EXTERNAL ASSESSMENT CENTRE REPORT TEMPLATE

Title: The MIST Therapy system for the promotion of wound healing in chronic and acute wounds

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Declared interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of NICE. Any errors are the responsibility of the authors.

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Abbreviations

CE	Conformité Européenne (European Conformity)
CRD	Centre for Review and Dissemination
DFU	Diabetic Foot Ulcer
EAC	External assessment centre
EED	Economic evaluation database
FDA	Food and Drug Administration
ITT	Intent to treat
MAUDE	Manufacturer and User Device Experience database
MeSH	Medical subject heading
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NLFU	Non-contact low frequency ultrasound
RCT	Randomised controlled trial
VAS	Visual analogue scale

Note on use of page numbers

Section numbers and page numbers in this external assessment centre report refer to the manufacturer's submission document unless otherwise stated.

1. SUMMARY

1.1 Scope of the submission

This report assesses the submission to NICE by the manufacturer (Celleration Inc, USA) for the MIST Therapy system (generator and applicator). The MIST Therapy system is a non-contact device that delivers low energy, low intensity ultrasound to the wound bed via a continuous, sterile, saline mist in order to promote wound healing. The mist is intended to act as a conduit for transmitting ultrasonic energy to the wound, transferring energy to a beneficial depth to promote healing by cleansing, reducing the bioburden and stimulating tissue granulation.

Specifically, the submission considers patients with chronic “hard to heal” wounds and acute wounds, in accordance with the scope issued by NICE. The report includes an assessment of the evidence for the clinical effectiveness, meta-analysis and the cost implications, submitted by the manufacturer.

1.2 Summary of submitted clinical effectiveness evidence

The key source of evidence on clinical effectiveness relating to patients with chronic, “hard to heal” and acute wounds were 10 studies; two RCTs [1, 2] and eight peer reviewed prospective or retrospective observational studies, with no control group in most studies [3 -10]. All the studies were conducted in hospitals or referral centres in the USA and all received some funding by the manufacturer, Celleration.

The studies followed treatment with the MIST therapy as an adjunct to standard of care. On average, treatment times were 2 or 3 times per week for 3 to 7 minutes with a mean duration ranging from 3 to 21 weeks. The studies show that the MIST therapy system appears to have a beneficial effect on wound healing and debridement which contributes to wound healing.

None of the studies demonstrated the long term outcome of wounds treated with MIST Therapy.

All of the studies were in patients 18 years and above.

No adverse events were attributed to the MIST Therapy system.

The safety of the health professionals and the patient due to aerosols created during the treatment using the MIST Therapy system were addressed in a separate technical in-vivo evaluation [11], which demonstrated that treatment of wounds with the MIST Therapy system did not “cause an aerosolisation and the standard attire in clinical settings was shown to be sufficient in preventing contamination.

The MIST Therapy system is portable and can be used in primary care, community hospitals or GP surgeries by nursing staff after minimal training.

1.3 Summary of submitted economic evidence

The literature searches conducted by the manufacturer do not identify any relevant economic studies. However, a number of studies related to wound closure or trauma that may have included the economic benefit of an earlier state of wellness were used to provide the data for the cost model.

1.3.1 Strengths

Through no faults of the authors, there is very little adequate evidence - only two small imperfect RCTs have been done.

1.3.2 Weaknesses

The assessment, 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.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

The authors appear to have garnered most of the salient human evidence. Bacterial burden and blood supply are prognostic factors. The submitted

evidence indicates that the clinical judgement of infection is often incorrect. In total, Celleration has on file over 200 publications on the MIST Therapy, which includes 104 unpublished single case studies held on Celleration patient registry and eight published case series in magazine “Thoughts on Therapy” funded by Celleration. The remainder consists of case series, posters and abstracts, and educational assessment of clinical uses on various wound aetiology and not large enough to provide statistical outcome data and which were excluded by Celleration from the final submitted clinical evidence. However, there is a plausible theory behind the use of MIST and animal experiments appear promising.

1.4.2 Weaknesses

Only two of the publications are randomised controlled trial of limited quality. Most of the other studies were either prospective or retrospective observational studies. The author of the report distinguishes between randomised and non-randomised design, but not between studies using historical controls and those (the majority) with no controls at all *i.e.* where the patient is their own control over time.

1.4.3 Areas of uncertainty

The effectiveness of MIST remains uncertain. Because the degree of (any) effectiveness (see below) remains highly uncertain, any calculation of cost effectiveness must be highly uncertain. The clinical effectiveness evidence is based on studies undertaken in clinics in the USA where MIST Therapy has been widely used for a number of years. However, the care pathways in the USA are similar to those in the UK.

1.5 Key issues

The meta-analysis submitted by Celleration acknowledges its limitations and stated that “first, all studies were either prospective or retrospective observational studies and are subject to the limitations inherent with non-randomised designs.” However, the analysis is largely based on changes within patients, rather than comparison between groups, and is therefore of

very little value. This applies in particular to the sections on health economics as discussed below.

The main limitation is that there are only two small RCTs comparing MIST Therapy with no MIST Therapy. Moreover, duration of follow up is generally inadequate with few reports on outcome beyond 9 weeks post treatment. Less serious issues consist of the limited range of ulcer types in the studies and failure to consider other promising new treatments apart from MIST - a point to which we return.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The submission quite properly focuses on chronic hard to heal wounds, including diabetic foot ulcers, arterial ulcers, pressure ulcers and venous ulcers. Celleration state that MIST therapy is also indicated for acute wounds such as traumatic wounds, post-surgical wounds and burns, but this is not the issue here. Common symptoms of ulceration include pain, exudate and odour, and these symptoms are frequently associated with poor sleep, loss of mobility and social isolation.

Relevant information is provided on the prevalence of venous, pressure and diabetic foot ulcers. Between 1.5 and 3.0 per 1000 people have active leg ulcers. Prevalence increases with age to about 20 per 1000 in people aged over 80 years. The prevalence of venous leg ulcers is estimated to be 150,000 in the UK with 28% of ulcers remaining open for more than 2 years. The prevalence of diabetic foot ulcers is estimated to be 84,000 in the UK annually and 5,000 diabetic patients undergo amputation annually. The prevalence of pressure ulcers is estimated to be 412,000 in the UK annually, 24% of which are grade 3 or 4 ulcers.

These figures appear to be consistent with NICE guidelines CG10 and CG29 [12, 13]. However, the prevalence of chronic ulceration is higher in people aged over 65, with 68% of all incidences occurring in this age group [14] and trends in the UK population over the next 20 years indicate an increase in people in this age group from 9.5 million to 13.0 million. At the same time the number of people with diabetes is expected to increase, and it is estimated that this will add approximately 25,000 new cases of foot ulceration a year.

