NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Medical technologies guidance

Assessment report summary

MIST Therapy system for the promotion of wound healing in chronic and acute wounds.

This assessment report summary has been written by technical analysts at NICE. It summarises the evidence that has been evaluated by the External Assessment Centre, and highlights key issues and uncertainties. The summary forms part of the information received by the Medical Technologies Advisory Committee (MTAC) when it formulates recommendations on the technology.

A list of the sources of evidence used to prepare this document is given in appendix A. The manufacturer's comments on factual inaccuracies in the assessment report and responses from the External Assessment Centre can be found in appendix D.

1 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.

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 at which point the generator switches off automatically.

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 is proposed to address these barriers to wound healing by stimulating the healing environment, actively treating the wound bed and promoting wound healing through wound cleansing and maintenance debridement by the removal of yellow slough, fibrin tissue, exudate and bacteria.

2 Proposed use of the technology

2.1 Disease or condition

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.

Between 1 and 3 people in every 1000 have active leg ulcers. Prevalence increases with age to about 20 people in every 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 annual cost to the NHS has been estimated at £300 million. This does not include the loss of productivity due to illness. 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 number of people with diabetes in the UK is predicted to increase over the next 20 years and it is estimated that this will result in an additional 25,000 new cases of foot ulceration a year.

The prevalence of pressure ulcers is estimated to be 412,000 in the UK annually, 24% of which are grade 3 or 4 ulcers (severe ulcers with tissue necrosis). Pressure ulcers represent a major burden of sickness and reduced quality of life for patients, their carers and their families. Often patients require prolonged and frequent contact with the health care system, and suffer much pain discomfort and inconvenience. The presence of pressure ulcers has been associated with a two- to four-fold increase of risk of death in older people in intensive care units (NICE Clinical guideline CG29).

The prevalence of chronic ulceration is highest in people aged over 65, with 68% of all incidences occurring in this age group. Trends in the UK population indicate that the number of people in the over 65 age group, will increase from 9.5 million to 13 million over the next 20 years.

2.2 Patient group

The MIST Therapy system is designed for use in patients with chronic, “hard to heal” and acute wounds including burns, pressure ulcers, leg ulcers, diabetic foot ulcers and surgical wounds. In addition, the MIST Therapy system is proposed for use as a wound bed preparation tool for biologics such as skin grafts.

Contraindictions: 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 malignancy.

2.3 Current management

Currently, a variety of advanced wound dressings are used to create the optimum wound healing environment for different types of wounds.

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.
- NICE encourages further research into the role of negative pressure wound therapy (e.g. VAC therapy) for open abdomen (Interventional procedures IPG322, 2009).

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.

2.4 Proposed management with new technology

The main comparators for the MIST Therapy system are 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 and compression bandaging. Treatment with the MIST Therapy system is estimated to take five to seven minutes to complete

and is performed when the wound dressings are changed three times a week. Therefore, the MIST Therapy system is an adjunct to advanced wound dressings and current care pathways are unlikely to be impacted by its use.

2.5 Equality and diversity issues

There were no equality issues identified that were deemed relevant to the production of guidance on the MIST Therapy system.

3 Issues for consideration by the Committee

3.1 Claimed benefits

Summary of claimed benefits addressed in the decision problem:

- MIST Therapy increases the closure of wounds by 40-70% within 6-12 weeks through accelerating the wound healing process.
- Case studies with MIST Therapy cover many indications including burns, pressure ulcers, leg ulcers, diabetic foot ulcers, surgical wounds and approximately 35,000 patients have been treated in the USA with excellent clinical results.
- MIST Therapy system improves healing rates thus reducing treatment time and may reduce associated costs including:
    - Hospital stay
    - Nursing time
    - Cost of wound dressings
    - Other technologies and surgical intervention
- MIST Therapy may be utilised for both in-patient and out-patient clinics and performed when the dressings are changed three times a week. Treatment is quick to administer with most treatments taking 5-7

minutes, ensuring convenient treatment sessions within normal clinical appointment times.

- Studies show that the recurrence rate of ulcers following the use of MIST is minimal which may be due to the effect MIST has on the collagen deposition during wound healing
- MIST Therapy enables bioburden reduction to a much greater depth of penetration than a wound dressing and stimulates faster healing. Therefore, the use of MIST Therapy should reduce the use of silver dressings and topical antibiotics and as a result, decrease the high treatment burden and the risk of silver or antibiotic resistance for the patient.
- MIST Therapy is painless and does not increase the risk of exposure to hazardous bacteria aerosols for the clinician or patients.
- A case series on the combined use of Negative Pressure Wound Therapy (NPWT) and MIST Therapy for treatment of infected surgical wounds showed a reduction in treatment time, a reduction in wound volume by 99-100% and a reduction in wound surface area by 82-100% in 4 to 12 weeks (Liguori *et al*., 2008). There are also a number of unpublished case studies for MIST used without NPWT which show excellent results and savings of approximately 37% to 50% over previous NPWT treatment.
- When yellow slough is present in wounds, MIST Therapy may be used as an alternative to expensive Hydrosurgery systems to cleanse the wound and facilitate healing. It can also be used at the patient's bed-side.

3.2 Issues for the consideration

In summary, the clinical evidence supports the case that the use of MIST Therapy can promote wound healing in chronic wounds.

The cost model reported that when MIST Therapy is used as an adjunct to standard wound care. The cost savings are £1563 per patient when compared against the standard wound care for leg ulcers, £2374 per patient against the standard wound care for diabetic ulcers and £2925 per patient when compared against the standard wound care for pressure ulcers.

The treatment cost for the MIST Therapy system is £7,626 per patient for 26 weeks based on 3 treatments per week regardless of the type of ulcer being treated. This cost includes the rental and consumable costs of treatment three times per week, wound dressing costs and nursing time (£50 per visit). The annual rental price of the MIST Therapy system is £7500.

One in vivo study reports that there is no risk of bacterial aerosolisation to clinician or patient when using MIST Therapy.

3.3 Main issues

- The two randomised controlled trials indicated that MIST Therapy can significantly improve wound healing in lower extremity chronic wounds although both studies contained less than 100 patients and there were limitations in the methodology.

- The other non-randomised clinical studies support that MIST Therapy can promote wound healing although only three of the studies contained comparison groups and all of the studies had small populations.

- In general, there are relatively few evidence-based treatment strategies for wound care owing to the outcomes of wound healing being difficult to measure. Wounds are a complex physiological condition which do not occur in isolation and the number of different types of wounds with various methods of treatment is large.

