



Review report of MTG5: The MIST Therapy system for the promotion of wound healing

Produced by:

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This medical technology guidance was published in July 2011.
All medical technology guidance is reviewed 3 years after publication.

This review report summarises new evidence and information that has become available since this medical technology guidance was published, and that has been identified as relevant for the purposes of this report. This report will be used to inform NICE's decision on whether this guidance needs to be updated at this time.

Acknowledgements

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1. Original objective of guidance

To assess the clinical and cost effectiveness of the MIST Therapy system for the promotion of wound healing.

2. Current guidance recommendations

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.

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.

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.

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.

NICE will review this guidance when new and substantive evidence becomes available.

3. Methods of review

The Birmingham and Brunel Consortium External Assessment Centre (EAC) previously undertook a literature review in June 2014 on this technology to inform NICE about the evidence available for updating the MTG5 guidance. For this previous EAC review, NICE provided searches covering the period from October 2010 to November 2013. Further to the NICE searches the EAC carried out an update search covering the intervening period from November 2013 to end of May 2014, on MEDLINE, EMBASE and CINAHL, using the NICE search strategy limited to human studies and English language papers only. The EAC also ran a focused search to identify any systematic reviews or HTAs published from November 2013 to end of May 2014 on the Cochrane Library's CDSR, DARE and HTA databases and using a systematic reviews filter on MEDLINE, MEDLINE In-Process and EMBASE. The focused search was supplemented by examining other sources of best evidence (e.g. TRIP, guidelines websites, AHRQ, CADTH) and looking for any ongoing research via trials registers.

For the current review, NICE updated the original literature searches with a search date limit from December 2013 to December 2015. The EAC re-ran the searches using the NICE initial search strategy to cover the period from December 2015 to February 2016 in order to identify any evidence available since the NICE's updated searches. Searches were limited to studies in English language and on humans. Details of literature search strategies are provided in Appendix C.

Thus, the current review incorporates the evidence from the findings of the previous EAC review in 2014, evidence identified from the NICE's update searches and, most recent, the EAC's update searches, together with evidence from any relevant studies identified by the product manufacturer since the production of the MTG5 guidance.

The process of results screening and study selection was performed by two reviewers independently based on the scope of the MTG5 guidance, using the inclusion and exclusion criteria in table 1 below. Relevant systematic reviews, meta-analyses, clinical trials and observational studies were eligible for inclusion. Data were extracted by one reviewer and independently checked for accuracy by a second. Data were synthesised narratively.

Table 1. Inclusion/exclusion criteria

	Inclusion	Exclusion
Population	Patients with chronic, “hard to heal” and acute wounds.	Patients in whom the use of therapeutic ultrasound was for any purposes other than wound healing or debridement.
Intervention	MIST Therapy system, which is: • Non-contact • Low-intensity (0.1 to 0.8 W/cm²)* • Low-frequency (40 kHz) *Power transferred per unit area; in this case watts transferred per square centimetre.	Therapeutic ultrasound that is not delivered through the MIST Therapy System. These include: • Devices that transfer ultrasound through direct contact with the patient’s skin or through bathing in water • High-frequency ultrasound (usually in MHz)
Comparator	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. Any other wound care interventions including Negative Pressure Wound Therapy and combinations of treatments with MIST Therapy.	-
Outcome	• Clinical outcomes (e.g. rate of healing, time to heal, wound size, wound volume, wound area, wound closure, pain score, quality of life, recurrence); • Surrogate outcomes (e.g. bioburden); Service utilisation (e.g. treatment time); Adverse events and safety related complications; • Economic outcomes (e.g. costs of treatment, cost-effectiveness).	No relevant outcomes reported.
Study design	Systematic reviews, meta-analyses, clinical trials, observational studies (such as cohort, case series and case-control studies, and single case reports), and qualitative studies where relevant.	• Narrative reviews, commentaries, editorials, letters and opinions that do not report any relevant new data; • Conference abstracts with no sufficient information indicating the device used was the MIST Therapy system, or without relevant outcome data.

4. New evidence

4.1. Changes in technology

The MIST Therapy systems have been updated with a new version of the technology called the UltraMIST System. This new version of the device has a CE mark, performs the same function and uses the same mode of action as

the MIST Therapy systems evaluated in the MTG5. The cost of the technology has not changed. Detailed comparison of the two versions is presented in table 2 below.

Table 2. Versions of the device

Characteristic	Current Version	New Version
Device Name	MIST[®] Therapy System (Generator, Treatment Wand and Applicator)	UltraMIST[®] System (Generator, Treatment Wand and Applicator)
510(k) Number	Traditional 510(k) K050129	Traditional 510(k): K140782
Model Number	CP-80004 (Generator + Treatment Wand) CP-80011 (Applicator kit)	CP-80030 (Generator + Treatment Wand) CP-80031 (Generator only) CP-80033 (Treatment Wand only) CP-80034 (Applicator)
Classification Regulation Product Code Name	Class II 21 CFR §878.4410 NRB Low Energy Ultrasound Wound Cleaner	Same
Indications for Use (per K050129)	“The MIST Therapy System produces a low energy ultrasound generated mist used to promote wound healing through wound cleansing and maintenance debridement by the removal of yellow slough, fibrin, tissue exudates and bacteria.”	“MIST Therapy Systems produce a low energy ultrasound generated mist used to promote wound healing through wound cleansing and maintenance debridement by the removal of yellow slough, fibrin, tissue exudates and bacteria.”
Performance Standards Met	IEC 60601-1, 2 nd Ed. IEC 60601-1-2 UL 60601-1	IEC 60601-1, 3 rd Ed. IEC 60601-1-2 UL 60601-1
Therapeutic Agent	Mechanical Energy (Ultrasound pressure)	Same
Applicators	Injection molded PC / ABS polymer	Same
Enclosures	Powder coated sheet metal and fabricated / machined ABS / PVC	Injection molded PC / ABS UL94 V-0 rated polymer
IV tubing	NA for MIST Therapy System	Extruded Class VI, phthalate free polymer
Supply Voltage	115/230VAC selectable	100-240VAC Universal input
Power Supply Input Frequency	50/60Hz	50-60Hz Universal input
Power Supply Input Rating	50 VA (fuse limited)	100 watts (fuse limited)
System Control	Microprocessor control with Ultrasound feedback control loop	Same
Distal Displacement of Radiation Surface (transducer tip)	65 ± 10 microns	Same

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Acoustic Frequency	40 ± 1 kHz	Same
Radiation surface diameter and material	0.390 in. ± 0.001 in Titanium allot (TI-6AL-4V)	Same
Saline Flow Rate	18 ± 2 mL/min	Same
Saline Source (0.9% Normal Sterile NaCl)	Bottle directly mounted to applicator (supplied in kit)	User provided IV Bag remotely connected to applicator via IV tubing
Control of Saline Flow	Valve in applicator to turn flow on and off, head pressure (gravity) used to control saline flow	Peristaltic pump used to control saline flow, start, and stop
Applicator distal face material and geometry	Injection molded PC/ABS polymer and compound curvature	Same
Single-use disposable Applicators	Sterile, Single-Use	Same
Packaging and Labeling	System: Non-sterile, reusable Applicator: Sterile per ISO 11607	Same
Method of Sterilization	Gamma radiation	Same
Shelf Life / Product Life Cycle	System: 5 years Applicator: 2 years in sterile packaging	Same
Treatment Parameters (see following table)	Algorithm used to calculate treatment time based on wound size (3-20 minutes)	Same

4.2. Changes in care pathways

No specific references are given to NICE guidance or NICE pathways in the current management section of MTG5.

NICE guideline [NG19] [Diabetic foot problems: prevention and management](#) was updated in August 2015. NG19 recommends one or more of the following as standard care for treating diabetic foot ulcers: offloading; control of foot infection; control of ischaemia; wound debridement; and wound dressings.

