor found a cost-saving of £684 per patient on average associated with the early use of EXOGEN. Anyway, this result was not robust to sensitivity analysis conducted by the EAC. They found that different methods of estimating healing rates from the available clinical data reversed the conclusions. With the EAC best estimate, early use of EXOGEN for delayed union resulted in £500 more expensive than waiting for surgery at non-union. For the non-union costing model, the sponsor assumed equal healing rates with EXOGEN and surgery. Together, this assumption and the sponsor's estimate of the cost of surgery gave a cost-saving for EXOGEN around £2310. This is a much larger difference than in the delayed union model. The EAC best estimate of the cost-saving with EXOGEN versus surgery in non-union is lower than that of the sponsor which was £1,164 cost saving on average per patient.

Patient population

The submitter assumes that all patients in the patient population have the diagnosis "nonunion fracture". That means every patient in the analysis has gone through a treatment of fractures that has failed to show normal progression to healing within nine months. The length of the time a fracture is classified as a nonunion varies. However, nonunion is here defined as a fracture that has failed to heal nine months after fracture.

Choice of comparator

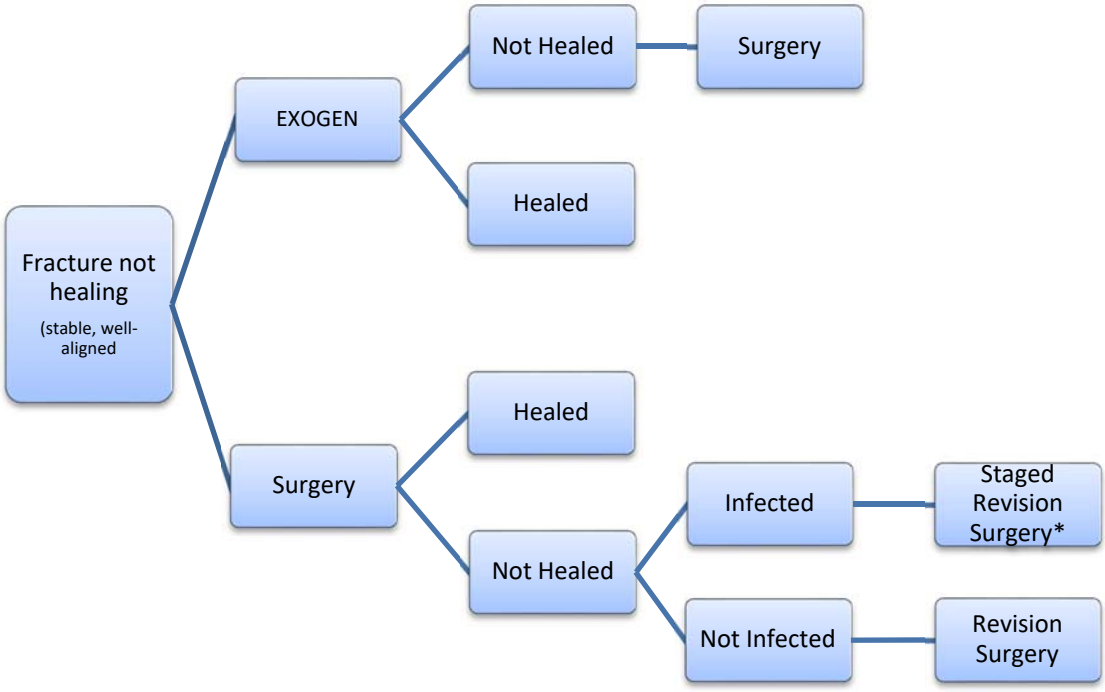
The new intervention is EXOGEN™. The patient with nonunion fracture may start using EXOGEN™ followed by surgery if the fracture does not heal in six months.

The comparator in the analysis is fracture surgery followed by further surgery if the fracture does not heal within six months.

Type of analysis and decision model

The submitter performed a cost-effectiveness analysis for EXOGEN™. They submitted one "nonunion fracture model" created in Excel. This model was adapted from Taylor et al. (2009) (61). The analysis adopted a simple Markov approach based on a 1-year time horizon and monthly cycles. The sponsor claims that the chosen schematic is in line with proposed and clinical pathways of care and follow management of nonunions.

The submission provides a simple model as an attempt to illustrate the gold standard strategy, surgery, in one arm and the other strategy, EXOGEN™, in the other arm. The model contains four different health states: not healed (nonunion fracture), healed fracture, minor infection and deep infection (osteomyelitis).



Figur 3: The figure is a schematic illustration of the model submitted from Bioventus.

All nonunion fracture patients begin in the health state "Fracture not healing". Patients in the EXOGEN™ pathway have EXOGEN™ as baseline treatment and patients in the surgery pathway have surgery as baseline treatment. In both pathways, if healing has not occurred within six months, it is assumed that further surgery is performed. In the surgery arm, patients in a not healed health state are at risk of infection. Based on that model, patients in a not healed health state from surgery health state are offered revision surgery.

Comments from the Norwegian Institute of Public Health

The model does not take into account that patients who undergo surgery in the EXOGEN™ arm also may be infected or not infected.

The model seems correct for patients who undergo the not-invasive EXOGEN™ treatment in the first six months, but it seems not correct for patients who fail to heal within six months in the nonunion fracture state, and, therefore, go through surgery after treatment with EXOGEN™.

The clinical and epidemiological data

The submitter estimates similar healing rates and similar time to healing of nonunions for surgical treatment as they found reported in the clinical studies. The potential of adverse events and complications profiles for each treatment arm, such as infection and methods of further surgical interventions were generated in their literature search. These have been quantified to make them relevant to the scope.

The model includes four potential health states: 1) healed, 2) not healed (nonunion fracture), 3) minor infection and 4) deep infection (ostemyelitis). The submitter gives no clear defination on “minor infection”.

The efficacy

The submitted model is based on a time horizon of 12 months a monthly cycles. The submitter reported that the majority of fractures have healed during the 12 months’ time period. The submitted healing rate for patients following the EXOGEN™ arm is 86% in 6 months. This rate is based on the results from the study by Zura et al. (2015) (8) and is the mean value of all different kinds of nonunion fractures. Healing rate for the surgery arm is also 86% within 6 months. This rate is based on the results from the study by Gebauer et al. (2005) (27). The submitter concidered that the remaining 14% of the patients who are not healed in either the EXOGEN™ arm or the surgery arm duering the 6 months period receive surgery, and then 14 % of those who receive surgery do not get healed. Based on the submitted doucmentation there will still be 2% patients with nonunion fracture in the end of the 12 months’ time period in each arm.

The model uses an infection rate of 1.2%, and assumes that about 54% of the infections are deep infections. These rates are based on the British population (Surveillance of sugical site infections in NHS hospitals in England: 2014 to 2015) (59). The submitter did not find any Norwegian data sources or registers, but assumes these rates based on the British population`s infection rate to be comparable to the Norwegian population. The submitted efficacy data are presented in table 7.