- No adverse events specific to the use of MIST Therapy have been reported in the published literature.

- The results of the cost analysis show a potential cost saving per patient if MIST Therapy is used as an adjunct to standard wound care driven by the reduced healing time. Wound care presents a high treatment burden to the NHS and therefore, the potential cost savings from the use of MIST Therapy could result in significant savings to the NHS. The costs of standard wound care were calculated from population based costs and incidence taken from NHS annual statistics for complex wounds. The costs represent the annual cost of treating a complex wound.

- The initial cost analysis submitted by the Manufacturer assumes that all types of ulcer will be treated with MIST for 26 weeks. Additional analysis showed that the wound healing time using MIST Therapy would have to increase to 32 weeks for leg ulcers, 35 weeks for diabetic foot ulcers and 36 weeks for pressure ulcers before the use of MIST Therapy was no longer cost saving

- Additional analysis is being performed by the External Assessment Centre to identify evidence on the clinical effectiveness of treating acute wounds with MIST Therapy and on the use of MIST Therapy as an adjunct to negative pressure wound therapy or as an alternative to hydrosurgery. The cost analysis did not analyse the costs of wound care with MIST Therapy compared against standard wound care for acute wounds.

4 The evidence

4.1 Summary of evidence of clinical benefit

The clinical effectiveness of the MIST Therapy system was described by wound area, wound volume, % wounds healed, healing time, bioburden and pain reduction. This wide variety of outcome measures is typical of research in wound care because wound healing is a complex process.

The manufacturer's submission identified ten studies assessing chronic wounds: two randomised controlled trials (RCTs) and seven peer reviewed prospective or retrospective observational studies. The manufacturer has over 200 publications on MIST Therapy on file, which included 104 unpublished single case studies held on the manufacturer's patient registry and eight published case series in a magazine that is funded by the manufacturer. The remainder consists of case series, posters and abstracts.

No adverse events specific to the use of MIST Therapy were reported.

Randomised Controlled Trials

One randomised controlled trial compared the use of the MIST ultrasound system (intervention group) against a sham device that delivered a saline mist without the use of ultrasound (control group) in patients with a chronic diabetic foot ulcer (Ennis *et al*., 2005). The device treatment protocol for both groups was three times per week for four minutes per treatment in addition to the standard of wound care standard such as wound dressings and weekly debridement. After 12 weeks of care, the proportion of wounds healed (defined as complete epithelialisation without drainage) in the intervention group (n=27) was significantly higher than in the control group (n=28), 40.7% versus 14.3% respectively (P= 0.0366, Fisher's exact test).

The other randomised controlled study compared the use of the MIST therapy ultrasound system (intervention group) against no ultrasound therapy (control group) in patients with non-healing wounds and chronic critical limb ischemia (Kavros *et al*., 2007). Both groups received the standard of wound care including daily dressing changes and weekly wound debridement. MIST Therapy was administered three times per week for five minutes per treatment. In this study, wound healing was defined as greater than 50% reduction in wound volume from the index measurement after 12 weeks of treatment. The percentage of patients who achieved greater than 50% reduction in wound volume was significantly higher in the intervention group

(n=35) than in the control group (n=35), 69% versus 29% (P <0.01) respectively.

Non-randomised Controlled Studies

The one prospective observational study obtained data from 23 patients with chronic lower extremity wounds of any etiology who received MIST Therapy in addition to advanced wound care (Ennis *et al*., 2006). Chronic wounds in this study were defined as those that had been present for longer than four weeks and had failed to progress to at least 15% closure despite receiving standard of wound care for two weeks. Advanced wound care included moist wound dressings such as alginates and foam dressings. MIST Therapy was administered for 3-12 minutes per treatment depending on the area of the wound, 3 times per week. The main outcome measures used in this study were wound area, wound volume and proportion of wounds healed. Control data were obtained from a published, prospectively collected clinic database. Patient demographics and wound etiologies were comparable between this MIST Therapy study and historic control group. In the control group (n=218), patients with wounds that failed to improve during an initial two to four weeks of advanced wound care, were treated with electrical stimulation, megahertz-based ultrasound or a combination of the two. To make the results from the MIST Therapy study comparable to the control data, patients were transitioned from MIST Therapy to another treatment protocol if wound healing reached a plateau (2-4 consecutive weeks without a reduction in wound area or volume). This was termed “MIST-assisted healing”. The overall percentage of wounds healed using MIST Therapy was 69% compared against 72% in the control group. Wounds treated with MIST Therapy alone were healed in a mean of eight weeks (median time of seven weeks) compared against a mean of 18.71 weeks for wounds treated with “MIST-assisted healing” (P = 0.0005). Wounds in the control group were healed with a median time of ten weeks although a statistically significant number of these patients required wound-related hospitalisation and surgical

procedures to achieve wound closure compared to the MIST Therapy study (P= 0.04).

A retrospective analysis reviewed the medical charts of 163 patients who received MIST Therapy as an adjunct to the standard of wound care (intervention group) and 47 patients who received the standard of wound care alone (control group) (Kavros *et al*., 2008). All the patients had lower extremity chronic wounds of any etiology. Standard of wound care included advanced wound care dressings (silvers, collagens), debridement and interventions specific to wound etiology such as compression and revascularization. MIST Therapy was administered for 3-12 minutes per treatment depending on the area of the wound, 3 times per week for 90 days. The main outcome measures used in this study were wound volume and the proportion of wounds healed. The median wound volume for MIST-treated wounds at the start of therapy was 304 mm^3 and 0 mm^3 at the end of therapy; median wound volume for control wounds at the start of therapy was 368 mm^3 and 68 mm^3 at the end. The percentage of wounds healed using MIST Therapy was 53% over a mean of 147 days compared against 32% over a mean of 134 days in the control group (P=0.009).

A retrospective case series analysed the medical records of 51 patients who had lower extremity chronic ulcers and received treatment using MIST Therapy in addition to the standard of wound care (Kavros and Schenck., 2007). Patients received the standard of wound care (moist wound dressings, debridement and compression) for a mean of 9.8 ± 5.5 weeks (P<0.0001). Patients received MIST Therapy once their wounds failed to progress with the standard of wound care alone and were treated three to five times a week for a mean of 5.5 ± 2.8 weeks (P<0.0001). The chronic wounds in this study had been present for 3 to 18 months. The main outcomes measures in this study were wound volume and rate of wound volume reduction. The mean percent reduction in wound volume in the standard of wound care period was 37.3% ± 18.6% (P<0.0001) over 9.8 ± 5.5 weeks (P<0.0001) compared against 94.9% ± 9.8% over 5.5 ± 2.8 weeks (P<0.0001) in the MIST Therapy treatment

period. During the standard of wound care period, no wound closures were recorded compared against the MIST Therapy treatment period in which 26 of 51 chronic wounds proceeded to closure ($P<0.05$).

