# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

# Evaluation Pathway Programme assessment

# Specification for manufacturer/sponsor submission of evidence

**March 2010**

# Contents



# List of tables and figures

Please include a list of all tables and figures here with relevant page references.

## Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Clinical Excellence (NICE) as part of the Evaluation Pathway Progamme assessment process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented.

Use of the specification and completion of appendices 1 to 13 (sections 9.1 to 9.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document 'Evaluation Pathway Programme methods guide' (www.nice.org.uk), particularly with regard to the 'reference case'. Users should see NICE's 'Evaluation Pathway Programme process guide' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

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

**A submission should be as brief and informative as possible**. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. Confine yourself to completing the response sections and appendices only. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the submission. Appendices are not normally presented to the Medical Technology Advisory Committee. Any additional appendices should be clearly referenced in the body of the submission. **Appendices should not be used for core information that has been requested in the specification.** For example, it

is not acceptable to attach a key study as an appendix and to complete the clinical-effectiveness section with ‘see appendix X’. Clinical study reports and protocols should not be submitted, but must be made available on request.

Studies should be identified by the first author or study ID, rather than by relying on numerical referencing alone (for example, ‘Study 123/Jones et al.[126]’ rather than ‘One study[126]’).

For information on submitting economic models, disclosure of information and equality and diversity, users should see ‘Related procedures for evidence submission’, section 8.

# Section A – Decision problem

Section A is completed in conjunction with the Scope and Briefing note by the NICE Evaluation Pathway Programme Technical Team. Manufacturers and sponsors are requested to confirm the information presented in section A and complete/amend where appropriate, and submit in advance of the full submission (for details on timelines, see the NICE document 'Evaluation Pathway Programme process guide' – www.nice.org.uk). Information for use (IFU), a (draft) assessment report produced by the regulatory authorities (for example, CE marking)), and a (draft) technical manual for devices should be provided (see section 7.1, appendix 1).

## 1 Description of technology under assessment

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

The MIST Therapy system

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

The MIST Therapy system aims to promote wound healing in chronic, "hard to heal" and acute wounds by delivering low energy, low intensity ultrasound to the wound bed via a continuous saline mist. The mist generated has a relatively uniform droplet size and is intended to act as a conduit for transmitting ultrasonic energy to the treatment site, supporting energy transfer to a beneficial depth to reduce bioburden and stimulate cells.

Wound healing involves three phases: inflammation, proliferation and remodelling. In non-healing wounds, progression through the three phases is impeded and standard wound care becomes ineffective. The MIST Therapy system addresses these barriers to wound healing by stimulating the healing environment, actively treating the wound bed and accelerating the healing process. The MIST Therapy device also promotes wound healing through wound cleansing and maintenance debridement by the removal of yellow slough, fibrin tissue, exudate and bacteria.

The use of the MIST Therapy system has been shown to:

- have an anti-inflammatory effect in wounds with chronic inflammation.
- stimulate the production of chemical mediators which activate fibroblasts resulting in early release of growth factors.
- increase deposition of blood vessels providing a stronger more natural collagen in granulation tissue.
- decrease bioburden through mechanical stress, including Methicillin-Resistant *Staphylococcus aureus* (MRSA), Vancomycin-Resistant *Enterococcus* (VRE) and *Pseudomonas* species.
- increase blood flow.
- bathe and cleanse the wound painlessly.

The non-contact MIST Therapy device comprises a generator with user-friendly controls, a transporter head to transport energy, a single use applicator and a sterile saline bottle. After the wound surface area is selected on the MIST Therapy device, the appropriate treatment time is automatically determined. Once the applicator and saline bottle are attached, treatment commences. A continuous mist is delivered across the wound bed via slow even strokes. The distance between the applicator and the wound bed is 0.5cm to 1.5cm. An audible and visual bubbling may occur until the treatment is complete and the generator switches off automatically.

1.3 Does the technology have CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The British Standards Institution certified on the 25th April 2007 that the Celleration MIST Therapy system indicated for the promotion of wound healing meets the relevant quality assurance system for CE marking (CE 512325).

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the (draft) assessment report (for example, CE marking)). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

Response There are no issues or special conditions regarding the EC Certificate. It was issued by BSI Product Services on April 25, 2007, is still valid and will be valid until April 24, 2012.

1.5 What is the (anticipated) CE marking, including the indication for use.

Response The Celleration, Inc MIST Therapy system (generator and applicator) is considered a Class IIa Sterile, Active Therapeutical Device per MDD 93/42/EEC, Annex IX, Rules 9 and 11. The sterile saline (an accessory) is used for irrigation and is considered a medical device classified as IIa, per rule 4, section 1.4 of Annex IX. The germicidal wipes used for cleaning the Generator and equipment are considered a medical device and are classified also as IIa, per rule 4, section 1.4 of Annex IX.

The indication for use as specified by the FDA is: The MIST Therapy System produces a low energy ultrasound-generated mist used to promote wound healing through wound cleansing and maintenance debridement by the removal of yellow slough, fibrin, tissue exudates and bacteria.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

MIST Therapy's End-Stage Renal Disease Patients Presenting Wounds (Celleration) - NCT01125735. This study is not yet open for participant recruitment. Phase IV. Study start date: September 2010. Estimated completion date: May 2012

MIST, A comparative study of MIST Therapy, Versajet and Scalpel debridement in reducing bacterial contamination. This is an in vitro test mechanism: Initial statistical analysis: August 2010. Estimated Publication date Spring 2011.

Evaluation of clinical and biologic action of low frequency noncontact ultrasound treatment in chronic wounds. This study has enrolled all patients with ongoing data collection. Estimated completion date: November 2010.

Use of MIST Ultrasound Therapy to minimize oedema, bruising and scarring after cosmetic surgery procedures of the face and body. Study enrolment will begin in October 2010. Estimated completion: January 2011.

Effect of Non-Contact Low Frequency Ultrasound treatment on suspected deep tissue injury healing. Retrospective Analysis completed. Estimated publication late Spring 2011.

A Prospective Assessment of the effectiveness of MIST Therapy on Suspected Deep Tissue Injury. Start date November 2010, completion date June 2011.

Trillium Healthcare, AZ- A Comparative, Prospective, Randomized Study of MIST Therapy versus Negative Pressure Wound Therapy on the Rate of Healing and Economic Value in the Treatment of Full Thickness Wounds in the Long-term Acute Care Hospital and Skilled Nursing Setting. Patient enrollment began September 2010, estimated completion date April 2011.

UK experiences of MIST will be written up as a series of posters from evaluation centres in the UK including: Bradford Royal Infirmary; St Charles Hospital – London, Salford Diabetic Foot Clinic, Salford Complex Wound Clinic. St Charles Hospital was able to safe a diabetic patient's foot from amputation through the use of MIST. To be presented at Wounds UK, Harrogate, November 2010.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Response There are 12 devices available for evaluation within the UK and one device purchased. The MIST device and consumables are already available to purchase, however, a full launch will be carried out once Drug Tariff status is obtained for the consumable kits.

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

ResponseYes, the MIST Therapy System has been cleared by the FDA under 510(k) K032378 and 510(k) K050129. The indication for use is: “The MIST Therapy System produces a low energy ultrasound-generated mist used to promote wound healing through wound cleansing and maintenance debridement by the removal of yellow slough, fibrin, tissue, exudates and bacteria.”

1.9 Please complete the table below. If the list price of the technology(s) is not yet known, provide details of the anticipated list price, including the range of possible list prices.

Response

**Table A1 Unit costs of technology being appraised**

| | |
|---|---|
| List price (excluding VAT) | Device purchase price is £12,500<br>MIST may be rented quarterly or annually, annual rental is £7,500 (£625/month/£29 per working day) |
| Average selling price | |
| Range of selling prices | |
| Consumables (if applicable)<br>Per consumable: name, list price, average/range selling price, frequency | MIST Single Use Applicator Kit<br>Consumable price submitted to drug tariff is £35 each. |
| Service/maintenance cost and frequency (if applicable) | N/A |
| Anticipated life span of technology | 5 years |
| Average length of use per treatment | 5-7minutes |
| Average frequency of use | 3 times/week |
| Average cost per treatment | Dependent on number of treatments being carried out daily.<br>If 5 patients treated daily £40/patient/day |

1.10 Would this technology require changes to the way current services are organised or delivered?

Response MIST would require no additional services in usage. The treatment would be carried out following normal working practices within the clinic setting or the community at dressing change. In some instances it may be necessary to see the patients more frequently than in current practice as for optimum results treatment is recommended 3 times weekly, however, the clinical benefits should outweigh the implication of another clinic visit.

1.11 Would other facilities or technologies need to be acquired or used alongside the technology being considered, in order for the claimed benefits to be realised?

Response The standard dressing treatment would be utilised alongside MIST Ultrasound Therapy. No other technology has to be considered when implementing MIST.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements or a need for monitoring of patients over and above usual clinical practice for this technology?

Response No.  MIST is safe in use and can be used on a variety of wound types from chronic non-healing through to acute wounds.  The clinician should consider the clinical objectives alongside the product benefits.

1.13 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Advanced wound dressings will be used in conjunction with the MIST Therapy system.

1.14 Does the technology require additional infrastructure to be put in place?

No additional infrastructure is required.

# 2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being considered in the scope.

MIST Therapy system is indicated for chronic and “hard to heal” wounds including diabetic foot ulcers, arterial ulcers, pressure ulcers and venous ulcers. It is also indicated for acute wounds including traumatic wounds, post-surgical wounds and burns.

Common symptoms of ulceration include pain, exudate and odour, and these symptoms are frequently associated with poor sleep, loss of mobility and social isolation.

Leg ulceration is most commonly caused by venous hypertension resulting from valvular incompetence in the superficial, deep or perforating veins. Sustained venous hypertension causes swelling, restricted blood flow and damage to the skin and other tissues.

A pressure ulcer is an area of damage to the skin and underlying tissue that is caused by unrelieved pressure, friction and/or shear forces. A severe ulcer is susceptible to infection and may be life-threatening.

Foot ulceration is a common complication of diabetes. Gradual loss of sensation renders the foot susceptible to even minor trauma. Susceptibility to infection and peripheral vascular disease inhibit healing once injury has occurred and may lead to gangrene and amputation. The age-adjusted rate of lower-limb amputation is estimated to be 15 times higher in individuals with diabetes than in the general population.

2.2 How many patients are assumed to be eligible for treatment in England and Wales? Present separate results for any groups and subgroups considered in the scope. How are these figures derived? Also present results for the subsequent 5 years.

Between 1.5 and 3.0/1000 people have active leg ulcers. Prevalence increases with age to about 20/1000 in people aged over 80 years. Most leg

ulcers are secondary to venous disease; other causes include arterial insufficiency, diabetes and rheumatoid arthritis. The prevalence of venous leg ulcers is estimated to be 150,000 in the UK with 28% of ulcers remaining open for more than 2 years.

The prevalence of diabetic foot ulcers is estimated to be 84,000 in the UK annually and 5,000 diabetic patients undergo amputation annually.

The prevalence of pressure ulcers is estimated to be 412,000 in the UK annually, 24% of which are grade 3 or 4 ulcers.

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

Pressure relieving devices: the use of pressure relieving devices for the prevention of pressure ulcers in primary and secondary care Clinical Guideline CG7 October 2003. Review date: September 2010

Pressure ulcers: The management of pressure ulcers in primary and secondary care
Clinical Guideline CG29 September 2005. Review date: September 2010

Infection control, prevention of healthcare-associated infection in primary and community care
Clinical Guideline CG2 June 2003. Review date: September 2009

Prevention and treatment of surgical site infection
Clinical Guideline CG74 October 2008. Review date: October 2011

Type 2 diabetes: prevention and management of foot problems
Clinical Guideline CG10 January 2004. Review date: May 2011

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Most health economies develop their own regional wound care management guidelines although NICE has published guidance for specific types of wounds.

- One of the recommendations for the treatment of patients with grade 3-4 pressure ulcers is that optimum wound healing environment should be created by using modern dressings (for example, hydrocolloids, hydrogels, hydrofibres, foams, films, alginates, soft silicones) (NICE Clinical guideline CG29, 2005).

- NICE recommends that a structured approach is used to improve the management of surgical wounds and an appropriate interactive dressing is used surgical wounds that are healing by secondary intention (NICE Clinical guideline CG74, 2008).

- For the treatment and prevention of diabetic foot ulcers (NICE Clinical guideline CG10, 2004):

    - Patients with non-healing or progressive ulcers with clinical signs of active infection (redness, pain, swelling or discharge) should receive intensive, systemic antibiotic therapy.
    - In the absence of strong evidence of clinical or cost effectiveness, healthcare professionals should use wound dressings that best match clinical experience, patient preference, and the site of the wound, and consider the cost of the dressings.

- Wounds should be closely monitored and dressings changed regularly.
- Dead tissue should be carefully removed from foot ulcers to facilitate healing, unless revascularisation is required.

In general, wound care recommendations describe the options for treatment (e.g. debridation, intensive, systemic antibiotic therapy) but specific wound dressings and wound care interventions are not defined.

The MIST Therapy system would be used once standard wound care has failed to heal the wound or as an alternative method for debridement in acute wounds. Published reports indicated MIST Therapy provides optimal patient benefit for wounds that have failed to heal after 30 days. MIST Therapy in combination with standard of care dressing has been shown to

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Response Sharp debridement requires highly trained professionals to carry out the procedure which in some instances means that the treatment may not be carried out quickly. MIST is safe in a clinical professionals hands allowing debridement of yellow sloughy tissue to be carried out safely.

2.6 Please identify the main comparator(s) and justify their selection.

The most commonly used wound dressings for the different types of wounds have been identified as the main comparators:
Venous and arterial ulcers – compression bandaging
Other chronic and “hard to heal” wounds – foam dressings
Acute wounds – surgical debridement
Infected wounds – silver dressings

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Response The device utilises sterile saline and Ultrasound if the device is used correctly adverse events should not occur unless the patient is allergic to saline. Over 35,000 patient treatments have been carried out and only 14 adverse events have been reported over the past 5 years.

Please see contraindications in use: *Do not use near electronic implants/ prosthesis (e.g. Near or over the heart or over the thoracic area if the patient is using a cardiac pacemaker); on the lower back during pregnancy or over the pregnant uterus; over areas of malignancies.*

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Response

Location of care: Treatment may take place in acute or primary care. The device is portable which enable usage within both the clinical and home care settings. For optimum usage e.g. for greater patient throughput the ideal location of care would be: Complex wound clinics; Leg ulcer clinics; Diabetic foot ulcer clinics.

Staff usage: Treatment would be carried out during normal dressing changes, ideally 3 times per week, on small wounds the treatment takes between 5-7 minutes. MIST cleanses the wound during treatment, removing one of the standard treatment parameters.

Administration costs, monitoring and tests: No extra costs or tests are required.

Data sources, estimates and values: No further sources/costs should be required.

2.9 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Response N/A.

# 3 Equity and equality

*The National Institute for Health and Clinical Excellence (NICE) is committed to promoting equality and eliminating unlawful discrimination. We aim to comply fully with all legal obligations to:*
*• promote race and disability equality and equality of opportunity between men and women, and*
*• eliminate unlawful discrimination on grounds of race, disability, age, sex and gender, sexual orientation, and religion or belief in the way we carry out our functions and in our employment policies and practices.*

## *3.1 Identification of equity and equalities issues*

3.1.1 Please specify any issues relating to equality and diversity in NICE guidance, or protocols for the condition for which the technology is being used.

No relevant equality and diversity issues have been identified for MIST Therapy

3.1.2 Are there any equality and diversity issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the assessment)?

No relevant equality and diversity issues have been identified for MIST Therapy

3.1.3 How have the clinical and economic analyses addressed these issues?

Not applicable

# 4 Statement of the decision problem

In this section the decision problem that the submission addresses is specified in the second column, Final scope issued by NICE. This is derived from the final scope issued by NICE completed by the NICE Evaluation Pathway Programme Technical Team in the first instance and should state the key parameters that the information in the evidence submission will address. The manufacturer or sponsor should specify any additions and/or amendments to the decision problem and rationale in the third and fourth column.

| | Final scope issued by NICE | Decision problem addressed in the submission | Rationale if different from the scope |
|---|---|---|---|
| Population | Patients with chronic, “hard to heal” and acute wounds. | Use of a NLFU protocol with standard of care to reduce the time to healing resulting in a cost effective solution | |
| Intervention | MIST Therapy system | | |
| Comparator(s) | Advanced wound dressings: alginate, capillary action, charcoal, film, foam, honey, hydrocolloid, hydrocolloid fibrous, hydrogel sheets, iodine, low/non-adherent wound contact layer, silicone and silver.<br>Any other wound care interventions including Negative Pressure Wound Therapy and combinations of treatments with MIST Therapy. | Hydrosurgery systems<br>Sharp debridement (scalpel) | MIST is effective in breaking down slough and reducing bacterial burden |
| Outcomes | Outcome measures include rate of healing, wound size, wound volume, wound area, treatment time. wound closure, time to heal, pain score, quality of life and bioburden.<br>Adverse events and safety related complications. | Recurrence | Studies show no recurrence following MIST treatment |
| Cost analysis | Comparative cost analysis of the MIST Therapy system and the most relevant UK comparator:<br>Venous and arterial ulcers – compression bandaging<br>Other chronic and | MIST Therapy reduces the cost to achieve healing as described in studies provided herein. Using the MIST Therapy in combination with | |

| | | | |
|---|---|---|---|
| | "hard to heal" wounds – foam dressings<br>Acute wounds – surgical debridement<br><br>The cost analysis should consider the price of the technology including capital costs, debridement costs, consumables, staff, running and maintenance costs, length of treatment and time to heal. The costs associated with complications, adverse events and recurrence relating to the use of the device and the comparator should be considered.<br><br>Sensitivity analysis should be used to address all parameter and model uncertainties including time to heal and recurrence. This should also include assessment of impact of the price differential between advanced wound dressings and the MIST Therapy system. | standard of care results in an average cost savings in U.S dollars of $2,556/patient or $2,555,620/1,000 patients Driver (2010).<br><br>Cost modelling was conducted using the British<br>£ in a de novo cost analysis comparing clinical effectiveness of MIST Therapy and the standard of care for treating chronic wounds from the perspective of the UK/Wales NHS. Net benefit to the NHS in England is approximately £ 352 million per patient. | |
| Subgroups to be considered | None | | |
| Special considerations, including issues related to equity or equality | N/A | | |

# Section B – Clinical effectiveness and cost

# 5 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Evaluation Pathway Programme methods guide'. The review of the clinical evidence should be systematic and transparent and a suitable instrument for reporting such as the PRISMA Statement should be used (http://www.prisma-statement.org/statement.htm).

## *5.1 Identification of studies*

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 7.2, appendix 2.

Response All of the data included within the search are in the study library database of Celleration. The studies included were consistent with Medline data search.

## *5.2 Study selection*

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

**Table B1 Eligibility criteria used in search strategy**

| | **Clinical effectiveness** |
|---|---|
| Inclusion criteria | Population<br>Interventions<br>Outcomes<br>Study design<br>Language restrictions |
| Exclusion criteria | Population<br>Interventions<br>Outcomes<br>Study design<br>Language restrictions |

Pubmed database search results include only those publications specific to the following search terms: low-frequency, noncontact ultrasound; MIST Therapy; MIST; MIST Therapy ultrasound; acoustic pressure wound therapy; MIST ultrasound therapy; low-frequency ultrasound; low-frequency noncontact ultrasound; noncontact low-frequency nonthermal ultrasound therapy.

5.2.2 The numbers of studies included and excluded at each stage should be reported

Response There are over 199 studies carried out on MIST low frequency ultrasound which cover 2 RCT's and over 7 peer reviewed articles. There are many published trials, retrospective trials, case series reports and case studies held on file. Not all of these studies are available through data base searches however are available upon request. Any publications listed in database searches not specific to the search terms were excluded from the final search results

**Complete list of relevant studies (RCTs and non-RCTs)**

5.2.3 Provide details of **all** studies that compare the intervention with other therapies in the relevant patient group. Highlight which of these studies compare the intervention directly with the appropriate comparator(s) referred to in the decision problem. If there are none, please state this. The list must be complete and will be validated by

independent searches conducted by the External Assessment Group. This should be presented in tabular form. A suggested format is presented below.

**Table B2 List of relevant studies**
Table B2 is attached as an excel spreadsheet.

Response The studies included within this table include all independent and sponsored studies which Celleration Inc is aware of including those from the database search: RCT's, retrospective studies, in vivo studies, in vitro studies, case studies and posters. Due to the number of studies (n = 199) **Table B2 is attached as an excel spreadsheet.** These studies are all listed within the first two tables following which only those studies meeting the criteria of the various sections within this document are included.

5.2.4 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of study data required, this should be indicated.

Response Case series, case studies and in vivo/in vitro work have been excluded from the documentation requesting further information as no statistical significance can be gained from them, therefore 22 studies are include within the following reviews where appropriate. All the studies are available on request totalling 199.

## *5.3 Summary of methodology of relevant studies*

5.3.1 As a minimum, the summary should include information on the study(s) under the subheadings listed in this section. It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE.

**Methods**

5.3.2 Describe the study(s) design and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one study.

**Table B3 Comparative summary of methodology of the studies**
Table B3 is attached as an excel spreadsheet.

The studies included within this table include all independent and sponsored studies which Celleration Inc is aware of including: RCT's, retrospective studies, in vivo studies, in vitro studies, case studies and posters. Due to the number of studies (n = 199) **Table B3 is attached as an excel spreadsheet.**

**Participants**

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the study. The following table provides a suggested format for the eligibility criteria for when there is more than one study. Highlight any differences between the studies.

