

The MIST Therapy system for the promotion of wound healing

Medical technologies guidance

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Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties. Providers should ensure that governance structures are in place to review, authorise and monitor the introduction of new devices and procedures.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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1 Recommendations

NICE medical technologies guidance addresses specific technologies notified to NICE by manufacturers. The 'case for adoption' is based on the claimed advantages of introducing the specific technology compared with current management of the condition. This case is reviewed against the evidence submitted and expert advice. The medical technology guidance on the MIST Therapy system for the promotion of wound healing recommends further research. This recommendation is not intended to preclude the use of the technology in the NHS but to identify further evidence which, after evaluation, could support a recommendation for wider adoption.

- 1.1 The MIST Therapy system shows potential to enhance the healing of chronic, 'hard-to-heal', complex wounds, compared with standard methods of wound management. If this potential is substantiated then MIST could offer advantages to both patients and the NHS.
- 1.2 The amount and quality of published evidence on the relative effectiveness of the MIST Therapy system is not sufficient, at the time of writing, to support the case for routine adoption of the MIST Therapy system in the NHS.
- 1.3 Comparative research is recommended in the UK to reduce uncertainty about the outcomes of patients with chronic, 'hard-to-heal', complex wounds treated by the MIST Therapy system compared with those treated by standard methods of wound care. This research should define the types and chronicity of wounds being treated and the details of other treatments being used. It should report healing rates, durations of treatment (including debridement) needed to achieve healing, and quality of life measures (including quality of life if wounds heal only partially). It is recommended that centres using the MIST Therapy system take part in research that delivers these outcomes. Current users of the MIST Therapy system who are unable to join research studies should use NICE's audit criteria to collect further information on healing rates, duration of treatment and quality of life and publish their results.
- 1.4 NICE will review this guidance when new and substantive evidence becomes

available.

2 The technology

Description of the technology

- 2.1 The MIST Therapy system (Celleration) aims to promote wound healing in chronic, 'hard-to-heal' wounds and acute wounds by delivering low-energy, low-intensity ultrasound to the wound bed through a continuous saline mist. The mist is claimed to transmit the ultrasonic energy to the wound bed, to activate healing by the removal of slough, exudate and bacteria, and to stimulate tissue regeneration.
- 2.2 The MIST Therapy system comprises a generator, a single-use applicator and a sterile saline bottle. Wound surface area is measured and entered into the MIST Therapy system, which then calculates the appropriate treatment time. When the applicator and saline bottle are connected, the ultrasound system is activated and a continuous mist is delivered to the wound bed using a hand-held applicator. The distance between the applicator and the wound bed is 0.5 cm to 1.5 cm. Once the treatment is complete, the generator switches off automatically.
- 2.3 The MIST Therapy system is intended for use as an adjunct to standard wound care with dressings and other cleaning or debridement as necessary.
- 2.4 Each treatment is estimated to take 5 to 7 minutes to complete and is normally performed 3 times a week, at the same treatment session as the wound dressings are changed.
- 2.5 The annual rental price of the MIST Therapy system stated in the manufacturer's submission is £7,500.

Current management

- 2.6 Standard care for chronic, 'hard-to-heal' wounds normally involves the use of advanced wound dressings, which include: alginate, capillary action, charcoal,

foam, honey, hydrocolloid, hydrocolloid fibrous, hydrogel, iodine, low- or non-adherent wound contact layer, silicone and silver dressings. Venous leg ulcers are a common type of chronic wound and compression bandaging is a mainstay of treatment, provided that serious ischaemia is not present.

- 2.7 Standard practice in the management of chronic wounds also includes wound debridement to remove dead tissue, and systemic antibiotic therapy for patients with wounds showing clinical signs of infection.