Table 7: The submitted efficacy data

	The submitted data	**Reference**
Healing rate - Exogen	86%	(8)
Healing rate - Surgery	86%	See table 4

Healing time - Exogen	6 months	(8)
Healing time -Surgery	6 months	See table 4
Infection rate - Surgery	1.2%	(65)
Not healed - Exogen	14%	(8)
Not healed - Surgery	14%	See table 4

Comments from the Norwegian Institute of Public Health

Based on the weak evidence as found in the chapter of clinical effect, the healing rates seem to be unclear. It also appears that the time horizon is somewhat too short to capture all important outcomes in the model. It is uncertain whether the model captures the infections after surgery in the EXOGEN™ arm. Expert opinion suggests the infection rate based on the British population is somewhat too low in order to reflect a Norwegian patient group. They think the infection rate is varying between 1% and 4%. We adjusted the infection rate to 2.5% in our model, and kept the proportion of deep infections.

The costs

The submission presents the resource use involved in the two procedures, 1) invasive surgical treatment and 2) EXOGEN™ treatment, by quantifying the unit costs to construct a total cost. The submitter estimates potential cost-savings by choosing the second option, EXOGEN™ treatment. They did include the health care costs only. No societal costs were included as the submitter was not able to fully identify and quantify the complex societal needs of nonunion fracture patients. The estimates are based on clinical opinions, Norwegian diagnosis related groups (DRGs) (66), the official price list to the communal primary health care sector (67), (deductible for patients) and other sources. Some sources were unclear in the submission file.

The submitter assumed that only patients who have stable, well-aligned fractures might undergo EXOGEN™ treatment. This matches the observations from the study by Zura et al. (2015) (8).

Resources used in the submission

- EXOGEN™ device – NOK 19,200. The price is given by the manufacturer, Bioventus.

- General Practitioner-visit – NOK 190. The patient pays a deductible based on the official list price to the communal primary health care sector (67).

- Outpatient cost - NOK 978.53. This cost is based on DRG-code: DRG 908A «Outpatient consultation of fracture, disclation or soft tissue injury in arm, leg or pelvic. » (66). This cost is quantified by 1.

- Cost of nonunion surgery – NOK 52,580 (weighted average). The sponsor estimated the average of the indicative cost based on inpatient DRG-prices* (64,114 NOK) and the indivative cost based on day case DRG-prices** (24,317 NOK). The DRGs are listed up below this section. The calculation are based on ISF regulation (2014) (66) and quantified by 1.

* Indicative inpatient DRGs used to generate DRG cost (66)

- Surgery of humerus bone & knee / leg / foot, except the knee joints surgery > 17 with complications and comorbidities (cc)
- Surgery of humerus bone / elbow / forearm except shoulder prosthesis without/cc
- Surgery of wrist / hand / without/cc or debridement of upper limb
- Surgery of pelvic / hip / femur except prosthesis surgery > 17 without/cc
- Surgery humerus bone & knee / leg / foot, except the knee joints surgery > 17 without/cc
- Surgeries of ankle & foot

** Indicative Day case DRGs used to generate DRG cost (66)

- Surgery of humerus bone & knee / leg / foot, outpatient surgery treatment
- Surgery of humerus bone / elbow / forearm except shoulder prosthesis, outpatient surgery treatment
- Surgery of wrist / hand excl larger joint surgery, outpatient treatment
- Surgery of pelvic / hip / femur except hip, outpatient surgery treatment
- Surgery of humerus bone & knee / leg / foot, outpatient surgery treatment
- Surgeries of ankle and foot, outpatient surgery treatment

- Cost of x-ray – NOK 227. The submitter based this cost on DRG 908R (66): «Orthopedic diagnostic ultrasound». The sponsor claims in the submission file that non procedure related costs, such as x-ray, are assumed to be the same in both treatment arms and excluded from the model.

- Costs related to wheelchair, crutches and physiotherapy – NOK 0. The submitter assumes that non-related costs are the same in both treatment arms and excluded from the model

- Infection management cost – NOK 31,043. The submitter bases this cost on DRG-code: DRG 242C «Specific inflammatory joint and spine diseases wihtout/cc». The calculation are based on ISF regulation (2015) (68) and quantified by 1.

- Stabilising temporary fixator – NOK 15,000.

- External fixation – NOK 26,430.

- Syntetic bone graft – NOK 4,863. The sponsor assumes that all nonunion surgery management includes the use of autologous iliac crest bone graft or synthetic graft.

- Operating room cost (removal of metalwork and debridement) except costs related to physicians – NOK 30,600. The submitter assumed the average operating room time for nonunion surgery to be 3 hours. The operating room cost is based on a Swedish report, «Region Skåne Inställda operationer Revisionsrapport KPMG AB Mars 2012» (69). The report informs that one hour is estimated to cost NOK 10,200.

Average hotel costs – NOK 132,000. The submitter calculated the average hotel costs based on data supplied by the Norwegian directorate of health for the hotel costs during 2013-2014. The average unit cost is calculated as NOK 4,125 and quantified by 32 hotel nights.

- I/V Clindamycin – NOK 3,630. The submitter assumes that patients administred intravenousv antibiotics are kept in hospital because antibiotic treatment regime involves dosing every 6 hours and close monitoring which is difficult to manage in a community setting. The sponser states that it is very difficult to determine the average length of time that a patient will require intravenous antibiotics. Based on product prescribing information and expert opinion they assumed that 3 weeks as inpatient is a minimum time that a patient will be required to be treated. They base this assumpion on the lack of provision of community intravenous services. They calculated the price based on 450-900 mg intravenous infusion every eight hours for 4-6 week plus (70).

- The total calculated cost related to deep infection will be NOK 243,123 based on the submitted model. By removing the double counted operating room cost the submitted deep infection cost will be about NOK 212,513.

Comments from Norwegian Institute of Public Health

All resources used in the submission had a reference to a source, but there were some confusion regarding how they were calculated and where the sources were taken from. Not all resources used in the submission were related to Norwegian conditions.

The EXOGEN™ device price is given by the manufacturer, but it is not completely clear weather this given price includes costs linked to staff traning or the device only. Regarding the cost related to the GP-price, the submitter did not multiply this price by 2 which is recommend in Guidelines for the economic evaluation of health technologies (71). The correct cost in the model would be NOK 380.

We calculated the DRG-prices based on 2014, 2015 and 2016 unit prices. DRG-prices have not changed much during the last three years. Based on “ISF regulation, 2016” (72) the correct costs related to outpatient cost will be NOK 1,052, the correct weighted average cost of nonunion surgery will be NOK 56,425, the infection management cost will be NOK 32,571

and the cost of x-ray will be NOK 1,725. They claimed that the x-ray price would be about NOK 227.

Expert opinions agreed that the use of x-ray is assumed to be the same in both EXOGEN™ arm and surgery arm. This may indicate that a patient treated by EXOGEN™ will be exposed to the same quantity of radiation as a patient treated by surgery. Costs related to wheelchair, crutches and physiotherapy are the same in both treatments, but the resources used in their spreadsheet model differ between the treatment arms. However, this will not affect the results. The cost related to infection management is more unclear. The submitter describes the infection management cost as «minor infection» in the submission and in the model as «major infection», while the «major infection» in the submission is given the name «deep infection» in the submitted model. This creates confusion regarding what kind of infection it concerns. Expert opinion suggested that «minor infection» may be a superficial infections, hence «minor infection» based on this specific DRG-code may be too weak.

Expert opinion suggested variation in the given price regarding stabilizing temporary fixator considering metalwork and debridement. External fixation may cost as little as NOK 9,000, but also as much as NOK 40,000. The price of synthetic bone graft depends on what kind of nonunion fracture site it is and our expert questioned whether this assumption may be generalized. Iliac crest bone grafts or synthetic grafts are more common for patients treated for nonunion fracture in tibia or radius.