**Table B4 Eligibility criteria in the studies**

| Study no. | Primary study | Inclusion criteria | Exclusion criteria |
|---|---|---|---|
| Study 1 | Ultrasound Therapy for Recalcitrant Diabetic Foot Ulcers: Results of a Randomized, Double Blind, Controlled Multicenter Study | Diabetes Type 1 or 2 with a chronic diabetic foot ulcer (>30 days in duration), Wagner grade 1 or 2 ulcer on plantar surface of the foot without exposure to bone, muscle, ligaments or tendons were considered. No clinical signs of infection and not taking antibiotics. At least 18 years of age. Recorded glysosylated haemoglobin value of <12 within 30 days of the study start day. Wound size >1cm$^2$ and <16cm$^{2.}$ Following screening those with a toe/brachial index has to be >0.7. | Ulcers secondary to non-diabetic aetiology. Gangrene located anywhere on the index foot. Patient has received radiation or chemotherapy within the past 6 months any oral, intravenous or topical antibiotic used within the past 7 days. Any use of cytokine or growth factory therapy in the past 7 days. Significant medical condition that would impair healing (other than diabetes). Patients with known or suspected osteomyelitis. Wounds that would require surgical correction in order for the index ulcer to heal. Use of corticosteroids or immunosuppressive drugs 7 days before the study or if anticipated that patient may require use during the course of the trial. Patients on renal or peritoneal dialysis. History of, or current, alcohol or drug abuse. Patients in whom offloading device is contra-indicated or who cannot be appropriately fitted. Patients with known HIV-positive status, cancer, hepatitis, or bleeding disorder. |

| Study no. (acronym) | Primary study ref. | Inclusion criteria | Exclusion criteria |
|---|---|---|---|
| Study 2 | Treatment of Ischemic Wounds with Noncontact Low-Frequency Ultrasound: The Mayo Clinic Experience, 2004-2006 | Wounds were present for minimum of 8 weeks before enrolment. Documented chronic critical limb ischemia as determined by transcutaneous oximetry (≤ 40 mm Hg) and included those with diabetes mellitus, chronic renal failure, prior vascular reconstructive surgery and osteomyelitis. | Patients undergoing chemotherapy and those who were unable or unwilling to attend 3 treatment sessions per week. |
| Study 3 | | n/a | n/a |
| Study 4 | The Effect of Noncontact, Low Intensity, Low-Frequency Therapeutic Ultrasound on Lower-Extremity Chronic Wound Pain: A Retrospective Chart Review | Ongoing painful, chronic, non-healing, lower extremity wounds of various causes. (the wounds had been present on average for 17 months, range 5 weeks to 96 month) | n/a |
| Study 5 | Expedited Wound Healing with Noncontact, Low-frequency Ultrasound Therapy in Chronic Wounds; A Retrospective Analysis | Below the knee lower extremity wounds of varied aetiology. | Those that did not meet the criteria of 3x treatments a week, had significant discontinuity of treatments, did not complete the treatment regimen or had participated in a previous study of MIST therapy in critical limb ischemia at the wound centre were excluded |
| Study 6 | Noncontact Ultrasound Therapy for Adjunctive Treatment of Non-healing Wounds: Retrospective Analysis | Aged over 18, had a non-healing wound of any aetiology and received non-contact ultrasound therapy at least 2 times per week during the study period. Non-healing wounds were those that had failed to progress to at least 15% closure in the prior 2 weeks of therapy. Wounds were selected on the basis of the need for cleansing and debridement. | If therapy was provided fewer than 2 times per week, their life expectancy was less than 6 months or non-contact ultrasound therapy was contraindicated when an electrical implant or prosthesis is located near the treatment site or the treatment site is on the lower back during pregnancy, over the uterus during pregnancy or over an area of malignancy. |

| Study no. (acronym) | Primary study ref. | Inclusion criteria | Exclusion criteria |
|---|---|---|---|
| Study 7 | Adjunctive Use of Acoustic Pressure Wound Therapy for Treatment of Chronic Wounds - A Retrospective Analysis | Aged over 18 years with a non-healing wound of any aetiology who had received ultrasound therapy to the wound a minimum of 2 times per week during the study period. Non-healing wounds were those that had failed to progress with at least 15% closure in the prior 2 weeks of therapy. | If therapy was provided fewer than 2 times per week, their life expectancy was less than 6 months or non-contact ultrasound therapy was contraindicated when an electrical implant or prosthesis is located near the treatment site or the treatment site is on the lower back during pregnancy, over the uterus during pregnancy or over an area of malignancy. In general, contraindications for the use of any ultrasonic device would also include use on epiphyseal plates of children. |
| Study 8 | A Retrospective Analysis of Acoustic Pressure Wound Therapy: Effects on the Healing Progression of Chronic Wounds | Aged over 18 years with a non-healing wound of any aetiology who had received ultrasound therapy to the wound a minimum of 2 times per week during the study period. | If therapy was provided fewer than 2 times per week, their life expectancy was less than 6 months. |
| Study 9 | Evaluation of Clinical Effectiveness of MIST Ultrasound Therapy for the Healing of Chronic Wounds | Chronic wounds of any aetiology on the lower extremity if they had been present for longer than 4 weeks and had failed to improve despite the clinic's standard approach for wound care during a 2-week period. Failure to improve was defined as less than 15% reduction in wound area. Were enrolled despite the presence of multiple comorbidities. Patients were 18 years or older. | Patients with clinical signs of infection or those taking antibiotics were excluded from the study. Were unable to achieve 3 visits per week for treatment or the need for urgent revascularisation. |

| Study no. (acronym) | Primary study ref. | Inclusion criteria | Exclusion criteria |
|---|---|---|---|
| Study 10 | Use of Non-Contact Low Frequency Ultrasound In the Treatment of Chronic Foot and Leg Ulcerations: A 51 Patient Analysis | Chronic non-healing wounds of 3 to 18 months duration. Patient's comorbidities or previous failure in ulcer therapy did not exclude them. Patients were not excluded if osteomyelitis was present. | n/a |
| Study 13 | Acoustic pressure wound therapy for management of mixed partial- and full-thickness burns in a rural wound center | Mixed partial thickness burns involving the trunk, extremities or both averaging 7% of total body area (range: 1% to 24%) | n/a |
| Study 11, 12, 14 - 199 | No inclusion / exclusion criteria's were set for these studies | n/a | n/a |

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups.

**Study 1: RCT, diabetic foot ulcers.** The study demographics did not differ between the two treatment groups, however, the initial mean wound area was larger in the sham treatment group than ultrasound ($p<0.05$). A cox proportional hazards regression analysis was carried out, results show the effect of the treatment variable to be statistically significant ($p=0.0061$) even with the inclusion of the important effects of the other variables. And statistically significant ($P=0.0287$) when all the variables were forced into the model.

Ultrasound is not contraindicated for infected wounds but because investigator consensus on the clinical signs and symptoms that would define an infection in the patient population was found to be sufficiently difficult to ascertain it was decided to exclude infected wounds from the study.

**Study 2: RCT, Ischemic wounds**. The demographic, baseline and arterial characteristics did not differ significantly between groups. A difference in $TcPO_2$ was observed (63% vs. 57%) which was not statistically significant.

**Outcomes**

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the study protocol as primary or secondary, and whether they are relevant with reference to the decision problem. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one study.

**Table B5 Primary and secondary outcomes of the studies**

| Study no. (acronym) | Primary outcome(s) and measures | Reliability/validity/ current use in clinical practice | Secondary outcome(s) and measures | Reliability/validity/ current use in clinical practice |
|---|---|---|---|---|
| Study 1 | Determine the safety and efficacy of a new, non-contact, kilohertz ultrasound therapy for the healing of recalcitrant diabetic foot ulcers | *p*= 0.0366, currently being used in over 600 sites in the US | Complete wound closure, bacterial reduction , reduction of surgical/sharp debridement's | Healing rates, *p* = 0.05; Reduced sharp/surgical debridement, *p*= 0.05 |

| Study no. (acronym) | Primary outcome(s) and measures | Reliability/validity/ current use in clinical practice | Secondary outcome(s) and measures | Reliability/validity/ current use in clinical practice |
|---|---|---|---|---|
| Study 2 | 50% wound healing at 12 weeks | *p*=0.001 | the predictive value of baseline $TCPO_2$ | Determination of $TCPO_2$ in the dependent position can provide valuable information regarding a patient's likelihood of healing. |
| Study 3 | Effects of noncontact ultrasound on wound bacteria levels | 50% reduction in bacteria in 2 weeks | Wound healing | 26% reduction in area, 20% reduction in volume in 2 weeks |
| Study 4 | Reduction of wound pain after ultrasound therapy | *p*=0.0003, | Reduction of narcotics for pain | 1/3 of patients had a lack of narcotic prescription |
| Study 5 | Proportion of wounds healed and wound volume reduction | *p*= 0.009 | The rate of healing | The slope of regression line in the MIST arm was steeper than the slope of in the control arm. *p*= .002 |
| Study 6 | MIST Therapy impact on non-healing wounds | Wound area was reduced by 79%. *P*< .0001 | Increased granulation tissue, improved peri-wound area, reduction in fibrin slough, reduction in exudate, improvement in patient pain score | 46% of patients had granulation tissue post MIST versus 32% prior. P< 0.0001; Improved peri-wound tissue 75% after versus 20% prior. P< 0.001; Reduction in fibrin/slough was 55% after versus 27% prior. P=0.0116; Reduction of exudate 88% versus 73% post MIST. P=0.002 |

| Study no. (acronym) | Primary outcome(s) and measures | Reliability/validity/ current use in clinical practice | Secondary outcome(s) and measures | Reliability/validity/ current use in clinical practice |
|---|---|---|---|---|
| Study 7 | Wound healing | Wound area reduced by 88%, *p*< 0.0001 volume reduced by 100%, *p*< 0.0001; 38% of wounds healed in 6.8 weeks | Increased granulation tissue, improved peri-wound area, reduction in fibrin slough, reduction of eschar, reduction in exudate, improvement in patient pain score | 54% increase in granulation tissue. *P*<0.0001; 41% decrease in slough, *p*< 0.006; 100% decrease in eschar, *p*=0.39; 27% increase in wounds without exudate, *p*=0.006; 29% Normal periwound skin, *p*=0.0001; 78% Reduction in pain, *p*<0.0001. |
| Study 8 | Wound healing | Wound area was reduced by 92%, *p*<0.0001. 24% of wounds healed in 4.2 weeks | Increased granulation tissue, Reduction of wound slough, reduction of eschar, reduction of pain | 52% increase in granulation tissue, *p*<0.0001; 44% increase in wounds without slough, *p*<0.001; 22% increase in wounds without slough, *p*=0.02; 78% Reduction of pain, *p*< 0.0001 |
| Study 9 | Determine the incidence of wound closure | 69% of wounds healed, mean time 7 weeks, *p*>0.05 | Area and volume reduction, microcirculation , reduction of hospital admissions | No hospital admission in MIST treated patients, *p*= 0.04; Area and volume reduction decreased as indicated through the healing numbers |
| Study 10 | Wound healing in chronic ,recalcitrant lower-leg and foot ulcerations | 94.9% wound volume reduction, *p*< 0.0001 | Recurrence of original wounds 30 months post treatment, treatment frequency | There was 0 recurrence, patients that received treatments 5x/week (56%) had higher rates of healing versus 3x/week (40%). |
| Study 11 | n/a | n/a | n/a | n/a |
| Study 12 | Removal of necrotic tissue | Wound healed in 6.5 weeks | Preparation for grafting | Graft was not required as wound healed. |

| Study no. (acronym) | Primary outcome(s) and measures | Reliability/validity/ current use in clinical practice | Secondary outcome(s) and measures | Reliability/validity/ current use in clinical practice |
|---|---|---|---|---|
| Study 13 | Healed wounds | All burns healed (1-45 weeks) | Non-hypertrophic scars, repigmentation, | Pliable, nontrophic scars developed in 86% of the patients, regimentation was seen in 79% of patients |
| Study 14 | Wound healing | Complete closure in 10 weeks | Pain reduction | Pain reduced gradually over time, patient was pain and narcotic free by 6 weeks |
| Study 15 | Wound preparation for closure | 2 or 3 underwent successful surgical closure | Speed healing of infected post surgical wounds | 4-12 weeks of combined NPWT and APWT Therapy resulted in 99-100% wound volume reduction and 82-100% wound area reduction, reduced size by 60% |
| Study 16 | Accelerated healing and pain relief | Wound area reduced 76% in 3 weeks, pain was reduced to 0 in 5 of 6 subjects | Enhance granulation tissue formation, reduce exudate, reduce fibrin and slough | Complete epithelialization was achieved in 1-3 weeks, minimal serous fluid, reduced fibrin, slough and eschar |
| Study 17 | Wound bed preparation for subsequent therapies | APWT was effective in preparing wounds for subsequent therapy | Presence of granulation tissue, reduction in wound area, reduction in wound volume | 4/5 wounds had 100% granulation, wound area decreased by 97%, wound volume decreased by 99% |
| Study 18 | Preparation for surgical closure | Reduced time to closure by 9-16 days | n/a | n/a |
| Study 19 | Non-surgical debridement and bioburden reduction | 70% of wound surface was covered with granulation tissue after 7 months | Reduction in wound size | Wound size decreased from 1.1% to 31.3% after 37 treatments. |
| Study 20 | Healed wounds | 4/6 wounds healed after 22 days and 5-13 APWT treatments | n/a | n/a |
| Study 21-24 & Studies 27-196 | | | n/a | n/a |

| Study no. (acronym) | Primary outcome(s) and measures | Reliability/validity/ current use in clinical practice | Secondary outcome(s) and measures | Reliability/validity/ current use in clinical practice |
|---|---|---|---|---|
| Study 25 | Improved wound healing with combined therapies | Reduction in wound volume or closure was achieved in 2-3 weeks, NLFU was performed 1-3 times per week | Reduction in necrotic tissue and slough, improved granulation tissue, improved periwound tissue, decreased wound exudate, decreased pain | There was noted reduction in fibrin and slough in all cases, there was improved granulation and periwound tissue in all cases, some subjects demonstrated a decrease in wound exudate, and those patients who reported pain at onset had a reduction in pain. |
| Study 26 | Improved wound healing or closure with combined therapies | Combined therapy of HVPC and APWT demonstrated healing in a mean of 17.6 weeks where the mean onset was 30.7 weeks | Reduction in necrotic tissue and slough, as well as 100% granulation tissue | All wounds demonstrated a reduction in necrotic tissue |
| Study 197 | Animal model to assess the effects of low frequency ultrasound | Positive effects were noted | Collagen deposition and the prevalence of blood vessels | Significantly more blood vessels were present in the treatment versus the sham group, p=0.05 |
| Study 198 | Ultrasound would differentially affect the intercellular signalling pathways in wound healing in the animal model | Ultrasound treated fibroblasts exhibited a much earlier release of growth factors | n/a | n/a |
| Study 199 | Accelerated healing & Debridement | Significant improvement in wound bed | n/a | Wound reduction of 41-73% in 10-14 weeks in recalcitrant leg ulcers |

**Statistical analysis and definition of study groups**

5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of

how the analysis took account of patients who withdrew. The following table provides a suggested format for presenting the statistical analyses in the studies when there is more than one study.

**Table B6 Summary of statistical analyses in studies**

| Study no. | Primary study ref. | Hypothesis objective | Statistical analysis | Sample size, power calculation | Data management, patient withdrawals |
|---|---|---|---|---|---|
| Study 1 | Ultrasound Therapy for Recalcitrant Diabetic Foot Ulcers: Results of a Double Blind, Multicenter RCT | Determine the effectiveness of Ultrasound therapy for healing diabetic foot ulcers | Fisher's exact test, two sample t-test, Cox proportion hazard regression, simple frequency test | 55 patients; p= 0.036 | Case report, clinical monitors, central data processing, SAS software. Intent to treat group 133 subjects, 12 did not meet criteria, 24 treated less than 10 weeks, 42 protocol violations |
| Study 2 | Treatment of Ischemic Wounds with Noncontact Low-Frequency Ultrasound: The Mayo Clinic Experience, 2004-2006 | Noncontact, low frequency ultrasound will impact healing chronic ulcers in the ischemic patient | Mann-Whitney *U* test for quantitative analysis of baseline demo & clinical characteristics; Wilcoxom sum-rank test for transcutaneous oxygen measurements; Chi square test for proportion of patients healed | 70 patients, 35 treated with ultrasound therapy, 35 in standard of care; p<0.001 63% in treatment group vs. 29% in control group | Data was collected on case report forms and complied by the facility staff; JMP 4.0 statistical software was used for analysis |
| Study 3 | The Impact of Noncontact, Nonthermal Low-Frequency Ultrasound on Bacterial Counts in Experimental and Chronic Wounds | The use of low frequency ultrasound will reduce bacteria in chronic wounds, the results from in vitro work could be duplicated in humans | Descriptive stats of bacteria quantities in CFU/g of tissue; 4x 107 pre-treatment versus 2 x 107 post 2 weeks treatment | 11 subjects | Data was collected on case report forms by the investigative site staff; Data collection was monitored by sponsor staff |

| Study no. | Primary study ref. | Hypothesis objective | Statistical analysis | Sample size, power calculation | Data management, patient withdrawals |
|---|---|---|---|---|---|
| Study 4 | The Effect of Noncontact, Low Intensity, Low-Frequency Therapeutic Ultrasound on Lower-Extremity Chronic Wound Pain: A Retrospective Chart Review | MIST Therapy administered to patients with painful non-healing wound will reduce the patient's pain | Wilcoxon signed - rank test, 1 tailed p=0,003; 2 tailed p=0.007 | 15 subjects; p=0.0003 | Retrospective data collected on case report forms by investigative site |
| Study 5 | Expedited Wound Healing with Noncontact, Low-frequency Ultrasound Therapy in Chronic Wounds; A Retrospective Analysis | Low frequency ultrasound will improve wound healing over standard of care in chronic lower extremity wounds | Mann-Whitney is of baseline demo & clinical characteristics; Chi square test for proportion of patients healed; Fisher exact test for small counts; One-way ANOVA for rate of healing/slope of regression | 210 subjects; p= 0.009 for wound healing; p=.002 Slope of regression | Case report forms were completed by the investigative site staff ; JMP 4.0 statistical software |
| Study 6 | Noncontact Ultrasound Therapy for Adjunctive Treatment of Non-healing Wounds: Retrospective Analysis | Time to healing in chronic wounds would be improved | Wilcoxon signed - rank test for paired comparisons with continuous variables, McNemar test for paired comparisons with categorical variables | 76 subjects; p<.0001 for granulation and periwound tissues; p=0.0116 for reduction of fibrin; p=0.0002 for exudate reduction; p<.0001 reduction in wound size | Case report forms were completed by the investigative site staff ; SAS version 9.1.3 |

| Study no. | Primary study ref. | Hypothesis objective | Statistical analysis | Sample size, power calculation | Data management, patient withdrawals |
|---|---|---|---|---|---|
| Study 7 | Adjunctive Use of Acoustic Pressure Wound Therapy for Treatment of Chronic Wounds - A Retrospective Analysis | Improved healing will be seen with low frequency ultrasound | Wilcoxon signed - rank test for paired comparisons with continuous variables, McNemar test for paired comparisons with categorical variables; | 41 subjects with 52 wounds; p<0.0001 for area, volume, granulation, periwound tissue and pain; p=.006 decreased fibrin | Data was compiled by the investigative site personnel; Statistical analysis was done using SAS version 9.1.3 |
| Study 8 | A Retrospective Analysis of Acoustic Pressure Wound Therapy: Effects on the Healing Progression of Chronic Wounds | Chronic wounds will heal faster with low frequency ultrasound | Wilcoxon signed - rank test for paired comparisons with continuous variables, McNemar test for paired comparisons with categorical variables; | 48 subjects; p<.0001 increase granulation, decrease fibrin, decrease wound size; p=0.02 decrease eschar | Data was compiled by the investigative site personnel; Statistical analysis was done using SAS version 9.1.3 |
| Study 9 | Evaluation of Clinical Effectiveness of MIST Ultrasound Therapy for the Healing of Chronic Wounds | Wounds treated with MIST Therapy will heal faster | Kaplan-Meier method | 23 subjects with 29 lower extremity wounds; p=0.04 with MIST alone; p=.005 with MIST plus another therapy | Data was compiled by the investigative site personnel; Statistical was done by investigative site personnel. |
| Study 10 | Use of Non-Contact Low Frequency Ultrasound In the Treatment of Chronic Foot and Leg Ulcerations: A 51 Patient Analysis | Low frequency ultrasound will improve the rate of wound healing in the recalcitrant lower extremity ulcer | Statistical method other than covariance is not mentioned in study | 51 subjects; p<.0001 for healing, SOC versus MIST, reduction of wound volume | Data was compiled through retrospective review by the site investigative staff |

| Study no. | Primary study ref. | Hypothesis objective | Statistical analysis | Sample size, power calculation | Data management, patient withdrawals |
|---|---|---|---|---|---|
| Study 11-199 | Variety of case series and case studies on various wound aetiologies - not large enough study groups to provide statistical outcome data | | | | |

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Response

| Study no. | Primary study ref. | Sub Group Analysis |
|---|---|---|
| **Study 1** | Ultrasound Therapy for Recalcitrant Diabetic Foot Ulcers: Results of a Randomized, Double Blind, Controlled Multicenter Study | Biopsies were carried out to review the bioburden and despite a lack of clinical signs of infection they demonstrated a significant bioburden. Quantitative culture biopsies, 86% of the ultrasound treated wounds and 93% of sham treated wounds demonstrated $>10^5$ aerobic bacteria/gram of tissue (pre-specified). |
| **Study 2** | Treatment of Ischemic Wounds with Noncontact Low-Frequency Ultrasound: The Mayo Clinic Experience, 2004-2006 | $TcPO_2$ were evaluated to assess the potential to heal ischemic wounds. $TcPO_2$ levels 20-40mm/Hg and less than 20mm/Hg effect on wound healing (pre-specified) |
| **Study 3** | The Impact of Noncontact, Nonthermal Low-Frequency Ultrasound on Bacterial Counts in Experimental and Chronic Wounds | All results were pre-specified |
| **Study 5** | Expedited Wound Healing with Noncontact, Low-frequency Ultrasound Therapy in Chronic Wounds; A Retrospective Analysis | Slope of regression to look at speed of healing (pre-specified) |
| **Study 6** | Noncontact Ultrasound Therapy for Adjunctive Treatment of Non-healing Wounds: Retrospective Analysis | Multiple clinical symptoms of non-healing wounds, granulation and periwound tissue, fibrin, and exudate; Pain reduction |
| **Study 7** | Adjunctive Use of Acoustic Pressure Wound Therapy for Treatment of Chronic Wounds - A Retrospective Analysis | Multiple clinical symptoms of non-healing wounds, granulation and periwound tissue, fibrin, and exudate; Pain reduction |
| **Study 8** | A Retrospective Analysis of Acoustic Pressure Wound Therapy: Effects on the Healing Progression of Chronic Wounds | Multiple clinical symptoms of non-healing wounds, granulation and periwound tissue, fibrin, and exudate; Pain reduction |

| Study no. | Primary study ref. | Sub Group Analysis |
|---|---|---|
| **Study 9** | Evaluation of Clinical Effectiveness of MIST Ultrasound Therapy for the Healing of Chronic Wounds | Optimum duration of treatment; effect of low frequency ultrasound on microcirculatory flow |
| **Study 10** | Use of Non-Contact Low Frequency Ultrasound In the Treatment of Chronic Foot and Leg Ulcerations: A 51 Patient Analysis | The effect of ultrasound on microbes; 30 month survivorship for recurrence of ulceration. |
| **Study 197** | Effects of ultrasound delivered through a mist of saline to wounds in mice with diabetes mellitus | Assessment of histological findings in MIST treated and sham group |
| **Study 198** | Physiological effect of ultrasound mist on fibroblasts | Assessment of growth factors |

5.3.8

**Participant flow**

Where applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who were lost to follow-up or withdrew from the study.