2.2 Critique of overview of current service provision

The scope describes the comparator as advance wounds dressings used to create the optimal wound healing environment for different types of wounds. These include: alginate, capillary action, charcoal, film, foam, honey,

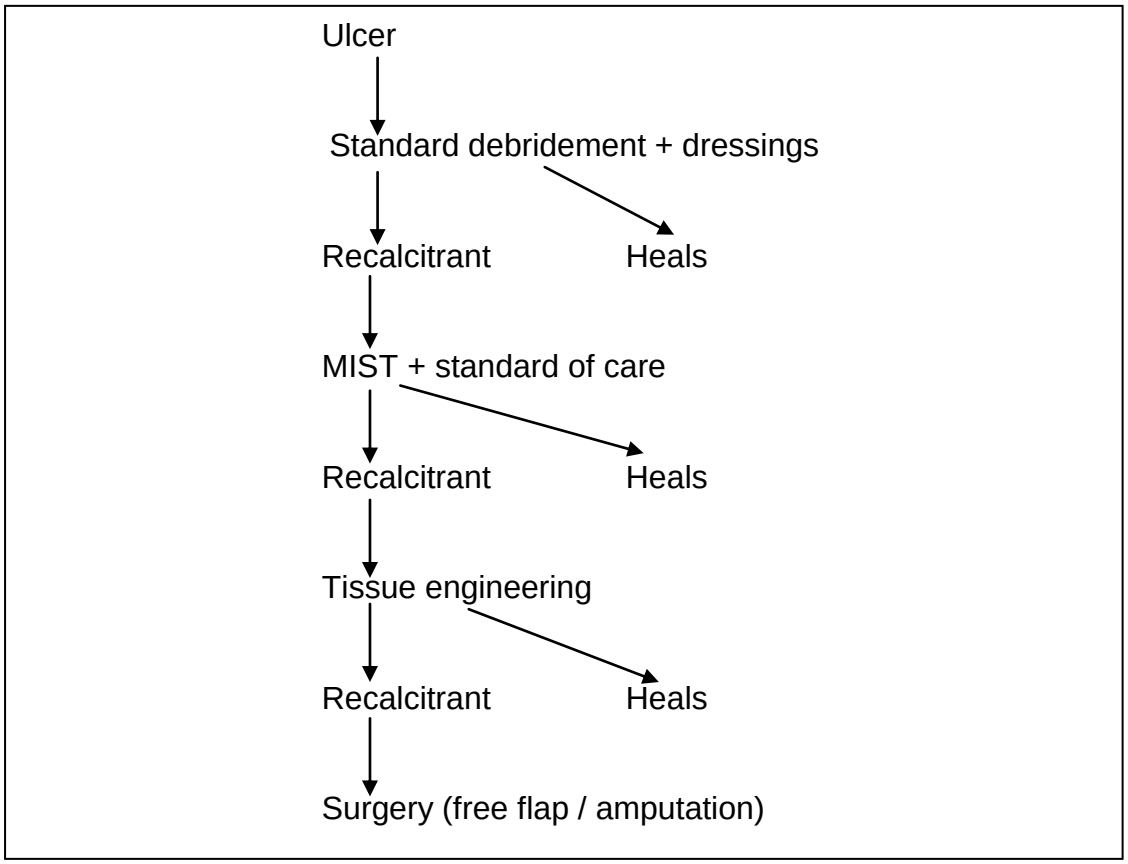
hydrocolloid, hydrocolloid fibrous, hydrogel sheets, iodine, low/non-adherent wound contact layer, silicone and silver and compression bandaging. Celleration's submission points out that generally wound care management is developed in line with regional guidelines for debridement and antibiotic therapy, and NICE guidance for specific types of wounds [12, 13, 15].

The intervention, MIST Therapy System, has only become available in the UK recently and drug tariff approval for the single use applicator and sterile saline has been obtained.

Clinical experts report that the major constraint to the uptake of the MIST Therapy system is cost, and as it is a novel technology, additional staff training for its use may be necessary. The experts also felt that the evidence for the clinical and cost effectiveness of the MIST Therapy as an adjunct to standard of care was limited, and were of the opinion that the technology would probably be of most use in treating recalcitrant wounds after all conventional treatment had failed. Such evidence as there is, relates to this group, and this group is the focus of the report. This is well justified in our view.

Celleration states that MIST Therapy is an adjunct to advanced wound dressings and therefore it is unlikely to impact on the current care pathways. Other new therapies, especially regenerative medicine, are not discussed. A potential future pathway is shown in figure 1.

Figure 1: Potential care pathway



The idea is that greater costs are justified by greater relative effectiveness in populations defined by failure of less expensive treatments. The implications are that, ideally, the whole pathway should be considered in clinical and health economic studies. For example, if MIST has even small beneficial effects it may repay the investment by offsetting expensive subsequent treatments.

3 Critique of definition of decision problem

3.1 Patient population

Patients with chronic, “hard to heal” and acute wounds including venous and arterial ulcers were outlined as being relevant in the scope issued by NICE. Most patients in these studies had lower limb ulcers. Subgroups were not considered as part of the submission. That said they may be important. While ulcers have common factors such as infections, distinguishing between problems such as venous hypertension versus microvascular disease might affect relative effectiveness of different treatments. Furthermore treatments differ by ulcer type *e.g*. pressure dressings in venous ulcers versus negative pressure in large traumatic wounds.

3.2 Intervention

In the submission, the intervention considered is the MIST Therapy system. It is argued that MIST actively treats the wound bed, accelerating the healing process. Its potential uses include chronic and “hard to heal” wounds such as diabetic foot ulcers, arterial ulcers, pressure ulcers, venous ulcers and acute wounds including traumatic wounds, post-surgical wounds and burns.

MIST Therapy uses noncontact ultrasound technology to atomise and deliver saline as a continuous mist, which is applied via slow even strokes to the site of treatment. The distance between the applicator and the wound bed is 0.5 to 1.5cm. The treatment time is automatically determined by the MIST Therapy system for the wound surface area. Most treatments take 5 to 7 minutes and are recommended when wound dressings are changed, typically three times a week.

The manufacturer submission states that the Celleration MIST Therapy system indicated for the promotion of wound healing meets the relevant quality assurance system for CE marking (CE 512325). The EC Certificate issued by BSI Product Services is valid until April 24, 2012.

According to the manufacturer, MIST Therapy system (generator and applicator) is considered a Class IIa Sterile, Active Therapeutical Device per

MDD 93/42/EEC, Annex IX, Rules 9 and 11. The sterile saline, an accessory, used for irrigation and the germicidal wipes used for cleaning the Generator and equipment are both considered a medical device classified as IIa, per rule 4, section 1.4 of Annex IX.