We considered the submitted operating room cost to be too low with respect to Norwegian contitions. We considered DRG points taken from the performance-based financing (in Norwegian: Innsatsstyrtfinansiering (ISF)) regulation, 2016 (72) to be a better way to calculate operating room costs. By using DRG 209 F and DRG 209 G (ISF regulation, 2016 (72)) we calculated the cost to be about NOK 118,711 to 185,493. The average of these DRGs is NOK 152,102. However, the submitted operating room cost is counted twice, both in the submission and in the model. We corrected this in the submitted model. Our expert thinks the operation room time may differ between 1 and 3 hours and an average operating room time based on Norwegian conditions would be about 2 hours.

There are few Norwegian hospital hotels, and big variations among the organization of the hospitals and the primary health care services. According to our expert, a patient may stay for two weeks at a hospital after a surgical treatment followed by intravenous antibiotic treatment at home. One patient day is in 2016 calculated to be NOK 4,505 (72). Two weeks will be NOK 63,070.

We considered the price related to intravenous antibiotics (Clindamycin) to be applicable, but even though our expert expresses that Clindamycin is still a way to treat patients with major infections in Norway, such treatment may increasingly be managed by homecare. However, according to expert opinions, «Cloxacillin» is the most used treatment option (73). This

treatment can last for 12 weeks or longer and may be administred at home by a nurse, or by health professionals in a nursing home. This medical treatment, 2 g / 10 vials Cloxacillin in 12 weeks, will cost among NOK 3,007 (73).

The total calculated cost for deep infection will be about NOK 264,472 based on our changes in resource use and unit costs. This is a higher cost than the submitted cost of NOK 243,123.

Health related quality of life

The submitter describes four different health states: healed (health state 1), not healed (health state 2), minor infection (health state 3) and major infection/ osteomyelitis (health state 4).

Health state 1 has a QALY weight factor of 0.88 (74). Health state 2 has a QALY weight factor of 0.68 (75). Health state 3 has the same QALY weight as Health state 2, 0.68, because the submitters did not find any literature on minor infections. Health state 4 has a QALY weight factor of 0.53 Lee et al. (2010) (76).

Comments from the Norwegian Institute of Public Health

We considered that there is uncertainty associated with the weight factor related to health state 1 as this factor is based on "prior to injury" and not when the nonunion fracture is actually healed. We also think there might be some difference between health state 2 and health state 3 regarding the health related quality of life (HRQoL) factor. It may depend on what kind of infection the patient is affected by in Health state 3.

The studies used different instruments to measure the HRQoL which might affect the outcomes. The SPRINT study Briel et al. (2011) (74) used a generic preference instrument, health utility index 3 (HUI3), and Schottel et al. (2015) (75) used the direct measurement instrument time trade off (TTO). Lee et al. (2010) (76) did not describe how they estimated their QALY weight factor on osteomyelitis.

Cost-effectiveness analysis

The submitted model was based on a cohort of 956 patients. They assumed, based on a Scottish cross-sectional epidemiological study, 18,54 fractures per 100,000 population (77). The time frame was one year, so they did not discount costs and effects. Other details (healing rate, healing time, infection rate, health related quality of life and costs) are mentioned in the earlier sections.

Results from the submitted model are reported in the table below (see table 8). The results suggest that EXOGEN™ is cost-saving.

Table 8: The cost-effectiveness results based on submitted model

Measure	Mean cost per patient (NOK)	Mean QALY per patient	Incremental costs	QALY gained	ICER
EXOGEN™	NOK 31,947	0.86	- NOK 35,175	0.007	Dominant

The submitted result indicates that treatment with EXOGEN™ is dominant, which means the intervention costs less and is at least as effective as the comparator.

Comments from the Norwegian Institute of Public Health

The submitter has constructed a straightforward simple model. They did not discount costs and effects because the model assumes monthly cycles over a 12 months timeframe. The costs and effects are achieved during a year. Discounting is not necessary because of the short timeframe, but in long run both costs and effects should be discounted by 4% according to Norwegian guidelines. However, there is uncertainy whether a one year time horizon is sufficient to catch up all differences in costs and health outcomes. Although they assume equal healing with EXOGEN™ and surgery based on the weak clinical effectiveness finidings. Because of the infection rate (1.2%) in the surgery arm there is high costs related to the propotion of this cohort being unhealed after one year.

No probabilistic sensitivity analysis were performed by the submitter as the model were built without any distribution related to the particular input parameter values. A probabilistic sensitivity analysis allows the modeler to quantify the level of confidence in the output of the analysis, in relation to uncertainty in the model inputs. However, a deterministic one-way sensitivity analysis were provided by the submitter (see table 9).

Table 9: Submitted one-way sensitivity analysis based on the base-case model

Relative risk (healing rate)	EXOGEN™	Surgery	Cost difference (EXOGEN - Surgery)
0.5 (72%)	NOK 31947.45	NOK 75431	- NOK 43483
1.0 (86%)	NOK 31947.45	NOK 67122	- NOK 35175
1.5 91%	NOK 31947.45	NOK 64155	- NOK 32207
2.0 (93%)	NOK 31947.45	NOK 62968	- NOK 31020
2.5 (96%)	NOK 31947.45	NOK 61187	- NOK 29240

Varying relative risk in surgery compared with Exogen

The submitted one-way sensitivity analysis shows that the magnitude of the estimated cost savings declines as surgery becomes more effective than EXOGEN™. Even if the healing rate with surgery is over twice that with EXOGEN™, the latter still appears to be cost saving. This is because EXOGEN™ is a considerably cheaper product than a surgical procedure.

Budget impact analysis

The submitter calculated potential savings as the difference in total costs of the two options. The submitter claimed: "The cost consequences do not include any adverse event management and reflect the cost of surgical intervention or treatment with EXOGEN™. Equally, there are no additional costs associated with the adoption of EXOGEN™ as this treatment fits into existing routine clinical practice". However, procurement of the EXOGEN™ device will provide an additional charge.

The submitter calculated cost saving results in each year. They emphasize however, that they assumed a finite population and it is not antipicipated that the availablility of EXOGEN™ will lead to an increased number of patients in the total cohort. Their key assumptions are based on the original analysis from several studies (8;30) which report consistent healing rates for EXOGEN™ of 86%. Gebauer et al. 2005 (27) reported comparable healing rates for surgery compared with EXOGEN™, this underpins the submitters' budget impact modelling. The submitter assumed that the maximum patient share will be reached within four years (see table 10 and 11). For the patient share if the new technology is not adopted the submitter based the shares on the current situation, which means that some patients are actually treated by EXOGEN™ device in today's health care services.

Table 10: Patient shares used in the submitted budget impact analysis

	Total patient share if EXOGEN™ is adopted			Total patient share if EXOGEN™ is not adopted		
	Year 1	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**
EXOGEN™	7%	15%	30%	3%	6%	9%
Surgery	93%	85%	70%	97%	94%	91%

The table illustrates how many patients who will undergo EXOGEN™ treatment and surgical treatment if or if not EXOGEN™ treatment is adopted.

By using a total number of 383 patients per year (see appendix 5), the EXOGEN™ price of NOK 19 200 and the average DRG surgery costs of NOK 52,580 (mentioned in the costs-section), the submitter calculated the yearly costs over three years.