Case Studies

One retrospective observational study reviewed the medical charts of 76 patients who had a non healing wound of any etiology and received non-contact ultrasound therapy (MIST Therapy) as an adjunct to conventional wound care (Bell and Cavorsi., 2008). Non-healing wounds were defined as those that failed to progress to at least 15% closure within the two weeks prior to therapy. The non healing wounds in this study had been present for a median of 8 weeks, although the range spanned from 2 to 332 weeks. Conventional wound care included moist wound dressings, selective debridement and compression. MIST Therapy was administered for a mean of 5.1 minutes per treatment for a mean of 2.3 times per week. Most of the non-healing wounds were located on the lower extremities and the main outcome measure used in this study was wound area. The median wound area was reduced by 79% during the use of MIST Therapy (2.5 to 0.6cm^2). The proportion of patients with greater than 75% healthy granulation tissue increased from 32% at the start to 46% at the end of MIST Therapy treatment. The patient-reported mean pain rating (0 = no pain, 10 = intense pain) decreased by a mean of 1.8 points during MIST Therapy treatment ($P=0.001$).

Another retrospective observational study reviewed the medical charts of 41 consecutive patients who had a non healing wound of any etiology and received acoustic pressure wound therapy (MIST Therapy) in addition to conventional wound care (Cole *et al*., 2009). Non-healing wounds were defined as those that failed to progress to at least 15% closure within the two weeks prior to therapy. The non healing wounds in this study had been present for a median of 8 weeks. Conventional wound care included moist wound dressings, debridement and interventions specific to wound etiology. MIST Therapy was administered for a mean of 3.7 minutes per treatment for a

mean of 2.5 times per week. Most of the non-healing wounds were located on the lower extremities and the main outcome measure used in this study was wound area. The median wound area was reduced by 88% (mean: 60%) during the use of MIST Therapy. The proportion of patients with greater than 75% healthy granulation tissue increased from 26% (n=12) at the start to 80% (n=41) at the end of MIST Therapy treatment. The patient-reported mean pain rating (0 = no pain, 10 = intense pain) decreased by a mean of 2.9 points during MIST Therapy treatment (P<0.0001). The percentage of wounds that healed completely was 38% (n=20) in a mean of 6.8 weeks of MIST Therapy treatment.

A retrospective review of medical charts from 48 consecutive patients who had a chronic wound of any etiology and received acoustic pressure wound therapy (MIST Therapy) as an adjunct to physical therapy wound management was conducted (Haan *et al*., 2009). Physical therapy wound management included debridement, optimum wound dressings, compression, negative pressure wound therapy and pulsed lavage with suction. The chronic wounds in this study had been present for a mean of 23 weeks (range 0 to 220 weeks) and most of the wounds were located on the lower extremities. MIST Therapy was administered for a mean of 4.1 minutes per treatment for a mean of 2.1 times per week. The main outcome measures used in this study were wound area, pain and proportion of wounds healed. The visual analog scale (VAS) was used to measure pain reported by 42 patients. The VAS (0 = no pain, 10 = intense pain) decreased from a mean of 3.6 to 0.8 during the MIST Therapy treatment, a mean reduction of 2.6 points (P<0.0001). The median wound area was reduced by 92% from the start to the end of MIST Therapy. The proportion of wounds with greater than 75% healthy granulation tissue increased from 37% to 89% (n=41) during the use of MIST Therapy treatment (P<0.0001). The percentage of wounds that healed completely during the study period using MIST Therapy treatment was 24% (n=12) in a mean of 4.3 weeks.

A retrospective case study of medical records from 15 consecutive patients with painful, chronic lower extremity wounds of various etiology was conducted (Gehling et al., 2007). All patients were treated with MIST Therapy to promote wound healing of their chronic wounds. Treatment was delivered to the wound three times per week for three to five minutes. Wounds had been present for a mean of 17 months (range 5 weeks to 96 months) before the start of MIST Therapy treatment. The main outcome in this study was pain. The pain described by patients was not related to clinical signs of infection and the pain was of greater than one month duration and greater than score five on a scale of 0 to 10 (0=no pain, 10=extreme pain). Mean pain scores decreased by 80% from pre-treatment to post-treatment with MIST Therapy (8.07 ± 1.91 and 1.67 ± 1.76 respectively, P=0.0003). Patients reduced or discontinued their use of narcotic analgesics within two weeks of starting treatment with MIST therapy.

One study included pre-clinical data and a prospective case series of 11 patients to study the use of MIST Therapy in controlling wound bacterial colony counts in chronic wounds (Serena *et al*., 2009). Eleven consecutive patients with pressure ulcers that contained 10^5 CFU/g of tissue received MIST Therapy three times a week for a mean duration of four minutes per treatment. Patients were treated with MIST Therapy for two weeks in addition to moist wound dressings. No antiseptics, antibiotics, silver or antimicrobial dressings were used in during the study. The mean pre-treatment bioburden was 4 x10^7 compared against 2 x 10^7 after two weeks of treatment with MIST Therapy. During the treatment period with MIST Therapy, mean wound area decreased by 26% and mean wound volume decreased by 20%.

4.2 Summary of economic evidence

The submitted economic evidence comprised an unpublished study, a conference poster and a new cost analysis to assess the costs and savings to the NHS of using the MIST Therapy system.

[redacted]

The conference poster described an economic evaluation based on a case series of five patients with pressure ulcers (Anaeme *et al.,* 2009). The primary outcome measure was the reduction in wound size over two months. Cost savings were estimated from the direct costs of using MIST Therapy compared against negative pressure wound therapy. The use of MIST Therapy and standard wound care resulted in a reduction in the size of pressure ulcers by 34% with an average saving of $1,310 per patient, with savings per patient ranging from $563-$2187.

4.2.1 Model Structure

For the purpose of cost analysis, three different wound dressings were considered to be the most relevant NHS comparators for the different types of wounds: compression bandaging for venous and arterial ulcers; foam dressing for other chronic and hard to heal wounds; surgical debridement for acute wounds.