3 Clinical evidence

Summary of clinical evidence

- 3.1 The main outcome measures for the promotion of wound healing using the MIST Therapy system are rate of healing and percentage of wounds healed. Also relevant are wound size, wound volume, wound area, level of bacterial contamination (bioburden), treatment time, pain score, quality of life, recurrence and adverse events.
- 3.2 The manufacturer's submission described almost 200 reports on the clinical use of the MIST Therapy system. The external assessment centre considered that 10 studies (2 randomised controlled trials and 8 peer-reviewed observational studies, of which 2 were prospective) were the key sources of evidence in the evaluation of the clinical effectiveness of the MIST Therapy system.
- 3.3 In 1 randomised controlled trial, 70 patients with non-healing wounds and chronic critical limb ischaemia had standard wound care and treatment with the MIST Therapy system (intervention group, n=35) or standard wound care alone (control group, n=35) for 12 weeks (Kavros et al. 2007). The MIST Therapy system was used for 5 minutes per treatment, 3 times per week. Standard wound care included daily dressing changes and weekly wound debridement. The study reported that 63% of wounds healed (healing defined as a greater than 50% reduction in wound volume) in the intervention group compared with 29% in the control group ($p<0.01$).
- 3.4 In the second randomised controlled trial, 133 patients with diabetes and chronic foot ulcers were treated using the MIST Therapy system (intervention group, n=70) or a sham device (control group, n=63) for 10 weeks (Ennis et al. 2005). Wounds were treated 3 times per week, with 4 minutes use of the active or sham device, in addition to standard wound care with dressings and weekly debridement as needed. The study reported that, based on the intention-to-treat analysis, 26% of wounds healed in the intervention group compared with 22% in the control group (not statistically significant).

- 3.5 The one prospective observational study of 23 patients with chronic lower-extremity wounds of any aetiology treated by the MIST Therapy system (the intervention group) reported that 69% of wounds healed with a mean healing time of 8 weeks (median 7 weeks) (Ennis et al. 2006). These were compared with 218 patients with chronic wounds treated previously by electrical stimulation or megahertz ultrasound (the historical control group) in whom 72% of wounds healed with a mean healing time of 18.7 weeks (median 10 weeks) ($p=0.0005$ in favour of the MIST group). The proportion of patients in the historical control group admitted to hospital for wound treatment (including surgical procedures) was significantly higher than in the MIST group ($p=0.04$). The MIST Therapy system was used for 3 to 12 minutes per treatment depending on the area of the wound, 3 times per week. All patients received standard wound care including daily dressing changes and weekly wound debridement. Patient demographics and wound aetiologies were comparable between the intervention group and the historical control group.
- 3.6 A retrospective analysis reviewed the medical charts of patients with chronic lower-extremity wounds of any aetiology who were treated using the MIST Therapy system and standard wound care for 90 days (intervention group, $n=163$) or standard wound care alone (control group, $n=47$) (Kavros et al. 2008). The MIST Therapy system was used for 3 to 12 minutes per treatment depending on the area of the wound, 3 times per week. Standard wound care included advanced wound care dressings (silver, collagens) and debridement. The study reported that 53% of wounds healed in the intervention group with a mean healing time of 147 days compared with 32% in the control group, which had a mean healing time of 134 days ($p=0.009$). At the start of treatment, the median wound volume in the intervention group and the control group was 304 mm^3 and 368 mm^3 respectively. The median wound volume in both groups decreased during treatment to a final volume of 0 mm^3 in the intervention group and 68 mm^3 in the control group.
- 3.7 A retrospective case series analysed the medical records of 51 patients with chronic lower-extremity ulcers that had been present for 3 to 18 months. Patients had standard wound care for a mean of 9.8 plus or minus 5.5 weeks followed by the MIST Therapy system for a mean of 5.5 plus or minus 2.8 weeks (Kavros and Schenk 2007). Patients received treatment using the MIST Therapy system when their wounds failed to improve with standard wound care alone and were treated

3 to 5 times a week (duration of each treatment was not stated). Standard wound care comprised moist wound dressings, debridement and compression. The study reported a 94.9% plus or minus 9.8% reduction in wound volume during the period with the MIST Therapy system compared with a 37.3% plus or minus 18.6% reduction during the period with standard wound care alone ($p < 0.0001$). No wound closed using standard wound care alone compared with 26 out of 51 wounds closing (51%) during treatment with the MIST Therapy system.