The submitted budget impact model shows differences between the two scenarios in each of the relevant years of the analysis (see table 11). They estimated cost savings each year.

Table 11: The submitted budget impact

Budget impact	Year 1	Year 2	Year 3
+ Cost if the New technology is adopted	19,243,222	18,220,459	16,302,778
- Cost without adoption of the New Technology, i.e. Current situation	19,754,603	19,371,067	18,987,531
Total cost	-511,381	-1,150,608	-2,684,753

The table illustrates potential cost savings by introducing EXOGEN™ as the difference in total costs of the two options. All costs: in Norwegian kroner.

Comments from the Norwegian Institute of Public Health

We noticed that the budget impact model created by the submitter did not take the total patient costs into account. The submitter have only used the EXOGEN™ device cost (NOK 19,200) or the one time surgery treatment cost (NOK 52,580) in the model. By only using the EXOGEN™ device cost or the one time surgical treatment cost they did not take into account infections that may occur in both arms if the individuals are "not healed". Based on their clinical effectiveness findings, 14% of the patients in both arms are not healed after 6 months. Their budget impact model does not capture this. However, the Norwegian Institute of Public Health finds it difficult to assume that the submitted considered healing rate of 86% for patients with nonunion fractures using EXOGEN™ is a reasonable estimate, based on the weak evidence.

Discussion

We have performed a single technology assessment of the use of EXOGEN™ ultrasound bone healing system as a Class II A Medical Device for the management of patients with nonunion fractures. The submission came from Bioventus LLC.

We have reviewed the submission file and evaluated it in accordance with the PICO (Population, Intervention, Comparator and Outcomes/endpoints). We have conducted our own searches for literature, selection of studies, quality assessment of the included studies, data extraction, GRADE assessment of the quality of the evidence for the effect estimates of the endpoints related to EXOGEN™ ultrasound bone healing system, and for surgery by evaluating the submitted evidence, as well as health economic evaluations for both strategies.

Efficacy

The submitter has submitted documentation supporting the literature search and a presentation of the evidence. However, neither the submitter nor we identified any studies that directly compared EXOGEN™ to other treatment alternatives, foremost surgery as the standard treatment option today. This means that none of the included studies met our PICO. A critical appraisal from the submitter of the quality of the evidence for the estimates of the specific endpoints (GRADE) is also lacking.

The evidence for the efficacy and safety came from 12 different observational studies involving EXOGEN™ treatment. None of these studies included a comparator. Nineteen different studies focusing on surgery, where one of the publications was a RCT – comparing surgery to shockwave treatment. The other 18 publications were observational studies. From these publications, we have reviewed the efficacy and safety endpoints up to one year.

Our single technology assessment is based on 10 of the 12 different EXOGEN™ studies reviewed by the submitter to examine the efficacy and safety endpoints. Two of the 12 studies were excluded because they did not include patients with nonunion fractures, but only patients affected by delayed union fractures. During the assessment period, we were in contact with both the submitter and a clinical expert. Both parts presented additional literature. A propensity-matching study focusing on delayed union factures, four systematic reviews focusing on various fracture sites and type of fractures (9;10;36;37), and an article presenting several case series were included in this report.

For the endpoints related to the surgery strategy, we based our analysis on the same 19 studies as found by the submitter.

Based on clinical expert opinion, there is no good or widely accepted definition of "fracture healing". According to the selected studies, both treatment strategies gave equal endpoints for healing rates and healing time. For EXOGEN™ 86% (the studies showed values between 63%-100%) is healed with a healing time of six months (94.7-360 days), and for surgery 86% (the RCT showed a healing time 180 days, and the different observational studies showed values between 63 and 180 days). In both treatment arms, 14% of the patients affected by nonunion fractures would experience revision surgery. According to our clinical expert, several fractures designated as nonunions will be healed without any treatment. Due to a not well-defined diagnosis and uncertain prognosis it is important to insist on comparative studies, preferably randomized controlled trials.

The safety endpoints are related to the device, system, treatment failures and the procedure's adverse events. In both treatment strategies, 14% of the patients affected by nonunion fracture would experience revision surgery in the end of six months. No adverse events were reported by the studies of EXOGEN™ treatment. The main adverse event associated with surgical treatment is infection. Expert opinion suggested the infection rate to be between 1% and 4%.

Regarding the radiation aspects, expert opinion suggested that x-ray is necessary in both treatment options. A patient has to undergo radiographic examination to confirm the need of any of the treatment options. There exists no direct comparative study of EXOGEN™ to other treatment alternatives for nonunion fractures, but we acknowledge the concept that it may possibly lead to reduced exposure to X-ray.

In addition to the lack of studies that directly compared EXOGEN™ to surgery, weaknesses of the selected studies are:

- *Few patients to follow-up:* The study populations varied between 15 and 767 patients in the various EXOGEN™ studies. Eight of the ten studies included less than 100 individuals. In the surgery studies, the study populations ranged from 15 to 122 patients, and only one study out of 19 studies included more than 100 participants.

- *Mixture of delayed union fracture and nonunion fracture:* Some studies included both nonunion and delayed union fractures. "Delayed union fracture" is when a fracture takes longer than usual to heal, unlike nonunion fractures where a fracture healing does not occur within six to nine months.

- *Different fracture sites:* The included studies reported patients with various fracture sites. Long-bones as tibia, femoral and fibula of the legs; humerus, radius and ulna of the arms; metacarpal bones; clavicles, and short-bones as scaphoid and ankle.

- *Lack of events/patients:* Some of the studies have a very limited study period, especially where the study populations are less than 20 patients.

- *Different definitions/outcome:* Several studies disagreed in their definitions of "nonunion fracture". For example, some of the studies defined a nonunion fracture as a failure of fracture to unite at a minimum of 6 months from fracture; other studies defined a nonunion fracture as a fracture with a minimum fracture age of 8 months or 9 months.

-*Lack of patient important outcomes:* Several studies did not report how the patients felt or functioned with or without the device during the study periods.

Cost-effectiveness

The submitter performed economic evaluation by developing a simple model with four different health states: "Not healed" (nonunion fracture), "healed fracture", "minor infection" and "deep infection" (osteomyelitis). However, according to the submitted model infections may only occur in the surgery arm. The model does not take into account that patients who undergo surgery in the EXOGEN™ arm also may be infected or not infected. Further, the submitter gives no clear defination on "minor infection". Our clinical experts think a better way to describe this health state is "superficial infections".

The submitter provided a base-case analysis over a time horizon of one year. The submitter calculated that the base-case incremental cost-effectiveness ratio for EXOGEN™ compared with surgery treatment would be dominant, which means the intervention costs less and is at least as effective as the comparator. The submitted incremental costs would be NOK -35,175 and QALY gained would be 0.007. The submitter assumed that the maximum patient share (30% of the patients with nonunion fractures) will be reached within four years, and that it will be cost savings each year by adopting EXOGEN™.

However, there were some uncertain points to consider regarding the submission. First, the submitter tested the impact of the healing rate for surgery by varying the relative risk of surgery compared with EXOGEN™ in a deterministic one-way sensitivity analysis of patients entering the economic model. Bioventus found that the magnitude of the estimated cost savings declines as surgery becomes more effective than EXOGEN™, but EXOGEN™ is still cost-saving in all scenarios. Even if the healing rate with surgery is over twice that with EXOGEN™, the latter still appears to be cost saving. This is because EXOGEN™ is a considerably cheaper product than a surgical procedure. The Norwegian Institute of Public Health finds it difficult to assume that the submitted considered healing rate of 86% for

patients with nonunion fractures using EXOGEN™ is a reasonable estimate, based on the weak evidence.