Negative pressure wound therapy should be considered after surgical debridement for diabetic foot ulcers, on the advice of the multidisciplinary foot care service. Dermal or skin substitutes as an adjunct to standard care can be considered when treating diabetic foot ulcers, only when healing has not progressed, and on the advice of the multidisciplinary foot care service.

NICE guideline [CG179] [Pressure ulcers: prevention and management](#) was updated in April 2014. CG179 recommends an assessment of the need for debridement which takes into consideration the amount of necrotic tissue; grade, size and extent of the pressure ulcer; patient tolerance and any co-morbidities. Where a need for debridement is identified, autolytic debridement, using an appropriate dressing should be used. Where this is likely to take longer and prolong healing time, sharp debridement should be considered. Following a skin assessment, systemic antibiotics should be offered to adults with a pressure ulcer if there are any of the following: clinical evidence of systemic sepsis; spreading cellulitis; underlying osteomyelitis.

With respect to dressing, CG179 recommends that the type of dressing used should be made in consultation with the patient or carers, taking into account: pain and tolerance, position of the ulcer, amount of exudate, and frequency of dressing change. When treating grade 2, 3 and 4 pressure ulcers a dressing that promotes a warm, moist wound healing environment should be considered. Gauze dressing should not be used.

The updates to the relevant guidelines do not impact the recommendations in MTG5, in as much as the evaluation did not place MIST into a current pathway. The comparator in the scope was advanced wound dressings. This seems appropriate as dressing and antibiotic treatment would be standard care. However, the evaluation itself used national population estimates of treatment costs to populate the comparator (chronic, hard-to-heal wounds). The robustness of these costs has not been evaluated using an itemised (bottom up) cost approach, nor have the sources used to generate treatment population samples been rigorously appraised. The treatment population was broken down using figures for numbers of people in England and Wales with diabetic foot ulcers, pressure ulcers and leg ulcers, and there may be a

possibility of double counting. These variables could all have changed. There are a number of other criticisms of the approach taken by the company, principally on the assumed improvement in healing time with the technology. In light of these concerns it would seem likely that there would need to be changes to the modelled care pathway.

4.3. Results from MTEP MTG review

The guidance, section 1.3, recommended research to address the uncertainties on the efficacy of the MIST system at the time of publication. NICE commissioned 2 pieces of research in response to this.

Cedar conducted a randomised controlled trial (White et al. 2015) involving 36 patients, 17 of whom received standard of care plus MIST (intervention), and 19 standard of care alone (control). For the primary outcome measures of change in wound area and number of wounds reaching healing cut-off values (25%, 50% and 75% wound closure), patients in the intervention arm saw on average a larger improvement than those in the control group. However, the differences were small and statistically non-significant. For the secondary outcomes of infections and adverse events, there were also no statistically significant differences between the intervention and control. Index ulcers of 2 patients had healed at or before the end of the study, and remained healed at 90 days in the intervention group and 1 in the control. No statistically significant differences in changes in Cardiff wound impact schedule scores between week 1 and 13 were found between the intervention and control. Changes in health-related quality of life scores between week 1 and 13, change in pain scores between week 5 and 13, and mean scores from week 5 to 13, did not differ significantly between groups.

Newcastle and York conducted a bench test report (Keltie 2013) which had 4 aims:

- 1) to demonstrate the transmission of ultrasound through air and through the saline mist
- 2) to develop a technique to visualise the extent of ultrasound transmission within the saline mist
- 3) to determine if the range of ultrasound transmission through the mist is within the distance specified in the manufacturer's instructions for use
- 4) to determine the depth of ultrasound transmission through a tissue phantom.

This study found that the saline spray does not significantly attenuate the ultrasound transmitted by the MIST device. The device, as expected,

delivered ultrasound at distances exceeding the treatment range specified by the company of 5 to 15 mm. The calculated temporal average acoustic intensity of the MIST device on an axis 12.5 and 20 mm from the tip, corresponding with the limits of the recommended therapeutic range, was consistent with the temporal average intensity of the MIST device of 100–500 mW cm⁻² or less to the wound site. It was calculated that >99% of the incident intensity would be reflected at an air-tissue interface. While the MIST saline spray may alter this proportion (the figure is <1% for a water tissue interface), this is not the mode of operation by which the sound wave is transmitted in the saline spray generated by the MIST device. It is also not supported by the finding of no significant change in ultrasound transmission in the absence and presence of the saline spray. Further research was recommended with human patients or a phantom model (such as pig muscle) to evaluate the attenuation of low frequency ultrasound through tissue. This would involve testing in an open-air environment with a waterproof sensor or in the presence of a saline mist. The absorption rate at a wet tissue surface, as commonly found in wounds, should also be investigated.

4.4. New studies

The previous EAC review in 2014 had the searches covering the period from October 2010 to May 2014. From those searches 3 systematic reviews (Smith et al. 2014; Driver et al. 2011; Voigt et al. 2011), 2 RCTs (Yao et al. 2014; Olyaie et al. 2013) and 1 case series report (Norris and Henchy 2010) were identified to be relevant.

The NICE update searches from December 2013 to December 2015 obtained 643 hits, from which 1 systematic review (Smith et al. 2014) and 5 RCTs (Prather et al. 2015; White et al. 2015; Beheshti et al. 2014; Yao et al. 2014; Olyaie et al. 2013) were identified to be relevant. The systematic review and 2 of the RCTs (Yao et al. 2014; Olyaie et al. 2013) were previously identified by the EAC review in 2014.

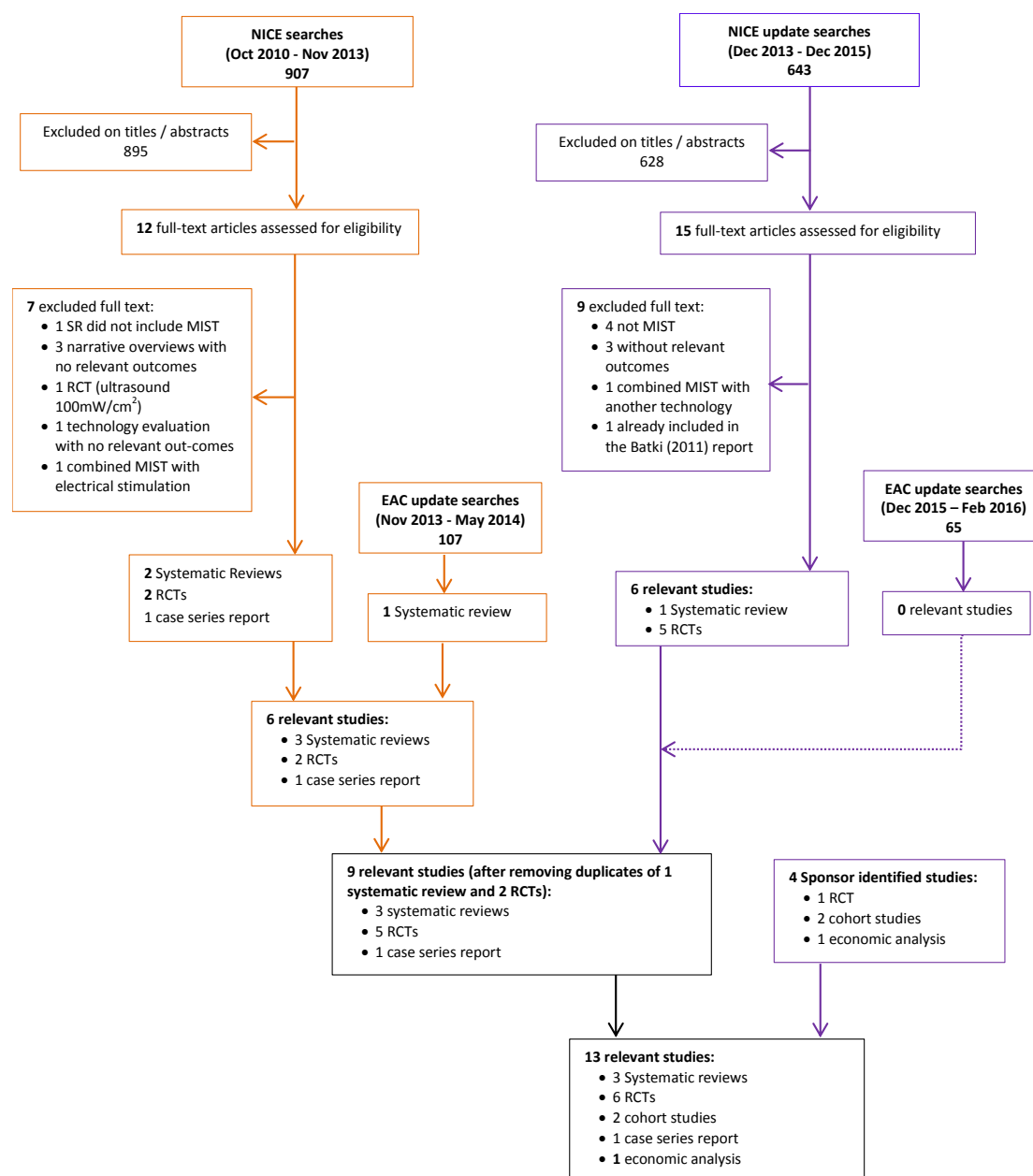
The most recent EAC update searches from December 2015 to Feb 2016 resulted in 65 hits, from which no relevant studies were identified.