- 3.8 One retrospective observational study reviewed the medical charts of 76 patients with non-healing wounds of any aetiology who were treated using the MIST Therapy system as an adjunct to standard wound care (Bell and Cavorsi 2008). Treatment was administered for a mean of 5.1 minutes per treatment for a mean of 2.3 times per week. The median duration of treatment was 4.3 weeks. Standard wound care included moist wound dressings, selective debridement and compression. The study reported that the median wound area was reduced by 79% (from 2.5 to 0.6 cm²) and the proportion of patients with greater than 75% healthy granulation tissue increased from 32% to 46% during treatment. The patient-reported mean pain rating (0 to 10; a higher score indicates more-intense pain) decreased by a mean of 1.8 points during treatment ($p = 0.001$).
- 3.9 Cole et al. (2009) described a retrospective observational study that reviewed the medical charts of 41 consecutive patients with non-healing wounds of any aetiology who were treated using the MIST Therapy system as an adjunct to standard wound care. Treatment was administered for a mean of 3.7 minutes per treatment for a mean of 2.5 times per week. Standard wound care included moist wound dressings, debridement and other interventions specific to wound aetiology. Mean wound area decreased by 60% (median 88%) and the proportion of patients with greater than 75% healthy granulation tissue increased from 26% ($n = 12$) to 80% ($n = 41$) during treatment. The percentage of wounds that healed completely was 38% ($n = 20$) with a mean healing time of 6.8 weeks. The patient-reported mean pain rating (0 to 10; a higher score indicates more-intense pain) decreased by a mean of 2.9 points during treatment ($p < 0.0001$).
- 3.10 Haan et al. (2009) described a retrospective review of medical charts from 48 consecutive patients who had a chronic wound of any aetiology treated using the MIST Therapy system and physical therapy wound management (including debridement, wound dressings, compression, negative-pressure wound therapy

and pulsed lavage with suction). Treatment was administered for a mean of 4.1 minutes per treatment for a mean of 2.1 times per week. The review reported that the median wound area decreased by 92% and the proportion of patients with greater than 75% healthy granulation tissue increased from 37% (n=18) to 89% (n=41) during treatment ($p<0.0001$). The percentage of wounds that healed completely was 24% (n=12) with a mean healing time of 4.3 weeks. The patient-reported mean pain rating (0 to 10; a higher score indicates more-intense pain) (n=42) decreased by a mean of 2.6 (3.6 to 0.8) points during treatment ($p<0.0001$).

- 3.11 A retrospective case study of medical records from 15 consecutive patients with painful, chronic lower-extremity wounds of various aetiologies treated by the MIST Therapy system reported a decrease in mean pain score (0 to 10; a higher score indicates more-intense pain) of 6.4 points (8.07 plus or minus 1.91 to 1.67 plus or minus 1.76, $p=0.0003$), which was an 80% reduction in patient-reported pain (Gehling et al. 2007). Patients reduced or stopped their use of pain killers within 2 weeks of starting treatment.
- 3.12 A prospective case series of 11 consecutive patients with chronic pressure ulcers reported bacterial colony counts in the chronic wounds (Serena et al. 2009). Treatment was administered for a mean duration of 4 minutes per treatment, 3 times a week. No antiseptics, antibiotics, silver or antimicrobial dressings were used during the study. The study reported that the mean wound bioburden decreased by 50% (from 4×10^7 to 2×10^7 colony-forming units per gram of tissue) during treatment. Mean wound area decreased by 26% and mean wound volume decreased by 20% during the treatment period.

Committee considerations

- 3.13 The committee considered that the evidence suggested real potential for the MIST Therapy system to enhance the healing of chronic wounds, but that overall the quality of the evidence was limited by small patient numbers and lack of appropriate comparison groups.
- 3.14 The committee noted that there was only one study comparing the MIST Therapy system and a sham device for the treatment of chronic wounds and judged the

study to be of low quality. In addition to more clinical studies, the committee considered that it would be useful to have more proof-of-concept evidence to demonstrate the transmission of ultrasound energy through a saline mist.

