NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Evaluation Pathway Programme assessment

Specification for manufacturer/sponsor submission of evidence

March 2010

Contents

List of tables and figures

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

Instructions for manufacturers and sponsors

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

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

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

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

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

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

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

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

Section A – Decision problem

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

1 Description of technology under assessment

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

moorLDI2-BI Burn wound assessment Imager. There are at present no different versions of this device which are CE marked as a medical device for burn wound assessment.

What is the principal mechanism of action of the technology?

The moorLDI2-BI includes a scan head, scan controller and a touch-screen panel computer, all mounted on a mobile stand that can be used in the ward, operating theatre, consulting room or special laser room. The scanner is mounted on a flexible arm and linked to the computer which has a bespoke software package with modules for imaging, storage, review and analysis.

In laser Doppler blood flow imaging, a low power Helium-Neon red laser beam is directed at the burn wound via a mirror. It is scanned in raster fashion across the burn area by rotating the mirror about vertical and horizontal axes. There is no direct contact with the tissue being assessed. Penetration depth is the full dermis. Laser light scattered from moving blood cells in the tissue undergoes a Doppler frequency shift, the average frequency shift being proportional to the average speed of the blood cells. Some of the scattered laser light is collected by the mirror and then focussed, by light-collecting lenses, on photodiode detectors. The resulting photocurrent is processed to calculate the blood flow in the tissue and this information is displayed as a colour-coded map of the wound area. Burn wound sizes from small (part of a

finger) to large (torso) can be mapped in this way. The scan takes from 80s to about 5 minutes depending on the size and required resolution of the wound.

Results are displayed as a colour-coded blood flow image and a colour video image of the burn wound. Healing potential results are also reported in three categories < 14 days, 14-21 days and > 21 days.

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

moorLDI2-BI was CE marked in 2003.

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

Not applicable. All CE marking is current and there are no special conditions.

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

moorLDI2 Burns Imager is CE marked as a burn wound assessment imager.

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

moorLDI2-BI relevant presentations at the next ANZBA meeting which Moor Instruments will attend. (Darwin, Australia 5-8 Oct, 2010.) Abstracts of the presentations are available. Publication in a journal is probable within the next 12 months.:

The effect of correct first aid treatment on the vasculature and cells within a burn
*Dr Leila Cuttle *, Ms Margit Kempf, Ms Pei-Yun Liu, Dr Gael Phillips, Dr Xue-Qing Wang*

Clinical relevance of Laser Doppler Imaging in adult burns
*Dr S R Jayalath, Dr Aruna Wijewardana *, Mr Peter Campbell, Dr John Vandervord*

MoorLDLS-B1 trial against MoorLDI2-B1 for burn wound depth assessment
*Ms Diane Ward *, Dr Queenie Chan, Dr Eric La Hei, Dr John Harvey, Prof Andrew Holland*

Ultrasound Assessed Thickness of Burn Scars In Association With Laser Doppler Determined Depth of Burns In Paediatric Patients
*Dr Xue-Qing Wang *, Julie Mill, Dr Olena Kravchuk, Prof Roy Kimble*

Papers submitted for publication in Burns Journal:

Pape SA, Baker RD, Wilson D et al.(Pre-publication). Burn wound healing time assessed by laser Doppler imaging (LDI) Part1: derivation of a dedicated colour code for image interpretation

Monstrey S.M, Hoeksema H, Baker R.D. et al (Pre-publication). Burn wound healing time assessed by laser Doppler imaging (LDI) Part2: Validation of a dedicated colour code for image interpretation

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

moorLDI2-BI Burns Imager is already used with the NHS.