3.3 Comparator

The possible comparator identified in the NICE scope were 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 any other wound care interventions, including negative pressure wound therapy and combination treatments with MIST Therapy. The evidence from the literature relates to situations where such standard of care and simple methods have failed so called “hard to heal” ulcers. MIST Therapy is an adjunct to the above methods not an alternative to them.

In the statement of the decision problem in the manufacturer submission, page 19, additional comparators are stated as hydrosurgery systems and sharp debridement with a scalpel. 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. However, if MIST is effective it may reduce the need for further surgery.

For the purpose of cost analysis, the comparator for hard to heal wounds is:

- Venous and arterial ulcers – compression bandaging
- Other chronic and hard to heal wounds – foam dressing
- Acute wounds – surgical debridement.

The comparator choice for “hard to heal” wounds is consistent with the scope although the MIST Therapy was (quite properly) considered an adjunct to standard of care.

3.4 Outcomes

The outcomes included in the manufacturer submission are consistent with the scope. However, the manufacturer has included recurrence as an additional outcome measure. This is eminently sensible, since the personal and social effects include recurrence.

The safety of the MIST Therapy system was reported and adverse events are considered.

3.5 Time frame

Not applicable.

3.6 Other relevant factors

None identified

3.7 Equality and diversity issues

No equality and diversity issues were identified to be addressed in the submission for the use of MIST Ultrasound Therapy system.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description and critique of the manufacturer's identification and selection of studies.

Assessment of literature searches

The MIST Ultrasound Wound Therapy system is indicated in chronic and "hard to heal" wounds including diabetic foot ulcers, pressure ulcers and venous ulcers. It is also indicated for acute wounds including traumatic wounds, post-surgical wounds and burns. It promotes wound healing by delivering low energy, low intensity ultrasound to the wound bed via a continuous saline mist.

The following critique is based on the information provided in the submission in Appendix 2: Search strategy for section 5.1 (identification of studies) page 109.

The submission only included a search of one database, pubmed.gov, US National Library of medicine, National Institute of Health database, but this database would be expected to include the relevant literature. Celleration has not provided a detailed description of the search strategy used to identify relevant studies and it is unclear whether any synonyms or indexing terms were included.

The search strategy outlined in section 7.2.4 is inconsistent with the search terms given in section 5.2.1 page 22. The manufacturer's submission states that the search results only include publications with the following search terms:

- low-frequency, noncontact ultrasound
- MIST Therapy; OR MIST
- MIST Therapy ultrasound
- acoustic pressure wound therapy

- MIST ultrasound therapy
- low-frequency ultrasound
- low-frequency noncontact ultrasound
- noncontact low-frequency nonthermal ultrasound therapy

The search term “noncontact low-frequency nonthermal ultrasound therapy” did not appear in the search strategy in Appendix 2, section 7.2.4. However, the search terms ‘Ultrasound MIST and fibroblast’ and ‘Ultrasound MIST’ do appear in this section, but are not listed in 5.2.1, study selection process. The terms used in the search strategy, section 7.2.4, are not listed in the statement of the decision problem by the manufacturer.

When the EAC reran the search in PubMed.gov, the number of citations listed in section 7.2.4 all matched with one exception for the search term Ultrasound MIST and fibroblast. Celleration cite one publication for this search term whereas the EAC search did not reveal any.

The date limits applied to the search strategy in the submission and defined in section 7.2.3, are not systematically applied to all search terms. The following date limits were applied:

- within the last five years *i.e.* 2005 to 2010
- 2002 – 2007
- 2002 – 2004
- none

The searches for evidence on adverse events were reported in Appendix 4: Search Strategy for section 5.9 (Adverse events). Celleration have not conducted a separate search for adverse events and cite 2 studies sponsored by them to assess the safety of MIST Therapy [1, 10]. Celleration provided a summary of the adverse events reported in the two studies, including a table of adverse events across all the patient groups.

Use of inclusion/exclusion criteria in the selection of studies

Celleration in their submission, in Tables B2 and B3**,** included all 199 independent and sponsored studies of which they are aware of. The first table includes RCTs, retrospective studies, in vivo studies, in vitro studies, case studies, posters and animal studies.

Celleration state reasonably, that case studies, in vivo/in vitro work and posters were excluded from the documentation as no statistically useful can be gained from them, and they are available on request. Much of the literatures relates to mechanism of action and have presumably been adequately summarised in the available papers. However, case studies were not excluded – a particular point of criticism to which we refer frequently.

4.1.2 Table of identified studies. What studies were included in the submission and what were excluded?

The EAC feels that the submission would have significantly benefitted from the provision of a flow chart outlining Celleration's process for the inclusion and exclusions of studies.

Celleration were inconsistent and did not apply the exclusion criteria rigorously with respect to the eligibility of the 199 studies (Tables B2 and B3, provided separately as an Excel spreadsheet) for consideration of clinical effectiveness. Table B4 describes the eligibility criteria for 11 studies, whilst Table B5 outlines primary and secondary outcomes for 24 studies. Both tables list studies excluded according to the Celleration Inc criteria. A much more serious problem, however, is failure to distinguish between studies with no controls at all (*i.e*. case series) from those [5, 8, 9] that do at least have non-randomised controls. It is sometimes impossible to work out to what comparisons statistical results in the tables pertain.

Table B6 in the submission provides a summary of the statistical analysis of ten studies which Celleration have selected for meta-analysis.

Studies included in the clinical effectiveness and meta-analysis is listed below:

1. RCTs

- 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.
- 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.

2. Non-RCT comparison

- 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.
- 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.
- 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.

3. Case Series

- 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.
- 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.

- 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.

- 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.

The manufacturer submission identified relevant ongoing studies for the treatment of chronic and “hard to heal” wounds. These are shown in table 1 with the completion dates.

Table 1: Estimated completion dates of ongoing studies

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

In addition, the following two studies funded by Celleration in the USA and which may be relevant were identified by the EAC (source www.clinicaltrials.gov):

- Split Thickness Donor site Pilot Study. A prospective, randomized, controlled, pilot study of the MIST Therapy system of Split Thickness Donor Sites. Completion date January 2011.

- The effectiveness Study of MIST Therapy after cosmetic surgery procedures of the face and body. Outcome measure is pain and swelling assessments, reduction in wound healing complications and improvements in scarring. Completion date March 2011.

Include details of any relevant studies that were not included in the submission.