Response

**Study 1: RCT, diabetic foot ulcers.** 133 patients were eligible to enter the study and randomised and allocated to each treatment group. 8 patients were withdrawn as the wound size exceeded the study limits. 4 patients were withdrawn as their wounds were <4 weeks duration and additional 24 were lost to follow-up before completing the required 10 week course of therapy leaving 97 considered evaluable according to the study criteria. An interim audit resulted in 42 patients bring withdrawn due to protocol violations resulting in 55 patients for the efficacy analysis group.

**Study 2: RCT, Ischemic wounds.** 70 patients were randomly assigned to receive 12 weeks treatment, 35 MIST, 35 Control. There were no patient drop outs during the study.

**Study 5: Retrospective analysis on chronic wounds.** 325 patient records were retrieved for the record review. Of these 162 were excluded as they had not been treated 3x per week or had significant discontinuity of treatments. The remaining 163 patients met the inclusion criteria for MIST and similarly 92 matched control patients treated during the study period were identified.

## *5.4 Critical appraisal of relevant studies*

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should also be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the External Assessment Group.

5.4.2 Please provide as an appendix a complete quality assessment for each study. See section 7.3, appendix 3 for a suggested format. For the quality assessments use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd).

## *5.5 Results of the relevant studies*

5.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one study, tabulate the responses.

5.5.2 For each outcome for each included study, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim study data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that study. Analytical adjustments should be described to cater for the interim nature of the data.

Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.

- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Response

| **Study no.** | **Measurement** | **The size of the effect** | **Confinterval** | **Number of participants** | **Clearly indicate any Interim study data** | **Report any other analysis performed** |
|---|---|---|---|---|---|---|
| **Study 1** | % of healing | Control (Sham treatment group) overall had larger wounds | 95% | 133 intent to treat; 78 removed due to protocol deviations; 27 subjects ultrasound treated; 28 subjects in the sham group | Planned interim analysis was scheduled for 10/2003, revealed no significant differences between treatment regimens | Quantitative culture biopsies, 86% of the US treated wounds and 93% of sham treated wounds demonstrated >105 aerobic bacteria/gram of tissue (pre-specified |

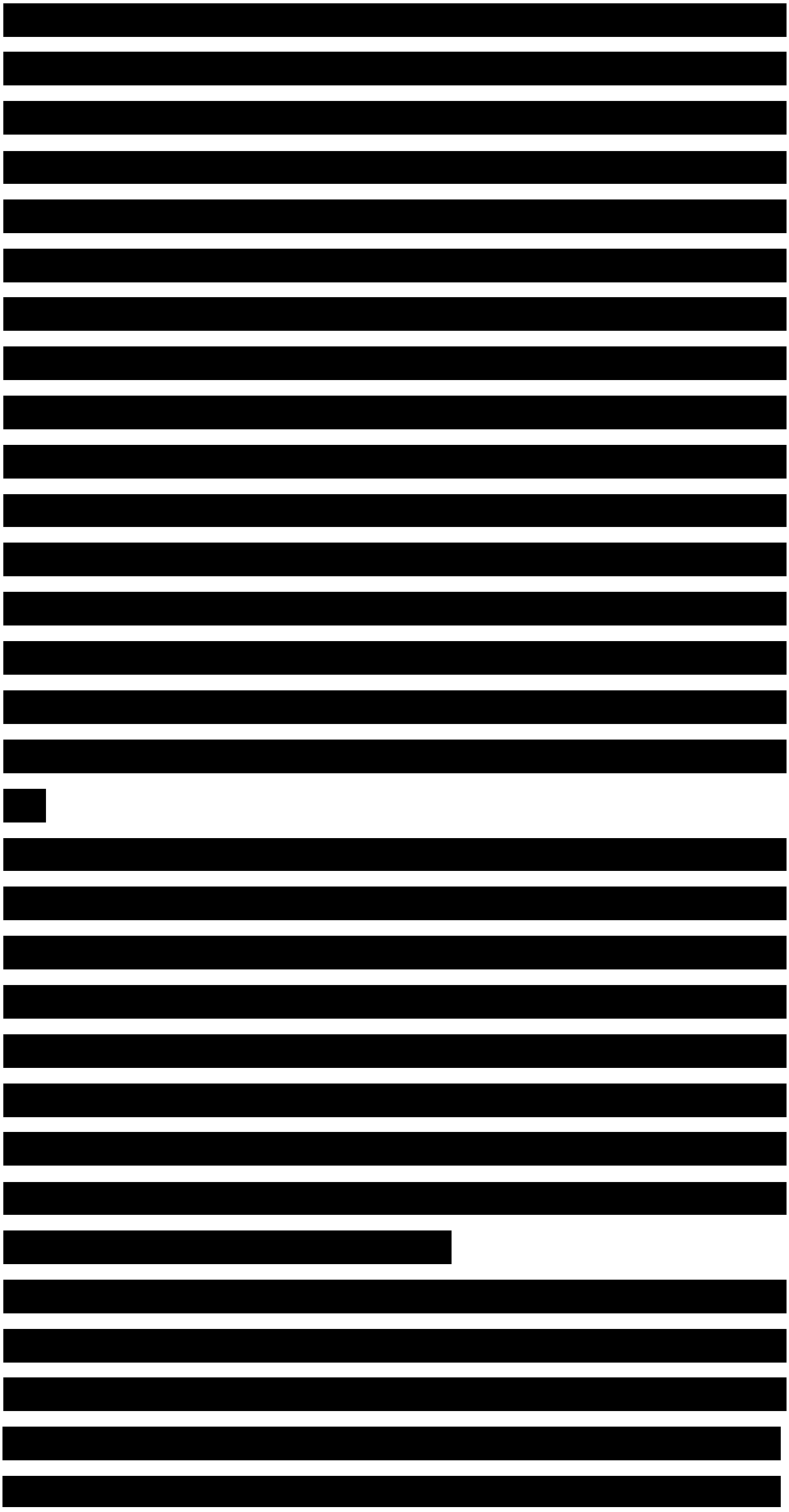
| Study no. | Measurement | The size of the effect | Confinterval | Number of participants | Clearly indicate any Interim study data | Report any other analysis performed |
|---|---|---|---|---|---|---|
| **Study 2** | 50% wound reduction in 12 weeks | There were no significant differences between the control and treatment group | 95% | 70 patients, 35 subjects ultrasound treated and 35 subjects in standard of care | | TcPO2 levels 20-40mm/Hg and less than 20mm/Hg effect on wound healing (pre-specified) |
| **Study 3** | CFU/gram of tissue | 4 combined studies, 1 pig model, 2 in vitro model and 1 in vivo model | 95% | 11 subjects in the in vivo portion of the study | In vitro Ultrasound penetration in wounded & intact skin, sham vs. treated; in vitro model stain and count live/dead bacteria; in vivo after 1 week, Ultrasound decease in bacterial counts | All results were pre-specified |
| **Study 4** | VAS pain scale | 15 Subjects ( 8 subjects vascular ischemia, 4 subjects sickle cell anaemia, 3 subjects venous stasis disease) | 95% | 15 Subjects | | |
| **Study 5** | % of healing | 163 subjects treated with MIST, 47 subjects in standard of care group; 51 ischemic subjects, 62 neuropathic subjects, 31 venous stasis subjects, 66 multi-factorial wounds | 95% | 417 intent to treat, 207 excluded due to lack of 3x/week treatment | | Slope of regression to look at speed of healing (pre-specified) |
| **Study 6** | % of healing | | 95% | 76 consecutive subjects, single arm, retrospective study | | Multiple clinical symptoms of non-healing wounds, granulation and periwound tissue, fibrin, and exudate; Pain reduction |

| Study no. | Measurement | The size of the effect | Confinterval | Number of participants | Clearly indicate any Interim study data | Report any other analysis performed |
|---|---|---|---|---|---|---|
| **Study 7** | % of healing | | 95% | 41 subjects, 52 wounds | | Multiple clinical symptoms of non-healing wounds, granulation and periwound tissue, fibrin, and exudate; Pain reduction |
| **Study 8** | % of healing | | 95% | 48 subjects, single arm, retrospective study | | Multiple clinical symptoms of non-healing wounds, granulation and periwound tissue, fibrin, and exudate; pain reduction |
| **Study 9** | % of wound healing | | 95% | 23 subjects, 29 wounds; prospective, non-comparative clinical outcomes trial | | Optimum duration of treatment; effect of low frequency ultrasound on microcirculatory flow |
| **Study 10** | % of wound healing | | 95% | 51 subjects, open label, nonrandomized, baseline-controlled clinical case series | | The effect of ultrasound on microbes; 30 month survivorship for recurrence of ulceration |
| **Study 25** | % of healing | | | 4 subjects, case series of chronic or delayed healing wounds | | |
| **Study 26** | % of healing | | | 10 subjects, non-healing wounds for a mean of 30.7 weeks, retrospective data collection | | |
| **Study 197** | impact on wound tissues | | | 50 mice, 27 ultrasound treated, 23 sham treatment | | Assessment of histology findings in MIST treated and sham group |
| **Study 198** | Effect on dermal fibroblasts | | | Dermal fibroblasts, 6 well plates for protein and 24 well plates for mitogenic factors | | Assessment of growth factors |
| **Study 11 -20** | These studies are educational assess of ultrasound, as well as small consecutive case series to demonstrate clinical uses of MIST Therapy | | | | | |
| **Study 21-24, 27-196 & 199** | Variety of case series and case studies on various wound aetiologies - not large enough study groups to provide statistical outcome data | | | | | |

## *5.6 Meta-analysis and evidence synthesis*

When considered appropriate, techniques for evidence synthesis such as meta-analysis, and indirect and mixed treatment comparisons can be used.

[redacted]



[redacted]

5.6.1 If evidence synthesis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Response Provided as above.

## *5.7 Adverse events*

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

5.7.1 If any of the main studies are designed primarily to assess safety outcomes, please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the studies, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each study should be provided in sections 7.4 and 7.5, appendices 4 and 5.

***Response*** Celleration sponsored two (2) clinical trials with primary study objectives to assess the safety of MIST Therapy. The following, and Table B7, provides a summary of the adverse event experience for both studies.

Ultrasound Therapy for Recalcitrant Diabetic Foot Ulcers: Results of a Randomized, Double Blind, Controlled, Multicenter Study: All 133 patients were included in the analysis of safety. This primary study objective was to compare the incidence of condition- or therapy-related adverse events among patients receiving MIST in relation to SHAM control through the 12-week treatment period.

A total of 193 adverse events were reported among the 133 patients; 111 adverse events among MIST patients and 82 events among SHAM patients. At least one adverse event was reported for 45 of the 70 (64.3%) MIST patients and 40 of the 63 (63.5%) SHAM control patients ($p = 0.9242$, Chi-Square Test). No statistically significant or clinically important differences were identified between the MIST treatment group and the SHAM control group in the incidence, severity, device-relatedness, or seriousness of adverse events.

The Impact of Noncontact, Nonthermal Low-Frequency Ultrasound on Bacterial Counts in Experimental and Chronic Wounds: All 18 enrolled patients were included in the analysis of safety. This primary study objective was to evaluate the occurrence of device- and/or treatment-related adverse events through the 2-week treatment period. Three (3) adverse events (17%) in 2 patients were reported among the 18 enrolled patients. Two (2) of these events were considered serious in nature, but none of the reported events were related to MIST Therapy or the MIST Therapy System.

5.7.2 Please provide details of all important adverse events. For each group, give the number with the adverse event, the number in the

group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

**Table B7 Adverse events across patient groups**

| System organ/ class/adverse events | Time period 1 | | | Time period 2 etc. – NA | | |
|---|---|---|---|---|---|---|
| | Intervention % of patients (n = 70) | Comparator % of patients (n = 63) | Relative risk (95% CI) | Intervention % of patients (n = x) | Comparator % of patients (n = x) | Relative risk (95% CI) |
| Ultrasound Therapy for Recalcitrant Diabetic Foot Ulcers: Results of a Randomized, Double Blind, Controlled Multicenter Study | | | | | | |
| **Coded Events** | | | | | | |
| Additional ulcer(s) | 20 | 14 | NA | | | |
| Cellulitis | 13 | 13 | NA | | | |
| Oedema | 4 | 5 | NA | | | |
| Erythema | 4 | 6 | NA | | | |
| Osteomyelitis | 4 | 5 | NA | | | |
| Pain | 7 | 10 | NA | | | |
| Tingling | 1 | 0 | NA | | | |
| Ulcer drainage | 1 | 2 | NA | | | |
| Ulcer enlargement | 3 | 3 | NA | | | |
| Ulcer infection | 19 | 14 | NA | | | |
| **Other Events** | | | | | | |
| Cardiovascular / Vascular | | | | | | |
| Cardiac | 1 | 2 | NA | | | |
| Endocrine | | | | | | |
| Hyperglycemia | 1 | 0 | NA | | | |
| Low blood sugar | 0 | 2 | NA | | | |
| Hematological | | | | | | |
| Bleeding | 1 | 0 | NA | | | |
| Hematoma | 1 | 0 | NA | | | |
| Pulmonary / Respiratory | | | | | | |
| Head cold | 1 | 0 | NA | | | |
| Shortness of breath | 0 | 2 | NA | | | |
| Sinus infection | 0 | 2 | NA | | | |
| Sore throat | 3 | 0 | NA | | | |
| Upper respiratory infection | 0 | 2 | NA | | | |
| Gastrointestinal | | | | | | |
| Abdominal cramping | 0 | 2 | NA | | | |
| Diarrhoea | 1 | 0 | NA | | | |
| Dyspepsia | 1 | 0 | NA | | | |
| Gallstone removal | 0 | 2 | NA | | | |
| GI problem | 1 | 2 | NA | | | |
| Stomach flu | 7 | 2 | NA | | | |
| Genitourinary | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Urinating difficulty | 1 | 0 | NA | | | |
| Urinary tract infection | 1 | 0 | NA | | | |
| Musculoskeletal | | | | | | |
| Ankle sprain | 1 | 0 | NA | | | |
| Charlie horse, leg | 1 | 0 | NA | | | |
| Foreign object under index ulcer | 1 | 0 | NA | | | |
| Leg cramps | 0 | 2 | NA | | | |
| Osteotomy | 1 | 0 | NA | | | |
| Plantar fasciitis | 0 | 2 | NA | | | |
| Tenderness left shin | 0 | 2 | NA | | | |
| Tendon lengthening | 4 | 2 | NA | | | |
| Integumentary | | | | | | |
| Abrasion | 1 | 5 | NA | | | |
| Blister | 3 | 2 | NA | | | |
| Burning sensation | 0 | 2 | NA | | | |
| Ecchymosis | 1 | 2 | NA | | | |
| Infection, axillary lymph node | 0 | 2 | NA | | | |
| Infection, great toe | 0 | 2 | NA | | | |
| Inflammation of abrasions | 0 | 2 | NA | | | |
| Itching | 1 | 0 | NA | | | |
| Recurrent ulcer, meta tarsal | 0 | 2 | NA | | | |
| Reopen | 1 | 0 | NA | | | |
| Sinus tract | 1 | 0 | NA | | | |
| Tinea pedis | 0 | 2 | NA | | | |
| Tunnelling | 0 | 2 | NA | | | |
| Undermining | 0 | 3 | NA | | | |
| Other conditions | | | | | | |
| Cataract | 1 | 0 | NA | | | |
| Chills | 1 | 0 | NA | | | |
| Ear pain, bilateral | 1 | 0 | NA | | | |
| Fever | 4 | 0 | NA | | | |
| Infection, eye | 1 | 0 | NA | | | |
| Thyroid tumour, benign | 1 | 0 | NA | | | |
| Trauma | 1 | 2 | NA | | | |
| The Impact of Noncontact, Nonthermal Low-Frequency Ultrasound on Bacterial Counts in | | | | | | |

| Experimental and Chronic Wounds | | | | | | |
|---|---|---|---|---|---|---|
| **System organ/ class/adverse events** | **Time period 1** | | | **Time period 2 etc. - NA** | | |
| | **Intervention % of patients (n = 18)** | **Comparator % of patients (n = 0)** | **Relative risk (95% CI)** | **Intervention % of patients (n =** x) | **Comparator % of patients (n =** x) | **Relative risk (95% CI)** |
| Change in mental status | 6 | NA | NA | | | |
| Fever | 6 | NA | NA | | | |
| Urinary Tract Infection | 6 | NA | NA | | | |
| NOTE: Counts and percentages represent incidence of Adverse Event within each patient. It does not account for multiple occurrences of the same event within patients.<br>CI, confidence interval<br>Adapted from European Public Assessment Reports published by the European Medicines Agency | | | | | | |

5.7.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Response Celleration maintains compliance with the Medical Device Reporting (MDR) requirements imposed by the Food and Drug Administration (FDA) on the medical device industry and users of medical devices. As the device manufacturer of the MIST Therapy System, Celleration must report deaths and serious injuries that the device has or may have caused or contributed to, report certain device malfunctions, establish and maintain adverse event files, and also submit to FDA specified follow-up. Celleration has received 14 reports of MDR events. No reports have been received indicating MIST Therapy may have caused or contributed to any deaths or serious injuries. Below is a summary of these events.

| Year | Number MDRs Filed |
|---|---|
| 2006 | 4 |
| 2007 | 3 |
| 2008 | 5 |
| 2009 | 2 |
| 2010 | 0 |

MDR events reported include:

- Transducer tip acoustic burn (n=11),

- Tingling in arm on user while using MIST (n=1),
- Patient allergy to saline (n=1),
- User sprayed herself in the face (n=1).

## *5.8 Interpretation of clinical evidence*

5.8.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Response The overall assessment of the clinical data associated with the MIST Therapy System demonstrates clinical effectiveness in the removal of fibrin and slough, the removal of bacteria, increasing granulation tissue in the bed of the wound, improved appearance of the periwound tissue, wound healing in a faster period of time than standard of care. Anecdotally there appears to be a reduction in wound pain when treated with MIST Therapy.

5.8.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Response The strength of the clinical evidence is the number of subjects involved in the clinical trials and the clinical effectiveness compared to standard of care. The technology has been shown to be effective in all types of chronic wounds, at anytime during the wound healing process. With bacterial burden being the primary factor in non-healing wounds MIST Therapy presents a significant contribution to improve the wound healing space. We have nearly 200 publications with supporting clinical data, our randomized, prospective, observational registries and retrospective report on over 500 patients, with more than 200 in control groups as well. Celleration's most significant limitation is only 2 of the publications are randomized controlled trials.

5.8.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical studies to the clinical benefits experienced by patients in practice.

Response There are over 6 million new wounds annually, many of them go on to heal, but nearly 50% of them do heal without incident. (Singer,1999)This may be related to a number of factors, including bacterial bioburden, the presence of slough and chronic inflammation. The use of MIST Therapy can reverse and/or impact these processes and assist with promoting wound

healing. The benefit to patients in clearly reducing any necrotic tissue, enhancing wound healing and as reported anecdotally reducing pain.

5.8.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the study, issues relating to the conduct of the study compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted.