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

moorLDI2- BI is registered with the FDA (510K K060976) and with Canada Health (Licence no. 75477) for use as a burn wound assessment imager

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

Table A1 Unit costs of technology being appraised

List price (excluding VAT)	
Annual lease price (assumes minimum lease period 2 years)	£22,000.00
selling price	£50,000.00
Consumables (if applicable) Per consumable: name, list price, average/range selling price, frequency	No consumables
Service/maintenance cost and frequency (if applicable)	Annual service and maintenance. Cost of service and maintenance plus all call out charges plus 1 group training course included in the lease fee. If the system is purchased the annual cost of service and maintenance including all call out charges is £8,000
Anticipated life span of technology	10 years
Average length of use per treatment	Preparing and setting instrument scan conditions approximately 20 minutes. Patient scanning time is in the range 1 to 5 minutes. Data insertion 5 minutes Image interpretation typically 15 minutes.
Average frequency of use	2 scans per patient day 2 or day 3 post burn.
Average cost per treatment	Assuming 250 scans per year then cost per scan per leased system is £88.00 This does not include the (hospital) operator's salary and hospital overheads cost.

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

This technology is an aid to decision-making and its use would not change the way current services are organized and delivered.

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

No other additional technologies or facilities need to be acquired or used alongside this technology.

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

No tests or investigations additional to usual clinical practice are required for patient selection and there are no particular administration requirements.

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

This device is an imager used to aid decision-making.

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

No additional infrastructure is required for use of moorLDI2-BI Burns Imager.

2 Context

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

This imager has been designed specifically for use with burns patients. In particular for patients admitted to hospital with burn wounds of mixed depth who require assessment of their wounds to support the choice of wound dressings and to decide which burn areas are deep enough to require grafting.

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

In the United Kingdom, about 175 000 people attend accident and emergency departments each year with burns from various causes. This represents about 1% of all emergency department admissions. Approximately 16,000 burns patients (40% children) are admitted to hospital each year and about 1000 of them need active fluid resuscitation. The number of burns related deaths average 300 a year. The source for this data:

National Burn Care Review Committee (Chairman Ken Dunn) Standards and Strategy for Burn Care Chapter 3, Sections 8 and 9, page 22.

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

No NICE guidance has been issued relating to the identification of burn depth and healing potential.

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

The technology is primarily relevant to the improvement of treatment decisions for patients with intermediate level burns. The moorLDI2 Burns Imager can be used 48-72 hours post-burn to identify the healing potential for individual burn wounds. This information can be used to develop an appropriate burn treatment plan.

The assessment of burn depth is a key decision that needs to be made in burn care treatment. However especially at the early stage it is difficult to distinguish the more superficial dermal burns which will heal well from deep dermal burns where a prolonged healing time will result in hypertrophic scarring. The diagnosis of burn depth is particularly difficult in children due to the prevalence of mixed depth scald burns, children's thin skin and their unpredictable response to injury. Strict categorization of burn depth is complicated by burn wound conversion where superficial burns may progress into deeper wounds due to progressive death of severely injured cells, oedema and tissue hyoxia.

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

Current clinical practice is divided between surgeons who prefer early excision and grafting and other surgeons who prefer more conservative early management. A problem with early surgery of intermediate thickness wounds is that decisions to graft, based on clinical assessment alone are wrong in a significant number of cases. On the other hand, conservative management will frequently delay surgery for patients with deeper burns that are not diagnosed by clinical assessment; this results in more, unnecessary and painful dressing changes.*

Best practice for the clinical assessment of burn wounds is not described; the accuracy of clinical assessment depends largely on individual experience.

> * '*Clinical examination correctly determined 66% of deep partial or full thickness burns between 36 and 72 h of injury compared to 90% using LDI. The LDI was also more specific; correctly diagnosing 96% of superficial partial thickness burns as opposed to 71% on clinical examination.'*
> *(Laser Doppler imaging prediction of burn wound outcome in children Burns 28 (2002) 11–171; A.J.A. Holland, H.C.O. Martin , D.T. Cass)*