The manufacturer also identified 4 studies that were considered relevant, including 1 RCT (Gibbons et al. 2015), 2 cohort studies (Honaker et al. 2012; Escandon et al. 2012) and 1 cost-effectiveness analysis (Amir 2014).

In total, 3 systematic reviews, 6 randomised controlled trials (RCTs), 2 cohort studies, 1 case series report and 1 report of a cost-effectiveness analysis were identified as relevant since the production of the NICE MTG5 guidance in July 2011.

Figure 1 displays a PRISMA flow diagram showing the study selection process. The studies identified by the NICE searches and excluded based on full-text paper assessment are listed in table 7 in Appendix B.

Figure 1 PRISMA flow diagram



Systematic reviews

Table 3 in Appendix B summaries the details of the 3 systematic reviews.

The Smith (2014) review included 10 studies. Eight of the 10 studies were already included in the Batki (2010) report, which was commissioned to support the MTG5 guidance. In the remaining 2 studies the technology used was Sonoca 180 which can be used in either a contact or noncontact manner, operates at 25 kHz frequency with a power output between 0% and 100%, and also uses saline as the coupling medium. It is unclear how similar the use of the Sonoca 180 was to the MIST Therapy system being assessed.

The Driver (2011) review included 8 studies, all of which were already included in the Batki et al. (2010) report.

The Voigt (2011) review included 8 studies, 3 of which used MIST therapy on healing of chronic wounds and the remaining 5 studies used other different types of low-frequency ultrasound. No separate analyses were conducted on the results of these 3 MIST studies. Of these 3 MIST studies, 2 were included in the Batki et al. (2010) report (Ennis et al. 2005; Kavros et al. 2007), while the other appeared to be a conference abstract (Park et al. 2011) which seemed to present the study reported in the full paper by Yao et al. (2014). This conference abstract by Park et al. is no longer available online.

Primary studies

Table 4 in appendix B outlines the details of the 6 RCTs and 3 observational studies.

The study by Gibbons et al. (2015) was a multicentre RCT comparing MIST plus standard care (n=41) with standard care alone (n=40) in adult patients with venous leg ulcers. Total follow-up period was 11 weeks. The primary outcome was mean percent ulcer area reduction from randomisation to week 4, which was statistically significantly higher in the MIST (61.6%) compared with that in the standard care alone group (45%). Reductions were also statistically significant greater in the MIST group compared with the control in median (65.7% versus 44.4%) and absolute wound area (9.0 cm² versus 4.1 cm²) as well as pain scores (from 3.0 to 0.6 versus 3.0 to 2.4).

The study by Prather et al. (2015) was a multicentre RCT comparing MIST plus standard care (n=16) with standard care alone (n=15) in patients with split thickness skin-graft donor sites. Follow up period was 5 weeks. The primary outcome measure was mean time to heal, which was significantly shorter in the MIST group (12.1 days) than in the standard care alone (21.3 days). All MIST subjects had epithelialised by 4 weeks, compared with 71% in

the standard care group. Recidivism rate within the 6-week follow-up was 8% in the MIST compared with 45% in the standard care group, but the difference did not reach statistical significance. There was no significant difference between the two treatment groups in pain score reduction. The MIST group had a statistically significant lower itching score at week 5 and 6. One (8%) subject in the MIST group required treatment for suspected infection during the study compared with 7 (50%) in the standard care group; statistical test of significance for this was not reported.

White et al. (2015) conducted a single centre RCT which compared MIST plus standard care (n=17) with standard care alone (n=19) in patients with chronic venous leg ulcers. Follow-up period was 13 weeks and then for those healed only there was a telephone follow-up 90 days later. The study found no statistically significant difference in the change from baseline to week 13 (or the point of healing) between the comparison groups, either in wound area, in health related quality of life score, or in reduction in pain score.

The Beheshti et al. (2014) study is a single centre RCT comparing the MIST therapy (n=30), high-frequency ultrasound therapy (HFU) (n=30) and standard treatment (n=30) for the healing of venous leg ulcers. Follow-up period was 6 months. The time duration of complete wound healing was statistically significant shorter in both ultrasound therapy groups compared with the standard treatment, and no statistically significant difference between the MIST and the HFU group. There was a statistically significant decrease in the size of ulcer, mean degree of pain and oedema in both ultrasound therapy groups after the 4-month visit in comparison to the standard treatment group; the difference was not significant between the MIST and HFU groups. No significant differences between groups in the recurrence of venous leg ulcers during a 6-month follow up after complete wound healing were observed.

The Yao et al. (2013) study was a single centre pilot RCT with 3 comparison groups in 12 patients with 12 non healing diabetic foot ulcers: MIST thrice per week (n=4), MIST once per week (n=4), and no MIST (n=4). Follow-up period was 5 weeks. The group receiving MIST thrice per week showed statistically significant wound area reduction at weeks 3, 4 and 5 compared to baseline, with the greatest percent area reduction (86%). The presence of wound area reduction in the group receiving MIST twice per week and that without MIST was 25% and 39%, respectively, but there were no statistically significant differences between these two groups over time.

The Olyaie et al. (2013) study was a single centre RCT comparing 3 treatment methods in outpatients with venous leg ulcers: MIST therapy (n=30), HFU therapy (n=30), and standard care (n=30). Total follow-up period was not clear but appeared to be at least 12 months. No significant differences at 2

months between the 3 groups in mean ulcer size, oedema, and pain score were observed. At 4 months significant differences were observed between the 3 groups in ulcer size, number of patients with decreases in oedema, and pain scores, with the MIST group having the best results, followed by the HFU group and then the standard care group. There were also statistically significant differences in time to complete wound healing, with the MIST group having the shortest time duration, followed by HFU and then standard care.

The Honaker et al. (2013) was a retrospective cohort study in 85 patients with 127 suspected deep tissue injuries. MIST plus standard care (43 subjects with 64 wounds) was compared with standard care (42 subjects with 63 wounds). Follow-up period was not clear. The MIST group had a statistically significant improvement in overall wound severity compared with the standard care group. A greater proportion of MIST patients were discharged home (21%) compared with the control arm (12%) and fewer were discharged to a long-term care facility (10% from the MIST group compared with 33% from the standard care group).

The study by Escandon et al. (2012) was a small prospective single arm cohort study of MIST treatment for patients with refractory venous leg ulcers (n=10). Follow-up period was 4 weeks. Following 4 weeks of MIST treatment, there was a statistically significant reduction in wound area, but no statistically significant reduction in individual and total bacterial counts, inflammatory cytokine expression, and pain score.