Response The pivotal DFU trial was performed in community hospitals to keep the intervention very close to clinical practice. Today MIST Therapy could be initiated as soon as the wound is identified as chronically inflamed, presents with a high bioburden, has persistent fibrin and slough or is painful. Patients in any patient care setting are suitable candidates for MIST Therapy with the most compelling criteria a wound recalcitrant to healing. Among the patients studied and reported on receiving MIST Therapy they include patients being seen in community wound clinic, a physician's office, an inpatient setting or a longer term patient care settings such nursing homes, rest home, warden assisted, respite, convalescent, elderly and special care homes in the UK. Essentially anywhere a patient may seek assistance with a non healing wound MIST Therapy can be delivered by a trained nurse, Wound Ostomy and Continence Nursing (WOCN), physical therapist, wound care physician, podiatrist, or a surgeon specialising in wound care.

# 6 Analysis of Cost

## *6.1 Published cost-effectiveness and cost evaluations*

**Identification of studies**

6.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and identify all unpublished data. Health economics studies should include all types of economic evaluation and cost studies, including cost analyses and budget impact analyses. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 7.6, appendix 6.

6.1.2 Response Identification of studies resulted from a complete search of specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

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

The PubMed.gov, US National Library of Medicine, National Institute of Health database and Cochrane Review were searched. PubMed comprises more than 20 million citations for biomedical literature from **MEDLINE**, life science journals, and online books.

.

**Description of identified studies**

6.1.3 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified

and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

**Table B8 Summary list of all evaluations involving costs**

| Study | Year | Country(ies) where study was performed | Summary of model | Patient population (average age in years) | Costs (currency) (intervention,comparator) | QALYs (intervention, comparator) (when referred to in the study) | ICER (per QALY gained) (if applicable) |
|---|---|---|---|---|---|---|---|
| Study 1E | 2010 | United States | Meta analysis using Markov analysis assigning patients to a varying stage of complexity for diabetic foot ulcer (DFU). Each degree of complexity was assigned a probability to time to healing using metrics derived from randomized controlled trials and large population cohort from Study 1,2,and 9 as described in Table B4, B5, B6, section 5.3.7 and 5.5.2. Population cohorts were patients with DFU treated with standard of care compared to patients treated with noncontact low-frequency ultrasound (NLFU) device delivering low-frequency (40 kHz), low-intensity (0.2 to 0.6 W/cm$^2$) ultrasound energy to the wound bed via a sterile saline mist as described herein. Time to healing for NLFU plus standard of care was derived from Study 1, 2, and 9 described herein. Data related to healing times, wound size and degree of severity at presentation for a standard of care population was derived from Stockl (2004) and Margolis (2002) and Margolis (1999) reporting on a control standard of care DFU patient population. | The 4 published studies used to develop the cost effectiveness analysis included patients ranging in age from 45 to 80 years of age. | The costs to treat the patients included supplies, antibiotics for those DFU that became infected, labor costs using U.S dollars. The compactor costs for achieving healing within a 12 week period for a cohort of 1,000 DFU patients was $10,351,324 for the standard of care patients and $7,795,703 for the MIST Therapy patients providing a net savings in U.S. dollars of $2,555,620. | QALYs were not reported. 41.0% of patients receiving NLFU plus standard of care wounds healed at 12 weeks compared to 18.8% of standard of care patients healed at 12 weeks. The net additional cost to treat 1 patient using standard of care compared to the new NLFU represents an additional cost to the payment system of U.S. $2,556 per patient. NLFU is dominant of the standard of care treatment for DFU. | 41% of NLFU patients were healed in 12 weeks. 18.8 % of standard of care patients healed at 12 weeks. Using the Markov approach to determine the incremental cost savings to move a patient to an improved level of health removes $2,555,620 from U.S. healthcare expenditure for a cohort of 1,000 patients. If each patient healed is allowed 1 additional year of health, Redekop (2004) noted a diabetic has a QALY of = 0.84 assigning that to the healed DFU patients and a QALY of a non healing DFU = 0.75 QALY one can estimate the gain of QALY/yr. Using these changes in QALY, achieving a greater level of health at less cost equates to a net savings. The ICER in U.S$ yields a (**savings)** per QALY gained with NLFU to $2,556/0.11 or $(23,236)/yr |

| Study | Year | Country(ies) where study was performed | Summary of model | Patient population (average age in years) | Costs (currency) (intervention,comparator) | QALYs (intervention, comparator) (when referred to in the study) | ICER (per QALY gained) (if applicable) |
|---|---|---|---|---|---|---|---|
| Study 2E | 2009 | United States | Study 50 describes a case series of 5 patients treated for decubitus ulcers (pressure ulcers) in a long- term acute- care setting treated with NLFU plus collagenase and moist bandages to attain a proper moisture balance. Within 2-5 weeks low frequency ultrasound resulted in improved tissue quality and marked reductions in area and volume that hastened either wound healing or readiness for flap procedures. Cost savings were compared vs. NPWT and avoidance of flap or graft procedures in 3 of 5 patients. | The patients ranged in age from 47 to 80 years of age. | Costs were measured in U.S.$. Costs to achieve wound closure in less time were compared to costs to achieve wound closure compared to a calculated cost of negative pressure wound therapy. The average savings per patient receiving NLFU ranged from $563 to $2187 yielding a reduction in wound size. | QALYS were not calculated however, the reduction of wound size and cost to achieve a reduction in wound size was reported for each patient. The average reduction in wound size across the 5 patients was 34% with a cost avoidance of $1,310 per patient. Despite the small sample size this correlates well with the meta analysis model Driver (2010). | N/A |

| Study | Year | Country(ies) where study was performed | Summary of model | Patient population (average age in years) | Costs (currency) (intervention,comparator) | QALYs (intervention, comparator) (when referred to in the study) | ICER (per QALY gained) (if applicable) |
|---|---|---|---|---|---|---|---|
| Study 3E | 2010 | UK | Economic modelling reporting on number of treated pressure ulcers, leg ulcers, diabetic foot ulcers in the UK and Wales and their associated costs to the NHS. Using incidence of disease numbers for chronic leg ulcers, diabetic foot ulcers, pressure ulcers, and the costs to UK/Wales to currently treat these patients is compared to the cost to use the MIST Therapy system in the UK/Wales in the patient care settings in which these patients would be treated.<br><br>The model is based upon peer reviewed publications showing the reduced time to healing for these chronic wounds. The data has been provided in this document. | In the economic model provided herein the age of the patient was not included rather the expressive of the disease was more critical to the cost to treat the patient. Margolis (2002) noted that the age of the wound is more predictive of the time to heal and is the age of the patient. | Costs were measured in British **£** from the cost perspective of the National Health Service (NHS). Extrapolating the number of patients treated annually in the UK/Wales with the average time to healing with MIST Therapy beyond the evidence of 12 weeks to 26 weeks the annual savings to the NHS to treat all patients presenting with a leg ulcer, DFU, or pressure ulcer represent a savings of £7,978. | In the Economic model QALYS were not included. To determine the benefit to the patient we are using the estimates for a QALY for wounds as reported by Rosser (1978) and applied by Marcario (2002) assigning 0.84 to a stage 3 and 0.73 to a stage 4. These measures are within range for DFU patient reported QALY. Using these measures we identified the patients gained 0.11 QALY/yr while removing costs from the system. | The ICER may be calculated using the incremental gain of 0.11QALY/yr used in Study 1E, and using the incremental (savings) calculated as the sum of net savings per wound type of (£2,659) to the NHS. The results in an ICER savings or benefit to the NHS of (£2.659)/0.11 or a savings of (£ 24,173)/yr due to reducing the time to healing by 50%. |
| ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s) | | | | | | | |

6.1.4 Please provide a complete quality assessment for each health economics study identified. Use an appropriate and validated

instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 7.7, appendix 7.

Response

| | **Study name Cost Effectiveness of Noncontact Low-Frequency Ultrasound for the Treatment of Diabetic Foot Ulcers. Driver VR 2010.** | |
|---|---|---|
| **Study question** | **Grade (yes/no/not clear/N/A)** | **Comments** |
| Study design | | |
| 1. Was the research question stated? | Yes | This analysis aimed to develop an economic model using large sample reported data when treating a DFU. |
| 2. Was the economic importance of the research question stated? | Yes | Focus was to measure the economic impact of closing a DFU in less time using NLFU plus standard of care than using only current standard of care. |
| 3. Was/were the viewpoint(s) of the analysis clearly stated and justified? | Yes | The viewpoint was from the cost of the healthcare provider to provide the care. The cost method was developed from the bottom up. |
| 4. Was a rationale reported for the choice of the alternative programmes or interventions compared? | Yes | Large patient registry including patients with DFU assigned to standard of care and a randomized controlled study of patients treated with NLFU plus standard of care. |
| 5. Were the alternatives being compared clearly described? | Yes | The patients in the model were assigned to different stages of wound progression at presentation based upon the staging previously described in published papers. |

[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

| | | |
|---|---|---|
| 6. Was the form of economic evaluation stated? | Yes | The form of economic evaluation was referenced to be related to U.S. national healthcare expenditures. |
| 7. Was the choice of form of economic evaluation justified in relation to the questions addressed? | Yes | Relevant costs were identified from peer reviewed papers. |
| Data collection | | |
| 8. Was/were the source(s) of effectiveness estimates used stated? | Yes | Previously published papers |
| 9. Were details of the design and results of the effectiveness study given (if based on a single study)? | Yes | This was a model derived from well designed and reported analysis of patients with DFU. |
| 10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)? | Yes | As reported in the referenced papers. |
| 11. Were the primary outcome measure(s) for the economic evaluation clearly stated? | Yes | The primary outcome measure was time to healing, or time to achieve a trajectory toward healing as defined in peer reviewed publications used to develop the economic model. |
| 12. Were the methods used to value health states and other benefits stated? | Yes | Health states were stratified as described by Stockl (2004) and Holzer (1998) relating stage to cost U.S.$ to achieve closure |
| 13. Were the details of the subjects from whom valuations were obtained given? | Yes | As reported in referenced peer reviewed published articles. |
| 14. Were productivity changes (if included) reported separately? | No | Productivity was not described yet inferred in the relationship to achieving healing. |
| 15. Was the relevance of productivity changes to the study question discussed? | No | |
| 16. Were quantities of resources reported separately from their unit cost? | No | |
| 17. Were the methods for the estimation of quantities and unit costs described? | Yes | As provided by Stockl (2004), Holzer (1998), and national U.S. statistics |
| 18. Were currency and price data recorded? | Yes | Price was based on U.S. currency |

| | | |
|---|---|---|
| 19. Were details of price adjustments for inflation or currency conversion given? | No | |
| 20. Were details of any model used given? | Yes | The modelling was described per published meta analysis ranking patients in DFU stage of presentation and healing. |
| 21. Was there a justification for the choice of model used and the key parameters on which it was based? | Yes | Justification was related to the meta analysis of Stockl (2004), Margolis (2002 and 1999). |
| Analysis and interpretation of results | | |
| 22. Was the time horizon of cost and benefits stated? | Yes | Time horizon was modelled to achieve healing until the modelled 1,000 patients would have healed. |
| 23. Was the discount rate stated? | No | |
| 24. Was the choice of rate justified? | Yes | The choice of costs was based upon claims data (Holzer 1998) and U.S. costs. |
| 25. Was an explanation given if cost or benefits were not discounted? | No | |
| 26. Were the details of statistical test(s) and confidence intervals given for stochastic data? | No | The mean time to healing was reported in the referenced papers. Healing rates for the NLFU plus standard of care and standard of care only were statistically significant as reported by their p values. |
| 27. Was the approach to sensitivity analysis described? | No | |
| 28. Was the choice of variables for sensitivity analysis justified? | N/A | |
| 29. Were the ranges over which the parameters were varied stated? | Yes | The parameters of achieving DFU healing were well described and provided in a Markov type model to estimate the costs to achieve healing for patients presenting with varying stages of DFU. |
| 30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?) | Yes | The alternatives provided have been well described in the referenced articles which were used to develop the cost effectiveness model. |

| | | |
|---|---|---|
| 31. Was an incremental analysis reported? | Yes | The final analysis to determine the cost to achieve closure of a population of 1,000 patients presenting with varying stages of DFU identified a net savings to the healthcare system of $2,555,620 for every 1,000 patients treated with NLFU for 12 weeks. |
| 32. Were major outcomes presented in a disaggregated as well as aggregated form? | Yes | Tables were provided as well as discussed in the paper. |
| 33. Was the answer to the study question given? | Yes | Using NLFU plus standard of care on a modelled patient population of 1,000 patients was found to provide a significant reduction in cost to treat patients. |
| 34. Did conclusions follow from the data reported? | Yes | The analysis of the parameters of the staging of the wound and their economic relevance related to healing was well defined. |
| 35. Were conclusions accompanied by the appropriate caveats? | Yes | The paper was focused on describing the cost effectiveness of achieving DFU closure comparing patients receiving NLFU plus standard of care and those receiving only standard of care. All relevant caveats were reported in the staging of the DFU at the time of presentation. Caveats related to infection and wound stage were well included in the model. |
| 36. Were generalisability issues addressed? | Yes | This paper focused on the cost to close a DFU comparing patients exposed to NLFU plus standard of care and standard of care only. To the extent that NLFU plus standard of care is able to prepare a wound bed to closure the results may be generalizable to other chronic wound bed scenarios. |
| Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination | | |

| | **Study name <u>Cost Effectiveness of Noncontact Low-Frequency Ultrasound for Non-healing Wounds in the Long-Term Acute-Care Hospital: A case series.</u> Anaeme KO, et. al.** | |
|---|---|---|
| **Study question** | **Grade (yes/no/not clear/N/A)** | **Comments** |
| Study design | | |
| 1. Was the research question stated? | Yes | This analysis aimed to develop an economic model using a small (5) case series of patients having pressure ulcers but not able to tolerate negative pressure wound therapy. |
| 2. Was the economic importance of the research question stated? | Yes | Focus was to measure the costs to achieve a reduction on pressure ulcer size without using negative pressure wound therapy and to include the importance of avoiding the need for a skin graft or return to the operating room. |
| 3. Was/were the viewpoint(s) of the analysis clearly stated and justified? | Yes | The viewpoint was from the actual costs to provide treatment from the perspective of the provider of the long-term acute-care centre. Costs were measured based on actual expenditure or cost of avoidance known when treating with negative pressure wound therapy for a series of days. |
| 4. Was a rationale reported for the choice of the alternative programmes or interventions compared? | Yes | The rational for the NLFU plus standard of care for the 5 patient case series was due to their intolerance to receiving negative pressure wound therapy. |
| 5. Were the alternatives being compared clearly described? | Yes | The alternatives in the 5 patient case series were NLFU plus standard of care, collagenase moist dressing. |
| 6. Was the form of economic evaluation stated? | Yes | Direct costs to provide the medical service as paid by the long-term acute-care centre. |
| 7. Was the choice of form of economic evaluation justified in relation to the questions addressed? | Yes | Relevant costs were identified from purchase invoices. |
| Data collection | | |

| | | |
|---|---|---|
| 8. Was/were the source(s) of effectiveness estimates used stated? | Yes | The effectiveness was measured as the percentage pressure ulcer reduction in size. |
| 9. Were details of the design and results of the effectiveness study given (if based on a single study)? | Yes | Simple collection of wound size and associated costs over a 2 month period. Patient selection was based on the patient's inability to tolerate negative pressure wound therapy. |
| 10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)? | N/A | |
| 11. Were the primary outcome measure(s) for the economic evaluation clearly stated? | Yes | The primary outcome measure was reduction in wound size over 2 months and the costs to treat compared to the costs if negative pressure wound therapy would have been used. |
| 12. Were the methods used to value health states and other benefits stated? | Yes | Case series of 5 patients in which 3 avoided the need for a graft, 1 was able to receive a graft and all avoided negative pressure wound therapy. |
| 13. Were the details of the subjects from whom valuations were obtained given? | Yes | Only details related specifically to their wound care. |
| 14. Were productivity changes (if included) reported separately? | No | Productivity was not described yet inferred in the relationship to achieving healing. |
| 15. Was the relevance of productivity changes to the study question discussed? | No | |
| 16. Were quantities of resources reported separately from their unit cost? | No | |
| 17. Were the methods for the estimation of quantities and unit costs described? | Yes | The unit of healing was provided as percent change and the cost savings was expressed in U.S. $. |
| 18. Were currency and price data recorded? | Yes | Price was based on U.S. currency. |
| 19. Were details of price adjustments for inflation or currency conversion given? | No | |
| 20. Were details of any model used given? | Yes | No modelling was used, rather direct measure of wound size reduction and costs to treat. |

| | | |
|---|---|---|
| 21. Was there a justification for the choice of model used and the key parameters on which it was based? | Yes | The justification of the case study was to compare healing in the absence of negative pressure wound therapy. |
| Analysis and interpretation of results | | |
| 22. Was the time horizon of cost and benefits stated? | Yes | Time horizon was reported over the 2 month study period. |
| 23. Was the discount rate stated? | No | |
| 24. Was the choice of rate justified? | N/A | |
| 25. Was an explanation given if cost or benefits were not discounted? | No | |
| 26. Were the details of statistical test(s) and confidence intervals given for stochastic data? | No | Straight forward collection of size reduction and direct costs compared to costs for negative pressure wound therapy resulting in an average savings per patient for the 5 patients receiving NLFU plus standard of care. |
| 27. Was the approach to sensitivity analysis described? | No | |
| 28. Was the choice of variables for sensitivity analysis justified? | N/A | |
| 29. Were the ranges over which the parameters were varied stated? | No | Straight forward collection of size reduction and direct costs compared to costs for negative pressure wound therapy resulting in an average savings per patient for the 5 patients receiving NLFU plus standard of care. |
| 30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?) | Yes | In this series of 5 patients the relevant alternatives were presented yet the patients could not tolerate the relevant alternative to NLFU plus standard of care, that being negative pressure wound therapy. |
| 31. Was an incremental analysis reported? | No | |
| 32. Were major outcomes presented in a disaggregated as well as aggregated form? | Yes | The outcome of wound size reduction and associated direct costs and avoided costs were presented in 1 Table. The costs of grafts or avoidance of a graft were not provided. |

| | | |
|---|---|---|
| 33. Was the answer to the study question given? | Yes | Using NLFU plus standard of care on a series of 5 patients that were intolerant to negative pressure wound therapy resulted in a reduction in size of their pressure ulcer by 34% with an average savings of $1,310 ranging from $563-$2187, |
| 34. Did conclusions follow from the data reported? | Yes | The conclusions followed from the 5 patient case series design and the measurements taken. |
| 35. Were conclusions accompanied by the appropriate caveats? | Yes | The conclusions were focused on the 5 patient series and did extrapolate to the potential savings to achieve pressure ulcer size reduction while avoiding complications. |
| 36. Were generalisability issues addressed? | Yes | The conclusion was generalised to patients receiving wound care treatment in a long-term acute-care centre and the impact this could have on total expenditures. |
| Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination | | |

| | **Study name De novo <u>Cost Effectiveness of Noncontact Low-Frequency Ultrasound Impact on the expenditures in the UK and Wales.</u>** | |
|---|---|---|
| **Study question** | **Grade (yes/no/not clear/N/A)** | **Comments** |
| Study design | | |
| 1. Was the research question stated? | Yes | This analysis aimed to develop an economic model using data from the NHS in the UK and Wales to measure the current annual expenditures to treat patients with venous leg ulcer, pressure ulcer or a DFU. Population based costs and incidence were reported based on published papers. |

| | | |
|---|---|---|
| 2. Was the economic importance of the research question stated? | Yes | The economic importance we was reported from the perspective of the NHS when comparing the cost benefit, or savings to the NHS by using NLFU plus standard of care to reduce the time to healing from the current 52 weeks to 26 weeks modelled from studies provided herein. |
| 3. Was/were the viewpoint(s) of the analysis clearly stated and justified? | Yes | The viewpoint was from the current costs incurred by the NHS to treat chronic wounds in the UK and Wales of £2.3bn - £3.1bn in 2005 (Posnett), 2008. |
| 4. Was a rationale reported for the choice of the alternative programmes or interventions compared? | Yes | The rational for cost to the NHS is based on improving the time to healing of the leg ulcers, pressure ulcers and DFU by supported in articles Study 1 Ennis, et. al. 2005, Study 2 Kavros, 2007, Study 5 Kavros, et. al., 2008, Study 9 Ennis, et. al., 2006, and Study 10 Kavros, et. al., 2007. |
| 5. Were the alternatives being compared clearly described? | Yes | The alternatives to treat the 3 dominant types of chronic wounds in the UK and Wales were defined and have been referenced in this report. The recommended new treatment protocol describes the use of NLFU plus standard of care shown to reduce the time to healing. |
| 6. Was the form of economic evaluation stated? | Yes | Total costs incurred by the NHS to treat all patients presenting with a chronic wound across all patient care settings. |
| 7. Was the choice of form of economic evaluation justified in relation to the questions addressed? | Yes | The costs to treat all patients in the UK and Wales presenting with chronic ulcers was compared to the reduction in total costs to the NHS if the NLFU plus standard of care treatment protocol is adopted in the UK and Wales. |
| Data collection | | |

| | | |
|---|---|---|
| 8. Was/were the source(s) of effectiveness estimates used stated? | Yes | The source of effectiveness was modelled knowing the number of patients having a chronic wound at any point in time with the current expenditures to develop a cost per patient. Then the cost to treat the patients resulting in a shorter time to healing was compared to the total costs. |
| 9. Were details of the design and results of the effectiveness study given (if based on a single study)? | Yes | The economic model is using Macro numbers and comparing the Macro economics of the current wound care practice in the UK and Wales to the known improvement in time to healing using the NLFU plus standard of care to treat chronic wounds. Studies provided herein demonstrate the large number of patients treated to date across the spectrum of chronic wounds such as venous leg ulcers, pressure ulcers, and DFU. |
| 10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)? | Yes | Tables have been provided to provide the logically flow if information to support the cost savings to the NHS. |
| 11. Were the primary outcome measure(s) for the economic evaluation clearly stated? | Yes | The primary outcome measure was reduction in wound size on an annual basis estimating the NLFU plus standard of care protocol will impact the healing of chronic wounds by a reduction in time to healing by 50%. Cost savings are reported on an annual basis to the NHS. |
| 12. Were the methods used to value health states and other benefits stated? | Yes | Health states are noted only as presence or absence of a chronic wound. |
| 13. Were the details of the subjects from whom valuations were obtained given? | Yes | These are large population cohorts. Information provided included average time to healing and the incidence of specific chronic diseases. |
| 14. Were productivity changes (if included) reported separately? | No | Productivity was not described yet inferred in the relationship to achieving healing. |