- 3.15 The committee recognised that the quality of evidence in the area of wound care is generally low and that the heterogeneity of chronic wounds poses a challenge. The committee was advised that the evidence supporting the clinical effectiveness of the MIST Therapy system was equal to or better than evidence for many other wound care interventions in current use in the NHS.
- 3.16 The committee noted that patients reported a reduction in pain and an improvement in health following MIST Therapy treatment. It was advised that even partial healing can result in reduction in pain and improvement in quality of life for some patients with chronic wounds.
- 3.17 The committee noted limited evidence on the rates of recurrence of chronic ulcers after MIST Therapy treatment. Further information on this longer-term outcome would be useful.
- 3.18 The committee noted that no adverse events specific to the use of the MIST Therapy system have been reported in the published literature or to the manufacturer.
- 3.19 The few available studies on use of the MIST Therapy system for acute wounds were small and lacking in statistical outcomes. The committee considered there was no substantial evidence to make a judgement on the clinical effectiveness of the MIST Therapy system for the treatment of acute wounds.

4 NHS considerations

System impact

- 4.1 NICE's guideline on pressure ulcers: prevention and management states that the cost of treating a grade 4 pressure ulcer is estimated to be £40,000 a year (Collier 1999). If the MIST Therapy system reduced the healing time of these wounds it could potentially offer substantial cost savings to the NHS, although most chronic wounds are likely to involve less prolonged and complex treatment.
- 4.2 The MIST Therapy system is claimed to enhance healing and decrease bioburden in wounds and might therefore reduce the use of antimicrobial dressings and systemic antibiotics. This could result in a reduction in the expenditure on wound dressings and in the risk of antibiotic resistance.
- 4.3 The committee was advised that the MIST Therapy system can be used in a community setting, where most chronic wounds are managed.

Committee considerations

- 4.4 The committee recognised that the MIST Therapy system potentially offers substantial cost savings to the NHS by reducing the length of time that chronic wounds require attention, and so decreasing costs associated with nursing time, wound dressings, hospital admissions and surgical interventions (including, occasionally, amputation).
- 4.5 The committee was advised by the expert adviser that patients have reported improvements in wellbeing after treatment with the MIST Therapy system and have shown greater willingness to attend clinics for treatment 2 to 3 times a week.
- 4.6 The committee noted that the use of the MIST Therapy system in a community setting could make it easier for patients with disabilities to access treatment, so

promoting equality.

5 Cost considerations

Cost evidence

- 5.1 The economic evidence for the MIST Therapy system comprised an unpublished cost-effectiveness study, a conference poster and a new cost analysis.
- 5.2 An unpublished study from the USA considered the economic impact of healing a foot ulcer in a patient with diabetes using the MIST Therapy system plus standard wound care compared with standard wound care alone (Driver 2010). The effectiveness of the 2 treatments was taken from peer-reviewed studies about foot ulcers in patients with diabetes and the primary outcome measure was defined as 'time to heal'. The study estimated that for every 1,000 patients treated for a 12-week period, the cost savings were US \$2,555,620. The savings associated with the MIST Therapy system resulted from the greater proportion of ulcers that healed or progressed towards healing within 12 weeks. The assumed difference in healing rate between the 2 treatments was large, and it was not clear how the costs attributed to each treatment were derived.
- 5.3 The conference poster described an economic evaluation based on a case series of 5 patients with pressure ulcers treated using the MIST Therapy system and standard wound care for 2 months (Anaeme et al. 2009). Cost savings were estimated from the direct costs of using the MIST Therapy system compared with negative pressure wound therapy as an adjunct to standard care. The cost calculations of negative pressure wound therapy were not described. The poster reported that mean wound area decreased by 34% during treatment with the MIST Therapy system. This was claimed to offer an average saving of US \$1,310, ranging from \$563 to \$2,187 per patient compared with the use of negative pressure wound therapy.
- 5.4 The cost model submitted by the manufacturer was based on an estimate of 600,000 leg ulcers, pressure ulcers and diabetic foot ulcers in the UK and an estimate of £2.3 billion to £3.1 billion as the total cost of treating chronic wounds in England and Wales in 2005 (Posnett and Franks 2008). The population-based costs and incidence were used to calculate an annual per-patient cost for each

type of ulcer. These costs per patient were compared with the cost of 26 weeks of treatment with the MIST Therapy system.