* *'The accuracies of burn depth assessments with LDI at days 0, 1, 3, 5 and 8 were 54.8%, 79.5%, 95%, 97% and 100% compared with the accuracies of clinical assessment alone of 40.6%, 61.5%, 52.5%, 71.4% and 100%, Based on the results of this study we recommend that ideally, all burns of intermediate depth should be analyzed with a combination of both LDI scanning and clinical evaluation. This combination of diagnostic techniques has shown to be more accurate than either technique alone in ensuring early appropriate management of the burn wound by avoiding unnecessary surgery and therefore reducing mortality, hospital stay and costs.'*
(Accuracy of early burn depth assessment by laser Doppler imaging on different days post burn; Burns 35 (2009) 36 – 45
*Henk Hoeksema *, Karlien Van de Sijpe, Thiery Tondu, Moustapha Hamdi,)*

* '*This audit confirmed that, in Caucasian adults, this scientific method is more accurate than clinical judgement in the assessment of burn depth. By using the LDI, the accuracy of burn depth assessment was found to be 97%, compared with 70% by clinical assessment alone.'*
(An audit of the use of laser Doppler imaging (LDI) in the assessment of burns of intermediate depth; Burns 27 (2001) 233–239; Sarah A. Pape, Costas A. Skouras, Phillip O. Byrne)

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

Clinical evaluation is the most widely used method of assessing burn wound depth. This method is based on the subjective, visual and tactile assessment of the external characteristics of a burn wound. The accuracy of this method relies almost entirely on the experience of the doctor.

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

Potential adverse events include damage to the retina of a patient not wearing the recommended eye protection and staring into the non-moving laser beam. This can only happen under an instrument fault condition. The eye is protected by blink reflex. All operators are trained in laser safety to avoid this occurrence and an additional factor is that the eye blink reflex provides some protection. No adverse events have been reported for this technology.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff

usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

The main resource use to the NHS associated with the moorLDI2-BI is with the system operation. Operators (generally nurses, healthcare assistants, physiotherapists, medical physics personnel etc) need to be specifically trained to operate the system effectively and safely. This training and assessment of competency requires 2 days of their protected time. There is also an aspect of training which relates to the safe and correct interpretation of the image in relation to diagnosis. This requires an additional 1 day of training plus mentoring by an experienced user. Interpretation is done by an experienced clinician assessing the burn wound blood flow image in combination with his/her clinical judgement.

The costs associated with the delivery of the training are included in the sale/lease price of the system. This however does not take into account hospital staff time into account and the costs that may be associated with this.

The location of the imaging will be on the wards, in theatre, out-patients dept – anywhere it is required, as it is a fully mobile system. Staff could be using the system as frequently as daily, depending on the number of patients admitted.

Administrative costs should be low as patient information, data and images are all stored internally within the system pc database and images are assessed on-site by clinicians. Scan reports are printed out by the operator and included in the patient file. External evaluation of images is not required assuming trained staff are available. Patient letters specifically related to the burns images do not have to be sent out.

Other costs to consider are the electricity required to power the system (less than 200W) and the colour ink for the printer. The combined cost of these is estimated to be less than £300 per year. If the moorLDI2-BI is networked with a specialist digital imaging database such as DICOM (Digital Imaging and Communications in Medicine) the associated administrative and IT costs would need to be taken into account.

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

There are no other significant costs

3 Equity and equality

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

3.1 Identification of equity and equalities issues

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

None identified

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

No equality and diversity issues have been identified.