| | | |
|---|---|---|
| 15. Was the relevance of productivity changes to the study question discussed? | No | |
| 16. Were quantities of resources reported separately from their unit cost? | No | |
| 17. Were the methods for the estimation of quantities and unit costs described? | Yes | The unit of healing was provided as percent change and the cost savings was expressed in British £. |
| 18. Were currency and price data recorded? | Yes | Price was based on British £. |
| 19. Were details of price adjustments for inflation or currency conversion given? | No | |
| 20. Were details of any model used given? | Yes | The model developed did include specific details related to the specific chronic incidence of disease and the costs to treat disease to the NHS. |
| 21. Was there a justification for the choice of model used and the key parameters on which it was based? | Yes | The justification of the economic model from the perspective of the NHS was to verify the cost savings to be achieved if the time to healing can be reduced as reported in the peer reviewed published literature regarding NLFU plus standard of care. |
| Analysis and interpretation of results | | |
| 22. Was the time horizon of cost and benefits stated? | Yes | Time horizon was reported over a 1 year period. |
| 23. Was the discount rate stated? | No | |
| 24. Was the choice of rate justified? | N/A | |
| 25. Was an explanation given if cost or benefits were not discounted? | No | Discounting was not provided as the model is projecting annual costs based upon current annual expenditures and healing. Healing is expected to occur within 1 year. |

| | | |
|---|---|---|
| 26. Were the details of statistical test(s) and confidence intervals given for stochastic data? | No | Straight forward collection of size reduction over time as reported in published papers combined with the reported total costs to the NHS compared to the cost to deliver the NLFU plus standard of care protocol to patients suffering from venous leg ulcers, pressure ulcers, and DFU in the UK and Wales. Costs are reported per patient reported to have a chronic wound in the UK and Wales. |
| 27. Was the approach to sensitivity analysis described? | No | |
| 28. Was the choice of variables for sensitivity analysis justified? | N/A | |
| 29. Were the ranges over which the parameters were varied stated? | Yes | The range of time is considered to be on an annual basis as reported by annual expenditures and annual incidence of chronic wounds to be treated. |
| 30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?) | Yes | The UK and Wales economic model is using the perspective of incidence of disease and expenditures to the NHS on an annual basis. Provided herein are the protocols currently used to treat chronic wounds under analysis. The comparison is using the current standard of care, which in the UK and Wales may vary across patients and care providers but nevertheless represents treatment protocols lacking NLFU plus standard of care protocols. The comparison across patients was focused on comparing patients in the current system being treated with the new technology and applying the reduced time to healing in conjunction with the lower cost to using the NLFU plus standard of care protocol. |

| | | |
|---|---|---|
| 31. Was an incremental analysis reported? | Yes | The incremental cost benefit to the NHS when adopting the NLFU plus standard of care protocol is a net savings of £1,563/ venous leg ulcer (UK); £2,374/ DFU (England only) and £2,925/ pressure ulcer (UK). |
| 32. Were major outcomes presented in a disaggregated as well as aggregated form? | Yes | Costs related to each wound type and then in total NHS savings was presented. |
| 33. Was the answer to the study question given? | Yes | Using NLFU plus standard of care in the UK and Wales when considered to reduce the time to healing by 50% of the majority of wounds results in a total annual savings of £352 million. |
| 34. Did conclusions follow from the data reported? | Yes | The conclusions followed from the data provided as evidenced in the tables reflecting total number of patients, costs to treat each chronic wound and then comparing the cost for NLFU plus standard of care in the model. |
| 35. Were conclusions accompanied by the appropriate caveats? | Yes | Caveats to the model include the use of the NLFU plus standard of care therapy to achieve the results. Additional caveats include the macro numbers used to compute the current standard of care provided to patients with chronic wounds in the UK and Wales. |
| 36. Were generalisability issues addressed? | Yes | The conclusion was generalised to patients in the UK and Wales who present for treatment to achieve healing for their venous leg ulcers, pressure ulcers or DFU. Of critical importance is the overall incidence of pressure ulcers treated in the UK and Wales with 63% of costs going to inpatient treatment and 66% of pressure ulcers being hospital acquired (Posnett, 2009). |

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

## *6.2 De novo cost analysis*

6.2.1 Please provide the rationale for undertaking further cost analysis in relation to the decision-problem.

Response Using wound healing data from the patients in the U.S that have received treatment using MIST Therapy, and understanding chronic wounds treated in the UK and Wales tend to receive similar standard of care treatment protocols; an economic model was developed to measure the cost benefit to the NHS if a protocol of MIST Therapy or NLFU plus standard of care treatment regimen was adopted.

**Patients**

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

Response Patients included in the De Novo analysis represent the incidence of chronic wounds experienced in the UK and in some cases Wales. The analysis considers the spectrum of wounds treated by the NHS including patients with venous leg ulcers, pressure ulcers and diabetic foot ulcers.

**Model structure**

6.2.3 Please provide a diagrammatical representation of the model you have chosen.

Response Diagrammatic model is based on a series of known data to bring together the current burden of cost incurred by the UK/Wales NHS. Chronic wounds represent a significant burden to the NHS which was estimated at £2.3bn - £3.1bn in 2005 Posnett,(2008).

**Leg ulcers.**

It is estimated that between 70,000 and 190,000 individuals have a venous leg ulcer at any one time Moffatt,( 2004). Leg ulcers cost the NHS up to £600m per year Logan (1997), however, the risk of infection and associated costs bring the average cost of a hard to heal wound to between £5,000 and £9,818 (HTA, 2004).

**Diabetic Foot Ulcers**

Foot ulcers represent a severe complication of diabetes and the most common cause of diabetes associated hospital admissions. The prevalence of foot ulcers in diabetes is between 4% and 10% and the annual population incidence is 1.0-4.1% (Singh, 2005). The incident rate is estimated at 84,000 diabetic

ulcers at any one time. Diabetic foot burden to the NHS is £600m per year with over 5,000 people undergoing leg, foot or toe amputations each year in the UK costing £252m (Boulton, 2005).

**Pressure Ulcers**

Approximately 412,000 individuals will develop a new pressure ulcer annually in the UK. Pressure ulcers cost the NHS between £1.4 - £2.1bn annually most of this is associated with nursing time with the cost of treating a pressure ulcer varying between £1,064 (grade 1) to £10,551 (grade 4) with costs increasing to over £20,000 for complex infected pressure ulcers.

**Annual Wound Estimates**

There are over 600,000 leg ulcers, diabetic foot ulcers and pressure ulcers annually in the UK costing the NHS in excess of £2.6bn.

**6.2.3 B1**

| | Number of wounds | Cost of Current Treatment | Average treatment cost | Hard to heal wound - Cost | Cost for a complex wound |
|---|---|---|---|---|---|
| **Leg Ulcers** (UK) | 150,000 | £600,000,000 | £4,000 | £9,189 | 5,000 to £14,000 per annum |
| **Diabetic Ulcers** (England only) | 84,000 | £348,000,000 | £4,143 | £10,000 | £10,000 to £50,000 if leading to amputation |
| **Pressure Ulcers** (UK) | 412,000 | £1,700,000,000 | £4,126 | £10,551 | £20,000 to £40,000 |
| **Total / average** | **646,000** | **£2,648,000,000** | **£4,099** | **£9,913** | |

**Hard to Heal Wound Estimates**

It is estimated that at least 28% of chronic wounds do not heal within 12 months.

Most grade 1 and 2 pressure ulcers heal within 12 weeks, however, 24% of pressure ulcers are grade 3 or 4 which are hard to heal.

There are at least 160,000 chronic hard to heal wounds taking over 12 months to heal annually. MIST is suitable for these chronic wound types with clinical studies showing MIST to improve healing outcomes and accelerate wound healing.

**6.2.3 B2**

| | Hard to Heal Wounds numbers | Hard to Heal Annual costs (per patient) | Total treatment costs |
|---|---|---|---|
| **Leg Ulcers** (UK) | 42,000 | £9,189 | £385,938,000 |
| **Diabetic Ulcers** (England only) | 23,520 | £10,000 | £235,200,000 |
| **Pressure Ulcers** (UK) | 98,880 | £10,551 | £1,043,282,880 |
| **Total / Average** | **164,400** | **£9,913** | **£1,664,420,880** |

## MIST Savings per Patient

The savings to the NHS for Hard to Heal wounds compare 52 weeks conventional treatment against 26 weeks MIST treatment.

MIST clinical studies have shown improved healing rates at twice the speed and half the time of conventional treatments, therefore, it has been assumed that if the treatment was carried out for a longer period, i.e., 26 weeks, it may facilitate complete healing.

**6.2.3 B3**

| **Wound Category Currently Treated in the UK/Wales and paid by NHS** | **Current annual costs to provide conventional standard of care for each wound type. Cost reported (per patient)** | **MIST Treatment Costs 26 weeks provided 3 times per week reported (per patient)*** | **Incremental savings using MIST reported (per patient)** |
|---|---|---|---|
| **Leg Ulcers** (UK) | £9,189 | £7,254 | £1,935 |
| **Diabetic Ulcers** (England only) | £10,000 | £7,254 | £2,746 |
| **Pressure Ulcers** (UK) | £10,551 | £7,254 | £3,297 |
| **Cumulative Average saving** | | | **£7,978** |

* MIST treatment costs include: 3 treatments per week (rental and consumable), dressing costs and nursing time (£50 per visit). Some patients may only require 2 treatments per week reducing the overall treatment cost. Average number of treatments per device per day @ 5, further cost efficiencies are realised with higher daily patient treatments.

## Savings to the NHS

If MIST healed wounds within 26 weeks compared to conventional treatment within 52 weeks, the total saving to the NHS in England would be over **£352m**.

**6.2.3 B4**

| Chronic would requiring medical treatment | Hard to Heal Wounds numbers | Conventional - Annual costs all hard to heal wounds | **England only savings*** | **England only savings*** | **England only savings*** |
|---|---|---|---|---|---|
| Leg Ulcers (UK) | 42,000 | £385,938,000 | **£54,884,361** | **£54,884,361** | **£54,884,361** |
| Diabetic Ulcers (England only) | 23,520 | £235,200,000 | **£55,836,480** | **£55,836,480** | **£55,836,480** |
| Pressure Ulcers (UK) | 98,880 | £1,043,282,880 | **£241,810,230** | **£241,810,230** | **£241,810,230** |
| **TOTAL COST** | **164,400** | **£1,664,420,880** | | | |
| **SAVING** | | | | £471,863,280 | **£352,531,070** |

Using the standard MIST Therapy protocol for patients have a chronic wound that has demonstrated failure to healing, the adoption of the MIST Therapy or NLFU treatment regimen may save on average £7,987 per patient with a hard to heal chronic wound annually. Given the high cost of treating patients in an inpatient setting additional cost savings may be attained by stabilising the patient underlying condition moving the wound toward healing and transferring the patient from an inpatient care setting to one with a primary care provider.

The published literature provided herein has been reported and demonstrates a MIST Therapy treatment regimen of 3 times per week for the duration necessary to cover the wound area, provides improved healing rates and wound reduction in 10 weeks compared to 20 weeks with standard care. Therefore, in developing this model we are applying the wound time to healing to the UK/Wales population allowing a time to healing of 26 weeks treatment.

The economic analysis provided herein reports the MIST Therapy treatment regimen may save the NHS £352m annually on wound care costs if adopted across both the Hospital and Community setting for all hard to heal chronic wounds. However, treatment may also be carried out within the chronic burns setting yielding yet additional opportunities.

6.2.4 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

Response The patient populations used in the UK/Wales perspective economic are expected to follow the treatment regimens as identified in section 2.4. The economic model included the recommendation provided by NICE that the current treatment protocols for the patients reported in the model were treated with standard of care only and NOT including the NLFU. Their treatment would follow the recommendations of NICE Clinical guideline CG29, 2005.

Patients included in the analysis having a diabetic foot ulcer would be expected to receive treatment and prevention as identified in NICE Clinical guideline CG10, 2004).

Patients included in the model having non-healing or progressive ulcers with clinical signs of active infection wound receive treatment following the NICE Infection control, prevention of healthcare-associated infection in primary and community care Clinical Guideline CG2 June 2003. Review date: September 2009.

Patients included in the study representing those with pressure ulcers would be expected to receive treatment along the guidelines of Pressure relieving devices: the use of pressure relieving devices for the prevention of pressure ulcers in primary and secondary care Clinical Guideline CG7 October 2003. Review date: September 2010

Pressure ulcers: The management of pressure ulcers in primary and secondary care Clinical Guideline CG29 September 2005. Review date: September 2010.

The economic model for use in the UK/Wales followed the current protocol for MIST Therapy to be initiated once standard wound care has failed to heal the wound, if the wound has not healed for 30 days, or as an alternative method for debridement in acute wounds. Published reports indicated MIST Therapy

provides optimal patient benefit for wounds that have failed to heal after 30 days.

The average daily cost to use MIST Therapy in the UK and Wales is provided in table 6.2.4 B1. MIST Therapy treatment regimen recommends treatment 3 times per week including the routine dressing change to maintain a moist wound bed.

| 6.2.4 B1 MIST Treatment costs | |
|---|---|
| | **Treatment costs** |
| **MIST annual rental** | **£7,500.00** |
| **Weekly rental** | **£144.23** |
| **Daily rental** | **£28.85** |
| Equipment: Cost per patient (based on 5 patients per day, 5 days a week) | £5.77 |
| **Consumable treatment cost (per patient treatment)** | **£35.00** |
| **Patient treatment cost** | **£40.77** |

6.2.5 Please define what the health states in the model are meant to capture.

Response The health states in the model have been designed to measure the current cost to treat chronic wounds in the UK and Wales using the current costs incurred by the NHS. The wound types under consideration in the model are; leg ulcers, diabetic foot ulcers, and pressure ulcers. The economic analysis is taking into account those incremental costs related to brining MIST into the treatment protocol.

6.2.6 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

Response The patients in the model are as reported to be receiving wound care treatment following the recommendations of the so noted NICE guidelines. In developing the costs associated with treatment one is considering the care provider to be following the NICE guidelines for patients seen in the UK and Wales.

6.2.7 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

**Table B9 Key features of analysis**

| Factor | Chosen values | Justification | Reference |
|---|---|---|---|
| Time horizon | 1 year annual expenditures | Information provided by the NHS and published reports provided annual incidence and annual expenditures | |
| Cycle length | MIST Therapy treatment was modelled for 26 weeks at 3 treatments per week | This is the protocol followed for patients having a chronic wound and has been reported to be effective in reducing the size of a wound leading to healing. | |
| Half-cycle correction | Not provided | | |
| Discount of 3.5% for costs | Not provided | Cost savings modelled by adopting the MIST Therapy model reflect a 25%-30% savings over current healthcare expenditures. | |
| Perspective (NHS/PSS) | NHS | Costs are reported by the NHS | |
| NHS, National Health Service; PSS, Personal Social Services. | | | |

**Technology**

6.2.8 Are the intervention and comparator(s) implemented in the model as per their CE marking as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Response They are implemented in the model per their CE marking.

6.2.9 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated

in the (draft) IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Response The treatment continuation rule used in the model is the same as described under section 2.4 through section 2.8 as provided herein.

## *6.3 Clinical parameters and variables*

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

6.3.1 Please demonstrate how the clinical data were implemented into the model.

Response The clinical data provided in the model were based on the clinical findings in Study 1 Ennis, et. al. 2005, Study 2 Kavros, 2007, Study

5 Kavros, et. al., 2008, Study 9 Ennis, et. al., 2006, and Study 10 Kavros, et. al., 2007. The cost of treatment for MIST Therapy is derived from incremental cost analysis captured during an activity based cost assessment, included reported costs published in Stockl, (2004).

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Response The clinical transition probabilities were calculated from the healing rates reported by Study 1 Ennis, et. al. 2005, Study 2 Kavros, 2007, Study 5 Kavros, et. al., 2008, Study 9 Ennis, et. al., 2006, and Study 10 Kavros, et. al., 2007. The clinical outcomes identified patients moving toward healing in less time than patients not receiving the MIST Therapy or NLFU plus standard of care treatment protocol. Using Kaplan Meyer Plots one can compare the percent of wounds that close using MIST and Standard of Care (SoC). Roughly 50% of the wounds are demonstrated to close at 12 weeks.

**Table 6.3.2 B1**

| Derivative Data from the KM Plots | | |
|---|---|---|
| | **MIST** | **SoC** |
| Fraction of ulcers that do not close in 12 weeks, Pnc: | **0.503** | **0.748** |
| Fraction of ulcers that close in 12 weeks, Pcl: | **0.497** | **0.252** |
| **Total Ulcer weeks per patient** | **9.019** | **10.488** |

Using Table 6.3.2 B1 table derived from the Study 1 Ennis, et. al. 2005 the economic analysis from the NHS expenditure perspective considers the annual treatment of wounds and estimates that wounds receiving the MIST Therapy protocol should heal within 26 weeks.

**Table 6.3.2 B2**

| Comparison MIST Treatment vs. Conventional Treatment | | | | | | | |
|---|---|---|---|---|---|---|---|
| Chronic wounds being treated | Annual conventional costs (per patient) | Conventional - Annual costs all hard to heal wounds | MIST Treatment Costs 26 weeks (per patient) | MIST - Annual costs all hard to heal wounds | Incremental Total saving using MIST (per patient) | Total saving using MIST all hard to heal wounds (UK) | **England only savings*** |
| **Leg Ulcers** (UK) | £9,189 | £385,938,000 | £7,626 | £320,292,000 | £1,563 | £65,646,000 | **£54,884,361** |
| **Diabetic Ulcers** (England only) | £10,000 | £235,200,000 | £7,626 | £179,363,520 | £2,374 | £55,836,480 | **£55,836,480** |
| **Pressure Ulcers** (UK) | £10,551 | £1,043,282,880 | £7,626 | £754,058,880 | £2,925 | £289,224,000 | **£241,810,230** |
| **TOTAL COST** | | **£1,664,420,880** | | **£1,253,714,400** | | | |
| **TOTAL SAVING** | | | | | | £410,706,480 | **£352,531,070** |

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Response The clinical trials carried out as described herein as reported in the following: Study 1 Ennis, et. al. 2005, Study 2 Kavros, 2007, Study 5 Kavros, et. al., 2008, Study 9 Ennis, et. al., 2006, and Study 10 Kavros, et. al., 2007 followed the wounds to healing. Further the cost effectiveness analysis of MIST Therapy to treat diabetic foot ulcers submitted by Driver, 2010 applies the healing rates of the MIST Therapy studies compares those outcomes with a large patient cohort receiving standard of care. The percent of patients healing in a similar period of time receiving the standard of care are depicted in the following table. The patients under the MIST Therapy or NLFU treatment regimen show 410 healing at 12 weeks compared to 188 healing in the same period of time.

**6.3.3 B3 Table 1. Case mix adjustment for ulcer responses under SC assuming a cohort of 1,000 patients (combined data from Stockl and Margolis)**

| Ulcer Severity Level | Healed at 12 Weeks | | Progressing Toward Healing at 12 Weeks | | Deteriorating or Not Progressing at 12 Weeks | | |
|---|---|---|---|---|---|---|---|
| | *SC* | *NLFU* | *SC* | *NLFU* | *SC* | *NLFU* | Total |
| 1 | 111 | 241 | 289 | 210 | 73 | 22 | 473 |
| 2 | 44 | 95 | 117 | 104 | 55 | 16 | 216 |
| 3 | 9 | 20 | 26 | 36 | 28 | 8 | 63 |
| 4 | 15 | 33 | 45 | 72 | 64 | 19 | 124 |
| 5 | 9 | 21 | 34 | 78 | 81 | 24 | 124 |
| Total | 188 | 410 | 511 | 500 | 301 | 89 | 1000 |

Reported by Driver (2010).

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

Response No the final outcomes were measured by taking an intermediate/or surrogate outcome. The studies provided herein Study 1 Ennis, et. al. 2005, Study 2 Kavros, 2007, Study 5 Kavros, et. al., 2008, Study 9 Ennis, et. al., 2006, and Study 10 Kavros, et. al., 2007 followed the patients for the intended time period or until healing occurred.

6.3.5 If clinical experts assessed the applicability of values available, or estimated or adjusted any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought.
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method(s) used to collect and collate the opinions.

The uncertainty around these values should be addressed in the sensitivity analysis.

Response The U.S. based cost effectiveness study as described in section 6 identified at Study 1E was developed by Vickie R Driver, MS, DPM, FACFAS Director, Clinical Research Foot Care, Endovascular and Vascular Services, Boston University Medical Center, Boston, MA. The analytical process was has been described under Study 1E.

Data to develop the economic analysis from the UK/Wales perspective was taken from referenced sources as noted in the references for section 6. Cost to achieve healing was referenced from Celleration, Inc, Eden Prairie, Minnesota and combined with standard of care costs as reported by Stockl, 2004.

No one was approached that did not complete an analysis reported herein. The data came from independent referenced sources, or peer reviewed publications resulting from randomized clinical trials.