Norris and Henchy (2010) reported 4 cases who received MIST treatment for non-healing leg ulcers in a UK leg ulcer clinic. The wound reduction rates were between 41–73% over a 10–14 week treatment period. Clinicians found the MIST Therapy system easy to use with minimal training. It was non-invasive, pain-free and did not result in discomfort or side-effects for the patients.

Economic evaluation

Amir (2014) reported a cost-effectiveness analysis of the MIST plus standard care compared with standard care alone for non-healing diabetic foot ulcers from a US healthcare system perspective. The key clinical parameter was healing rate for which data were taken from different trials. Cost data were derived from a study using claims data in the US during 2000 and 2001. The estimated cost saving over 12 weeks was \$2,016.324 per 1,000 patients. The saving was due to reduced time to heal, reduction in the costs of subsequent medical care and reduction in the chance of costly complications. Table 5 in Appendix B summarises this study.

Summary

Three relevant systematic reviews were identified which however do not include any new relevant primary studies.

Six RCTs have been published since the production of MTG5; all compared the MIST treatment with standard care (with 2 of the studies having a third arm with HFU therapy, and 1 study having two different MIST treatment frequency arms and a standard care arm). Sample sizes ranged from 12 to 90 patients (4 to 43 patients in each comparison arm). The follow-up period was 5 weeks in 2 RCTs, and 11 weeks, 13 weeks (or over), 6 months and 12 months (or over) in the other 4 RCTs. The RCTs reported on change in wound size, oedema, pain score and itching score, recurrence of ulcers, health-related quality of life, and time to healing.

Three observational studies were identified. One was a small retrospective cohort study comparing MIST plus standard care (43 subjects with 64 wounds) with standard care alone (42 subjects with 63 wounds) in overall wound severity and discharge destination. One was a prospective cohort study comparing changes in wound area, total bacterial counts, inflammatory cytokine expression and pain score of refractory venous leg ulcers before and after MIST treatment in 10 patients. One was a case series study reporting 4 cases of MIST treatment for non-healing leg ulcers.

One cost-effectiveness analysis from a US healthcare system perspective estimated cost saving of MIST plus standard care compared with standard care alone over 12 weeks.

4.5. Ongoing trials

Six registered trials were identified. Details of the trials are presented in table 6 in Appendix B.

Two (NCT01671748; ISRCTN24438635) of these trials are of the same study, which has now been completed and published as the RCT by White et al. (2015). One trial (NCT01214980) has been completed and published as the RCT by Pranthier et al. (2015). One trial (NCT01549860) has been completed and published as the RCT by Gibbons et al. (2015). See section 4.4 and table 4 in Appendix B for details of these published studies.

Of the remaining two trials, one (NCT01206855) is a RCT comparing MIST with standard care in subjects following cosmetic procedures. The target sample size is 3440. The primary outcome measures include reduction in swelling, bruising, firmness and pain, and the secondary outcome measure is patient satisfaction. The trial has been completed but it is unclear whether

there are any results available. The other trial (NCT02045303) is an open label study comparing contact ultrasound therapy (Sonoca-180) plus MIST with either Sonoca-180 or MIST Therapy alone. The population is subjects (n=20) with sub-acute and chronic lower extremity ulcers of various aetiologies requiring selective debridement. The primary outcome is total wound area; the secondary outcomes are total wound volume and percent slough. The estimated completion date is December 2015. It is unclear whether there are any results available.

4.6. Changes in costs

The MIST Therapy systems have been updated with a CE-marked new version of the technology, i.e. the UltraMIST Therapy system. This new version of the device performs the same function and uses the same mode of action as the MIST Therapy systems evaluated in the MTG5. The cost of the technology has not changed.

4.7. Other relevant information

None

5. Conclusion

As stated by the authors of the initial assessment report Batki et al. (2010), the limitation of the evidence in the initial assessment is that, it included only two small RCTs comparing MIST treatment with no MIST treatment. Most of the other studies were either prospective or retrospective observational studies. The meta-analysis was based on observational studies, where data were on changes within patients, rather than comparison between groups. The 6 RCTs identified in the current review, although with small sample sizes, provide more comparative data between groups.

In the studies assessed in the initial review report, duration of follow up was generally inadequate with few reports on outcome beyond 9 weeks post treatment. The newly identified studies in the current review provided more data beyond 9 weeks of follow-up, with the follow-up period being 11 weeks, 13 weeks (or over), 6 months and 12 months (or over) in 4 RCTs.

With regard to outcome measures, not all of the outcomes outlined in the NICE scope for the MTG5 were addressed in the studies considered in the meta-analysis in the initial assessment report, e.g. quality of life (QoL) and bioburden. Of the studies identified in the current review, two RCTs (Gibbons et al. 2015; White et al. 2015) measured QoL; one of them reported data on QoL (White et al. 2015). No studies identified in the current review reported outcomes on wound bioburden.

In the initial assessment report it was stated that due to limited data on the effectiveness of MIST, any calculation of cost effectiveness was uncertain. The cost-effectiveness analysis identified in the current review was based on the US healthcare system. The data on key clinical parameters were taken from different trials and data on cost were derived from US claims data during 2000 and 2001. The results of this analysis is therefore of limited applicability and value.

The additional studies on the effectiveness of MIST identified in the current review provide some limited extra comparative data with longer follow-up and may in part reduce the degree of uncertainty on the effectiveness of MIST but do not fully address the scope of the original assessment report.

Appendix A – Relevant guidance

NICE guidance – published

NICE guideline [NG19] [Diabetic foot problems: prevention and management](#).
Published date: August 2015

NICE medical technology guidance [MTG21] [The ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury](#).
Published date: November 2014

NICE guideline [CG179] [Pressure ulcers: prevention and management](#).
Published date: April 2014

NICE medical technology guidance [MTG17] [The Debrisoft monofilament debridement pad for use in acute or chronic wounds](#). Published date: March 2014

NICE interventional procedure guidance [IPG467] [Negative pressure wound therapy for the open abdomen](#). Published date: November 2013

NICE medical technology guidance [MTG5] [The MIST Therapy system for the promotion of wound healing](#). Published date: July 2011

NICE guidance – in development

None

Guidance from other professional bodies

Health Improvement Scotland. [Scottish Wound Assessment and Action Guide \(SWAAG\)](#). Published date: November 2014.

SIGN Guideline 116: [Management of debates](#). Date published: March 2010; updated: September 2013.

SIGN Guideline 120: [Management of chronic venous leg](#). Published date: August 2010.

Appendix B – Details of studies and ongoing trials

Table 3. Systematic reviews

Study ID	Objective	Data source	Selection criteria	Primary studies included
Smith et al. 2014	To examine the effect of noncontact low-frequency ultrasound on the healing of chronic wounds	CINAHL and PubMed were searched for studies published in English from 2000 to 2011	Population: patients with chronic wounds (defined as those present for more than 4 weeks) Intervention: noncontact low-frequency ultrasound used for wound debridement, either alone or as an adjunct to standard wound care. Comparator: not specified Outcome measure: wound healing quantified by one or more of the following methods: full epithelialisation, percent of wound area reduction, or the percent of participants who demonstrated a measurable reduction in wound size. Studies in which wound healing was not a primary outcome were excluded. Study design: not limited	Ten studies were included, of which 8 were already included in the report by Batki et al (2010), which was commissioned in 2011 to support the MTG5 guidance. In the remaining two studies the technology used was Sonoca 180 which can be used in either a contact or noncontact manner, operates at 25 kHz frequency with a power output between 0% and 100%, and also uses saline as the coupling medium. It is unclear how similar the use of the Sonoca 180 was to the MIST in the Batki (2010) report.
Driver et al. 2011	To summarise and quantify the effects of a noncontact low frequency ultrasound (NLFU) therapy on healing of chronic wounds.	PubMed and MEDLINE databases, “in January 2010 and again in October 2010”	Population: patients with chronic wounds Intervention: treatment with noncontact low-frequency ultrasound (NLFU) therapy (the MIST Therapy system) for at least 4 weeks Comparator: not stated Outcome measure: - percent reduction in wound area - percent reduction in wound volume - proportion of wounds healed - percent reduction in wound pain Study design: not specified	Eight studies were included, all of which were already included in the Batki (2010) report.
Voigt et al. 2011	To determine whether low-frequency ultrasound used as an adjunctive therapy improves	PubMed; Cochrane (CENTRAL); AHRQ; CADTH; CTAF; NIHR HTA; clinical guidelines websites including NICE, SIGN, NGC, ISCI, and	A pre-specified inclusion /exclusion criteria was used. Population: patients with chronic lower limb wounds of the following aetiology: venous insufficiency; diabetes (type 1 or 2); pressure/immobile patient; arterial occlusive disease; neuropathic insufficiency.	Included 8 studies on different types of low-frequency ultrasound, 3 of which used MIST therapy on healing of chronic wounds. No separate analyses were conducted on the results of these 3 MIST studies. Of these 3 MIST studies, 2 were