The submitted cost model used population based costs and incidence reported with reference to improving the “time to heal” of leg ulcers, pressure

ulcers and diabetic foot ulcers. The perspective was from the current cost incurred by the NHS to treat chronic wounds in the UK and Wales of £2.3-3.1 billion in 2005 (Posnett and Franks., 2008).

The economic model assumed the use of MIST Therapy would follow the current care pathway for the treatment of wounds; it would be initiated if standard wound care has failed to heal the wound, if the wound has not improved for 30 days or as an alternative method for debridement in acute wounds. The treatment regimen would be three times a week for the appropriate duration depending on the area of the wound. It was assumed that the treatment would take place at the same time as the changing of wound dressings during standard wound care. Published studies report improved healing rates and a reduction in wound size in 10 weeks using MIST Therapy as an adjunct to standard wound care compared against 20 weeks using standard wound care alone. In the model this data was used to apply a healing time of 26 weeks for MIST Therapy compared against 52 weeks of standard of wound care.

The unit costs associated with treatment using MIST Therapy in the economic model included annual rental of the technology, administration and consumable treatment costs. The manufacturer states that staffing costs are not necessarily incremental because the nurse would treat the wound and apply a new dressing for any treatment option. The cost of ordering, transporting, processing and stocking consumables was not included in the analysis. The energy cost and the cost of disposal of consumables was also not included in the analysis.

4.2.2 Costs

The treatment cost for the MIST Therapy system is £7626 per patient for 26 weeks based on 3 treatments per week. This cost includes the rental and consumable costs at around £41 per treatment, three times per week. The annual rental cost of MIST Therapy system is £7500 and consumables cost

£35 per treatment. The treatment cost for MIST Therapy also included, wound dressing costs at £7 per treatment and nursing time at £50 per visit.

The main cost savings included in the manufacturer's cost analysis were for reducing the time for a wound to heal compared to the standard of wound care alone.

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	£9,189	£7626	£1563
Diabetic Ulcers	£10,000	£7626	£2374
Pressure Ulcers	£10,551	£7626	£2925

The costs of standard wound care were calculated from NHS annual wound statistics for complex wounds.

4.2.3 Sensitivity Analyses

The manufacturer's cost analysis assessed the cost implications if treatment using MIST Therapy resulted in a faster healing time and reduced the number of weeks of wound care required.

The base case analysis assumed that treatment with MIST would be for 26 weeks. Additional analysis showed that wound healing time would have to increase to 32 weeks for leg ulcers, 35 weeks for diabetic foot ulcers and 36 weeks for pressure ulcers before the use of MIST Therapy was no longer a cost saving option.

No sensitivity analysis was undertaken to assess the impact on results of different prices for the MIST Therapy system and wound dressings.

4.2.4 Results

The MIST Therapy cost analysis showed that the average cost per patient over 26 weeks of treatment was estimated to be £7626 for leg, diabetic and pressure ulcers. The annual cost saving was £1563, £2374 and £2925 for treatment of leg, diabetic and pressure ulcers respectively, when compared against standard wound care alone.

4.3 Summary of technical evidence

[redacted]

5 Ongoing research

Study	Estimated completion date
MIST Therapy's End-Stage Renal Disease Patients Presenting Wounds. A Prospective, Randomized, Controlled Study.	May 2012
MIST, A comparative study of MIST Therapy, Versajet and Scalpel debridement in reducing bacterial contamination.	2010, published 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.	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.	January 2011
Effect of Non-Contact Low Frequency Ultrasound treatment on suspected deep tissue injury healing. Retrospective Analysis completed.	Publication date Spring 2011
A Prospective Assessment of the effectiveness of MIST Therapy on Suspected Deep Tissue Injury. Start date November 2010.	June 2011

Trillium Healthcare, AZ- A Comparative, Prospective, Randomised 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.	April 2011

No data from these studies has been included in the submission, assessment report or assessment report summary.

6 Author

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January 2011

Appendix A: Sources of evidence considered in the preparation of the assessment report summary

A Batki A.D., Nayyar P., Chen Y. and Lilford R.
Wolfson Applied Technology Laboratory (WATL)
The MIST Therapy system for the promotion of wound healing in chronic and acute wounds.
January 2011

B Submissions from the following manufacturer/sponsors:

H & R Healthcare on behalf of Celleration.

C Related NICE guidance

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

D References

Anaeme KO, Ferrin C, Hollis B. Cost Effectiveness of Noncontact Low-Frequency Ultrasound for Non-healing Wounds in the Long-Term Acute-Care Hospital: A case series. Presented at Clinical Symposium on Advances in Skin and Wound Care, San Antonio, Texas, USA October 2009.

Bell AL, Cavorsi J. Noncontact ultrasound therapy for adjunctive treatment of nonhealing wounds: retrospective analysis. *Phys Ther* 2008;88: 1517 - 1524.

Cole PS, Quisberg J, Melin MM. Adjuvant use of acoustic pressure wound therapy for treatment of chronic wounds: a retrospective analysis. *J Wound Ostomy Continence Nurs* 2009; 36: 171 -177.

Driver VR. Cost Effectiveness of Noncontact Low-Frequency Ultrasound for the Treatment of Diabetic Foot Ulcers. To be submitted for publication 2010.

Ennis WJ, Foremann P, Mozen N, et al. Ultrasound therapy for recalcitrant diabetic foot ulcers: results of a randomised, double-blind, controlled, multicenter study. *Ostomy Wound Manage* 2005; 51: 24 - 39.

Ennis WJ, Valdes W, Gainer M, et al. Evaluation of clinical effectiveness of MIST ultrasound therapy for the healing of chronic wounds. *Adv Skin Wound Care* 2006; 19: 437 - 446.

Gehling ML, Samies JH. The effect of noncontact, low-intensity, low-frequency therapeutic ultrasound on lower-extremity chronic wound pain: a retrospective chart review. *Ostomy Wound Manage* 2007; 53:44 - 50.

Haan J, Lucich S. A retrospective analysis of acoustic pressure wound therapy: effects on the healing progression of chronic wounds. *J Am Coll Cert Wound Spec* 2009; 1: 28 - 34.

Kavros SJ, Miller JL, Hanna SW. Treatment of ischemic wounds with noncontact, low-frequency ultrasound: the Mayo clinic experience, 2004-2006. *Adv Skin Wound Care* 2007; 20: 221 -226.