Second, there is uncertainty whether a one year time horizon is sufficient to catch up all differences in costs and health outcomes. Although the submitter assumes equal healing in both EXOGEN™ and surgery based on the weak clinical effectiveness findings, they also consider an infection rate of 1.2% with surgery. This results in a proportion of the cohort being unhealed after one year in the surgery arm. The cost related to infections are very high (submitted infection costs per patients with deep or superficial infections: NOK 128,595).

The submitter estimated that the total costs savings of implementing EXOGEN™ in Norway would be about NOK 2,684,753 in year three after adoption of EXOGEN™ in Norway. We noticed that the budget impact model created by the submitter did not consider the total patient costs. By only using the EXOGEN™ device cost or the one time surgical treatment cost, they did not take into account infections that may occur in both arms if the individuals that are “not healed”.

Considerations of the prioritization criteria in light of available evidence

The clinical evidence is very limited as stated earlier in this report. The main reason for this limitation is the lack of comparative studies. In turn this restricts the possibilities to consider the established prioritization criteria in Norway; i.e. benefit, resources and severity (78) with reference to the available clinical evidence on EXOGEN™ in the following way:

- **Benefit:** Cannot be considered due to insufficient clinical evidence.
- **Resources:** Cannot be considered due to insufficient clinical evidence. Based on the identified publications and clinical experts' opinions, we do not know if EXOGEN™ has any effect compared to surgery. In an economic evaluation, we need to know both the assumed costs and the assumed benefits of the particular technology (78) . As it is not possible to assess potential benefits of the technology in this case, we are subsequently unable to provide considerations related to this criterion.
- **Severity:** Estimated absolute shortfall (AS), as an expression of severity, would depend on the cost-effectiveness analysis, which we did not have sufficient evidence to perform.

The need for further research

We did not identify any studies comparing directly EXOGEN™ to other treatment alternatives, foremost surgery, nor sham. There is a need for improved evidence, preferably a randomized controlled clinical trial to assess the clinical effectiveness of EXOGEN™

compared to a relevant alternative. It can be mentioned that research in this field also explores options including cell-based therapies (79).

Conclusion

Efficacy

A recent systematic review based on high to moderate certainty evidence, concluded that LIPUS does not improve outcomes important to patients and probably has no effect on radiographic bone healing in patients with fresh fractures. The studies using patient history as control suggested that EXOGEN™ induces healing in nonunion fractures. Data from studies examining surgery as the treatment option also indicated that surgery induces healing of nonunion fractures. The certainty of the latter findings is however very low according to GRADE. Because of the low quality of the evidence, we do not know if EXOGEN™ promotes bone healing in patients with nonunion fractures. As the interventions have not been compared in the same study, using the same kind of patients, it is not possible to estimate or conclude on which treatment option that has the highest or fastest healing rate. Heterogeneity within the studies for each of the interventions does not favor pooling of the data to get more precise estimates of effect and safety

Cost-effectiveness

The submitter´s basecase suggested that the technology is dominant for individuals with non-union fracture, i.e. that EXOGEN™ is a cheaper and more effective technology than surgery. However, there are huge uncertainties concerning the input parameters and the assumptions related to the model. The submitter assumed equal healing with EXOGEN™ and surgery based on the low quality findings regarding clinical effectiveness. The one year time horizon is probably not sufficient to catch up all differences in costs and health outcomes (especially when it comes to infections caused by surgery in the EXOGEN™ arm).

Conclusion

The overall conclusion is that there are no rigorous high quality studies available to draw conclusions about the effectiveness of EXOGEN™ compared to surgery or other alternatives. The submitted calculated cost savings related to EXOGEN™ is also depending on the clinical effectiveness. There is a need for improving the evidence, preferably through a randomised controlled trial including patients with nonunion fractures in order to assess the clinical effectiveness of EXOGEN™compared to a relevant alternative.

Appendix

Appendix 1 – Submitter search details

The following search terms were used to identify relevant publications:

1) EXOGEN™ search terms
(((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 "ultrasonic"[MeSH Terms] OR "ultrasonics"[All Fields])))

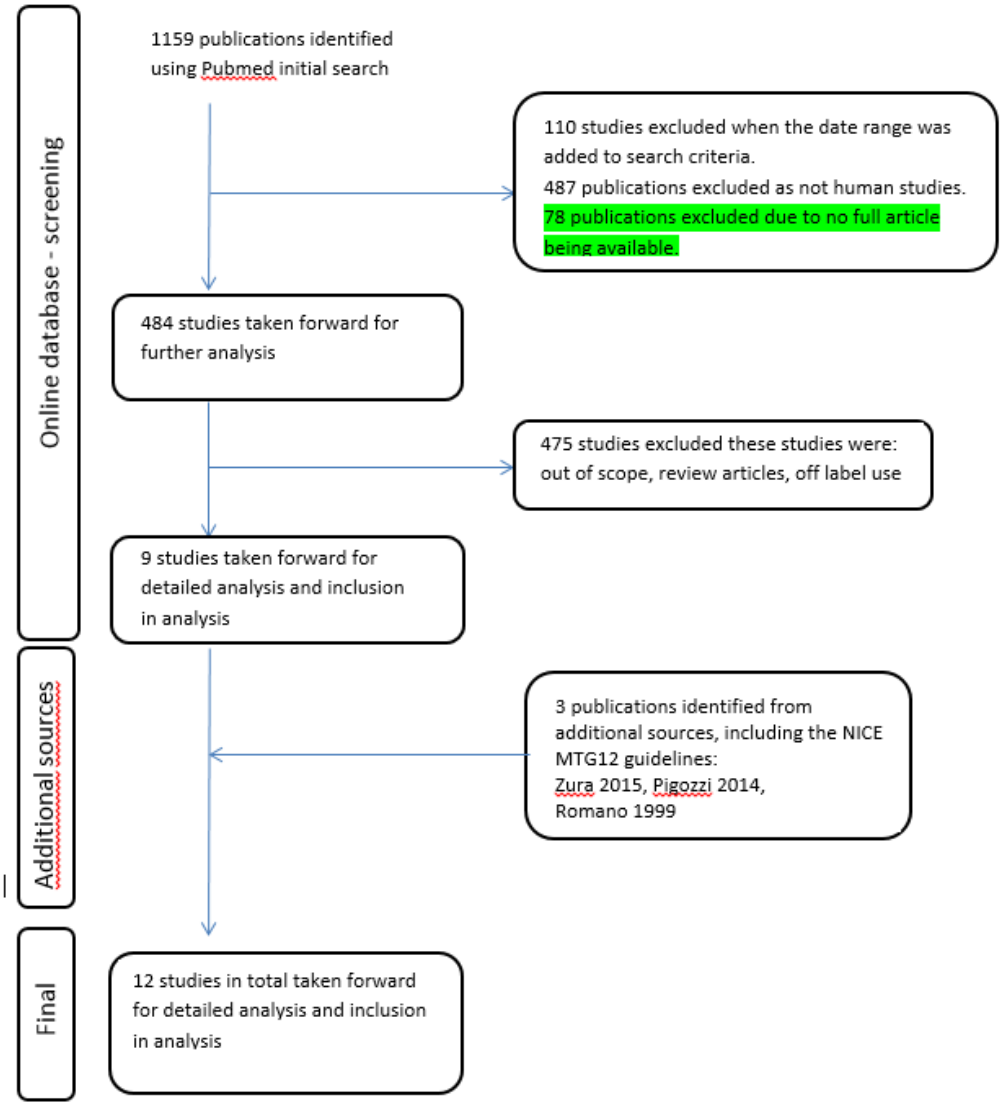
2) Comparator – Surgical treatment of nonunion
(nonunion*[Title] OR nonunion*[Title]) AND (surgical[Title] OR surgery[Title] OR treatment*[Title])