- 5.5 In the cost analysis, it was assumed that the use of MIST Therapy would follow the current care pathway for the treatment of wounds; it would be used if standard wound care had failed to heal the wound or if the wound had not improved within 30 days. The treatment would take place at the same time as the changing of wound dressings during standard wound care so it was assumed in the cost model that there would be no additional nurse visits. The additional nurse time taken to treat a patient with the MIST Therapy system alongside standard wound care was not analysed in the cost model. This analysis of differences in nurse time could not be undertaken owing to the different approaches used to calculate the cost of treatment with the MIST Therapy system and standard wound care.
- 5.6 For the purposes of the cost analysis, the effectiveness of the MIST Therapy system was described as mean time to healing. This was calculated as 14 weeks from a number of studies with different study design. In the cost model, a mean healing time of 26 weeks for the MIST Therapy system was assumed compared with 52 weeks for continual standard wound care.
- 5.7 The costs associated with treatment included annual rental of the MIST Therapy system, administration of the therapy, MIST Therapy consumables and dressings for standard wound care. The cost of ordering, transporting, processing and storing consumables was not included in the analysis. The energy cost and the cost of disposal of consumables was also not included in the analysis.
- 5.8 The annual total rental cost of the MIST Therapy system is £7,500.
- 5.9 The treatment cost for the MIST Therapy system is £7,626 per patient for 26 weeks based on 3 treatments per week. Rental cost per treatment was estimated to be £6 assuming one MIST Therapy system would be used on 5 patients per day 5 days a week. Its consumables cost was calculated to be £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.
- 5.10 The costs of standard wound care were calculated from NHS annual wound

statistics for complex wounds, and estimated total wound care costs in the UK for each ulcer type, to calculate an average cost per patient ('top down' approach). The costs of the MIST Therapy system were calculated from the estimated resource use per treatment ('bottom up' approach).

- 5.11 The MIST Therapy cost analysis showed that the average cost per patient over 26 weeks of treatment was estimated to be £7,626 for leg, diabetic foot and pressure ulcers. The main cost saving included in the manufacturer's cost analysis related to the reduction in the time for a wound to heal compared with standard wound care alone. The annual cost savings per patient were £1,563, £2,374 and £2,925 for the treatment of leg, diabetic foot and pressure ulcers respectively.
- 5.12 The sensitivity analyses reported that time to heal was the most important factor for the MIST Therapy system to be cost saving to the NHS.

Committee considerations

- 5.13 The committee was concerned that the approaches used to calculate the costs of treatment with the MIST Therapy system and with standard wound care were different. The costs of standard wound care were calculated from incidence and population-based costs ('top down' approach) in contrast to the costs of the MIST Therapy system, which were calculated from the annual rental cost of the device, consumables and treatment costs ('bottom up' approach).
- 5.14 The committee discussed the assumption used in the model of a healing time of 26 weeks for the MIST Therapy system compared with 52 weeks for standard wound care. It considered that a 50% reduction in healing time from using the MIST Therapy system was not adequately supported by the clinical evidence.
- 5.15 The committee considered that uncertainty about the conclusions of the cost model were related primarily to uncertainty about the relative clinical effectiveness of the MIST Therapy system in promoting wound healing. This was an important consideration in determining the committee's recommendation for further comparative research.

- 5.16 The committee was advised that exclusion from the cost model of amputation and other procedures with substantial long-term cost implications meant that cost savings of the MIST Therapy system were potentially underestimated.

6 Conclusions

- 6.1 The committee considered that the MIST Therapy system showed promise in the treatment of chronic wounds and its use was supported by expert opinion. The potential cost savings claimed for its use depend primarily on evidence of comparative effectiveness. The low quality of that evidence and consequent uncertainty about its relative effectiveness in healing wounds compared with standard care alone meant that the case for routine adoption in the NHS could not be supported at the time of writing.
- 6.2 The committee concluded that good quality studies are needed to substantiate the potential of the MIST Therapy system to offer advantages to patients and the NHS. The committee wished to give strong encouragement to further research on the use of the MIST Therapy system, compared with standard care alone, for treating chronic wounds.

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