The approach taken for the search strategies is at risk of missing potentially relevant studies. Additional search strategies carried out by the EAC for identification of clinical studies include searches of:

- EMBASE
- Medline
- Medline (R) IN Process
- Cochrane library
- CINAHL

using the terms used by Celleration in their PubMed search with appropriate limits activated where possible:

- low-frequency noncontact ultrasound;
- MIST Therapy; OR MIST
- MIST Therapy ultrasound
- acoustic pressure wound therapy
- MIST ultrasound therapy
- low-frequency ultrasound
- low-frequency noncontact ultrasound
- noncontact low-frequency nonthermal ultrasound therapy

The additional searches indicate that all the relevant studies using the MIST Therapy system are included in the submission.

4.1.3 Description and critique of manufacturers approach to validity assessment and details of the quality assessment of studies.

As stated above, the manufacturer did not assess the quality of the clinical effectiveness studies using appropriate criteria nor even described study methodology in a clear way. The checklist used was based on the criteria for risk of bias in RCTs, issued in guidance for undertaking reviews in healthcare, by the Centre for Reviews and Dissemination, University of York [16]. The checklist used to assess the quality of the studies does not cover certain aspects, such as whether follow-up was adequate. The main characteristics of the study quality are not captured. For example, they do not comment on lack of observer masking (blinding) or very small numbers in the second RCT [2]. They do not comment on possible bias caused by excluding the centres where Sham procedures were more successful in the first RCT [1]. The most important effectiveness information by a considerable margin comes from RCTs. However, in the submission Celleration state that the two RCTs have not been graded and their comments regarding the studies' approach to addressing the areas covered by the questions can be seen in table 2, alongside comments by the EAC.

Table 2: Critical appraisal of relevant clinical effectiveness studies

Ennis, Foreman, Mozen et al (1)		
Study question	**How is the question addressed in the study?**	**Comments by EAC**
Was randomisation carried out appropriately?	Yes	Prospective, randomised, double-Blind, controlled multicentre study. Randomization by computer generated randomization table supplied by the study sponsor (Celleration Inc) to the active ultrasound (MIST Therapy) or control (Sham) group.
Was the concealment of treatment allocation adequate?	Yes	
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	The baseline population demographics for the 55 patients in the final treatment group appear similar. However, the initial wound area was larger in the Sham group than the MIST group. Although the authors allow for this in the analysis, this difference emerged after the exclusions and therefore may have been a marker for confounding factors that could not be corrected for statistically.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	The clinician opening the randomisation envelopes and administering treatment knew the actual group status. Patients blinded using a modified dummy Sham device and placing a drape between them and equipment. Both MIST and Sham device turned on at the same time so that the same sound was heard. Patients blinded to the treatment, but this is hardly relevant. Therapist was not blinded. It is claimed that observer was blinded but therapist decided when the ulcer was healed. Blinding here is very unclear.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes. Explained and adjusted for	A total of 133 patients were enrolled, 55 patients remained after exclusion of 12 patients not meeting eligibility criteria, 24 lost to follow up and 42 treatment protocol violations with the Sham device at five centres. The ITT was null. The best sham outcomes were removed when the protocol violations were excluded. The effect size in the remaining “efficacy” cohort is huge.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No evidence of additional outcomes being measured but not reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	An intent-to-treat approach was used for data analysis on all 133 patient initially recruited and who had received >1 treatment and this was not significant.
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD’s guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table 2: Critical appraisal of relevant clinical effectiveness studies (cont'd)

Kavros, Miller, Hanna (2)		
Study question	**How is the question addressed in the study?**	**Comments by EAC**
Was randomisation carried out appropriately?	Yes	Prospective, open-label, parallel-group, controlled trial. Eligible patients were randomised into two groups receiving standard wound care (n = 35) or MIST Therapy plus standard wound care (n = 35). Patients were randomly assigned but the process was not explained.
Was the concealment of treatment allocation adequate?	No, was not a blinded RCT	
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Although baseline characteristics were similar, there appears to be more males than females in both groups and tissue oxygen levels were lower (worse) in the control group.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	Not blinded. Therapist was not blinded. The observer making complex volume measurements also did not appear to have been blinded which introduces a high risk of bias.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Photographs were taken of the wounds, but do not appear to have been used.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	All patients were followed up to the end of the study.
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

4.1.4 Description and critique of manufacturers outcome selection

The outcome measures addressed by the manufacturer's submission are considered to be appropriate. Relevant outcome measures as outlined in the NICE scope and provided in the manufacturer submission, were rate of healing, wound size, wound area, treatment time, wound closure, time to heal, pain score, quality of life and bioburden. In addition adverse events were also considered, with details provided in the appropriate section. The ten studies submitted in the clinical evidence measured several of these outcomes

All the outcomes specified in the NICE scope were addressed in the ten studies submitted in the clinical evidence.

4.1.5 Describe and critique the statistical approach used

The manufacturer included ten studies in the statistical analysis table in section 5.3.6 page 33. The statistical analysis of the ten clinical studies was inadequately reported by Celleration, and may be based on before and after comparisons (*i.e.* within patient). It seems that they mixed up different type of comparisons.

The statistical methods used in the independent meta-analysis are completely inappropriate. It is known that even hard to heal ulcers will improve with treatment. What was needed, but not provided, is a comparison between treatment with and without MIST Therapy. The test for publication bias is irrelevant in the context of simple within patient studies.

4.1.6 Summary statement about the review of clinical effectiveness

The submitted evidence was relevant to the decision problem, in terms of patient populations and interventations. However, the studies were not shown from the point of view of providing an unbiased measurement of incremental effectiveness. Of the studies included in section 5.5.2 two were randomised controlled trials [1, 2], with the remainder [3-10] mostly retrospective observational studies with historical controls or single arm studies. In addition, the manufacturer has included four studies [17-20] which lack evidence and based on the exclusion criteria should not be included.

The table in section 5.5.2, the manufacturer inaccurately reports that in the study by Kavros, Liedl *et al* [8] there are 417 patients in the intent to treat (ITT) analysis. However, this study is a retrospective, observational analysis, so it would be difficult to separate intended treatment from treatment received.

4.2 Summary of submitted evidence

Section 4.1.2, page 14, lists the ten studies [1-10] that Celleration has submitted for meta-analysis and as evidence for the MIST Therapy system. The findings of these studies, presented in the submission (pages 38-49), are summarised below.

4.2.1 Summary of results

MIST Therapy System is an adjunct to Standard of Care and is not a replacement for it. The primary outcome measures outlined in the scope have been addressed collectively in the ten studies submitted for the clinical evidence (Table 3).