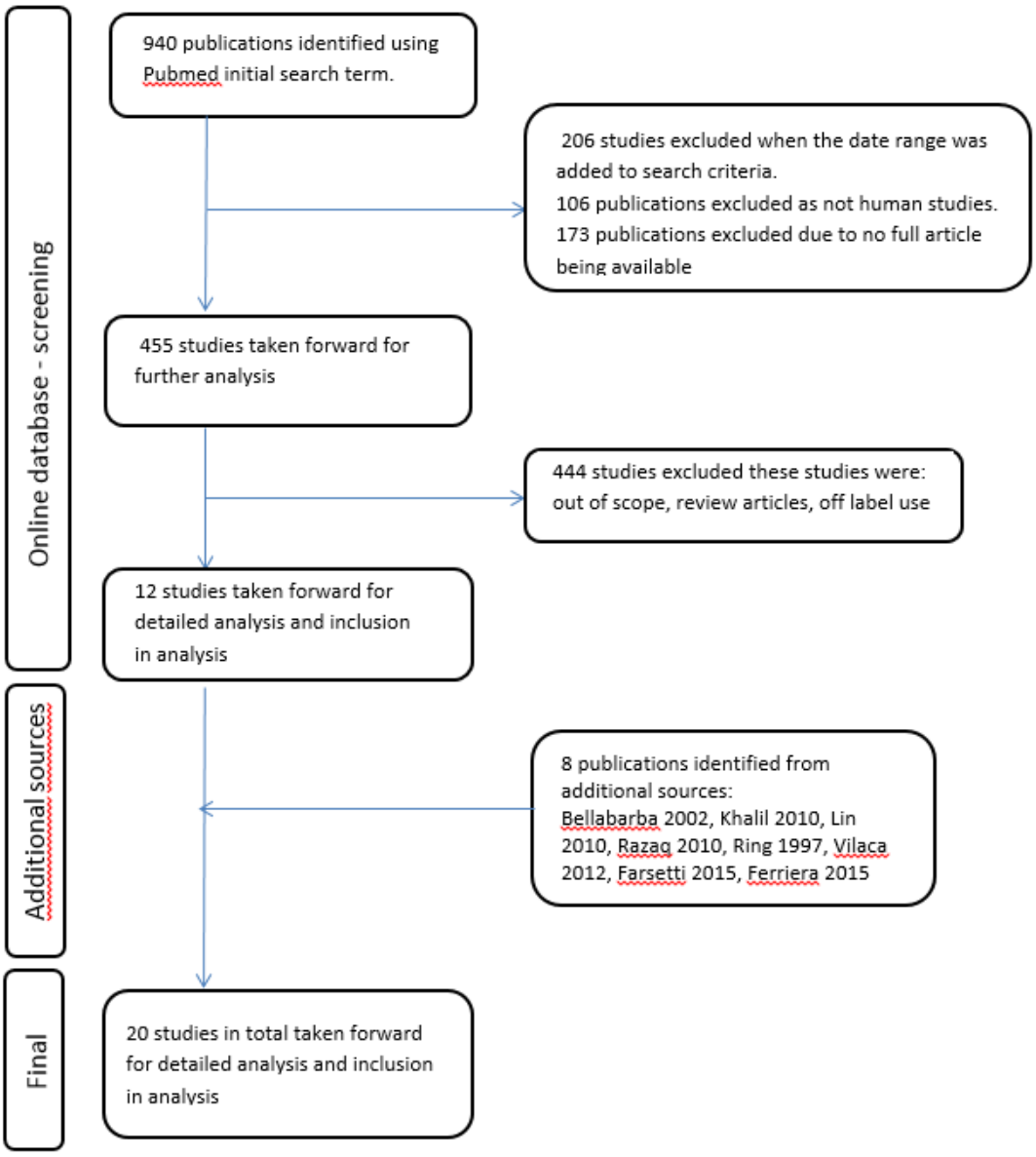
Table 12. Inclusion and Exclusion criteria EXOGEN™

Inclusion criteria	Population/patient group/indication	Nonunions
	Intervention	EXOGEN™ / Low Intensity Pulsed Ultrasound / Sonic Accelerated Fracture Healing System Surgery, surgical
	Comparison	N/A
	Endpoint	Healing rates, healing time
	Study design	Prospective Retrospective analysis of prospective data, provided data had not been previously published for the same analysis 12 or more patients in each series
	Linguistic limitations	English

Exclusion criteria	Specify whether there were any special exclusion criteria	Fresh fractures, fracture healing complications in children Those not in the scope Lack of healing data fewer than 12 patients Non-English No availability of a full article Pre 1992

Flow chart for EXOGEN™ studies





Appendix 2 – Our search strategy

Literature search: EXOGEN™ Single Technology Assessment

Databases: Ovid Embase, Ovid MEDLINE, Cochrane Library, PubMed, WHO International Clinical Trials Registry Platform (ICTRP)
Date: 2016.03.04
Results: 439 records (473 including duplicates)
Peer review: Gyri Hval Straumann, research librarian
Searched by: Ingrid Harboe, research librarian

Search strategies

Database: Embase 1974 to 2016 March 03,
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Date: 2016.03.04
Results: 369

#	Searches	Results
1	Fractures, Ununited/ use pmez [Medline]	5066
2	fracture nonunion/ use oemezd [Embase]	8913
3	Pseudarthrosis/	15869
4	(un-unite* or ununite* or non-unite* or nonunite* or nonunion* or non-union* or (delay* adj3 union*) or pseudarthrosis).tw.	33494
5	or/1-4	45963
6	Ultrasonic Waves/ use pmez [M]	108
7	ultrasound/ use oemezd [E]	127259
8	Ultrasonic Therapy/ use pmez [M]	8537
9	ultrasound therapy/ use oemezd [E]	7760
10	(ultraso* or (ultra adj1 so*) or ultra-so*).tw.	665989
11	(LIPU or LIPUS or PLIUS).tw.	674
12	(SAFHS or sonic accelerated fracture healing system).tw.	58
13	Exogen.tw.	361
14	or/6-13	695726
15	5 and 14	538
16	remove duplicates from 15	369
17	16 use pmez [M]	44
18	16 use oemezd [E]	325

Database: Cochrane Library
Date: 2016.03.04
All Results (39): Cochrane Reviews (18)
Other Reviews (5)
Trials (12)
Technology Assessments (3)
Economic Evaluations (1)