Study ID	Objective	Data source	Selection criteria	Primary studies included
	the outcomes of complete healing and reduction of size of chronic lower limb wounds	Wound Healing Society; various Journal websites; Google. All conducted on March (time period covering of the databases was not reported). Additional source: reference sections; E-mail inquiries to the manufacturers	Intervention: all types of low-frequency ultrasound (contact, as well as noncontact i.e. MIST) and high-intensity and low-intensity) as an aid to wound healing, specifically: - low frequency (20-30 KHz) and low intensity (0.1-0.5w/cm²) noncontact ultrasound (LFLNCU) - low frequency (20-30 kHz) and high intensity (50-60 w/cm²) contact ultrasound (LFHICU) Comparator: not specified Outcome measure: complete wound healing (primary) and wound area reduction (secondary) Study design: randomised controlled trial	included in the Batki (2010) report, while the other appeared to be a conference abstract.

Table 4. Primary studies

Study ID	Design and setting	Population	Intervention	Control	Outcomes	Statistics	Effect size
Gibbons et al. 2015	Multicentre RCT in the US; wound assessor and study authors were blinded; study personnel and participants were not blinded. Manufacturer sponsored	Patients aged 18 to 90 years with venous leg ulcers (n=81)	MIST plus standard care (n=41)	Standard care (n=40)	Primary outcome: percent ulcer area reduction from randomisation to the 4-week. Secondary outcome: actual wound area reduction, healing rates and times to healing, pain score, and QOL score (SF-36). Total follow-up period 11 weeks.	Fisher's Exact test or Student's t-test and the Wilcoxon Rank Sum tests; multivariate model	Percent ulcer area reduction (%) after 4 weeks: median 65.7 (IQR 48.4, 83.9) and mean 61.6 (SD 28.9) for MIST; median 44.4 (IQR 20.9, 68.1) and mean 45.0 (SD 32.5) for control; p=0.02. Absolute reduction in ulcer area (cm ²) after 4 weeks: mean 9.0 (SD 9.0) AND median 5.5 (IQR 3.3, 11.3) for MIST; mean 4.1 (SD 4.1) and median 3.1 (IQR 1.5, 6.2) for control; p=0.003. VAS pain score after 4 weeks: mean 2.0 (SD 2.4) and median 0.6 (IQR 0.1, 3.8) for MIST; mean 3.4 (SD 3.2) and median 2.4 (IQR 0.4, 5.9) for control; p=0.03. Reduction in VAS pain score after 4 weeks: mean 1.7 (SD 3.0) and median 0.5 (IQR 0.0, 2.9) for MIST; mean 0.0 (SD 2.3) and median 0.0 (IQT -0.8, 1.3) for

							control; p=0.01. Baseline median QOL scores were 38.9 for the physical component and 48.2 for the mental component. The scores improved in both arms after 4 weeks of treatment (no further details).
Prather et al. 2015*	Multicentre RCT in the US; wound assessor was blinded. Manufacturer funded.	Adult patients (age >18 years) with split thickness skin-graft donor sites (n=31)	MIST plus standard care (n=16)	Standard care (n=15)	Primary outcome: time to wound healing, defined as absence of drainage and full epithelialisation. Secondary outcomes: pain and itching scores (10-point scale); recidivism rates. Follow-up 5 weeks.	Fisher's exact test, Student's t-tests, and Kaplan-Meier time to heal analyses were performed. Analyses were intent-to-treat based.	Mean time to heal: MIST at 12.1 (SD 6.0) days vs. standard care at 21.3 (SD 14.7) days (p=0.04). All subjects in the MIST group had epithelialized by 4 weeks compared with 71% in the control. Recidivism rates: 8% for MIST vs. 45% for standard care (p=0.06). There was no significant difference between the two treatment groups in pain score reduction. The MIST group had a statistically significant lower itching score at week 5 (p=0.02) and week 6 (p=0.03). Treatment for suspected infection during the study: 1 (8%) for MIST group vs. 7 (50%) for standard care. There were 3 (9.1%) subjects reporting a single episode of discomfort with the MIST treatment.
White et al. 2015	Single centre open label RCT in the UK; outcome assessor was blinded. The manufacturer provided research grant and equipment loan but played no role in study conduction or study analysis.	Adult patients with chronic venous leg ulcers (n=36)	MIST plus standard care (n=17)	Standard care (n=19)	Primary: change in wound area 8 weeks after treatment. Secondary: incidence of infections; health-related quality of life; ulcer pain (VAS), HRQoL(CWIS). Follow-up 13 weeks (and then to those healed only a telephone follow-up 90 days later)	One-way between groups ANCOVA; non-parametric Mann-Whitney U-test; Fisher's exact test	Change in wound area: MIST 46.6% (SD 38.1); standard care 39.2% (SD 38.0); difference= -7.4% (95% CI -33.4 to 18.6); p=0.565. Actual change in wound area (cm ²): -6.2 (SD 5.5) for MIST; -5.3 (SD 5.5) for standard care; p=0.618 Change in HRQoL scores (MIST vs. control): - Well-being: 8.3 (SD 16.2) vs. 8.0 (SD 16.2); difference 0.4 (95% CI -10.6 to 11.4; p=0.943) - Physical symptoms and daily living: 10.4 (SD 10.7) vs. 5.8 (SD 10.7); difference 4.6 (95% CI -2.6 to 11.9; p=0.204) - Social life: 3.0 (SD 19.8) vs. -0.5 (SD 19.8); difference 3.5 (95% CI -10.0 to 17.0; p=0.601). Difference in adjusted pain reduction score: -9.1 (95% CI -19.23 to 1.06; p=0.078) (scores range 0 to 100).