**Summary of selected values**

6.3.6 Please provide a list of all variables included in the cost analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

**Table B10 Summary of variables applied in the economic model**

| Variable | Value | CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Age | A years<br>The meta analysis provided in Study 1E included patients with an average of 68.9 (Stockl, 2004). Average age for Level 1 69.2, level 2 68.4, level 3, 66.0, level 4, 69.5 and level 5 68.9. average age and 63.8 average age in (Margolis, 2002) reported an average age of 63.8 and noted that the time to healing was more a factor of the age of the wound rather than the age of the patient.<br>Study 1 Ennis reported on patient average age 56 for the treatment arm and 54 for the sham arm. | x to y (normal)<br>Stockl reported on age specific to the level of a wound. Age (years) level 1 69.2 range+/- 11.6, level 2 68.4+/- 11.7, level 3 66.0 +/- 14.1, level 4 69.5 +/- 11.7 and level 5 68.9+/- 11.8 with a p value of 0.008.<br><br>Study 1 treatment arm average age range: 56 +/-11 and the sham control arm average age 54 +/- 12. | Patient characteristics section 5.3.4.<br>These references used in the U.S. economic model are provided in the references for section 6. |
| Overall survival | B months<br>Time to healing was reported in the U.S. economic study, in the Study 2E case series and in Study 3E the UK/Wales perspective the model included estimates of all living patients requiring treatment. | x to y (Weibull) | Study results section 5.5 |
| Refer to section 6.3.8 for further assumptions and sources | | … | … |
| CI, confidence interval | | | |

6.3.7 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? What assumptions and/or techniques were used for the extrapolation of longer term differences in clinical outcomes between the intervention and its comparator?.

Response The costs reported in Study 1E and Study 3E are based upon currently reported costs from referenced sources and the cost to provide MIST Therapy to the patient following the recommended treatment protocol of 3 times per week to cover the surface area of the wound. The costs were not extrapolated beyond the time to heal since healing was achieved with MIST Therapy within the year being calculated for cost.

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Response

6.3.8B1

| **Leg Ulcers - UK Market Analysis** | |
|---|---|
| **Leg Ulcer Statistics** | |
| Total Population [1] | 61,399,118 |
| Population 65-74 | 5,057,700 |
| Population 75-84 | 4,721,400 |
| Population 65-84 | 9,779,100 |
| **Prevalence rates** | **Number of leg ulcers** |
| Prevalence rates of 1.2 to 3.2 per 1,000 people (mean 2.2) [2] | 613,993 |
| Prevalence of a History of Leg Ulcers in People Over 65 Years (3 to 4%) ( mean 3.5%) would result in 352,048 ulcers | 352,048 |
| 70,000 to 190,000* individuals in UK with venous ulcer, mean values result in 130,000 ulcers [3] | 130,000 |
| Quotes 150,000* venous leg ulcers in the UK [4] | 150,000 |
| *Arterial ulcers account for 20% of ulcers on average 26,000 to 30,000 ulcers which are excluded from the figures above [5] | 28,000 |
| Estimated number of leg ulcers in UK | 150,000 |
| | |
| **Cost to the NHS** | |
| Leg ulcer treatment cost to NHS estimates (conservative) [6] | £600,000,000 |
| mean treatment cost (number of wounds by cost to NHS) | £4,000 |
| | |
| **Supporting Data** | |

| |
|---|
| 55% of ulcers were unhealed after a year [3] |
| 45% of venous leg ulcers are hard to heal [7] |
| 1% of population may be effected by leg ulceration at some time during their lives [8] |
| Individual patient costs ranging from 1,100 to 5,000. 9 |
| Up to 50% of a district nurses time is spent dealing with leg ulcers and over a 5th of patients need daily treatment [10] |
| Treating a leg ulcer in hospital for 3 months would be in excess of **£14,000.** [11] |
| 28% of ulcers remain open for 2 or more years |
| Costs can rise to 10,800 euro's (£9,189) [7] |

1. UK Census 1997 - Population Statistics
2. Graham et al
3. Moffatt et al, 2004
4.Simon DA, McCollum CN, 2004
5.Prince S, Dodds SR, 2006
6.Logan, 1997
3. Moffatt et al, 2004
7. www.woundsolutions.com
8. Cullum N, 1994
9. Eccles NK, 4ulcercare
10.British Medical Journal report
11. Alister Campbell quote

6.3.8 B2

| **Diabetic Foot Ulcers - UK Market Analysis** | |
|---|---|
| **Diabetic Foot Ulcer Statistics** | |
| Total Population | 61,399,118 |
| People in ENGLAND with diabetes in 2008 (4.77% of population) | 2,442,000 |
| 400 new cases are diagnosed every day | |
| **Prevalence/Incidence rates** | **Number of diabetic foot ulcers** |
| **Prevalence in the diabetic population between 5 and 7%** | **84,000** |
| One in 20 develop a foot ulcer each year | 122,100 |
| Prevalence (4 to 10%) | 7.00% |
| Annual population incidence (1 - 4%) | 2.50% |
| Lifetime incidence | 25.00% |
| Estimated number of diabetic foot ulcers annually in England | 84,000 |

| **Cost to the NHS** | |
|---|---|
| £600m is spent on treating foot problems and £252m spent on amputation | 600,000,000 |
| £600m is spent on treating foot problems and £252m spent on amputation | 252,000,000 |
| Diabetic Foot Ulcer Costs to the NHS (minus cost of amputation) | £348,000,000 |
| mean treatment cost (number of wounds divided by cost to NHS) | £ 4,143 |

| **Supporting Data** |
|---|
| People with Type I and Type " diabetes are at risk of damage to the nerves and blood supply to their feet which can lead to foot ulcers and slow healing wounds. |
| By 2025 it is forecast that 3,605,000 people will have diabetes in England |
| 15% of people with diabetes will develop a lower-extremity ulcer of some sort |

| |
|---|
| 30% of ulcers heal after 20 weeks of good wound care but 70% remain unhealed |
| Diabetic foot ulcers have a 28% recidivism rate at 12 months |
| Approximately half of foot wounds will become infected during treatment |
| Non-healing neuropathic ulcers may eventually require amputation and are more likely to die than others with diabetes |
| 5,000 people with diabetes undergo leg, foot or toe amputation each year in the UK, equivalent to 100 per week. |
| Amputations cost the NHS around £13,500 each. |


1. UK Census 1997 - Population Statistics.
2. NHS Statistics
3. Gordois, 2003
4. NHS diabetes - foot care
5. Singh, N., et al 2005
6. Boulton A, 2005
7. National Diabetes NHS support team newsletter
8. Reiber GE, 1996
9. Margolis D et al, 1999
10. Redekop WK, 2003
11. Lavery, LA, 2007
12. Edelson GW, 1996
13. www.feetforlife.org


6.3.8 B3

| Pressure Ulcers - UK Market Analysis | |
|---|---|
| **Leg Ulcer Statistics** | |
| Total Population [1] | 61,399,118 |
| Population 65-74 | 5,057,700 |
| Population 75-84 | 4,721,400 |
| Population 65-84 | 9,779,100 |
| | |
| **Prevalence / incidence rates** | **Number of pressure ulcers** |
| Approximately 412,000 individuals will develop a new pressure ulcer annually in UK [2] | 412,000 |
| 1 in 23 of the over 65 population [2] | 425,178 |
| 1 in every 150 of general population [2] | 409,327 |
| Mean incidence in UK is 40 cases per 1000 hospital admissions [2] | |
| In 1999/2000 HOSPITAL patients with pressure ulcers amounted to [2] | 320,000 |
| Pressure ulcers in NURSING HOMES annually are likely to amount to [3] | 32,000 |
| Conservative estimate of 55,000 new cases with GP, COMMUNITY [4] | 55,000 |
| | |
| Estimated number of pressure ulcers | 412,000 |
| | |
| **Cost to the NHS** | |
| Cost to the UK is £1.4 - 2.1bn annually | £1.4 to £2.1bn |
| Conservative value of treating pressure ulcers in the UK | £1,700,000,000 |
| Mean treatment cost | £4,126 |
| | |
| **Supporting Data** | |
| Pressure ulcers are estimated to cost equivalent to 4% of NHS expenditure [2] | |
| 90% of costs is derived from Nursing costs [2] | |

| |
|---|
| The treatment costs vary from £1,064 (grade 1) to £10,551 (grade 4) [2] |
| A pressure ulcer with osteomyelitis may cost £20k to £24k [2] |
| Grade 3 and 4 ulcers make up 24% of the total number of pressure ulcers [2] |

1. UK Census 1997 - Population Statistics
2. Bennett G et al, 2004
3. DOH statistics & Bennett, 2004
4. Margolis DJ, 2002 & Bennett, 2004

Tables 6.3.8B4 and 6.3.8B5 wound statistics are taken from the most recent data available in terms of Prevalence and Cost to the NHS. See each category for background data and references.

6.3.8 B4

| NHS Annual Wound Statistics | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Annual wounds in the population requiring treatment** | **Number of wounds** | **Cost of Current Treatment** | **Average treatment cost** | **P value** | **Hard to heal wound - Cost** | **Cost for a complex wound** | **Estimated Hard to Heal Chronic Wounds** |
| **Leg Ulcers** (UK) | 150,000 | £600,000,000 | £4,000 | <.0001 | £9,189 | 5,000 to £14,000 per annum | 28% of leg ulcers |
| **Diabetic Ulcers** (England only) | 84,000 | £348,000,000 | £4,143 | <.0001 | £10,000 | £10,000 to £50,000 if leading to amputation | conservative estimate 28% |
| **Pressure Ulcers** (UK) | 412,000 | £1,700,000,000 | £4,126 | <.0001 | £10,551 | £20,000 to £40,000 | 24% of Pressure Ulcers are grade 3 or 4 |
| **Total / average** | **646,000** | **£2,648,000,000** | **£4,099** | | **£9,913** | | |
| **Standard deviation** | **804** | **£718,958,506** | **£78** | | **£685** | | |

6.3.8 B5

| **Conventional Care Treatment Costs for Hard to Heal Wounds** | | | | **CI** | **CI** | **p value** |
|---|---|---|---|---|---|---|
| **Hard to Heal Wounds** | **Hard to Heal Wounds numbers** | **Hard to Heal Annual costs (per patient)** | **Total treatment costs** | **Range of Total Costs** | | |
| **Leg Ulcers** (UK) | 42,000 | £9,189 | £385,938,000 | 384,943,170 | 387,022,830 | <0.0001 |
| **Diabetic Ulcers** (England only) | 23,520 | £10,000 | £235,200,000 | 234,160,170 | 236,239,830 | <0.0001 |
| **Pressure Ulcers** (UK) | 98,880 | £10,551 | £1,043,282,880 | 1,032,921,700 | 1,053,718,310 | <0.0001 |
| **Total / Average** | **164,400** | **£9,913** | **£1,664,420,880** | | | |
| **Stdev** | **39,277** | **£685** | **£429,694,112** | | | |

6.3.8 B6

| Comparison MIST Treatment vs. Conventional Treatment Per Patient | | | |
|---|---|---|---|
| **Chronic ulcers requiring treatment** | **Annual conventional costs (per patient)** | **MIST Treatment Costs 26 weeks (per patient)*** | **Total savings using MIST (per patient)** |
| **Leg Ulcers** (UK) | £9,189 | £7,254 | £1,935 |
| **Diabetic Ulcers** (England only) | £10,000 | £7,254 | £2,746 |
| **Pressure Ulcers** (UK) | £10,551 | £7,254 | £3,297 |
| **Cumulative average saving** | | | **£7,978** |

6.3.8 B7

| Population Comparison MIST Treatment vs. Conventional Treatment | | | | | |
|---|---|---|---|---|---|
| **Chronic ulcers requiring treatment** | **Conventional - Annual costs all hard to heal wounds** | **MIST - Annual costs all hard to heal wounds** | **Total saving using MIST all hard to heal wounds (UK)** | **England only savings*** | **P value** |
| **Leg Ulcers (UK)** | £385,938,000 | £320,292,000 | £65,646,000 | £54,884,361 | <0.0001 |
| **Diabetic Ulcers (England only)** | £235,200,000 | £179,363,520 | £55,836,480 | £55,836,480 | <0.0001 |
| **Pressure Ulcers (UK)** | £1,043,282,880 | £754,058,880 | £289,224,000 | £241,810,230 | <0.0001 |
| **TOTAL COST** | £1,664,420,880 | £1,253,714,400 | | | |
| **TOTAL SAVING TO NHS** | | | £410,706,480 | £352,531,070 | |

| Population Comparison MIST Treatment vs. Conventional Treatment | | | | | |
|---|---|---|---|---|---|
| **Chronic ulcers requiring treatment** | **Conventional - Annual costs all hard to heal wounds** | **MIST - Annual costs all hard to heal wounds** | **Total saving using MIST all hard to heal wounds (UK)** | **England only savings*** | **P value** |
| **Leg Ulcers (UK)** | £385,938,000 | £320,292,000 | £65,646,000 | £54,884,361 | <0.0001 |
| **Diabetic Ulcers (England only)** | £235,200,000 | £179,363,520 | £55,836,480 | £55,836,480 | <0.0001 |

## *6.4 Resource identification, measurement and valuation*

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables,

mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

**NHS costs**

6.4.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Response The tables providing this information are found in response to question 6.3.8 The estimate to provide MIST Therapy to patients in the UK and Wales is provided in this table 6.3.8 B6.
Table 6.4.1 provides an estimate of the QALYs to the NHS when using the MIST Therapy treatment regimen to treat the hard to heal wounds in the UK/Wales patient population.

6.4.1

| **UK/Wales Population** | **Cost Effectiveness Model From the Perspective of the NHS** | | | **QALYs[1,2]** |
|---|---|---|---|---|
| | | | | |
| **Subgroup Analysis** | **Cost of New Technology** | **Cost of Current Gold Standard** | **Net incremental Change -Savings** | **QALY/yr** |
| **Leg Ulcers (UK)** | £320,292,000 | £385,938,000 | -£65,646,000 | £596,781,818 |
| **Diabetic Ulcers (England only)** | £179,363,520 | £235,200,000 | -£55,836,480 | £507,604,364 |
| **Pressure Ulcers (UK)** | £754,058,880 | £1,043,282,880 | -£289,224,000 | £2,629,309,091 |
| **Net savings across all subgroups of chronic wounds** | | | -£410,706,480.00 | |
| | | | | |
| QALYs net gain from 0.11 going from a wound state of 0.74 to a healing state of 0.85 | | | | |


1. Redekop WK, Stolk EA, Kok E, Lovas K, Kalo Z, Busschbach JJ. Diabetic foot ulcers and amputations: estimates of health utility for use in cost-effectiveness analyses of new treatments. *Diabetes Metab*. 2004;30(6):549–556.
2. Rosser R, Kind P. A scale of valuations of states of illness: Is there a social consensus? Int J Epidemiol 1978;7:347–58.


(PbR) tariffs have not been included in the cost estimates as wounds resulting with and without CC are excluded from the list as noted in Table 17 in the Changes to the Exclusion List noted on Newly Excluded in 2010-11. Source: Payment Guidance by Results NHS 2010 -2011.

http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_112970.pdf.

6.4.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Response They are on the exclusion list for 2010 and 2011 and therefore would not be applied to the cost analysis.

**Resource identification, measurement and valuation studies**

6.4.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 7.9, appendix 9. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

Response The relevant data sources used in the De Novo cost analysis have been provided in section 6.3.8 with the source information referenced each of the tables for calculating the total number of each subgroup of chronic wound and their estimated costs including p values.

6.4.4 If clinical experts assessed the applicability of values available, or estimated or adjusted any values, please provide the following details[4]:

- the criteria for selecting the experts

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method(s) used to collect and collate the opinions.

The uncertainty around these values should be addressed in the sensitivity analysis.

Response All expert opinion and data used to develop the De Novo cost analysis have been heretofore referenced in section 6.3.8. The data was obtained from peer reviewed sources based upon published data or that maintained by the NHS.

**Intervention and comparators' costs**

6.4.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, technology costs should be cross-referenced to sections 1.9. Provide a rationale for the choice of values used in the cost model discussed in section 6.2.3. Uncertainty around prices in sensitivity analysis.

6.4.6

| MIST Only Treatment costs | |
|---|---|
| | **Treatment costs** |
| **MIST annual rental** | **£7,500.00** |
| **Weekly rental** | **£144.23** |
| **Daily rental** | **£28.85** |
| Equipment: Cost per patient (based on 5 patients per day, 5 days a week) | £5.77 |
| **Consumable treatment cost (per patient treatment)** | **£35.00** |
| Patient treatment cost | £40.77 |

The cost to provide the MIST Therapy is well defined and is typically administered by a clinician, a physician, podiatrist, physical therapist, wound care nurse, or a home care nurse. This model depicts only the incremental costs of the device. Nursing cost to administer are estimated to be £50.00.

These are not necessarily all incremental since the nurse would be treating the wound and applying a new dressing for any treatment option.

Table B11 Unit costs associated with the technology in the economic model

| **Items** | **Intervention (confidence interval) MIST Therapy** | **Ref. in submission** | **Comparator 1 (confidence interval) Current Standard of Care in UK / Wales** | **Ref. in submission** | **Etc.** |
|---|---|---|---|---|---|
| Technology cost annual rental | **£7,500.00 allocated to £28.75 per treatment or based upon 5 treatments per week for 5 patients the daily rental per procedure is estimated to be £5.77** | Celleration, Inc. Eden Prairie, Minnesota | Multiple modalities are currently used, therefore we are providing the modelled cost per patient | NICE treatment guidelines | |
| Mean cost of technology treatment | £40.77 per treatment for 26 weeks £7,254 venous leg ulcer, £7,254 diabetic foot ulcer, £7,254 pressure ulcer (p =<0.0001 all cases). | Celleration, Inc. Eden Prairie, Minnesota | £9,189 venous leg ulcer, £10,000 diabetic foot ulcer and £10,551 pressure ulcer (p =<0.0001 all cases) | NHS data, sources to develop cost per sub group provided in tables 6.3.8 | |
| Administration cost | Administration costs are estimated at £ 50.00 per treatment for an estimated cost for 26 weeks of $3,900. A portion of this time is not unique to MIST and would be done regardless of the treatment modality. | Per protocol of using the device. | Included in the total cost to deliver the standard of care as provided from national macroeconomic numbers. | | |

| Items | Intervention (confidence interval) MIST Therapy | Ref. in submission | Comparator 1 (confidence interval) Current Standard of Care in UK / Wales | Ref. in submission | Etc. |
|---|---|---|---|---|---|
| Monitoring cost | N/A | The monitoring and delivery are one in the same act. | Included in the comparator estimates | | |
| Tests | No additional tests are required specifically due to the MIST Therapy treatment | | Included in the comparator estimates | | |
| Total treatment for 26 weeks resulting in healing. Comparator cost is not specifically related to healing | £21,762 cumulative costs to treat the 3 categories of wounds for 26 weeks providing a net savings to achieve healing of £7,987 | | £29,740 cumulative costs to treat the 3 categories of wounds summed for treating the 3 wound types resulting in greater expense to the NHS. | | |

**Hard to Heal Wound Estimates**

It is estimated that at least 28% of chronic wounds do not heal within 12 months.

Most grade 1 and 2 pressure ulcers heal within 12 weeks, however, 24% of pressure ulcers are grade 3 or 4 which are hard to heal.

There are at least 160,000 chronic hard to heal wounds taking over 12 months to heal annually. MIST is suitable for these chronic wound types with clinical studies showing MIST to improve healing outcomes and accelerate wound healing.

| Chronic wound requiring an intervention | Hard to Heal Wounds numbers | Hard to Heal Annual costs (per patient) | Total treatment costs |
|---|---|---|---|
| **Leg Ulcers** (UK) | 42,000 | £9,189 | £385,938,000 |
| **Diabetic Ulcers** (England only) | 23,520 | £10,000 | £235,200,000 |
| **Pressure Ulcers** (UK) | 98,880 | £10,551 | £1,043,282,880 |
| **Total / Average** | **164,400** | **£9,913** | **£1,664,420,880** |

**MIST Savings per Patient**

The savings to the NHS for Hard to Heal wounds compare 52 weeks conventional treatment against 26 weeks MIST treatment. MIST clinical studies have shown improved healing rates at twice the speed and half the time of conventional treatments, therefore, it has been assumed that if the treatment was carried out for a longer period, i.e., 26 weeks, it may facilitate complete healing.

| Chronic wound requiring an intervention | Annual conventional costs (per patient) | MIST Treatment Costs 26 weeks (per patient)* | Total savings using MIST (per patient set) |
|---|---|---|---|
| **Leg Ulcers** (UK) | £9,189 | £7,254 | £1,935 |
| **Diabetic Ulcers** (England only) | £10,000 | £7,254 | £2,746 |
| **Pressure Ulcers** (UK) | £10,551 | £7,254 | £3,297 |
| **Cumulative saving** | | | **£7,978** |

* MIST treatment costs include: 3 treatments per week (rental and consumable), dressing costs and nursing time (£50 per visit). Some patients may only require 2 treatments per week reducing the overall treatment cost. Average number of treatments per device per day @ 5, further cost efficiencies are realised with higher daily patient treatments.

## Health-state costs

6.4.7 Please summarise, if appropriate, the costs included in each health state (Explanation of definition of health-state). Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost model. The health states should refer to the states in section 6.2.5.