ID	Search	Hits
#1	MeSH descriptor: [Fractures, Ununited] this term only	129
#2	MeSH descriptor: [Pseudarthrosis] this term only	22
#3	(un-unite* or ununite* or non-unite* or nonunite* or nonunion* or non-union* or (delay* near3 union*) or pseudarthrosis)	765
#4	#1 or #2 or #3	765
#5	MeSH descriptor: [Ultrasonic Therapy] this term only	756
#6	MeSH descriptor: [Ultrasonic Waves] this term only	0
#7	(ultraso* or ultra-sound* or ultrasonic* or ultra-sonic*)	23647
#8	(LIPU or LIPUS or PLIUS)	28
#9	(SAFHS or sonic accelerated fracture healing system)	3
#10	Exogen	11
#11	#5 or #6 or #7 or #8 or #9 or #10	23658
#12	#4 and #11	39

Database: PubMed (ahead of print articles)
Date: 2016.03.04
Results: 64 hits
Search ((((((((pubstatusaheadofprint) OR publisher [sb])))) AND ((((ultrasound[Title/Abstract] OR ultrasonic[Title/Abstract] OR exogen[Title/Abstract] OR "sonic accelerated fracture healing system"[Title/Abstract])))) AND fracture*[Title/Abstract])))) OR ((exogen[Title/Abstract]) AND fracture*[Title/Abstract])

Source: WHO International Clinical Trials Registry Platform (ICTRP)
Date: 2016.03.04
Results: 5 hits
Search: exogen

Appendix 3 – Quality assessment of studies using EXOGEN™

Literature search: EXOGEN Single Technology Assessment

Databases: Ovid Embase, Ovid MEDLINE, Cochrane Library, PubMed, WHO International Clinical Trials Registry Platform (ICTRP)
Date: 2016.03.04 plus update search 2018.02.06.
Total results: 527 records
439 records 2016.03.04 (473 including duplicates)
88 records 2018.02.06. (118 including duplicates)
Peer review: Gyri Hval Straumann, research librarian
Searched by: Ingrid Harboe, research librarian

Search strategies
Database: Embase 1974 to 2016 March 03,
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Date: 2016.03.04 plus 2018.02.06
Results**:** 369 plus 88

#	Searches	Results
1	Fractures, Ununited/ use pmez [Medline]	5066
2	fracture nonunion/ use oemezd [Embase]	8913
3	Pseudarthrosis/	15869
4	(un-unite* or ununite* or non-unite* or nonunite* or nonunion* or non-union* or (delay* adj3 union*) or pseudarthrosis).tw.	33494
5	or/1-4	45963
6	Ultrasonic Waves/ use pmez [M]	108
7	ultrasound/ use oemezd [E]	127259
8	Ultrasonic Therapy/ use pmez [M]	8537
9	ultrasound therapy/ use oemezd [E]	7760
10	(ultraso* or (ultra adj1 so*) or ultra-so*).tw.	665989
11	(LIPU or LIPUS or PLIUS).tw.	674
12	(SAFHS or sonic accelerated fracture healing system).tw.	58
13	Exogen.tw.	361
14	or/6-13	695726
15	5 and 14	538
16	remove duplicates from 15	369
17	16 use pmez [M]	44
18	16 use oemezd [E]	325

Database: Cochrane Library
Date**:** 2016.03.04 plus 2018.02.06
All Results (50): Cochrane Reviews (18 plus 1)
Other Reviews (5)
Trials (12 plus 9)
Technology Assessments (3 plus 1)
Economic Evaluations (1)

ID	Search	Hits
#1	MeSH descriptor: [Fractures, Ununited] this term only	129
#2	MeSH descriptor: [Pseudarthrosis] this term only	22
#3	(un-unite* or ununite* or non-unite* or nonunite* or nonunion* or non-union* or (delay* near3 union*) or pseudarthrosis)	765
#4	#1 or #2 or #3	765
#5	MeSH descriptor: [Ultrasonic Therapy] this term only	756
#6	MeSH descriptor: [Ultrasonic Waves] this term only	0
#7	(ultraso* or ultra-sound* or ultrasonic* or ultra-sonic*)	23647
#8	(LIPU or LIPUS or PLIUS)	28
#9	(SAFHS or sonic accelerated fracture healing system)	3
#10	Exogen	11
#11	#5 or #6 or #7 or #8 or #9 or #10	23658
#12	#4 and #11	39

Database: PubMed (ahead of print articles)
Date: 2016.03.04 plus 2018.02.06
Results: 64 plus 6 hits
Search ((((((((pubstatusaheadofprint) OR publisher [sb])))) AND ((((ultrasound[Title/Abstract] OR ultrasonic[Title/Abstract] OR exogen[Title/Abstract] OR "sonic accelerated fracture healing system"[Title/Abstract])))) AND fracture*[Title/Abstract])))) OR ((exogen[Title/Abstract]) AND fracture*[Title/Abstract])

Source: WHO International Clinical Trials Registry Platform (ICTRP)
Date: 2016.03.04 plus 2018.02.06
Results: 5 plus 10 hits
Search: exogen

Appendix 4 – Quality assessment of studies using EXOGEN™

Mayr 2000

Study name	Mayr 2000	
Study question	Response	How is the question addressed in the study?

	yes/no/not clear/N/A)	
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		

Gebauer 2005

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, nonunion 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		

Jingushi 2007

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		

Nolte 2001

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, nonunion type, fixation type present before, at the start of, and during ultrasound treatment.
Have the authors taken account of the confounding factors in	Yes	Data stratified by the patient and fracture characteristics.

the design and/or analysis?		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		

Lerner 2004

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		

Romano 1999

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		

Pigozzi 2004

Study name:	Pigozzi 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	All patients who met the inclusion criteria were included

Was the exposure accurately measured to minimise bias?	Yes	Patients followed the recommended 20 minutes and no other treatment was conducted
Was the outcome accurately measured to minimise bias?	Not clear	Information not provided
Have the authors identified all important confounding factors?	Yes	Complexities of biological, mechanical and anatomical factors are all noted
Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	
Was the follow-up of patients complete?	Yes	All patients were followed to healing
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		

Watanabe 2013

Study name: Watanabe 2013		
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 diagnostic criteria for a delayed union and nonunion are variable throughout the literature, and our definition for this study was derived in part from the US Food and Drug Administration's definition.
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?	Yes	
Have the authors identified all important confounding factors?	Yes	"We did not conduct a controlled double-blind since this study design would not be acceptable. It denies treatment to one study arm and it may be impossible to carry out in patients suffering with infected pseudoarthrosis. In all of the treated cases in this study, the course of fracture healing showed over a period of time that there was no change in the healing process in the presence of an infection and, therefore, the patient was his own control. The only new event

		that was introduced at the start of treatment was the use of low intensity pulsed ultrasound."
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?	Yes	"The cut-off values for success of LIPUS therapy were obtained by the calculation of sensitivities, specificities and the area under the curves obtained using receiver operating characteristics (ROC) analysis, if statistically significant differences were obtained in the ratio scale. Relative risk of failure of nonunion healing by LIPUS therapy and 95 % confidence interval were also calculated. Multiple logistic analyses were applied to find out the independent risk factors for failure of LIPUS therapy for delayed union and nonunion. Statistical significance was set at p\0.05. All statistical tests were performed using JMP software
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Zura 2015

Study name: Zura 2015		
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?	Yes	The authors tested whether patients were systematically lost to follow-up, potentially distorting results, by examining demographics of the patients lacking outcome information (Table 2). Patients lacking an outcome were on average 3.7 years younger ($p < 0.0001$), male ($p < 0.01$), and stopped using LIPUS 39 days sooner ($p < 0.0001$). Because these differences are not linked to worse outcomes, it suggests that the heal rate data were not biased in favour of healing by exclusion of patients with missing outcomes.