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Beheshti et al. 2014	Single centre RCT in Iran.	Patients with venous leg ulcers (n=90)	• MIST (n=30) • HFU (n=30)	Standard treatment (n=30)	Time of complete wound healing; wound size, pain and oedema (baseline; 2 and 4 months); recurrence of VLUs 6 months after complete wound healing. Total follow-up 6 months.	Student's <i>t</i> test, ANOVA, chi-square, or Fisher's exact test	Mean (SD) time duration of complete wound healing in the MIST, HFU and standard treatment group was 8.13 (1.40), 6.10 (1.47) and 5.70 (1.57) months, respectively ($p<0.0001$; for the difference between HFU and MIST $p=0.22$). Size of ulcer, mean degree of pain and oedema in both ultra sound therapy groups was decreased after the 4-month visit in comparison to the standard-treatment group ($p=0.01$, $p<0.0001$ and $p<0.0001$, respectively). No significant differences between the two ultrasound groups in changes in ulcer size in visit 1, 2 months after and 4 months after ($p=0.91$, 0.68 and 0.45, respectively). No significant differences between groups in the recurrence of VLUs during a 6-month follow up after complete wound healing ($p=0.37$).
Yao et al. 2013	Single centre pilot RCT in the US.	Adult patients (age 18–90 years) with non healing DFUs for 5 weeks (n=12 patients with 12 foot ulcers)	Group 1: MIST thrice/week (n=4) Group 2: MIST once/week (n=4)	Group 3: no MIST (n=4)	Percent area reduction (PAR) of each wound compared to baseline was evaluated weekly to week 5; Profiles of cytokines/proteinase/ growth factors in wound fluid and biopsied tissue. Total follow-up 5 weeks.	ANOVA tests with Bonferroni correction; Chi-square test or a Fisher's exact test; correlation analysis; repeated measures analysis	Group 1 showed statistically significant wound area reduction at weeks 3, 4 and 5 compared to baseline, with the greatest PAR, 86% ($p<0.05$). The PAR in groups 2 and 3 was 25% and 39%, respectively, but there were no statistically significant differences between group 2 and the control group over time.
Olyaei et al. 2013	Single centre RCT in Iran.	Outpatients diagnosed with chronic venous leg ulcers (n=90)	MIST group: (n=30) HFU group: (n=30)	Standard care (n=30)	Wound size, wound pain, lower leg oedema, and any side effects, assessed at baseline and after 2 and 4 months; time to healing.	Student's <i>t</i> -test, ANOVA, chi-square, or Fisher's exact test	At 2 months: no significant difference between the 3 groups in mean ulcer size, oedema, and pain score. At 4 months, mean (SD): - ulcer size: 2.72 cm² (2.16), 3.23 cm² (2.39), and 4.28 cm² (2.80) for MIST, HFU and standard treatment respectively ($p=0.04$) - proportion of patients with decreased oedema:

					Total follow-up unclear, but at least 12 months.		significantly higher in the MIST and HFU group compared to the standard treatment group (p=0.00) - pain scores: 3.26 (3.06), 3.96 (2.88), and 5.10 (1.88) in MIST, HFU, and standard treatment respectively (p=0.02) Time to complete wound healing, mean months (SD): 6.65 (1.59), 6.86 (2.04) and 8.50 (2.17) for MIST, HFU, and the control respectively (p=0.00).
Honaker et al. 2013	Retrospective cohort study in the acute care setting in a hospital in the US	Adult patients with suspected deep tissue injuries (n=85 patients with 127 wounds)	MIST plus standard care (n=43 with 64 wounds)	Standard care (n=42 with 63 wounds)	Wound severity before or after treatment; pressure ulcer staging at discharge; discharge destination. Follow-up period unclear.		The MIST group had a significantly reduced average wound severity score compared with the control group (2.52 difference, t=5.67, p<0.001). A greater proportion of MIST patients were discharged home (21%) compared with the control arm (12%) and a fewer were discharged to a long-term care facility (10% vs. 33%). There were no adverse events associated with patients that received MIST.
Escandon et al. 2012	Prospective single arm cohort in the US	Patients with refractory venous leg ulcers (n=10)	MIST (n=10)	Not applicable	Change over the 4-week treatment period in: wound closure; bacterial counts; expression of inflammatory cytokines; pain reduction. Follow-up 4 weeks.	Descriptive statistics; Pearson's correlation	Wound area: 38.3 cm² at baseline and 29.0 cm² at the last follow-up visit (45% mean reduction, p=0.0039). Individual and total bacterial counts: a decline in which is not significant. Inflammatory cytokine expression for all patients: a reduction which is not statistically significant. There was a correlation between healing and change in cytokine expression, which showed statistically significance for tumour necrosis factor (TNF)-α p=0.0395, IL-1α p=0.0351, IL-6 p=0.0508, IL-8 p=0.0990. Pain (VAS): 4 at the baseline and 2.7 by the end of the study; p=0.275.
Norris and Henchy 2010	Case series report, UK	Cases with non-healing leg ulcers and were	MIST	Not applicable	Wound reduction	Wound reduction	In summary, wound reduction rates were between 41-73% over the 10-14 week treatment period. Clinicians found the MIST Therapy system easy to use with minimal training. It was non-invasive, pain-free and

		treated with MIST in a UK leg ulcer clinic (n=4)					did not result in discomfort or side-effects for the patients.
Abbreviations: ANOVA, analysis of variance test; CWIS, Cardiff Wound Impact Schedule (5 point scale from 1 'not at all' to 5 'always'); DUF, diabetic foot ulcer; HUF, high-frequency ultrasound; IQR, interquartile range; n, number of patients; PAR, percent area reduction; HRQoL, health related quality of life; RCT, randomised controlled trial; SD, standard deviation; SF-36, Short Form (36) Health Survey; VAS, visual analogue scale; VLU, venous leg ulcer; vs, versus. * There is some discrepancy in the paper, as the number of patients randomised described in the figure 3 in the paper was 31, while the number of patients analysed in the tables in the paper was 32.							

Table 5. Economic analysis

Study ID	Population	Intervention and comparator	Form of analysis	Perspective	Time horizon	Data and source	Results
Amir 2014	Patients with non-healing diabetic foot ulcers	- MIST (3 times per week) plus standard care - Standard care	Cost-effectiveness analysis	US healthcare system	12 weeks	Published data on diabetic foot ulcer treatment costs, healing rates, and predictors of failure to heal. Rate of healed and progressed toward healing: 91 % with MIST and 70 % with standard care Rate of deteriorated or did not progress toward healing: 9% with MIST and 30% with standard care MIST treatment costs included the device, dressings, and staff time, based on 3 treatments per week, for an incremental cost of \$180 per week. Data source: Stockl et al. 2004; Ennis et al. 2005; Ennis et al. 2006; Margolis et al. 1999	Estimated cost saving over 12 weeks: \$2,016.324 per 1,000 patients. The savings were due to reduced time to heal, reduction in the costs of subsequent medical care and the chance for costly complications.

Table 6. Ongoing trials

Study ID	Design	Population	Intervention	Comparator	Primary outcomes	Secondary outcomes	Current status	Estimated completion date
NCT01671748	RCT	Subjects with varicose ulcer (n=47)	MIST	Standard care	Percentage change in wound area; Actual change in wound area	Overall health related quality of life; Change in ulcer pain between week 5; Incidence of wound infection; Number of non-serious adverse events; Wound recurrence rate	Published: White (2015)	Completed in Dec 2013
ISRCTN24438635	RCT	Subjects with non-healing venous leg ulcers (target n=40)	MIST	Standard care	The percentage and actual change in wound area (cm ²) between baseline and exit visits	The change in health related quality of life between baseline and exit visits	Published: White (2015)	Completed in Dec 2013
NCT01214980	RCT	Subjects requiring skin grafting due to burns, trauma, or chronic venous ulcers (n=156)	MIST	Standard care	Rate of wound healing	Time to full epithelialisation; Numeric pain score; Numeric itching score; Donor site recidivism rate	Published: Pranthier et al. 2015	Completed in Jul 2014
NCT01549860	RCT	Subjects presenting	MIST	Standard care	Wound area mean percent reduction	Change in pain VAS scores	Published: Gibbons et	Completed in Apr 2015

		with chronic lower extremity venous ulcers					al. 2015	
NCT01206855	RCT	Subjects following cosmetic procedures (n=3440)	MIST	Standard postoperative incision care	Reduction in swelling, bruising, firmness and pain; Reduction in wound healing complications; Improvements in scarring	Patient satisfaction	Completed	Completed in Dec 2013
NCT02045303	Open label comparative study	Subjects with sub-acute and chronic lower extremity ulcers requiring selective debridement (n=20)	Contact ultrasound therapy (Sonoca-180) plus MIST	Either Sonoca-180 or MIST Therapy alone	Total wound area	Total wound volume; percent slough	Unclear	Dec 2015