**Table B12 List of health states and associated costs in the economic model**

| Health states | Items | Value | Reference in submission |
|---|---|---|---|
| Health state 1 | Technology | £40.77 | |
| | Staff | £50.00 | Estimate of incremental time for nurse to use MIST and dress the wound. |
| | Hospital costs | £7.00 | MIST Therapy treatment does not require any additional hospital capital costs. The estimate of £7.00 reflects standard dressings that are used to bandage the wound after treatment. These costs would be incurred irrespective of any treatment provided to the wound area. Incremental costs are only associated with the technology. Total hospital costs may be reduced due to an earlier discharge to a less expensive patient care setting |
| | Etc. | | |
| | Total | £97.77 | Per treatment |
| Health state 2 | | | |
| Etc. | … | … | … |

Summaries have been provided bases on the macro level to treat venous leg ulcers, diabetic foot ulcers and pressure ulcers. The only incremental cost different than the current costs associated with the standard of care are the direct costs to provide MIST Therapy. The model considers MIST Therapy would replace current modalities not yielding the reduced time to healing.

**Adverse-event costs**

6.4.8 Please summarise the costs for each adverse event listed in section 5.7 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost model discussed in section 6.2.3. Adverse event and complications episodes. Include all adverse events and complications costs, both during and longer term post-treatment cost.

**Table B13 List of adverse events and summary of costs included in the economic model**

| Adverse events | Items | Value | Reference in submission |
|---|---|---|---|
| Adverse event 1 | Technology | Costs to manage the events as noted in section 5.7 would include the cost to treat the ulcers noted in the de novo study. For example any new ulcers during treatment would be expected to cost less than the ulcers treated after not healing for 30 days. | 5.7 |
| | Staff | | |
| | Hospital costs | | |
| | Etc. | | |
| | Total | | |
| Adverse event 2 | Technology | Cellulitis was noted as an adverse event and would be treated using antibiotics if identified early on while treating the patient. | |
| | Staff | | |
| Etc. | … | … | … |

The costs to treat the patients based upon the time to healing in the randomized clinical trial have been extracted from macro costs for the NHS to treat patients with a chronic wound of the leg, diabetic foot ulcer or a pressure ulcer. To the extent that those costs as well reflect the usual adverse events typically occurring to a patient already having a chronic wound, the cost to treat the event are inclusive of the total costs reported. The De Novo economic analysis therefore reflects the inclusive costs to treat the natural sequelae of disease progression. Adverse events captured in the randomized clinical trial for MIST Therapy as reported in section 5.7 are typical of a patient with a chronic wound and not uniquely related to the use of MIST Therapy, yet all adverse events noted during the clinical trial were recorded.

**Miscellaneous costs**

6.4.9 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

Response All costs have been noted.

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

Response The use of MIST Therapy provides a cost reduction opportunity by healing wounds in less time in a cost effective manner.

## *6.5 Sensitivity analysis*

This section should be read in conjunction with NICE's 'Evaluation Pathway Programme methods guide',

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

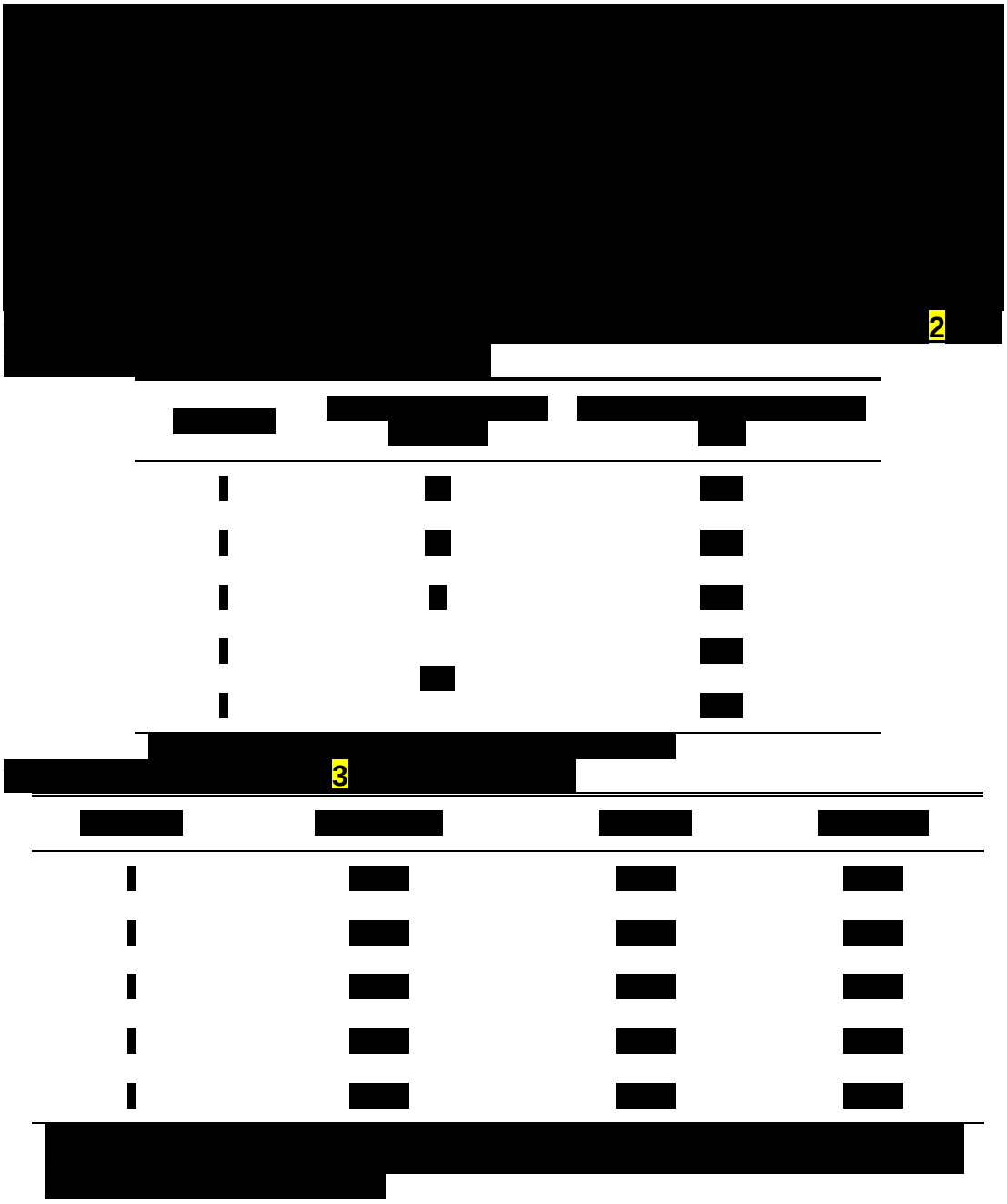
The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses.

All inputs used in the analysis will be estimated with a degree of imprecision.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.5.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

Response The assumptions used to develop the Study 1E model were based upon a large sample of patients 2,253 (Stockl 2004) and > 31,000 (Margolis, 2002). Using these large patient populations seeking treatment for diabetic foot ulcer(s) using the time to healing in the studies conducted by Study 1 Ennis, et. al. 2005, Study 2 Kavros, 2007, Study 5 Kavros, et. al., 2008, Study 9 Ennis, et. al., 2006, and Study 10 Kavros, et. al., 2007 as reported herein provide an effective comparator for determining the cost effectiveness of the treatment. The ability of MIST Therapy to bring a wound to closure in less time utilizes less resources resulting in a net cost savings and therefore is the dominant treatment option providing better outcome at less cost.



## *6.6 Results*

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Costs.
- Disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.

- A tabulation of the mean cost results.
- Results of the sensitivity analysis

**Clinical outcomes from the model**

6.6.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical studies. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

**Table B14 Summary of model results compared with clinical data**

| **Outcome** | **Clinical study result** | **Model result** |
|---|---|---|
| Progression-free survival achieving a healing state of the wound all subgroups | $C_1$ De Novo population based economic analysis | $R_{1\ MIST}$ Savings £7,987/patient or > £ 352 million in England only. £410,706,480 NHS |
| Post-progression survival N/A measures were taken on an annual basis since wounds heal in less than 1 year | $C_2$ | $R_2$ |
| Overall survival | $C_{1+2}$ | $R_{1+2}$ |
| Adverse event 1 | $C_3$… | $R_{3…N/A}$ |
| Etc. | … | … |

Reporting in the UK/Wales cost model

6.6.2 Please provide details of the disaggregated costs by health state, and costs by category of cost. Suggested formats are presented below.

**Table B15 Summary of costs by health state reflecting the economic model from the UK/Wales perspective for the population effected.**

| **Health state** | **Cost intervention (X)** | **Cost comparator (Y)** | **Increment** | **Absolute increment** | **% absolute increment** |
|---|---|---|---|---|---|
| Health state 1 (HS1) Improving the time to healing a chronic wound | $X_{HS1}$ **£1,253,714,400** | $Y_{HS1}$ **£1,664,420,880** | $X_{HS1} – Y_{HS1}$ -£410,706,480 | $\|X_{HS1} – Y_{HS1}\|$ £410,706,480* | $\|X_{HS1} – Y_{HS1}\|$/ (Total absolute increment) = 100% |
| HS2 | $X_{HS2}$ | $Y_{HS2}$ | $X_{HS2} – Y_{HS2}$ | $\|X_{HS2} – Y_{HS2}\|$ | $\|X_{HS2} – Y_{HS2}\|$/ (Total absolute increment) |
| … | … | … | | … | … |
| Adverse event 1 (AE1) | $X_{AE1}$ | $Y_{AE1}$ | $X_{AE1} – Y_{AE1}$ | $\|X_{AE1} – Y_{AE1}\|$ | $\|X_{AE1} – Y_{AE1}\|$/ (Total absolute increment) |
| AE2 | $X_{AE2}$ | $Y_{AE2}$ | $X_{AE2} – Y_{AE2}$ | $\|X_{AE2} – Y_{AE2}\|$ | $\|X_{AE2} – Y_{AE2}\|$/ (Total absolute increment) |
| **Total** | **$X_{Total}$** | **$Y_{Total}$** | **$X_{Total} – Y_{Total}$** | **Total absolute increment** | **100%** |
| Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee | | | | | |

*For costs attributable to £352,531,070 reflect costs for England only

**Table B16 Summary of costs by category of cost**

| Item | Cost intervention (X) | Cost comparator (Y) | Increment | Absolute increment | % absolute increment |
|---|---|---|---|---|---|
| Technology cost | $X_{tech}$ $£_{40.77}$ | $Y_{tech}$ $£_{72.00}$ | $X_{tech} – Y_{tech}$ $£_{-31.21}$ | $\|X_{tech} – Y_{tech}\|$ £31.21 | $\|X_{tech} – Y_{tech}\|$/ (Total absolute increment) 100% |
| Mean total treatment cost. Using population data to develop a in incremental cost per patient on average across all subgroup of wounds | $X_{treat}$ £7,254 | $Y_{treat}$ £9,913 | $X_{treat} – Y_{treat}$ -£2,659 | $\|X_{treat} – Y_{treat}\|$ £2,659 | $\|X_{treat} – Y_{treat}\|$/ (Total absolute increment) 100% |
| Administration cost. Component of treatment cost | $X_{admin}$ | $Y_{admin}$ | $X_{admin} – Y_{admin}$ | $\|X_{admin} – Y_{admin}\|$ | $\|X_{admin} – Y_{admin}\|$/ (Total absolute increment) |
| Monitoring cost. Monitoring is intrinsic to providing the therapy | $X_{mon}$ | $Y_{mon}$ | $X_{mon} – Y_{mon}$ | $\|X_{mon} – Y_{mon}\|$ | $\|X_{mon} – Y_{mon}\|$/ (Total absolute increment) |
| Tests | $X_{tests}$ | $Y_{tests}$ | $X_{tests} – Y_{tests}$ | $\|X_{tests} – Y_{tests}\|$ | $\|X_{tests} – Y_{tests}\|$/ (Total absolute increment) |
| Etc. | … | … | … | … | … |
| **Total** | **$X_{Total}$** | **$Y_{Total}$** | **$X_{Total} – Y_{Total}$** | **Total absolute increment** | **100%** |
| Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee | | | | | |

## Base-case analysis

6.6.3 Please present your results in the following table. List interventions and comparator(s) from least to most expensive.

**Table B17 Base-case results per treatment**

| Technology | Total costs (£) |
|---|---|
| MIST Therapy provided 3 time per week | £293 |
| UK/Wales per patient incremental savings | £2,659/savings per patient treated |
| UK UK/Wales population treatment net savings | £410,706,480 |

**Sensitivity analyses**

6.6.4 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Response Straight forward approach comparing cost to deliver the treatment over a population of 656,000 patients in the UK and Wales is comparing the average cost to treat using standard of care against the cost savings of achieving an improved time to healing. The improved time to healing on a smaller population of patients was significant using Study 1 Ennis (2005) demonstrating 40.7% of the wounds healed at 10 weeks compared 14.3% of Sham controls (p=0.0366).

6.6.5 Please present the results of PSA.

Response

6.6.6 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Response The scenario analysis from the U.S. perspective identified a cost savings per patient of $2,556 with a gain of 0.11 QALY/yr resulting in a net gain of $23,236/yr of improved health and saving cost to the health system. Redekop,(2004).

The UK/Wales perspective, using the same net gain in QALY/yr of 0.11 results in a savings per patient of £2,659 equating to a QALY of £24,173 to the NHS.

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

Response

6.6.8 What are the key drivers of the cost results?

Response Study 6 Bell et. al. (2008) using MIST Therapy impact on non-healing wounds identified the wound area was reduced by 79%. P< 0.0001. The treatment MIST therapy increased granulation tissue, improved peri-wound area, reduction in fibrin slough, reduction in exudate, improvement in patient pain score with 46% of patients granulation tissue post MIST versus 32% prior ( P< 0.0001). Improved peri-wound tissue 75% after versus 20% prior (P< 0.001). Reduction in fibrin/slough was 55% after versus 27% prior (P=0.0116). Reduction of exudate 88% versus 73% post MIST (P=0.002). The De Novo population based economic model from the NHS perspective considers costs to treat the hard to heal wounds compared to the less time to heal resulting from the new intervention MIST Therapy or NLFU plus standard of care.

## *6.7 Validation*

6.7.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

Response The validation of the data provided has been described at each point in the cost analysis.

## *6.8 Subgroup analysis*

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics.

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

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

6.8.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical effectiveness or cost due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

Response The De Novo UK/Wales perspective cost analysis included the dominant chronic wounds treated and paid by the NHS defined as the subgroups venous leg ulcers, diabetic foot ulcers and pressure ulcers. Tables found in 6.2.3 B1 and 6.2.3 B2 provide examples of the costs to treat these three wound types showing a close similarity in per wound treatment costs for the common chronic wound and the hard to heal chronic wounds.

6.8.2 Please clearly define the characteristics of patients in the subgroup.

Response This has been provided in previous tables relative to their incidence, cost and total numbers in the UK and Wales

6.8.3 Please describe how the statistical analysis was undertaken.

Response This was not a stochastic model based upon a small observation from the UK and Wales. Rather the De Novo analysis is a population based analysis showing p values indicating we have reached a high level of statistical significance. Using large numbers of patients used in the model is essentially sampling the total incident population. The data used is a reliable source to determine incidence, prevalence, and costs to the NHS.
What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.6.3 (Base-case analysis).

Response The subgroups are represented as patients having a venous leg ulcer, diabetic foot ulcer or a pressure ulcer. Tables are in 6.3.8.

6.8.4 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

Response This UK/Wales analysis did not include post surgical or trauma wounds other than those that may be included in leg ulcers. Adding this population to the model would likely continue to demonstrate the cost effectiveness of the MIST Therapy reduction in time to healing. The MIST Therapy treatment protocol based upon peer reviewed patient time to healing, was found to be cost effective in the complex high volume patients having venous leg ulcers, diabetic foot ulcers and pressure ulcers. The sample

represents the majority of chronic wounds. One would expect from the cost differences that MIST Therapy would as well prove cost effective for patients having post surgical chronic wounds or traumatic wounds that fail to heal after 30 days.

## *6.9 Interpretation of economic evidence*

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

Response The results are consistent with the literature in the MIST Therapy reduces the time to healing and therefore removes cost to treat chronic wounds from the healthcare systems in the U.S. and to the NHS.

6.9.2 Is the cost analysis relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

Response Yes the cost analysis is relevant to all patients that may express a chronic wound.

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

Response The main strengths of the analysis are the large patient populations used to derive the economic models. The clinical trials reporting the healing rate were from a small sample but did yield statistically relevant reduction in time to healing for approximately 50% of the patients receiving the wound treatment.
The weakness of the economic model are; it has been developed De Novo from the perspective of the NHS using macroeconomic data modelling clinical results from randomized controlled double clinical trials conducted in the U.S. The NICE guidelines for treating patients with diabetic foot ulcers, pressure ulcers and venous leg ulcers indicate the standard of care treatment protocols in the UK and Wales are similar to those practiced in the U.S., therefore one could expect to see similar reductions in time to healing and promotion of granulation tissue.

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

Response Analyses could be conducted measuring the costs to treat patients with chronic wounds post surgery or due to trauma. Statistical measures have

been provided about the treatment cost and their means. The population of wound patients was used in the estimate not a representation of the population. Given the large population used one could provide a range of likely costs in those cases in which MIST Therapy may take longer than 26 weeks to heal the patient. The low incremental cost of MIST Therapy dominates most economic models since a slight reduction in time to healing over the standard of care will continue to demonstrate a positive return for investment in the technology.

The macro cost estimates provide a good general baseline. Additional refinement of patient care setting costs could be provided. MIST Therapy may be provided in any patient care setting with the incremental costs similar across all sites of care. The cost benefit of MIST Therapy could be higher if we modelled the reduction in length of stay of pressure ulcer patients treated as inpatients.

## References

Please use a recognised referencing style, such as Harvard or Vancouver.

Response


1. Alister Campbell quote

2. Bennett G. Dealey C. Posnett J. The cost of pressure ulcers in the UK. Age and Ageing 2004; 33: 230–235. British Geriatrics Society 2004; all rights reserved.

3. British Medical Journal report

4. Carter MJ. Cost-effectiveness Research in Wound Care: Definitions, Approaches, and Limitations. Ostomy and Wound Management. 2010;.(565):11.

5. Cullum N. Leg ulcer treatments: a critical review (Part 2). Nurs Stand. 1994 Oct 5-11;9(2):32-6.

6. Driver VR. Cost Effectiveness of Noncontact Low-Frequency Ultrasound for the Treatment of Diabetic Foot Ulcers. Submitted for publication. 2010.

7. Eccles NK, 4ulcercare.

8. Holzer SE, Camerota A, Martens L, Cuerdon T, Crystal-Peters J, Zagari M. 1998 “Costs and duration of care for lower extremity ulcers in patients with diabetes.” Clin Ther. 1998 Jan-Feb;20(1):169-81.

9. Marcario A. Dexter F. Is Noncontact Normothermic Wound Therapy Cost Effective for the Treatment of Stages 3 and 4 Pressure Ulcers? Ostomy and Wound Management. 2002 April:3. http://www.woundsresearch.com/article/299

10. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: the association of wound size, wound duration, and wound grade on healing. Diabetes Care. Oct 2002;25(10):1835-1839.

11. Margolis DJ, Kantor J, Berlin JA. Healing of diabetic neuropathic foot ulcers receiving standard treatment. A meta-analysis. Diabetes Care. May 1999;22(5):692-695.

12. Moffatt CJ. Franks PJ. Doherty DC et al. Prevalence of leg ulceration in a London population. Q J Med. 2004 91: 431-437.

13. Posnett J, Franks PJ. Nurs Times. The burden of chronic wounds in the U.K. 2008 Jan 22-28;104(3):44-5. Smith & Nephew Wound Management, Hull.

14. Redekop WK, Stolk EA, Kok E, Lovas K, Kalo Z, Busschbach JJ. Diabetic foot ulcers and amputations: estimates of health utility for use in cost-effectiveness analyses of new treatments. Diabetes Metab. 2004;30(6):549–556.

15. Rosser R, Kind P. A scale of valuations of states of illness: Is there a social consensus? Int J Epidemiol 1978;7:347–58.

16. Stockl K, Vanderplas A, Tafesse E, Chang E. Costs of lower-extremity ulcers among patients with diabetes. Diabetes Care. Sep 2004;27(9):2129-2134.

17. UK Census 1997 - Population Statistics

**18.** Vowden K, Vowden P, Posnett J. The resource costs of wound care in Bradford and Airedale primary care trust in the UK. J Wound Care. 2009 Mar;18(3):93-4, 96-8, 100 passim**.**

19. www.woundsolutions.com (HTR 2004)

20. Singer, A. J., Clark, R. A. (1999) Cutaneous wound healing. *N. Engl. J. Med.* **341**,738-746

21. Posnett, J., Franks P.J., The burden of chronic wounds in the UK. Nursing times, 2008, 104 (3) 44-45

22. Moffatt. C. J., eta al. Prevalence of leg ulceration in a London population. QJM, 2004, 97 (7) 431-437

23. Logan. R., Common skin conditions of the skin and feet. Medicine, 1997, 25 (8) 23-27

24. Singh. N., Preventing foot ulcers in patients with diabetes. JAMA, 2005, 293; 217-228

25. Boulton A. J., et al. The global burden of diabetic foot diseases. Lancet, 2005, 366, 1719-1724

# 7 Appendices

## *7.1 Appendix 1*

7.1.1 IFU, scientific discussion or drafts.

## *7.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)*

The following information should be provided.

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

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

Response The PubMed.gov, US National Library of Medicine, National Institute of Health database, and Cochrane Review were searched. PubMed comprises more than 20 million citations for biomedical literature from **MEDLINE**, life science journals, and online books.

7.2.2 The date on which the search was conducted.

Response Search conducted on 14 October 2010

7.2.3 The date span of the search.

Response Searches spanned from 1994 – present.