Have the authors identified all important confounding factors?	Yes	This cohort is perhaps the largest group of consistently defined chronic nonunion fractures in the literature. By contrast, most case series are small, reporting a few dozen patients. In addition, bias can be significant in case series because they are often written when a clinician notices something out of the ordinary:
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?	Yes	Conservatively, only p-values <0.01 were reported, since a large sample size is prone to yield statistical significance in the absence of clinical significance; using a smaller p-value threshold reduces this risk. Ninety-five percent confidence intervals (CIs) were calculated for percent-healed point estimates. All data were analyzed using SAS software, v9.3 (Cary, NC).
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Roussignol 2012

Study name: Roussignol 2012		
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 inclusion criteria met the 2002 AFSSAPS (French medical product safety authority) recommendations
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?	Yes	Consolidation was checked clinically (absence of pain on axial and rotational stress) and radiologically on plain AP and lateral views at 6 months (continuity of at least three cortices). Radiological consolidation was confirmed by an independent investigator.
Have the authors identified all important confounding factors?	Not clear	
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	See above

Was the follow-up of patients complete?	Yes	Patients were followed up at 6 weeks, and 3 and 6 months after initiation of stimulation. AP and lateral X-rays views were taken at each consultation, plus CT at 3 and 6 months. At each consultation, the patient was asked to indicate the transmitter site and compliance was checked by a monitor on the device, which showed the number of treatment cycles the patient had performed at home.
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	Precision of analysis is not stated
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Data are extracted from the Norwegian patient register

Helsedirektoratet God helse - gode liv

Contacts with pseudoathrosis (ICD-10-code M84.1) as main diagnosis and at least on surgical procedure electively treated at publicly funded Norwegian somatic hospitals in year 2013.

		Unique patients				All contacts						
Health region (Norwegian *Helseregion)*	Hospital	In-patient care	Day-care	Out-patient care	Total	In-patient care	Day-care	Out-patient care	Total	Average length of stay (for in-patient contacts)	Average contact cost (in Norwegian kroner)	Summarized contact cost (in Norwegian kroner)
West	Haukeland	25	2	2	29	26	2	2	30	4.2	62,043.6	1,861,306.7
	Voss	2	0	0	2	3	0	0	3	1.7	57,513.7	172,541.2
	Haugesund	4	5	1	10	4	5	1	10	3.0	41,813.8	418,138.2
	Stord	1	2	0	3	1	2	0	3	1.0	25,535.4	76,606.1
	Førde	6	0	0	6	6	0	0	6	5.3	85,560.5	513,363.3
	Stavanger	36	6	1	43	37	6	2	45	4.0	78,032.3	3,511,453.6
	Haraldsplass	4	0	0	4	4	0	0	4	3.0	43,638.2	174,553.0
	Total	78	15	4	97	81	15	5	101	3.9	66,613.5	6,727,962.0
Middle	St Olavs hospital - Trondheim	8	12	1	21	8	12	2	22	9.0	46,127.9	1,014,813.5
	St Olavs hospital - Orkdal	1	1	0	2	1	1	0	2	2.0	73,095.3	146,190.6
	Ålesund	5	3	3	11	5	3	10	18	3.2	18,110.6	325,990.0
	Molde	3	2	0	5	3	2	0	5	4.7	76,795.4	383,977.1
	Kristiansund	4	0	0	4	4	0	1	5	3.3	50,886.6	254,433.2
	Sykehuset Levanger	4	2	0	6	4	2	1	7	1.5	35,237.4	246,662.1
	Sykehuset Namsos	0	2	0	2	0	2	0	2		17,968.1	35,936.2
	Total	25	22	4	51	25	22	14	61	4.9	39,475.5	2,408,002.7
North	UNN Tromsø	8	2	2	12	8	3	2	13	3.1	63,782.8	829,175.9
	UNN Narvik	0	1	0	1	0	1	0	1		22,011.4	22,011.4
	UNN Harstad	3	3	0	6	3	4	0	7	3.3	37,818.4	264,728.8
	Nordlandssykehuset - Bodø	14	4	0	18	14	4	2	20	3.1	46,999.1	939,982.6
	Nordlandssykehuset - Vesterålen	1	1	0	2	1	2	0	3	1.0	20,880.6	62,641.8
	Nordlandssykehuset - Rana	0	1	0	1	0	1	0	1		24,141.6	24,141.6
	Helse Finnmark - Hammerfest	1	1	0	2	1	1	0	2	3.0	41,241.8	82,483.7
	Helse Finnmark - Kirkenes	1	0	0	1	1	0	0	1	3.0	42,089.9	42,089.9
	Total	28	13	2	43	28	16	4	48	3.1	47,234.5	2,267,255.8
South-East	Sykehuset Innlandet - Elverum/Hamar	10	4	0	14	10	4	1	15	4.4	64,061.9	960,928.9
	Sykehuset Innlandet - Kongsvinger	2	0	0	2	2	0	0	2	3.0	55,028.6	110,057.1
	Sykehuset Innlandet - Tynset	1	1	0	2	1	1	0	2	2.0	104,357.0	208,714.1
	Sykehuset Innlandet - Lillehammer	7	1	0	8	7	1	0	8	2.6	46,305.8	370,446.8
	Drammen	7	5	1	13	8	5	2	15	5.9	33,248.6	498,728.4
	Bærum	8	1	0	9	8	1	0	9	1.6	52,148.9	469,340.4
	Kongsberg	4	2	0	6	5	2	0	7	3.2	80,195.8	561,370.3
	Ringerike	2	1	0	3	2	1	0	3	.5	30,032.3	90,096.9
	Skien/Porsgrunn	7	3	0	10	7	3	0	10	4.3	52,251.5	522,515.0
	Rjukan	5	1	0	6	5	1	0	6	3.2	59,611.0	357,665.9
	Sykehuset Østfold	9	7	4	20	9	7	6	22	3.8	34,711.6	763,654.5
	Akershus	20	15	0	35	22	15	4	41	5.0	48,983.6	2,008,325.7
	OUS (kan ikke splittes)	23	14	2	39	23	14	9	46	5.1	40,537.8	1,864,738.6
	Kristiansand	11	3	0	14	11	3	1	15	4.7	67,746.3	1,016,194.2
	Arendal	4	0	1	5	4	0	1	5	3.5	65,166.4	325,832.2
	Flekkefjord	3	2	0	5	3	2	0	5	2.3	47,273.3	236,366.4
	Sykehuset i Vestfold (kan ikke splittes)	9	1	0	10	9	1	0	10	2.8	47,364.0	473,640.1
	Martina Hansens hospital	1	0	0	1	1	0	1	2	6.0	14,299.5	28,599.1
	Lovisenberg	2	0	0	2	2	0	0	2	3.0	66,330.1	132,660.3
	Diakonhjemmet	5	0	1	6	5	0	2	7	2.6	63,312.4	443,187.0
	Betanien Telemark	1	0	0	1	1	0	0	1	62.0	185,440.3	185,440.3
	Total	141	61	9	211	145	61	27	233	4.4	49,907.7	11,628,502.2
Total		**272**	**111**	**19**	**402**	**279**	**114**	**50**	**443**	**4.2**	**51,990.3**	**23,031,722.7**

Only elective

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