Table 7. Excluded studies based on full-text paper

Study ID	Reason for exclusion
Excluded from the results of NICE searches Oct 2010 - Nov 2013	
Cullum N, Al KD, Bell-Syer-Sally EM. Therapeutic ultrasound for venous leg ulcers. <i>Cochrane Database of Systematic Reviews</i> 2010; (6).	Did not include studies on MIST
Butcher G, Pinnuck L. (2013) Wound bed preparation: ultrasonic-assisted debridement. <i>British Journal of Nursing</i> , 22(6):S36-S43.	Narrative overview without relevant outcomes
Gray D, Stang D. Ultrasound-assisted wound debridement device. <i>Wounds UK</i> 2010; 6(4):156-162.	Narrative overview without relevant outcomes
Madhok BM, Vowden K, Vowden P. (2013) New techniques for wound debridement. <i>International Wound Journal</i> , 10(3):247-251	Narrative overview without relevant outcomes
Samuels JA, Weingarten MS, Margolis DJ, Zubkov L, Sunny Y, Bawiec CR et al. (2013) Low-frequency (<100 kHz), low-intensity (<100 mW/cm(2)) ultrasound to treat venous ulcers: a human study and in vitro experiments. <i>Journal of the Acoustical Society of America</i> , 134(2):1541-1547.	Device was not MIST
Lasko J, Kochik J, Serena T. (2010) Combining acoustic pressure wound therapy with electrical stimulation for treatment of chronic lower-extremity ulcers: a case series. <i>Advances in Skin & Wound Care</i> , 23(10):446-449.	MIST was combined with electrical stimulation
Keltie K, Reay CA, Bousfield DR, Cole H, Ward B, Oates CP et al. (2013) Characterization of the ultrasound beam produced by the MIST therapy, wound healing system. <i>Ultrasound in Medicine & Biology</i> , 39(7):1233-1240.	Technology evaluation with no relevant outcomes
Excluded from the results of NICE searches Dec 2013 - Dec 2015	
Amini S, ShojaeeFard A, Annabestani Z et al. (2013) Low-frequency ultrasound debridement in patients with diabetic foot ulcers and osteomyelitis. <i>Wounds-A Compendium of Clinical Research & Practice</i> , 25 (7): 193-198	Device was not MIST
Li X, Liu S, Lai X et al. (2009) A Pilot Study of Ultrasonically-assisted Treatment of Residual Burn Wounds. <i>Wounds-A Compendium of Clinical Research & Practice</i> 21 (10): 267-272.	Device was not MIST
Maher SF, Halverson J, Misiewicz R et al. (2014) Low-frequency ultrasound for patients with lower leg ulcers due to chronic venous insufficiency: a report of two cases. <i>Ostomy Wound Management</i> , 60 (2): 52-61	Device was not MIST
Samuels JA, Weingarten MS, Margolis DJ, Zubkov L, Sunny Y, Bawiec CR et al. (2013) Low-frequency (<100 kHz), low-intensity (<100 mW/cm(2)) ultrasound to treat venous ulcers: a human study and in vitro experiments. <i>Journal of the Acoustical Society of America</i> , 134(2):1541-1547.	Device was not MIST
Keltie K, Reay CA, Bousfield DR, Cole H, Ward B, Oates CP et al. (2013) Characterization of the ultrasound beam produced by the MIST therapy, wound healing system. <i>Ultrasound in Medicine & Biology</i> , 39(7):1233-1240.	Technology evaluation with no relevant outcomes
Madhok BM, Vowden K, Vowden P (2013) New techniques for wound debridement. [Review]. <i>International Wound Journal</i> , 10 (3): 247-251	Overview with no relevant outcomes
Unger PG (2014) Effect of noncontact low-frequency ultrasound on wound healing. <i>Journal of Acute Care Physical Therapy</i> , 5 (2): 51-52	Expert opinion with no relevant outcomes

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Jeffers AM, Maxson PM, Thompson SL et al. (2014) Combined negative pressure wound therapy and ultrasonic MIST therapy for open surgical wounds: a case series. <i>Journal of Wound, Ostomy, & Continence Nursing</i> 41 (2): 181-186	Combined MIST with another technology
Haan J, Lucich S (2009) A retrospective analysis of acoustic pressure wound therapy: effects on the healing progression of chronic wounds. <i>Journal of the American College of Certified Wound Specialists</i> , 1 (1): 28-34.	Already included in the initial assessment report Batki et al. (2010) which supported the MTG5 guidance

Appendix C – Literature search strategy

NICE search strategy for the searches covering the period Oct 2010 – Nov 2013

Search strategy used for Ovid MEDLINE(R) <1946 to November Week 3 2013>

- 1 (low* adj4 frequen* adj4 non?contact* adj4 ultrasound*).tw.
- 2 MIST.tw.
- 3 (acoustic* adj4 pressur* adj4 wound* adj4 therap*).tw.
- 4 (low* adj4 frequen* adj4 ultrasound*).tw.
- 5 (ultrason* adj4 assist* adj4 wound*).tw.
- 6 UAWD.tw.
- 7 or/1-6
- 8 limit 7 to english language
- 9 limit 8 to ed=20101014-20131231
- 10 low-frequency noncontact ultrasound.tw.
- 11 (MIST therapy or MIST).tw.
- 12 MIST therapy ultrasound.tw.
- 13 acoustic pressure wound therapy.tw.
- 14 MIST ultrasound therapy.tw.
- 15 low-frequency ultrasound.tw.
- 16 ultrasound MIST.mp. and fibroblasts.tw. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
- 17 ultrasound MIST.tw.
- 18 or/10-17

- 19 limit 18 to english language
- 20 limit 19 to ed=20101014-20131231
- 21 9 not 20

EAC search strategy used for the searches covering the period 11 Nov 2013 – May 2014

Search strategy used for MEDLINE

- 1 (low* adj4 frequen* adj4 non?contact* adj4 ultrasound*).tw.
- 2 MIST.tw.
- 3 (acoustic* adj4 pressur* adj4 wound* adj4 therap*).tw.
- 4 (low* adj4 frequen* adj4 ultrasound*).tw.
- 5 (ultrason* adj4 assist* adj4 wound*).tw.
- 6 UAWD.tw.
- 7 or/1-6
- 8 limit 7 to english language
- 9 limit 8 to ed=20131101-20140531

NICE search strategy for the searches covering the period 11 Dec 2013 – 31 Dec 2015

Database: MEDLINE

- 1 (low* adj4 frequen* adj4 non?contact* adj4 ultrasound*).tw.
- 2 MIST.tw.
- 3 (acoustic* adj4 pressur* adj4 wound* adj4 therap*).tw.
- 4 (low* adj4 frequen* adj4 ultrasound*).tw.
- 5 (ultrason* adj4 assist* adj4 wound*).tw.
- 6 UAWD.tw.
- 7 or/1-6

- 8 limit 7 to english language
- 9 limit 8 to ed=20131211-20151231
- 10 Animals/ not Humans/
- 11 9 not 10

Database: Medline in-Process

- 1 (low* adj4 frequen* adj4 non?contact* adj4 ultrasound*).tw.
- 2 MIST.tw.
- 3 (acoustic* adj4 pressur* adj4 wound* adj4 therap*).tw.
- 4 (low* adj4 frequen* adj4 ultrasound*).tw.
- 5 (ultrason* adj4 assist* adj4 wound*).tw.
- 6 UAWD.tw.
- 7 or/1-6
- 8 limit 7 to english language
- 9 limit 8 to ed=20131211-20151231
- 10 Animals/ not Humans/
- 11 9 not 10

Database: Embase

- 1 (low* adj4 frequen* adj4 non?contact* adj4 ultrasound*).tw.
- 2 MIST.tw.
- 3 (acoustic* adj4 pressur* adj4 wound* adj4 therap*).tw.
- 4 (low* adj4 frequen* adj4 ultrasound*).tw.
- 5 (ultrason* adj4 assist* adj4 wound*).tw.
- 6 UAWD.tw.
- 7 or/1-6

- 8 limit 7 to english language
- 9 limit 8 to dd=20131211-20151231
- 10 Nonhuman/ not human/
- 11 9 not 10

Database: EconLit

- 1 (low* adj4 frequen* adj4 non?contact* adj4 ultrasound*).tw.
- 2 MIST.tw.
- 3 (acoustic* adj4 pressur* adj4 wound* adj4 therap*).tw.
- 4 (low* adj4 frequen* adj4 ultrasound*).tw.
- 5 (ultrason* adj4 assist* adj4 wound*).tw.
- 6 UAWD.tw.
- 7 or/1-6
- 8 limit 7 to english language [Limit not valid; records were retained]