7.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example,

MeSH) and the relationship between the search terms (for example, Boolean).

Response

| Search # | Term searched | Limits Activated | Results (# citations) |
|---|---|---|---|
| 1 | low-frequency noncontact ultrasound | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 10 |
| 2 | MIST Therapy OR MIST | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 28 |
| 3 | MIST Therapy ultrasound | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 9 |
| 4 | acoustic pressure wound therapy | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 11 |
| 5 | MIST ultrasound Therapy | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 6 |
| 6 | low-frequency ultrasound | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 24 |
| 7 | low-frequency noncontact ultrasound | None | 18 |
| 8 | ultrasound MIST and fibroblasts | Animals, In Vitro, published in 2002 - 2007 | 1 |
| 9 | ultrasound MIST | Animals, Clinical Trial, Meta-Analysis, Case Reports, Clinical Trial, Phase I, Clinical Trial, Phase II, Comparative Study, Evaluation Studies, In Vitro, Journal Article, Technical Report, Core clinical journals, Nursing journals, Publication Date from 2002 to 2004 | 1 |

7.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Response NA

7.2.6 The inclusion and exclusion criteria.

Response Pubmed database search results include only those publications specific to the following search terms: low-frequency, noncontact ultrasound; MIST Therapy; MIST; MIST Therapy ultrasound; acoustic pressure wound therapy; MIST ultrasound therapy; low-frequency ultrasound; low-frequency noncontact ultrasound; noncontact low-frequency nonthermal ultrasound therapy. Any publications listed in database searches not specific to the search terms were excluded from the final search results.

7.2.7 The data abstraction strategy.

Response Publications included in or excluded from the database search results were confirmed by a review of the publication abstracts.

Database search results, with appropriate publications excluded from final listing.

1. Combined Noncontact, Low-Frequency Ultrasound and Medical Honey for the Treatment of Chronic Wounds: A Case Series.

Chernev I, Liguori PA, Senno SL, Peters KL, Bowers JM.

J Wound Ostomy Continence Nurs. 2010 Jun 20. [Epub ahead of print]PMID: 20571471 [PubMed - as supplied by publisher]Related citations

2. The impact of noncontact, nonthermal, low-frequency ultrasound on bacterial counts in experimental and chronic wounds.

Serena T, Lee SK, Lam K, Attar P, Meneses P, Ennis W.

Ostomy Wound Manage. 2009 Jan;55(1):22-30.PMID: 19174586 [PubMed - indexed for MEDLINE]Related citations

3. Acoustic pressure wound therapy in the treatment of stage II pressure ulcers.

Thomas R.

Ostomy Wound Manage. 2008 Nov;54(11):56-8.PMID: 19037138 [PubMed - indexed for MEDLINE]Related citations

4. Expedited wound healing with noncontact, low-frequency ultrasound therapy in chronic wounds: a retrospective analysis.

Kavros SJ, Liedl DA, Boon AJ, Miller JL, Hobbs JA, Andrews KL.

Adv Skin Wound Care. 2008 Sep;21(9):416-23.PMID: 18769168 [PubMed - indexed for MEDLINE]Related citations

5. Clinical effectiveness of noncontact, low-frequency, nonthermal ultrasound in burn care.

Waldrop K, Serfass A.

Ostomy Wound Manage. 2008 Jun;54(6):66-9.PMID: 18579927 [PubMed - indexed for MEDLINE]Related citations

6. Acoustic pressure wound therapy in the treatment of a vasculopathy-associated digital ulcer: a case study.

Fleming CP.

Ostomy Wound Manage. 2008 Apr;54(4):62-5.PMID: 18480507 [PubMed - indexed for MEDLINE]Related citations

7. Acoustic pressure wound therapy for management of mixed partial- and full-thickness burns in a rural wound center.

Samies J, Gehling M.

Ostomy Wound Manage. 2008 Mar;54(3):56-9.PMID: 18456962 [PubMed - indexed for MEDLINE]Related citations

8. Wound closure and gradual involution of an infantile hemangioma using a noncontact, low-frequency ultrasound therapy.

Serena T.

Ostomy Wound Manage. 2008 Feb;54(2):68-71.PMID: 18401909 [PubMed - indexed for MEDLINE]Related citations

9.Treatment of ischemic wounds with noncontact, low-frequency ultrasound: the Mayo clinic experience, 2004-2006.

Kavros SJ, Miller JL, Hanna SW.

Adv Skin Wound Care. 2007 Apr;20(4):221-6.PMID: 17415030 [PubMed - indexed for MEDLINE]Related citations

10.The effect of noncontact, low-intensity, low-frequency therapeutic ultrasound on lower-extremity chronic wound pain: a retrospective chart review.

Gehling ML, Samies JH.

Ostomy Wound Manage. 2007 Mar;53(3):44-50.PMID: 17395987 [PubMed - indexed for MEDLINE]Related citations

11.Evaluation of clinical effectiveness of MIST ultrasound therapy for the healing of chronic wounds.

Ennis WJ, Valdes W, Gainer M, Meneses P.

Adv Skin Wound Care. 2006 Oct;19(8):437-46.PMID: 17008814 [PubMed - indexed for MEDLINE]

12. Is ultrasonic mist therapy effective for debriding chronic wounds?

Ramundo J, Gray M.

J Wound Ostomy Continence Nurs. 2008 Nov-Dec;35(6):579-83. Review.PMID: 19018197 [PubMed - indexed for MEDLINE]Related citations

13.Getting misty over wound care. Learn how therapy with ultrasound waves and saline mist can help your patient's wound heal.

Kent DJ.

Nursing. 2007 Sep;37(9):36-7. No abstract available. PMID: 17728650 [PubMed - indexed for MEDLINE]Related citations

14. Adjuvant use of acoustic pressure wound therapy for treatment of chronic wounds: a retrospective analysis.

Cole PS, Quisberg J, Melin MM.

J Wound Ostomy Continence Nurs. 2009 Mar-Apr;36(2):171-7.PMID: 19287265 [PubMed - indexed for MEDLINE]Related citations

15.Acoustic pressure wound therapy to debride unstageable pressure ulcers in the acute care setting: a case series.

Medrano S, Beneke MJ.

Ostomy Wound Manage. 2008 Dec;54(12):54-8.PMID: 19104124 [PubMed - indexed for MEDLINE]Related citations

16.Low-frequency, therapeutic ultrasound treatment for congenital ectodermal dysplasia in toddlers.

Caswell D, McNulty BM.

Ostomy Wound Manage. 2008 Oct;54(10):58-61.PMID: 18927484 [PubMed - indexed for MEDLINE]Related citations

17.Negative pressure wound therapy combined with acoustic pressure wound therapy for infected post surgery wounds: a case series.

Howell-Taylor M, Hall MG Jr, Brownlee Iii WJ, Taylor M.

Ostomy Wound Manage. 2008 Sep;54(9):49-52.PMID: 18812625 [PubMed - indexed for MEDLINE]Related citations

18. Acoustic pressure wound therapy to facilitate granulation tissue in sacral pressure ulcers in patients with compromised mobility: a case series.

Schmuckler J.

Ostomy Wound Manage. 2008 Aug;54(8):50-3.PMID: 18716342 [PubMed - indexed for MEDLINE]Related citations

19.Combination of negative pressure wound therapy and acoustic pressure wound therapy for treatment of infected surgical wounds: a case series.

Liguori PA, Peters KL, Bowers JM.

Ostomy Wound Manage. 2008 May;54(5):50-3.PMID: 18493094 [PubMed - indexed for MEDLINE]Related citations

20.Use of noncontact low-frequency ultrasound in the treatment of chronic foot and leg ulcerations: a 51-patient analysis.

Kavros SJ, Schenck EC.

J Am Podiatr Med Assoc. 2007 Mar-Apr;97(2):95-101.PMID: 17369314 [PubMed - indexed for MEDLINE]Related citations

21. Physiological effects of ultrasound mist on fibroblasts.

Lai J, Pittelkow MR.

Int J Dermatol. 2007 Jun;46(6):587-93.

Department of Dermatology, Mayo Clinic College of Medicine, Rochester, Minnesota 55905, USA.

22. Effects of ultrasound delivered through a mist of saline to wounds in mice with diabetes mellitus.

Thawer HA, Houghton PE.

J Wound Care. 2004 May;13(5):171-6.

Faculty of Health Sciences, University of Western Ontario, Canada.

## *7.3 Appendix 3: Quality assessment of RCT(s) and non-RCT(s) (section 5.4)*

7.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

The two RCT's have not been graded. Please find below how the questions are addressed by the study in our opinion.

| **Study question** | **Study 1** | **Study 2** |
|---|---|---|
| Was randomisation carried out appropriately? | Yes | Yes |
| Was the concealment of treatment allocation adequate? | Yes | No, was not a blinded RCT |
| Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease? | Yes | Yes |
| Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)? | Yes | No |
| Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for? | Yes, explained and adjusted for | No |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | No | No |
| Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | Yes | No |
| Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination | | |

Response

## *7.4 Appendix 4: Search strategy for section 5.9 (Adverse events)*

The following information should be provided.

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

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

Response The PubMed.gov, US National Library of Medicine, National Institute of Health database was searched. PubMed comprises more than 20 million citations for biomedical literature from **MEDLINE**, life science journals, and online books. All publications that were obtained were within the Celleration study library, therefore, no unknown adverse events are available to include within this section.

7.4.2 The date on which the search was conducted.

Response The full search was conducted on 14 October 2010.

7.4.3 The date span of the search.

Response The searches spanned from 2002 – present.

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

Response The related searches provided the following results, the adverse events are reported separately within section 5.

| Search # | Term searched | Limits Activated | Results (# citations) |
|---|---|---|---|
| 1 | low-frequency noncontact ultrasound | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 10 |
| 2 | MIST Therapy OR MIST | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 28 |

| | | | |
|---|---|---|---|
| 3 | MIST Therapy ultrasound | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 9 |
| 4 | acoustic pressure wound therapy | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 11 |
| 5 | MIST ultrasound Therapy | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 6 |
| 6 | low-frequency ultrasound | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 24 |
| 7 | low-frequency noncontact ultrasound | None | 18 |
| 8 | ultrasound MIST and fibroblasts | Animals, In Vitro, published in 2002 - 2007 | 1 |
| 9 | ultrasound MIST | Animals, Clinical Trial, Meta-Analysis, Case Reports, Clinical Trial, Phase I, Clinical Trial, Phase II, Comparative Study, Evaluation Studies, In Vitro, Journal Article, Technical Report, Core clinical journals, Nursing journals, Publication Date from 2002 to 2004 | 1 |

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

Response n/a

7.4.6 The inclusion and exclusion criteria.

Response Pubmed database search results include only those publications specific to the following search terms: low-frequency, noncontact ultrasound; MIST Therapy; MIST; MIST Therapy ultrasound; acoustic pressure wound therapy; MIST ultrasound therapy; low-frequency ultrasound; low-frequency noncontact ultrasound; noncontact low-frequency nonthermal ultrasound therapy. Any publications listed in database searches not specific to the search terms were excluded from the final search results. All studies are held

on file with Celleration and any adverse event reporting is stated within section 5.7 to 5.8.

7.4.7 The data abstraction strategy.

Response See notes for the medical data base search. All studies are held with Celleration and as such are listed in detail within section 5.5. If further information is required please advise bearing in mind time difference with the USA.

## *7.5 Appendix 5: Quality assessment of adverse event data in section 5.9 (Adverse events)*

7.5.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Response Celleration sponsored two (2) clinical trials with primary study objectives to assess the safety of MIST Therapy. Table B7, provides a summary of the adverse event experience for both studies.

Ultrasound Therapy for Recalcitrant Diabetic Foot Ulcers: Results of a Randomized, Double Blind, Controlled, Multicenter Study: All 133 patients were included in the analysis of safety. This primary study objective was to compare the incidence of condition- or therapy-related adverse events among patients receiving MIST in relation to SHAM control through the 12-week treatment period.

A total of 193 adverse events were reported among the 133 patients; 111 adverse events among MIST patients and 82 events among SHAM patients. At least one adverse event was reported for 45 of the 70 (64.3%) MIST patients and 40 of the 63 (63.5%) SHAM control patients (p = 0.9242, Chi-Square Test). No statistically significant or clinically important differences were identified between the MIST treatment group and the SHAM control group in the incidence, severity, device-relatedness, or seriousness of adverse events.

The Impact of Noncontact, Nonthermal Low-Frequency Ultrasound on Bacterial Counts in Experimental and Chronic Wounds: All 18 enrolled patients were included in the analysis of safety. This primary study objective was to evaluate the occurrence of device- and/or treatment-related adverse events through the 2-week treatment period. Three (3) adverse events (17%) in 2 patients were reported among the 18 enrolled patients. Two (2) of these events were considered serious in nature, but none of the reported events were related to MIST Therapy or the MIST Therapy System.

## *7.6 Appendix 6: Search strategy for cost-effectiveness and cost studies (section 6.1)*

The following information should be provided.

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

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

Response The PubMed.gov, US National Library of Medicine, National Institute of Health database, Cochrane Review, National Institute for Health and Clinical Excellence website, and Google search were searched. PubMed comprises more than 20 million citations for biomedical literature from **MEDLINE**, life science journals, and online books.

7.6.2 The date on which the search was conducted.

Response October 28-November 17, 2010

7.6.3 The date span of the search.

Response The date span included 1992-2010

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

| Search # | Term searched | Limits Activated | Results (# citations) |
|---|---|---|---|
| 1 | low-frequency noncontact ultrasound | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 10 |
| 2 | MIST Therapy OR MIST | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 28 |
| 3 | MIST Therapy ultrasound | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 9 |
| 4 | acoustic pressure wound therapy | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 11 |
| 5 | MIST ultrasound Therapy | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 6 |
| 6 | low-frequency ultrasound | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 24 |
| 7 | low-frequency noncontact ultrasound | None | 18 |
| 8 | ultrasound MIST and fibroblasts | Animals, In Vitro, published in 2002 - 2007 | 1 |
| 9 | ultrasound MIST | Animals, Clinical Trial, Meta-Analysis, Case Reports, Clinical Trial, Phase I, Clinical Trial, Phase II, Comparative Study, Evaluation Studies, In Vitro, Journal Article, Technical Report, Core clinical journals, Nursing journals, Publication Date from 2002 to 2004 | 1 |

| | | | |
|---|---|---|---|
| 10 | Cost effectiveness wounds | Guidance documents, Journal articles, Manuscripts, Evaluation Studies, public information database | 10 |

Response

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

Response Comparison of treatment cost estimates to the Agency for Healthcare Quality and Resource database, private hospital records to verify accuracy of range of cost to treat a hard to heal wound discounted to reflect costs in the UK and Wales.

## *7.7 Appendix 7: Quality assessment of cost-effectiveness and cost studies (section 6.1)*

| | **Study name** | |
|---|---|---|
| **Study question** | **Grade (yes/no/not clear/N/A)** | **Comments** |
| Study design | | |
| 1. Was the research question stated? | Yes | |
| 2. Was the economic importance of the research question stated? | Yes | |
| 3. Was/were the viewpoint(s) of the analysis clearly stated and justified? | Yes | |
| 4. Was a rationale reported for the choice of the alternative programmes or interventions compared? | Yes | Sometimes vague |
| 5. Were the alternatives being compared clearly described? | Yes | Standard of care way typically stated yet the exact details of standard of care were not often defined |
| 6. Was the form of economic evaluation stated? | Yes | In the wound care literature not always well stated |
| 7. Was the choice of form of economic evaluation justified in relation to the questions addressed? | Yes | |
| Data collection | | |

| | | |
|---|---|---|
| 8. Was/were the source(s) of effectiveness estimates used stated? | No | Effectiveness of healing a wound within a time period was not well defined. |
| 9. Were details of the design and results of the effectiveness study given (if based on a single study)? | Yes | For those few studies identified |
| 10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)? | No | |
| 11. Were the primary outcome measure(s) for the economic evaluation clearly stated? | Yes | |
| 12. Were the methods used to value health states and other benefits stated? | Yes | In the few instances the information was reported |
| 13. Were the details of the subjects from whom valuations were obtained given? | Yes | Very few papers providing original QALY data. |
| 14. Were productivity changes (if included) reported separately? | No | |
| 15. Was the relevance of productivity changes to the study question discussed? | No | |
| 16. Were quantities of resources reported separately from their unit cost? | No | |
| 17. Were the methods for the estimation of quantities and unit costs described? | No | |
| 18. Were currency and price data recorded? | Yes | Only a few such papers identified for wounds |
| 19. Were details of price adjustments for inflation or currency conversion given? | Yes | |
| 20. Were details of any model used given? | Yes | |
| 21. Was there a justification for the choice of model used and the key parameters on which it was based? | Yes | |
| Analysis and interpretation of results | | |
| 22. Was the time horizon of cost and benefits stated? | Yes | |

| | | |
|---|---|---|
| 23. Was the discount rate stated? | Yes | The discount rate was used in those cases in which the time horizon for patient or health system benefit was being determined over 1 year. |
| 24. Was the choice of rate justified? | Yes | |
| 25. Was an explanation given if cost or benefits were not discounted? | Yes | |
| 26. Were the details of statistical test(s) and confidence intervals given for stochastic data? | Yes | Did not find many stochastic analyses of wound healing. |
| 27. Was the approach to sensitivity analysis described? | Yes | |
| 28. Was the choice of variables for sensitivity analysis justified? | Yes | |
| 29. Were the ranges over which the parameters were varied stated? | Yes | |
| 30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?) | Yes | Generally not well defined in the published data |
| 31. Was an incremental analysis reported? | Yes | |
| 32. Were major outcomes presented in a disaggregated as well as aggregated form? | NA | |
| 33. Was the answer to the study question given? | Yes | |
| 34. Did conclusions follow from the data reported? | Yes | Varied by paper |
| 35. Were conclusions accompanied by the appropriate caveats? | Yes | |
| 36. Were generalisability issues addressed? | Yes | |
| Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination | | |

## *7.8 Appendix 8: Search strategy for section 6.4 (Measurement and valuation of health effects)*

The following information should be provided.

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

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

Response The PubMed.gov, US National Library of Medicine, National Institute of Health database, Cochrane Review, National Institute for Health and Clinical Excellence website, and Google search were searched. PubMed comprises more than 20 million citations for biomedical literature from **MEDLINE**, life science journals, and online books.

7.8.2 The date on which the search was conducted.

Response October 28-November 17, 2010

7.8.3 The date span of the search.

Response The date span of the search was from 1992-2010

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

Response

| Search # | Term searched | Limits Activated | Results (# citations) |
|---|---|---|---|
| 1 | low-frequency noncontact ultrasound | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 10 |
| 2 | MIST Therapy OR MIST | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 | 28 |

| | | | |
|---|---|---|---|
| | | years | |
| 3 | MIST Therapy ultrasound | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 9 |
| 4 | acoustic pressure wound therapy | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 11 |
| 5 | MIST ultrasound Therapy | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 6 |
| 6 | low-frequency ultrasound | Humans, Animals, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Evaluation Studies, In Vitro, Journal Article, Lectures, Multicenter Study, English, Core clinical journals, Nursing journals, published in the last 5 years | 24 |
| 7 | low-frequency noncontact ultrasound | None | 18 |
| 8 | ultrasound MIST and fibroblasts | Animals, In Vitro, published in 2002 - 2007 | 1 |
| 9 | ultrasound MIST | Animals, Clinical Trial, Meta-Analysis, Case Reports, Clinical Trial, Phase I, Clinical Trial, Phase II, Comparative Study, Evaluation Studies, In Vitro, Journal Article, Technical Report, Core clinical journals, Nursing journals, Publication Date from 2002 to 2004 | 1 |
| 10 | Cost effectiveness wounds | Guidance documents, Journal articles, Manuscripts, Evaluation Studies, public information database | 10 |
| 11 | QALY wounds | Journal articles, Manuscripts, Books, Evaluation Studies | 4 |

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

Response

7.8.6 The inclusion and exclusion criteria.

Response Any studies related to wound closure or trauma that may have included the economic benefit of an earlier state of wellness.

7.8.7 The data abstraction strategy.

Response Articles and resources identified and relevant have been noted under the references section of 6.

## *7.9 Appendix 9: Resource identification, measurement and valuation (section 6.4)*

The following information should be provided.

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

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

Response The PubMed.gov, US National Library of Medicine, National Institute of Health database, Cochrane Review, National Institute for Health and Clinical Excellence website, and Google search were searched. PubMed comprises more than 20 million citations for biomedical literature from **MEDLINE**, life science journals, and online books

7.9.2 The date on which the search was conducted.

Response October 18-November 17, 2010

7.9.3 The date span of the search.

Response The date span of the search included 1994-2010

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

Response

| Search # | Term searched | Limits Activated | Results (# citations) |
|---|---|---|---|
| 1 | Cost effectiveness wounds | Guidance documents, Journal articles, Manuscripts, Evaluation Studies, public information database | 10 |
| 2 | QALY wounds | Journal articles, Manuscripts, Books, Evaluation Studies | 4 |

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

Response

7.9.6 The inclusion and exclusion criteria.

Response Inclusion criteria included those studies that provided any economic information related to wound healing. NHS population data and cost data were used.

7.9.7 The data abstraction strategy.

Response All relevant articles that aided the analysis have been included in the references section of 6.

# 8 Related procedures for evidence submission

## *8.1 Cost models*

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

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Medical Technology Advisory Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission.

There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

## *8.2 Disclosure of information*

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

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

information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in red and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been

put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

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

## *8.3 Equity and equality*

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

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE’s responsibility in this respect, including

when considering subgroups and access to recommendations that use a clinical or biological criterion.

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