Table 3: Summary of outcome measures in the ten studies submitted for the evidence

Study	Wound area	Wound volume	% healed	Healing time	Bioburden	Pain reduction	Adverse events	Quality of life
Ennis (1)	✓	**x**	✓	✓	✓	**x**	✓	**x**
Kavros (2)	**x**	✓	✓	**x**	**x**	**x**	**x**	**x**
Bell (3)	✓	**x**	✓	✓	**x**	✓	✓	**x**
Cole (4)	✓	✓		✓	**x**	✓	**x**	**x**
Ennis (5)	✓	✓	✓	✓	**x**	**x**	**x**	**x**
Gehling (6)	**x**	**x**	**x**	**x**	**x**	✓	**x**	**x**
Haan (7)	✓	**x**	✓	✓	**x**	✓	✓	**x**
Kavros (8)	**x**	✓	✓	✓	**x**	**x**	**x**	**x**
Kavros, (9)	**x**	✓	**x**	✓	**x**	**x**	**x**	**x**
Serena (10)	✓	✓	**x**	**x**	✓	**x**	✓	**x**

All but two of the studies were either prospective or retrospective observational studies and are subject to the limitations and possible bias inherent with non-randomised designs. Only three studies had a control arm using a sham device, one of which used historical controls from a previous study. 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.

The treatment duration with the MIST Therapy ranged from 0.4 to 25 weeks, with a mean healing time ranging from 3.6 to 21 weeks. There was no long term follow up of the patients to study the reoccurrence of a wound healing.

Pain was measured in four studies [2, 3, 6, 7] and relied on self-measurement using a visual-analogue scale at each patient visit. However, in two of the studies the information was not available on all the enrolled patients at the start and end of the study.

All the included studies received some funding from Celleration Inc and all were conducted in the USA. However, there is no reason why the results would not be transferrable in the UK given that the standard treatments are similar as are the types of ulcer and comorbodities.

Clinical observation and small case studies have also indicated that the use of MIST therapy reduces pain and infection in chronic wounds (Table B2, Manufacturer submission).

4.2.2 Critique of submitted evidence syntheses

The submission includes two RCTs which indicated that MIST Therapy can significantly promote healing in lower extremity wounds; although, both studies contained a relatively small number of participants, 55 and 70 respectively, and both had significant shortfalls in their methodology/conduct. Eight nonrandomised studies also support the use of MIST Therapy to improve wound healing and decrease healing time. However, non-random allocation of treatment, lack of appropriate comparison groups and the small populations used in the individual studies limit the evidence.

Of the two RCTs, the study by Ennis et al [1] was conducted across 23 centres. Also in this study, protocol violation occurred in 5 centres, with a subsequent loss of 42 patients from the trial. This indicates a poorly designed protocol. The efficacy study systematically removed patients who did relatively better on average with the sham procedure.

Adverse Events

Celleration sponsored two clinical trials [1, 10] with the primary objective to assess the safety of MIST Therapy. A summary of the adverse events reported in the two studies, including a table of adverse events across patient groups, is provided in the submission (Section 5.7). One hundred and ninety three adverse events were reported in the study by Ennis et al [1], and 18 in the study by Serena et al [10].

Ennis et al [1], reported 45 adverse events (64%) in the patients treated with MIST Therapy and 40 adverse events (64%) in the Sham control groups (p = 0.9242, Chi-Square Test). However, the EAC are unclear on how these numbers were derived in the submission, as they are not cited in the published study and the EAC are unable to verify this data from the information in table B7.

Serena et al [10] reported three adverse events during a two week treatment period of 18 patients, two of these were considered serious in nature, but were unrelated to the MIST Therapy. However, the published study does not discuss these adverse events as an outcome in the main body of the publication, and only states in the abstract that no adverse incidents occurred.

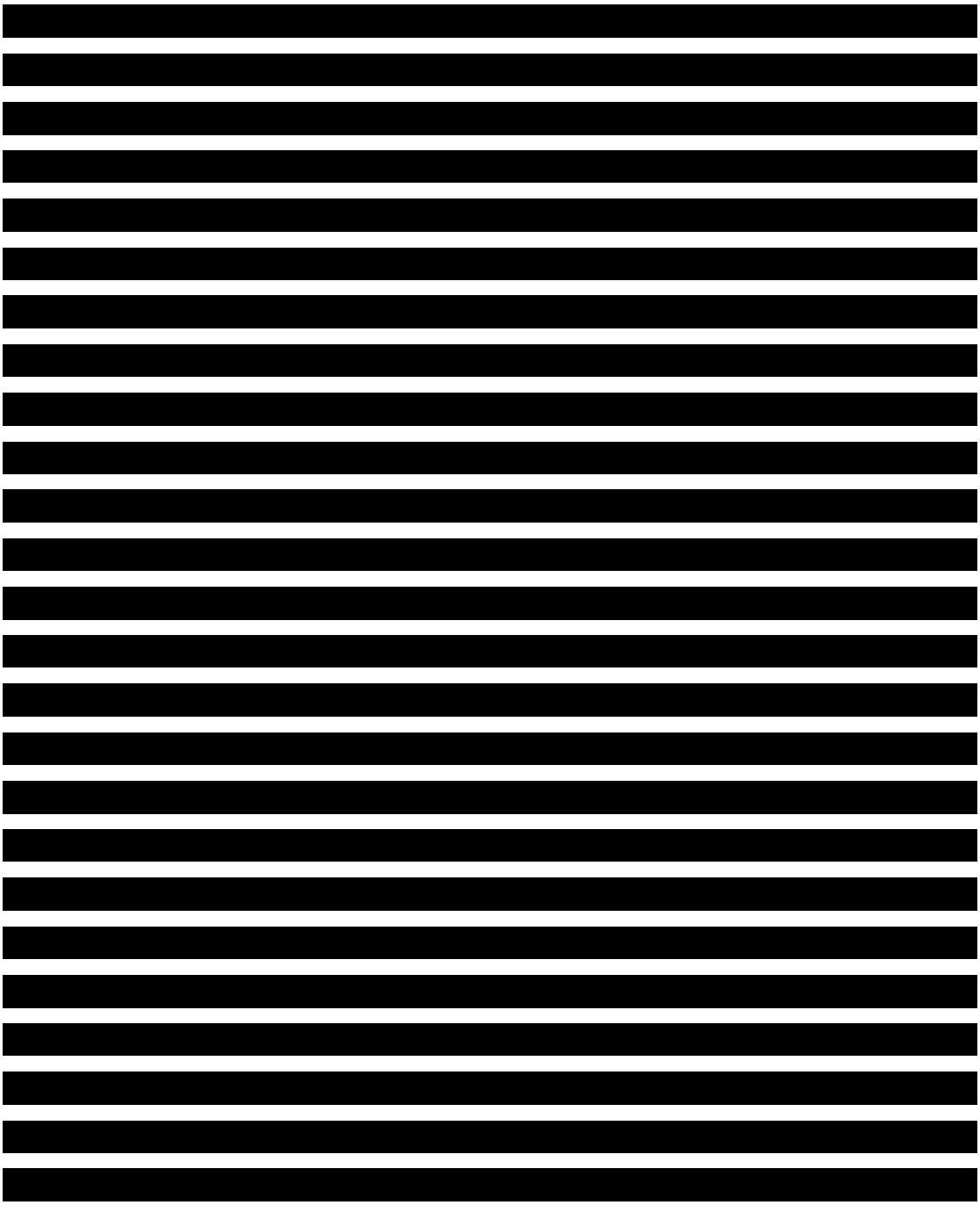
Bell et al [3] looked at treatment related adverse events during the study period and reported one events, a rash, which was classified as non-serious and unrelated to the MIST Therapy system. Haan *et al* [7] report that there were no treatment related adverse events.