Kavros SJ, Schenck EC. Use of noncontact low-frequency ultrasound in the treatment of chronic foot and leg ulcerations: a 51-patient analysis. *J Am Podiatr Med Assoc* 2007; 97: 95 - 101.

Kavros SJ, Liedl DA, Boon AJ, et al. Expedited wound healing with noncontact, low-frequency ultrasound therapy in chronic wounds: a retrospective analysis. *Adv Skin Wound Care* 2008;21:416 - 423.

Lam K. An in vitro evaluation of the bacterial aerolisation when using the MIST Therapy system to treat wounds inected with Staph aureus and Pseudomonas aeruginosa. January 2008.

Posnett J, Franks PJ. The burden of chronic wounds in the U.K. Nursing Times 2008; 104 (3):44-45.

Serena T, Lee SK, Lam K, et al. The impact of noncontact, nonthermal, low-frequency ultrasound on bacterial counts in experimental and chronic wounds. *Ostomy Wound Manage* 2009; 55: 22-30.

Appendix B: Comments from professional bodies

Royal College of General Practitioners
John Hedges, General practitioner

Foot in Diabetes UK
Paul Chadwick, Podiatrist

An Bord Altranais, the Irish nurses' association
Rachel Henchy, Sister

Royal College of Nursing

Ray Norris Tissue Viability Nurse

Wound Alliance UK
Sylvia Stanway Tissue Viability Nurse

Four expert advisers had direct involvement with the use of MIST Therapy and one expert would like to use the technology.

Four expert advisers thought MIST Therapy was thoroughly novel and one expert adviser thought it was a significant modification on existing technology.

Three expert advisers thought MIST Therapy would offer additional benefits over current practice by reducing pain and increasing the rate of wound healing. One expert adviser also stated MIST therapy is a more effective treatment of wound infections and decreases levels of exudate. Another expert thought that MIST Therapy would offer a quality of life improvement to patients.

Two expert advisers thought the level of evidence for MIST therapy was moderate and the three other expert advisers thought it had limited evidence.

Four expert advisers who had direct involvement with the use of MIST Therapy thought the benefits were likely to be realised in practice and five expert advisers thought the likely obstacle was budget limitation.

One expert adviser who had direct involvement with the use of MIST Therapy stated that there was real progress being made in healing wounds where other treatments had not been successful. Patients with wounds that have failed to heal in over 5 years are close to healing since commencing MIST Therapy.

One expert adviser stated that recalcitrant wounds which had not healed using conventional treatment, healed completely when MIST Therapy was used.

One expert adviser stated that it is one of the first wound healing technologies which appears to deliver its claims.

Appendix C: Comments from patient organisations

The following organisations were contacted for commentary:

British Skin Foundation
Changing Faces
Counsel and Care
CritPaL - Patient Liaison Committee of the Intensive Care Society
Diabetes UK
ICU Steps
Let's Face It
MRSA Action UK
National Concern for Healthcare Infection (NCHI)
Royal College of Surgeons Patient Liaison Group
Skin Care Campaign
The Patients Association

No response was received.

Appendix D: Manufacturers' comments and External Assessment Centre responses

The table below summarises factual inaccuracies identified by the manufacturer in the assessment report and their proposed amendments. The final column contains a response from the External Assessment Centre.

Issue 1

Summary of submitted clinical effectiveness evidence	The Ennis, et. al. pivotal clinical trial resulting in FDA approval did produce the following results. Weekly wound evaluations. 40.7% of MIST treated wounds healed compared to 14.3% in the sham group (P=0.0366, fisher's exact test); Kaplan Meier survival analysis results found a mean time to healing of 9.12 (SD 0.58) weeks and a median of 11 weeks (SD 0) for MIST compared to a mean of 11.74 (SD 0.22) and a median of 12 weeks (SD 0.82) for sham treatment (log range P <0.0144). Given the inherent complexity in blinding a clinician to the use of a device we point out the duration of the follow up to wound closure is within the standards for other published wound clinical literature. The patients were followed to healing.	Published wound clinical trials report outcomes within 4 wks, 3 months and rarely 6 months follow up period. Ennis, et. al 2005, reported a mean time to closure of 40.7 % of the patients at 9.12 weeks. For a wound clinical trial follow up to 12 weeks showing healing is later reporting on 8 months is longer than most. NICE guideline "*Surgical site infection prevention and treatment of surgical site infection National Collaborating Centre for Women's and Children's Health Commissioned by the National Institute for Health and Clinical Excellence October 2008"* in sections 7.2, 7.4, 7.6 and Appendix G reported on comparative studies for wound treatments. The time to follow wound treatments relative to the end point of SSI infection were short resulting in no additional information provided in the guideline. Ennis, et. al 2004 flaws considered, does however report on a set of diabetic foot ulcer patients followed to healing. Blinding for the MIST therapy system is difficult, yet accomplished at some clinical trial sites. We recommend despite the flaws of this study in the realm of published wound clinical trials the data are useful upon which we could then build the economic argument.	The issue listed by the manufacturer is NOT a factual inaccuracy of the EAC report. The proposed amendment and its justification do not provide substantive evidence or argument. No amendment is required.

Issue 2

1.3.2 Weaknesses The assessment,	The follow up paper of Ennis, et. al. (2006) does provide an 8 month follow up of the patients comparing them to	The evidence used in the economic analysis did depend upon the clinical trial	The issue listed by the manufacturer is NOT a

including the economic assessment, is based on effectiveness parameters that are derived from observed studies. Worse, much of this evidence is based on before and after studies on the same patients. The entire report and its conclusion therefore rest on sticky foundation.	a similar set of standard set of patients during the same time period. The finding, in a wound clinical trial it is customary to follow the same patient for the duration off the study period. The historic controls treatment was compared to those patients receiving the MIST therapy. There was a statically significant difference in the hospital resources used to treat these patients. It was these differences used to develop the economic model. Given the high cost in the UK to treat this population MIST therapy on a comparative basis provided a cost savings alternative to safe, effective, and pain free debridement for hard to heal wounds. Main outcome measures: wound healing, area and volume reduction and microcirculatory flow. Overall 69% of the wounds in the study were healed using an intent-to-treat model. Median time to healing was 7 weeks with ultrasound therapy. Historic controls were healed with a median time to healing of 10 weeks; however a statistically significant number of these patients required wound-related hospitalization and surgical procedures to achieve closure compared with the wounds in the present study. Baseline $TcPo_2$ testing was performed along with Perimed PIM 2 scanner for microvascular status. Laser Doppler imaging was used for wound measurements.	information. The Ennis paper provided insight into a comparative set of patients not receiving MIST Therapy. The paper, albeit not perfect in terms of a the gold standard for an RCT, did however provide evidence that suggests patients treated with MIST Therapy experience a reduction in wound size related to healing in less time than a similar set of patients not treated with MIST therapy. Given the method of delivering MIST therapy, a blinded control group does not lend well to the best designed clinical trial. The patients reported where the blind was not broken provided an acceptable comparative cohort.	factual inaccuracy of the EAC report. The proposed amendment and its justification do not provide substantive evidence or argument. No amendment is required.