Database: Cochrane Library

- #1 (low* near/4 frequen* near/4 non?contact* near/4 ultrasound*):ti,ab,kw
(Word variations have been searched)
- #2 MIST:ti,ab,kw (Word variations have been searched)
- #3 (acoustic* near/4 pressur* near/4 wound* near/4 therap*):ti,ab,kw
(Word variations have been searched)
- #4 (low* near/4 frequen* near/4 ultrasound*):ti,ab,kw (Word variations
have been searched)
- #5 (ultrason* near/4 assist* near/4 wound*):ti,ab,kw (Word variations
have been searched)
- #6 UAWD:ti,ab,kw (Word variations have been searched)
- #7 #1 or #2 or #3 or #4 or #5 or #6 Publication Year from 2013 to 2015

Database: PubMed

#11	Add	Search (#9 OR #10)
#10	Add	Search (publisher [sb] AND #7)
#9	Add	Search (#7 and #8)
#8	Add	Search ("2015/12/19"[Date - Entrez] : "3000"[Date - Entrez])
#7	Add	Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
#6	Add	Search UAWD[Title/Abstract]
#5	Add	Search (ultrason*[Title/Abstract] AND assist*[Title/Abstract] AND wound*[Title/Abstract])
#4	Add	Search (low*[Title/Abstract] AND frequen*[Title/Abstract] AND ultrasound*[Title/Abstract])
#3	Add	Search (acoustic*[Title/Abstract] AND pressur*[Title/Abstract] AND wound*[Title/Abstract] AND therap*[Title/Abstract])
#2	Add	Search MIST[Title/Abstract]
#1	Add	Search (low*[Title/Abstract] AND frequen*[Title/Abstract] AND non?contact*[Title/Abstract] AND ultrasound*[Title/Abstract])

**EAC search strategies for the searches covering the period
Dec 2015 – Feb 2016 (and to update the NICE 2015 searches
which covered 11 Dec 2013 – 31 Dec 2015)**

Database: Ovid MEDLINE(R) <1946 to February Week 2 2016>

- 1 (low* adj4 frequen* adj4 non?contact* adj4 ultrasound*).tw.
- 2 MIST.tw.
- 3 (acoustic* adj4 pressur* adj4 wound adj4 therap*).tw.
- 4 (low* adj4 frequen* adj4 ultrasound*).tw.
- 5 (ultrason* adj4 assist* adj4 wound*).tw.
- 6 UAWD.tw.
- 7 or/1-6

- 8 limit 7 to english language
- 9 (201512\$ or 201601\$ or 201602\$).ed.
- 10 8 and 9
- 11 animals/ not humans/
- 12 10 not 11

***Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
<February 23, 2016>***

- 1 (low* adj4 frequen* adj4 non?contact* adj4 ultrasound*).tw.
- 2 MIST.tw.
- 3 (acoustic* adj4 pressur* adj4 wound adj4 therap*).tw.
- 4 (low* adj4 frequen* adj4 ultrasound*).tw.
- 5 (ultrason* adj4 assist* adj4 wound*).tw.
- 6 UAWD.tw.
- 7 or/1-6
- 8 limit 7 to english language
- 9 (201512\$ or 201601\$ or 201602\$).ed.
- 10 8 and 9
- 11 animals/ not humans/
- 12 10 not 11

Database: Embase <1974 to 2016 February 23>

- 1 (low* adj4 frequen* adj4 non?contact* adj4 ultrasound*).tw.
- 2 MIST.tw.
- 3 (acoustic* adj4 pressur* adj4 wound adj4 therap*).tw.
- 4 (low* adj4 frequen* adj4 ultrasound*).tw.
- 5 (ultrason* adj4 assist* adj4 wound*).tw.
- 6 UAWD.tw.
- 7 or/1-6
- 8 limit 7 to english language
- 9 (201552\$ or 201601\$ or 201602\$ or 201603\$ or 201604\$ or 201605\$ or 201606\$ or 201607\$ or 201608\$ or 201609\$).em.

- 10 8 and 9
- 11 animal/ not human/
- 12 10 not 11

**Database: Cochrane Library (CDSR issue 2 of 12 2016, CENTRAL Issue 1 of 12 2016, DARE and EED Issue 2 of 4 2015, HTA issue 1 of 4 2016)
(Searched on 24 February 2016)**

- #1 (low* near/4 frequen* near/4 non?contact* near/4 ultrasound*)
- #2 MIST
- #3 (acoustic* near/4 pressur* near/4 wound* near/4 therap*)
- #4 (low* near/4 frequen* near/4 ultrasound*)
- #5 (ultrason* near/4 assist* near/4 wound*)
- #6 UAWD
- #7 #1 or #2 or #3 or #4 or #5 or #6 Online Publication Date from Dec 2015 to Feb 2016

Database : EconLit (EBSCO)

- S1 (low* near/4 frequen* near/4 non?contact* near/4 ultrasound*) 18
- S2 MIST 0
- S3 UAWD 0
- S4 acoustic* near/4 pressur* near/4 wound* near/4 therap* 3
- S5 (low* near/4 frequen* near/4 ultrasound*) 0
- S6 ultraso* near/4 assist* near/4 wound* 35
- S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6 Limiters - Published Date: 20150101-20151231 2

Database: PubMed (Searched on 25 February 2016)

- #1 Search (((low frequenc* ultraso*[Title/Abstract]) OR ultraso* assis*[Title/Abstract]) OR acoustic press*[Title/Abstract]) OR (MIST[Title/Abstract] OR UAWD[Title/Abstract])
- #2 Search wound*[Title/Abstract]
- #3 #1 AND #2
- #4 (#3) AND ("2015/12/01"[PDAT] : "2016/02/29"[PDAT])

Trials register searches 2016 update

CT.gov (searched 25/2/2016)

Search terms and limits:

wound | ultrasound | received from 12/01/2015 to 02/29/2016

MIST | received from 12/01/2015 to 02/29/2016

ulcer* | ultrasound | received from 12/01/2015 to 02/29/2016

healing | ultrasound | received from 12/01/2015 to 02/29/2016

WHO ICTRP searched 25/2/2016

Search terms and limits:

wound | ultrasound received from 12/01/2015 to 02/29/2016

healing | ultrasound received from 12/01/2015 to 02/29/2016

ulcer* | ultrasound received from 12/01/2015 to 02/29/2016

MIST received from 12/01/2015 to 02/29/2016

Possible additional studies resulting from trials:

Also checked whether further publications had been issued for relating to trials listed in NICE's December 2015 MTEP reviews search template.

NCT02045303 No publications

NCT01206855 No publications

NCT01214980 Prather JL, Tummel EK et al. Prospective Randomized Controlled Trial Comparing the Effects of Noncontact Low-Frequency Ultrasound with Standard Care in Healing Split-Thickness Donor Sites. *J Am Coll Surg*. 2015 Aug; 221(2) :309-18. doi: 10.1016/j.jamcollsurg.2015.02.031. Epub 2015 Mar 14.
<http://www.ncbi.nlm.nih.gov/pubmed/25868409>

NCT01549860 No publications

NCT01671748 No publications

ISRCTN24438635 No publications

Adverse events sources.

Database: FDA MAUDE database update searches 25/2/2016

Search terms:

Celleration

MIST

Wound healing

Wound ultrasound

Ulcer healing

All limited by date 1/12/2015 – 29/2/2016

No results for any of these

Database: FDA Medical Devices update searches 25/2/2016

Search terms:

Celleration

MIST

Wound healing

Wound ultraso*

Nothing more recent than previously reported

Database/website: MHRA update searches 25/2/2016

Search terms:

Celleration

MIST

Wound healing

Wound ultraso*

Nothing more recent than previously reported

Appendix D – References

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