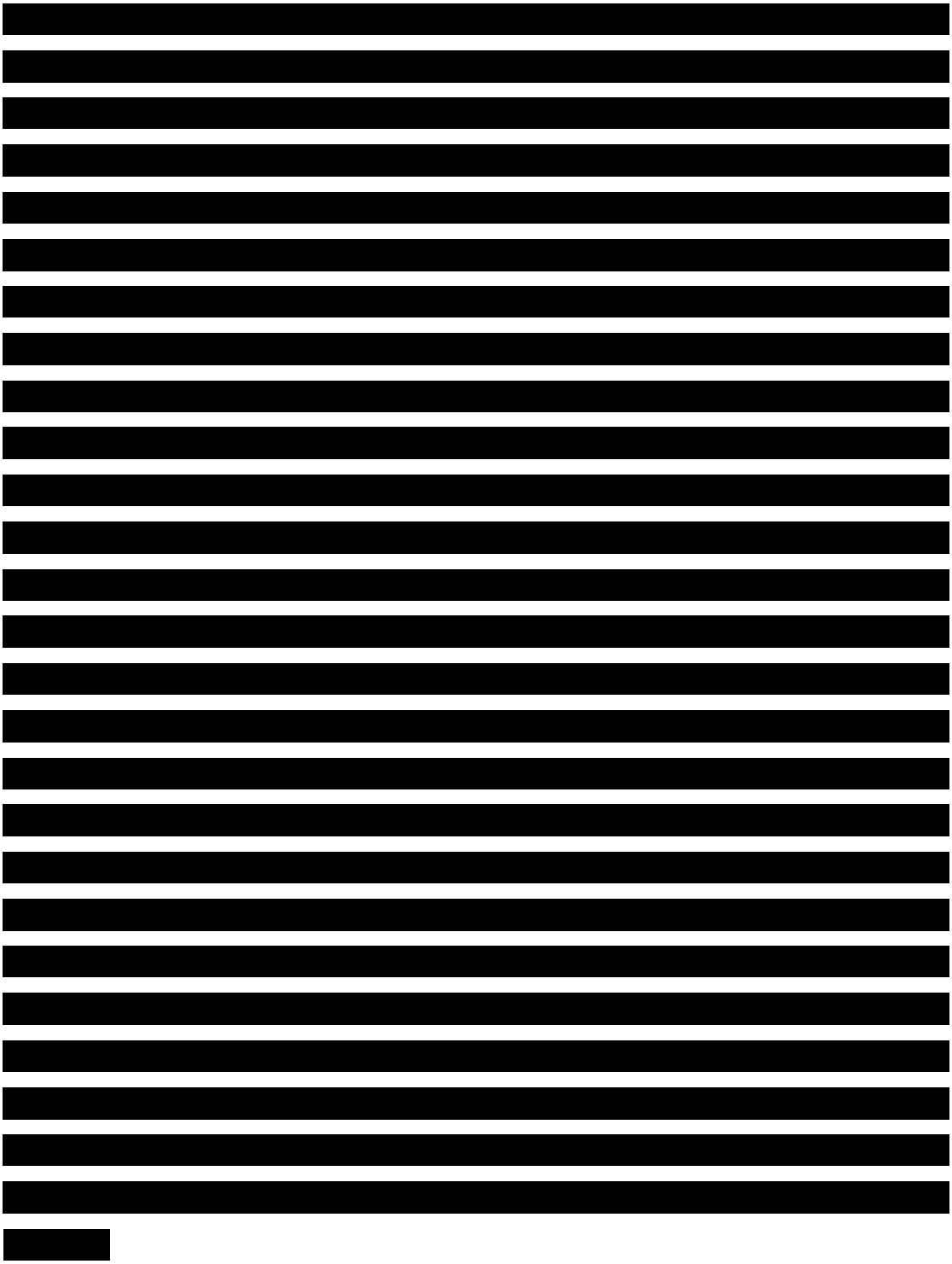
Safety

The safety of the health professionals and the patient due to aerosols created during the treatment using the MIST Therapy system were not addressed in the studies, but evidence was submitted in a separate technical in-vivo

evaluation [11]. This study demonstrated that treatment of wounds with the MIST Therapy system did not *"cause an aerosolisation of bacteria from the wound site as measured by the placement of agar media plates arranged in locations and at distances stimulating a patient, a clinician and a neighbour."* Universal safety precaution, such as the standard attire in clinical settings was shown to be sufficient in preventing contamination.

4.2.2.1 Meta-analysis and evidence synthesis





5 ASSESSMENT OF COST ANALYSIS

5.1 Overview of manufacturer's economic assessment

5.1.1 Methods

This section assesses the cost analysis submitted by the Manufacturer regarding the use of MIST Therapy System for the treatment of "hard to heal" chronic and acute wounds. The manufacturer submission includes:

- A description of the literature search undertaken for the identification of cost and cost effectiveness studies in relation to the MIST Therapy System
- A description of the *de novo* cost analysis, which included a summary of the model, patient population, model parameters, assumptions, data sources and sensitivity analysis
- A summary of the variables applied in the economic model
- An Excel file showing the UK market analysis for leg ulcers, diabetic foot ulcers and pressure ulcers
- An Excel file containing additional information including costs for treatment using MIST Therapy or comparators.

A summary of the relevant areas of the submission document for the cost analysis can be seen in table 4.