Issue 3

1.4.2 Weaknesses The author of the report distinguishes between randomised and non-randomised design, but not between studies using historical controls	Accept patients as their own control for wound healing when the design of the study provides two dichotomous groups, MIST Therapy or non MIST Therapy receiving good standard of care. The wound healing environment is highly dependent upon the patient's unique overall health, behaviours, attention to treatment regimen, and therefore does provide an excellent laboratory type	With respect to the complexities of conducting RCT wound clinical trials using a device that is obviously being used or not, presents problems that may be addressed by retrospective review and using patients healing as their own control.	We cannot find this publication and is not relevant to the EAC statement. The issue listed by the manufacturer is NOT a factual inaccuracy of the EAC report. The proposed

and those (the majority) with no controls at all *i.e.* where the patient is their own control over time.	control for healing. A comparative group of similar patients following the treatment regimen in the same manner, yet controlled for experimental versus standard of care is an effective model. Retrospective case reports of patients having similar wound aetiology, match for co morbid conditions, and treatment regimens varying MIST or non MIST does produce information that can be used in the clinic.	The NHS, Ghatnekar O, Willis M, Persson U, ***Cost –Effectiveness of treating deep diabetic foot ulcers with Promogran in four European countries***, concluded: "The treatment of diabetic non-superficial foot ulcers with Promogran in conjunction with good wound care (GWC) resulted in more healed ulcers and a shorter time than GWC alone. It was also a cheaper treatment option from the perspective of the healthcare provider." These findings were based upon 1 RCT – with limitations, survey of 5 other papers and expert opinion used to develop a Markov Model. While we recognize NHS provides review and opinion, the data presented in the Celleration application has more robust data and used a straight forward method of modelling demonstrating a significant clinical and economic benefit.	amendment and its justification do not provide substantive evidence or argument. No amendment is required.

Issue 4

2.1 **Critique of manufacturer's description of underlying health problem** These figures appear to be consistent with NICE guidelines CG10 and CG29 [12, 13]. The manufacturer has not provided data for the subsequent 5 years.	As noted using the information from the MIST Therapy RCT, other published articles on healing from standard of care treatments the 5 year cost benefit can be modelled.	Modelling of outcomes is allowed. There is very little published information on the cost effectiveness of the standard of care in closure of hard to heal wounds. The data used to develop the de nove model were obtained from both the US and UK using standard databases. Modelling of the time to healing can include the cost of MIST Therapy with the healing time less than standard in 40.7 % of patients.	Amendment noted and the sentence "The manufacturer has not provided data for the subsequent 5 years" will be amended.

Issue 5

3.3 Comparator The rationale being the MIST therapy is effective in breaking down slough and reducing bacterial burden. We differ on this point. Debrided tissue should be removed before treatment	The FDA approval for the MIST Therapy treatment is intended to provide a low energy ultrasound through the affect of cavitations; the MIST Therapy device promotes wound healing through wound cleansing and maintenance debridement by the removal of yellow slough, fibrin tissue, exudate and bacteria. If the clinician should choose to debride areas of the wound bed prior to MIST Therapy and follow with their dressing regimen of choice MIST Therapy is being used as an adjunct to enhance wound healing. MIST Therapy is not promoted as a substitution of all levels of debridement.	Providing clarification on the intended and actual use of MIST Therapy.	The issue listed by the manufacturer is NOT a factual inaccuracy of the EAC report. The proposed amendment and its justification do not provide substantive evidence or argument. No amendment is required.

Issue 6

4.1.1 Description and critique of the manufacturer's	The date limits applied to the search strategy in the submission and defined in section 7.2.3, are not	The dates included the economic references which were not specific to MIST Therapy or any of the key MIST	The issue listed by the manufacturer is NOT a factual inaccuracy of the

identification and selection of studies.	systematically applied to all search terms.	Therapy search terms. Data from 1992 includes all references use to develop the economic analysis.	EAC report. We are unsure of what amendments the manufacturer requires us to make.

Issue 7

4.1.2. **Inclusion and exclusion of studies**	MIST is a relatively new technology, therefore case series and posters were included to deliver evidence across a broad spectrum of wound conditions and results. All studies were included where relevant to highlight product benefits in use.	Following discussions with NICE it was recommended to include all studies within the Clinical Evidence section including posters and case series to support the extensive usage in other clinical settings and to support the healing results in complex wounds.	There is nothing wrong in including studies of various design/publication status. The key is to have explicit criteria for selecting the studies of greatest relevance and presenting them in a systematic way. This is lacking in the submission. The issue listed by the manufacturer is NOT a factual inaccuracy of the EAC report. The proposed amendment and its justification do not provide substantive evidence or argument. No amendment is required.

Issue 8

4.1.3 **Description and critique of manufacturers approach to validity assessment and details of the quality assessment of studies.**	The studies provided herein reflect what is available to provide a basis for understanding the impact the MIST Therapy treatment may have on patients. Since the technology is new we have used what is available and compared that to the current metrics of standard of care. The evidence, based upon lack of data from the perfect RCT, continues to trend toward a clinical afforded the patient and the healthcare system.	As provided in guidance for completing the NICE submission we provided the data available. In the tables describing the information obtained from the clinical studies were recognized the deficiencies were apparent, yet the paper were published in well regarded wound care journals. RCT in wound care have inherent problems yet the RCTs provided, problems notwithstanding do trend toward improved patient outcomes.	The issue listed by the manufacturer is NOT a factual inaccuracy of the EAC report. The proposed amendment and its justification do not provide substantive evidence or argument. No amendment is required.

Issue 9

4.1.5 **Describe and critique the statistical approach used**	Please clarify what you would have preferred in Table B6. [redacted]	If provided with greater detail we welcome to adjust table B6 as you recommend. [redacted]	We have already provided suggestions for possible approaches in the EAC report The issue listed by the manufacturer is NOT a factual inaccuracy of the EAC report. The proposed amendment and its justification do not provide substantive evidence or argument. No amendment is required.

Issue 10

4.2.1 **Summary of results.** In our opinion sham devices are not necessary as long as the observer is blinded. The exception would be when pain and quality of life are unknown.	Given what the MIST Therapy system looks like and how it is used, the only possible control would be for patients to be evaluated by a care provider having no knowledge of which patient received MIST Therapy. This was conducted in the RCT. Given the limited number of defined personnel working in an ambulatory wound clinic, or inpatient setting, it would be difficult for the personnel to not have such knowledge due to the shortage of personnel and the need to document the patient's care. The best measure available to measure the progression of healing of a wound is the change in size, the time to healing, or additional interventions. The only other macro measure would be to compare patients receiving MIST Therapy with patients that had not received MIST Therapy.	Please provide further insight in how you would recommend the data provided and captured thus far be used to develop a macro economic model.	We have already provided suggestions in the EAC report. The issue listed by the manufacturer is NOT a factual inaccuracy of the EAC report. The proposed amendment and its justification do not provide substantive evidence or argument. No amendment is required.

Issue 11

4.2.1 **There was no long term follow up of the patients to study the reoccurrence of a wound healing.**	The objective of the use of MIST Therapy is to bring a wound to closure. The studies have demonstrated that patients receiving MIST Therapy healed in less time, demonstrated a reduction in wound size, or required fewer interventions. The recidivism of a chronic wound is the result of the patient's overall health status, life style, and injury. Perhaps one could model the likelihood of recidivism using historical data based upon wound type subgroup. This was provided in the economic model, presenting that not all wound would heal. Kavros (APMA 2007) reported a 30 month survivorhip survey on his 51 patient study. 43/51 patients were survivors. 38 (88%) did not have an incident of further ulceration, 5 (12%) did develop a subsequent ulcer,	Few studies related to the treatment of chronic wounds follow the patients long enough to document with certainty the incidence or probability or recidivism of a healed wound.	We are unsure of the amendments the manufacturer requires us to make.

	however in a different location than the index ulcer recorded in the study.		

Issue 12

4.2.2.1 **Meta-Analysis and evidence synthesis , Lack of systematic search of literature and explicit criteria for selecting studies into the meta-analysis**	An independent literature search of PubMed and Medline was performed by the author. The articles were found independently and in duplicate. In general, funnel plots are used as an assessment of whether studies with larger sample sizes (and smaller N) report larger effect sizes than would be expected. That is, if reporting bias is occurring, then reported effect sizes should be on either side of the meta-analyzed point estimate for studies with larger standard errors.	The literature search was done independently of the manufacturer and the description has been provided.	The independent search was not mentioned in the meta-analysis document provided. The key issues here are lack of explicit criteria for selecting studies into the meta-analysis and most importantly, lack of control groups. No amendment is required.

Issue 13

4.2.2.1 **Lack of Control groups**	[redacted]	[redacted]	The issue listed by the manufacturer is NOT a factual inaccuracy of the EAC report. The proposed amendment and its justification do not provide substantive evidence or argument. No amendment is

	[redacted]		required.

Issue 14

4.2.2.1 **Lack of clearly defined patients population and comparator**	[redacted]	[redacted]	The issue listed by the manufacturer is NOT a factual inaccuracy of the EAC report. The proposed amendment and its justification do not provide substantive evidence or argument. No amendment is required. Clearly defining patient population and comparator is vitally important, as exemplified by the specifications in the scope issued by NICE.

Issue 15

4.2.2.1 **Lack of sufficient**	[redacted]	The methodology is explained, the overall assessment of healing uses measures of volume, area, and pain, support the	The statement with regard to potential confounders supports the concern that

description of the characteristics of the patients/wounds and assessment of the methodology of included studies	[redacted]	effectiveness of MIST Therapy.	EAC raised with regard to lack of high quality RCTs and prospective studies for reliably estimating clinical effectiveness. The issue listed by the manufacturer is NOT a factual inaccuracy of the EAC report. The proposed amendment and its justification do not provide substantive evidence or argument. No amendment required.

Issue 16

5.2. **Effectiveness of MIST. In Summary**	The Ennis DFU trial reported there were 133 patients enrolled at 23 sites. Twelve (12) did not meet the eligibility criteria (8 patients had wounds beyond the size Limits and 4 had wounds less that 4 weeks duration. Twenty-Four (24) were lost to follow –up prior to the 10 week course of therapy. There were 42 patients with protocol violations. This left 55 evaluable patients. The 42 protocol deviations were related to inverting treatment distances between the “sham” and treatment group. Hence all of these sites were excluded to keep that data clean and comparable	The decision to exclude patients was made prior to any data analysis. This study is a randomised, double-blind trial, the highest of clinical standard. The chronic wound at risk for limb loss is an extremely difficult patient to study due to the urgency of healing.	The issue listed by the manufacturer is NOT a factual inaccuracy of the EAC report. The proposed amendment and its justification do not provide substantive evidence or argument. No amendment required.

Issue 17

4.2.2.1 Other issues	[redacted]	[redacted]	The issue listed by the manufacturer is NOT a factual inaccuracy of the EAC report. The proposed amendment and its

			justification do not provide substantive evidence or argument. No amendment required.

Issue 18

5.1.1 Overview of manufacturer's economic assessment: Methods Limits quoted in section 7.8.4, page 126 can only be applied to PUBMED. The date limits were inconsistently reported; in section 7.8.3 it was stated as 1992 to 2010 and in section 7.9.3 it was reported as 1994 to 2010.	Point taken the correction should note data range from 1992-2010. Date limits were more the result of information searched rather than entering a limiting range. Dates prior to 2004 would indicate data on studies not associated with a MIST Therapy treatment. The search words included, cost effectiveness and wounds, QALY and wounds, and wounds. An additional document not identified within the submission includes from the Database of Abstracts of Reviews of Effects (DARE). Authors McGaughey H, Dhamija S, Oliver L, Porter-Armstrong A, McDonough S. "Pulsed electromagnetic energy in management of chronic wounds: as systematic review" September 29, 2010 despite small studies and few RCTs: under Authors' conclusions" *There was strong evidence to suggest that pulsed electromagnetic energy had a positive effect on the rate of wound healing; the degree to which it was clinically significant was less conclusive.* " There were very few papers identified assigned quality adjusted live years to any studies involving wounds.	Date range should read 1992-2010 to include metrics captured for the cost model. All date ranges should reflect 1992-2010. Please include the reference for McGaughey, et.al. (2010).	The issue listed by the manufacturer is NOT a factual inaccuracy of the EAC report. The EAC has seen the DARE review of the paper which states that "their conclusion of strong evidence for improved rate of wound healing appeared somewhat over-optimistic considering all the studies were small and all appeared to have methodological flaws that could impact on the reliability of results. In light of this, the authors' conclusions should be interpreted with caution." The proposed amendment and its justification do not provide substantive evidence or argument. No amendment required.