Table 4: Summary of key information for cost analysis

	Reference in submission document	Key tables/figures in submission document
Review of literature	Pages 53, 54, 89, 90, 120 – 128 (Appendix 6 to 9)	Tables B8, pages 55-57
Model structure	pages 71 - 74	Tables section 6.2.3 B1 to B4
Transition probabilities	pages 78 to 82	Tables 6.3.2 B1 and B2, 6.3.3 table B3, 6.3.6 table B10
Time horizon	Page 76	Table B9
Adverse events	Page 94	Table B13
Resources use and costs	Pages 87 -93	Tables B11 and B12
Sensitivity analysis	Page 95 to 96	Table 6.5.2 B1 and 6.5.2 B2
Results	Pages 97 to 102	Tables B14 to B17

Identification of studies

The search strategy for cost-effectiveness studies were reported in Appendix 6: Search Strategy for cost-effectiveness and cost studies (section 6.1), pages 120 -122. The submission includes a search of PubMed.gov, US National Library of Medicine, National Institute of Health database, Cochrane Review, National Institute for Health and Clinical Excellence website, and Google search.

The search terms used were:

- cost effectiveness AND wounds
- QALY AND wounds

The search terms were limited to those listed above and the EAC noted the absence of any subject index headings (MeSH).

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.

The search strategy for Appendix 8: measurement and Valuation of health effects; and Appendix 9: Resource identification, measurement and valuation, suffer from the same issues as above.

According to the manufacturer submission page 126, these searches yielded 10 and 4 results respectively. The manufacturer's inclusion criteria was any studies related to wound closure or trauma that may have included economic benefit, or studies that provided any economic information related to wound healing. However, there are no details listed of the 14 studies, but on pages 126 and 127 the manufacturer states that articles and resources identified as relevant have been included in the 25 references listed in section 6 (page 106 to 107).

The submission did not include the search strategy applied to each database and the EAC assumes that the same search strategy was applied in all the databases.

5.1.2 Results

The base case results presented in Table B17, section 6.6.3 of the submission are shown in terms of cost of the MIST Therapy being provided three times per week per patient. In addition, incremental cost savings per patient treated and the net savings to the NHS in the UK/Wales population are also given. A breakdown of costs associated with the annual rental of the technology, administration and consumable treatment costs. According to the manufacturer, staff costs are not necessarily incremental as the nurse would be treating the wound and applying a new dressing for any treatment option.

In addition to the base case results, sensitivity analyses were also presented in the submission (section 6.5).

5.1.3 Model validation

The manufacturer states that the de novo cost model is based on using "Macro numbers and comparing the Macro economics of the current wound care practice in the UK and Wales to the known improvement in time to healing using the NLFU plus standard of care to treat chronic wounds". In the

submission the manufacturer used population based costs and incidence reported with reference to improving the time to healing of the leg ulcers, pressure ulcers and DFU [1, 2, 5, 8, 9]. The perspective was from the current costs incurred by the NHS to treat chronic wounds in the UK and Wales of £2.3bn - £3.1bn 2005 [25].

5.2 Critique of approach used

Costs of MIST

There are two types of salient health service cost:

- Direct costs consisting of device cost (rental cost or purchase cost amortized over a number of years) and cost in staff time. The cost in staff time consists of the time required to use MIST given that a patient would be having a dressing change anyway and the cost of any additional treatment sessions that would not have been scheduled but for the need for MIST.

- The indirect costs associated with delayed or accelerated healing with contingent effects on health service costs. Were a broader societal, rather than narrow or health service perspective to be taken, then patient costs or savings would also have to be factored in.

The obvious difficulty here is that the less expensive items (the device itself and the 10 or so minutes required for its use) are known with a high degree of certainty while the more important costs (especially down stream savings contingent on effectiveness in promoting healing) are very poorly calibrated.

Effectiveness of MIST

It is here that real problems arise. Only two RCTs exist. While the controlled before and after studies may provide a measure of assurance that MIST is effective, it would be very unsound to use this type of study as a measure of effectiveness. As a general rule, the calibration of effectiveness would be ascertained by pooling the results of RCTs. However in this case we have only two RCTs and they both have serious problems as stated above.

In summary:

There are only 2 RCTs.

One of these RCTs by Ennis *et al* [1] has a curious and large number of post randomisation exclusions where the excluded cases had a less good outcome under MIST than in the included cases. This throws grave doubts on the study, especially as far as measurement of the magnitude of effectiveness is concerned.

Between the two RCTs, only 125 patients are included in the measurement of effectiveness used by the authors.

The second RCT by Kavros, Miller *et al.* [2] generates concerns over the risk of observer bias in a rather complex unmasked assessment of ulcer volumes as described above.

The trials deal with a restricted set of wounds and do not include venous ulcers.

The long and short of all this is that we do not have a reliable effectiveness measure.

To this must be added further issues:

- The outcome measures in the RCTs (and other studies) are clinical – wound healing, pain and so on. Quality of life is not measured in the studies. This means that a model has to be created to link trial results and the results of separate studies describing the relationship between wound characteristics and quality of life.
- Follow up is short in the above studies. Not only does this have implications for measures of effectiveness but also for cost since there is no tally of resource use that might provide, for example, a measurement of follow up visits required as a result of any positive long term benefit of MIST. In addition there is no measurement of (any) reduction in the need for additional high technology or

expensive treatments such as regenerative medicine, free flap tissue grafts or amputations.

5.3 Results included in manufacturer's submission

The results of the model are reported in pages 97 to 104 of the manufacturer submission. The MIST treatment cost analysis showed that the average per-patient cost over 26 weeks was estimated to be £7254 in leg, diabetic and pressure ulcers (section 6.4.6, page 92). Depending on the type of ulcer, the manufacturer calculates that this equates to an annual cost saving per patient of between £1935 and £3297 when compared to conventional treatment.

The results section of the submission mainly comprised tables with no explanation surrounding these. The base case results are given in Table B17, section 6.6.3 of the submission. However, the manufacturer has not listed the interventions and comparator(s) from least to most expensive as required by NICE.

5.4 Comment on validity of results presented with reference to methodology used

The evaluation report deals with the issues as outlined:-

5.4.1 Overview

The report identifies three papers dealing with health economic issues. Appendix 6 gives the data-bases searched and limits used. It is not clear how the relevant articles were then identified from all papers returned.

Three relevant articles are identified and discussed. No notice whatever is taken of the above points about the fragility of the effectiveness parameters, yet more than half of the 133 page report is devoted to health economic issues. Given the fragile, poorly calibrated effectiveness measure, this lengthy analysis must be regarded as a castle built on sand. The report is also very difficult to read, perhaps because of the restrictive nature of the reporting template.

5.4.2 Studies identified

The three studies identified were:

- [redacted]

- Study 2E, Anaeme et al, 2009 [27] is based on a case series. Moreover, the series consisted of only 5 cases. Patients had (quite properly) been given other treatments apart from MIST. In my opinion use of this study design to calculate cost effectiveness is risible but no scepticism is expressed. That said, it is possible to complete the pro-forma without divulging this obvious flaw.