Issue 19

5.5. **Can clarification be provided on "therefore it is likely to prove cost – effective, even if the magnitude of (any) effect is rather small"**	Could you please clarify what is meant by "small"	In the terms of the patient groups studied, small numbers may still be in excess of 40,000. It would be useful for the group to understand what is exactly being stated here for the expert panel.	The short term solution in the EAC report will allow the estimation of the minimum effect that needs to be demonstrated for the MIST therapy to be cost effective. (page 39, section 5.5 EAC report). No amendment required.

Issue 20

5.2 Critique of approach used **Costs of MIST**	The direct costs of the device were amortized and incrementally added to the total cost. The nursing time was added in addition to all costs directly and specifically related to the use of MIST Therapy. The model included the episode of time as reported in the RCT rather than including all downstream costs. The use of MIST Therapy was the dominant economic option; therefore additional cost savings downstream will add greater cost effectiveness.	The high benefit in cost savings in using MIST allows for added benefit if one wants to bring in reduced downstream costs. For example we did not include in the model the resulting avoidance of operation room, and surgical interventions resulting from a wound continuing to move to a more critical phase. Avoidance of emergency room admission was not modelled in as well. Once the new technology reaches the level of dominance shown by the low cost of using MIST Therapy, the economic value in terms of QALY has been demonstrated.	Only dominant if you accept the effectiveness parameter and we have explained why this is very uncertain. No amendment required.

Issue 21

5.2 Critique of approach used **Costs of MIST** **Effectiveness of MIST**	The effectiveness did use modelling to extrapolate to a larger population the healing rates identified in the Ennis, et. al. 2007, and Kavros 2007 and the retrospective study from Ennis et. al 2006 and Kavros 2008. The retrospective studies, albeit not RCT, followed patients seen for wound treatment and compared a similar set of patients not receiving MIST therapy. Given	The high benefit in cost savings in using MIST allows for added benefit if one wants to bring in reduced downstream costs. For example we did not include in the model the resulting avoidance of operation room, and surgical interventions resulting from a wound continuing to	**With reference to 1st paragraph column 2**: See previous comment on uncertainty of short term let alone long term effectiveness estimates. **With reference to 2nd**

	the consistency of the outcomes, the integrity of the authors, we did find the data supportive of the findings of the RCT and useful for developing a cost effectiveness model. While we agree the gold standard for a CEA is an RCT for comparing the new technology to the current standard of care (which in wounds with the variation in treatment modalities would need to be controlled), including a QALY EQ-5D instrument, and collection of current associated costs and measures of utility from the societal perspective. Funds are limited and do not always allow for such a study. We used a QALY method for patients with diabetic foot ulcers and venous leg ulcers and applied those to the patient outcomes in the model.	move to a more critical phase. Avoidance of emergency room admission was not modelled in as well. Once the new technology reaches the level of dominance shown by the low cost of using MIST Therapy, the economic value in terms of QALY has been demonstrated. If a Bayesian approach to the use of the data and applying a Markov model to measure downstream benefits or recidivism rates is allowed, we welcome the opportunity to further test the data gathered from our RCT and with your guidance information from retrospective review studies for the wound sub groups.	**paragraph column 2** We have problems with the input values used in the model. Not the QALY model itself. **With reference to 1st paragraph column 3** Again only if the effectiveness parameter is accepted. No amendment required.

Issue 22

5.3 Results reported in manufacturer's submission.	The comparator costs are listed under section 6.4.6 Table B 11. Pages 92-94. Items noted under the comparator column reflect the sum of average costs to treat patients in the UK and Wales without MIST Therapy. The combinations of unique treatment methods for patients and each type of wound would be exhaustive yet yield on average the costs we provided as representative of patients not treated with MIST Therapy, therefore using the current standards of care.	The costs for comparators reflect average costs for patients receiving the current standard of care and not having their wound treated with MIST Therapy.	Please clarify what point the manufacturer is trying to make and the amendment they require us to make.

Issue 23

5.4.2 Studies identified	The articles cited as sources for the development of the economic analysis were commented on in Table 7.7 Limitation of the paper were noted. The basis for the variance in length to time to heal was more predicated on the results from Ennis, et. al.2005, Margolis (2002, 1999) and Stockl (2004).	The papers cited are used to introduce limits in the model. The article by Anaeme was not used for any specific metric, rather to show trends in reduced costs in a long term acute care setting when the wound size is reduced.	We agreed that the product shows promise.

	[redacted]	The economic analysis was build upon inference from studies that were not perfect, yet with the low incremental cost of MIST Therapy and the clinical benefits that are consistently reported, the product show promise in reducing the cost of treating hard to heal wounds.	

Issue 24

5.4.3. De novo cost analysis	The justification provided in 6.2.1 was to provide the basis for perspective of the analysis. It is recognized that the analysis did bring into the model different wounds experienced by the population of the UK and Wales. A longer sensitivity analysis could be provided comparing predicted rates of recidivism, varying times to healing, avoidance of adverse outcomes, and societal benefits.	If additional data is sought to extrapolate healing over a longer horizon please advice.	We do not criticise the idea of stratifying cost utility analyses by type of ulcer. On the contrary we think this is a good idea.

Issue 25

5.5 Summary of uncertainties and issues	As noted we welcome the opportunity to conduct the Bayesian analysis with agreed to metrics with NICE and conduct the Markov model to determine downstream cost minimization for the UK and Wales.	Using approved modelling with a combination of data obtained in the RCT, non MIST healing found in the published literature and supported by a panel of experts regarding the metrics would provide additional credence to the economic model.	It is likely that MIST would not have to have a very large magnitude of effect size in order to be cost-effective, given its modest cost and possible large down-stream savings contingent upon slightly improved healing rates. (Reference: Cosh, E., Girling, A, Lilford, R., McAteer, H.L. & Young, T. 2007. Investing in New Medical Technologies: A decision framework. Journal of Commercial Biotechnology. 13 (4):236-

			271.)