- Study 3E, *de novo* cost model, 2010, (section 6.2, manufacturer submission). The description of the method is not easy to understand but effectiveness is calibrated in terms of average time to healing across a series of papers with completely different study designs. A mean difference of 14 weeks in time to healing is derived. Most ulcers in the RCTs had not healed completely, so this is an extremely uncertain parameter. Again massive savings are claimed, but this is inevitable, given the effectiveness parameter assumed.

5.4.3. De novo cost and subsequent analyses

The report does not attempt to justify this analysis (section 6.2.1, manufacturer submission). This justification could have been made on many sound bases:

- Sensitivity analysis to cover less 'penicillin like' effect sizes
- The need to include a broader spectrum of ulcer types.
- Longer term modelling with sensitivity analyses.

The analysis does, in the event, cover different ulcer types. The authors provide a breakdown of NHS costs per year in treatment across all ulcer types. They then sensibly break these ulcers down into hard to heal categories (where MIST would apply) and estimate cost by ulcer type. This is all very reasonable but they run into trouble when they calculate cost-effectiveness, because they base this on the idea that "clinical studies have shown improved healing rates at twice the speed and half the time of traditional treatments". This is an unjustified statement given the above caveats.

They extrapolate further, without providing any intellectual basis, and claim an heroic 26 week average difference in duration of required treatment. They do not seem to have included possible extra visits – in some of the studies patients who would only have attended 2 times per week were asked to come 3 times per week. This might normally be a significant point, but in this study, it is dwarfed by the effectiveness assumptions.

To take the effectiveness estimate from Driver's meta-analysis [25] where all patients were compared before and after care (that included but was not confined to MIST therapy) renders these conclusions, worthless.

There follows a long series of specific questions, such as how expert advisers were selected, on which further comment would be possible. However, such an exegesis risks deflecting attention from the main problem. The sensitivity analyses requested in the form provided an opportunity to test their

conclusions over a wide range of less heroic yet plausible effectiveness estimates. This was not done. Instead they went in the opposite direction using a case series by Bell et al [3], which does not even have retrospective controls. This yields an obvious over-estimate since its use in a model implies implausibly that none of the patients who healed after the MIST Therapy treatment would otherwise have done so.

5.5 Summary of uncertainties and issues

This evaluation report is unreliable for the reasons indicated.

None of this means that MIST is not effective or, indeed, not cost-effective.

MIST has a plausible theoretical rationale based on in-vitro and in-vivo biological studies.

All results (save the intention to treat analysis on Ennis' RCT) are positive, and it appears not to have harmful effects.

It is thus a priori likely that it is effective (although it is unlikely that it is as effective as claimed).

It is not a costly treatment as it can (mostly) be given at the time of dressing changes. Any effectiveness cuts down suffering, the cost of repeat visits and more extreme therapies (including major surgery) and patient costs.

Therefore it is likely to prove cost-effective, even if the magnitude of (any) effect is rather small.

I recommend a short term and a long term solution.

Short term - a Bayesian estimate of effectiveness based on a global assessment of the evidence should be used to inform an economic analysis. Sensitivity analysis should be performed across a composite 'prior' - a prior in which individual expert priors are consolidated.

Long term - the HTA programme should be asked to consider sponsoring a trial forthwith.

6 Additional work undertaken by the External Assessment Centre

Provide rationale for undertaking additional work, description of methods and results.

- Additional literature search in order to investigate the reliability of the manufacturer's literature searches used to identify the clinical data. Details of these are provided in Section 4.1.2, along with a detailed critique of the literature searches in Sections 4.1.1 and 5.1.1.
- Search FDA, MAUDE for adverse events related to MIST Ultrasound Therapy.
- For cost-effectiveness and cost evaluations, the manufacturer's submission included a search of the pubmed.gov, US National Library of medicine, and National Institute of Health databases. Additional literature searches were conducted in Medline, Medline (R) In process, Embase, Cochrane Library, Cochrane Wounds Group and CINAHL databases.
- Comments have been provided alongside the manufacturer's clinical appraisal of the included effectiveness studies (section 4.1.3, Table 2).
- In the manufacturer's submission, the list of future ongoing studies using the MIST Therapy System, from which evidence is likely to be available in the next year, included studies presented at Wounds UK conference, Harrogate, November 2010. The EAC were able to obtain the PowerPoint presentation and the three posters to assess the data from the UK perspective [21-24]. The findings were similar to those reported in studies conducted in the USA.

7 Discussion

7.1 Summary of clinical effectiveness issues

The literature search for the clinical effectiveness studies relating to MIST Therapy System for chronic “hard to heal” wounds was restricted only one database (PubMed.gov), but this database would be expected to include all relevant literature.

The included studies on which the clinical effectiveness was based were all conducted in the USA with all or some funding provided by Celleration Inc. However, there is no reason why the results would not be transferrable in the UK given that the standard treatments are similar as are the types of ulcer and comorbodities. Of all the submitted evidence, only two are RCTs and both have methodological weakness. The remaining non-randomised and mostly uncontrolled studies cannot provide reliable estimates of treatment effects. Therefore there remains significant uncertainty with regard to the clinical effectiveness of the MIST Therapy system.

Not all of the outcomes outlined in the NICE scope were addressed in the studies considered in the meta-analysis *e.g.* quality of life and bioburden.

7.2 Summary of cost issues

MIST has a plausible theoretical rationale based on in-vitro and in-vivo biological studies.

All results (save the intention to treat analysis on Ennis’ RCT) are positive, and it appears not to have harmful effects.

It is thus a priori likely that it is effective (although it is unlikely that it is as effective as claimed)

It is not a costly treatment as it can (mostly) be given at the time of dressing changes. Any effectiveness cuts down suffering, the cost of repeat visits and more extreme therapies (including major surgery) and patient costs.

Therefore it is likely to prove cost-effective, even if the magnitude of (any) effect is rather small.

It is recommended that in the:

- **Short term** - a Bayesian estimate of effectiveness based on a global assessment of the evidence should be used inform an economic analysis. Sensitivity analysis should be performed across a composite 'prior' - a prior in which individual expert priors are consolidated.

- **Long term** - the HTA programme should be asked to consider sponsoring a trial forthwith.

7.3 Implications for guidance and research

The submission has presented evidence that suggests the MIST Therapy System is an effective and cost effective treatment that promotes healing of chronic and acute "hard to heal" wounds. However, critical appraisal of the submission reveals some weakness and limitations in the evidence.

Further more robust, multicentre studies with large sample size are needed to determine the clinical effectiveness and cost benefits of using Ultrasound MIST therapy compared to standard of care. It would also be useful to conduct subgroup analysis to assess whether MIST Therapy reduces antibiotic prescribing, pain and improves quality of life.

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