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

Not applicable

4 Statement of the decision problem

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

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Patients with intermediate level burns		
Intervention	moorLDI2-BI Burn wound assessment Imager		
Comparator(s)	Clinical assessment of burns biopsy, ultrasound, injection of vital dyes to stain living tissue, fluoroscein injection, thermography	Other techniques, other than clinical assessment, are either invasive (biopsy, injection of dyes or fluoroscein) or only sample a small part of the burn (biopsy, ultrasound), or outputs require more expert interpretation (biopsy, ultrasound), or are not accurate (e.g. convection cooling effect on thermography).	Clinical assessment is the only other technique used routinely in most burn centres. Other techniques are not considered to be practical for routine use in their current form.
Outcomes	Burn depth and healing potential within 14 or 21 days. Sensitivity, specificity, positive predictive value, negative predictive value of wound healing potential before 14 or 21 days. Length of hospital stay, number of operations and their duration, number of dressing changes, wound complications	Prediction of healing time: within 14 or 21 days or not healing within 21 days. Burn depth is not an outcome but it is recognized that burn depth strongly influences healing time. No change to other areas of scope.	Skin blood flow assessed by LDI enables healing time prediction regardless of age, burn site, %TBSA etc. Burn depth is not a functional assessment and is not independent of these parameters.
Cost analysis	Comparative cost analysis of the use of moorLDI2 –BI Burn wound assessment Imager with clinical assessment and the use of clinical assessment alone for decision-making in the treatment of burn wounds. Cost analysis should account for hospital and clinic care, staff training, long-term burn management and other relevant costs.	Cost minimization analysis is proposed.	Data is not readily available for QALY analysis. Most benefits are in the early, treatment phase. Active scar management treatment and care costs, required after skin grafting, can be significantly reduced when inappropriate surgery is prevented
Subgroups to be considered	None identified		
Special considerations, including issues related to equity or equality	None identified		

Section B – Clinical effectiveness and cost

5 Clinical evidence

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

5.1 Identification of studies

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

Moor Instruments continuously review the clinical literature related to burn depth assessment and use of the moorLDI2-BI Laser Doppler Imaging for this assessment.

Searches for literature are conducted in accordance with MEDDEV (2.7.1 Dec 2009, 2007/47/EC amending 93/42/EEC).

This review reflects the ongoing process of Moor Instruments Ltd to continuously search and evaluate both published and unpublished. Literature related to the clinical use of Laser Doppler Imaging in burn depth assessment and other related clinical fields.

The availability of published independent clinical studies has further advanced the clinical evidence available.

5.2 Study selection

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

Table B1 Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	Population – Burn Injuries Interventions – Laser Doppler Imaging of burn wounds with CE Marked 510K FDA Equipment. Outcomes – any of the following: time to healing, scarring, length of stay, cost reduction, time to surgery, treatment decision Study design – audits, clinical studies, pilot studies, observational studies, cohort study, statistical studies Language restrictions – English Level of results available – fully published articles in the press
Exclusion criteria	Population – Non-burn injuries Interventions – non-use of Laser Doppler Imaging, use of Laser Doppler Imagers without CE marking/510K FDA. Outcomes – Other than those listed above Study design – None Language restrictions – Languages other than English Level of results available – unpublished audits and posters

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

21 relevant studies are included of which 19 are clinical observational studies, one is an experimental study and one study presents an extensive statistical analysis of a clinical study. 10 of the studies were published in peer reviewed journals, and another is in press. These 11 studies are included in our review. The remaining 10 studies, excluded from our review, are published as

abstracts of oral or poster presentations at national and international burns meetings.

All 21 studies are referenced in table B2.

See appendix A for a full bibliography.

5.2.3 Provide details of **all** studies that compare the intervention with other therapies in the relevant patient group. Highlight which of these studies compare the intervention directly with the appropriate comparator(s) referred to in the decision problem. If there are none, please state this. The list must be complete and will be validated by independent searches conducted by the External Assessment Group. This should be presented in tabular form. A suggested format is presented below.

Table B2 List of relevant studies

Study no. (acronym)	Intervention	Comparator	Population	Primary study ref.
1 Hoeksema *et al* INCLUDED	Laser Doppler Imaging	Laser Doppler Imaging and Clinical assessment	Intermediate burns	Burns, 2009, 35, 36 - 45
2 Mill *et al* INCLUDED	Laser Doppler Imaging	Laser Doppler Imaging and wound outcome	Paediatric burns	Burns 2009,35, 824, 831
3 Brown *et al* INCLUDED	Laser Doppler Imaging	Laser Doppler Imaging and Histology	Vesicant burns	Burns 1998, 24, 692-698
4 Kim *et al* INCLUDED	Laser Doppler Imaging	Laser Doppler Imaging and clinical assessment	Burns	J.B.C.R 2010 March/April, 328-332
5 Pape *et al* INCLUDED	Laser Doppler Imaging	Laser Doppler Imaging and Clinical assessment and biopsy	Intermediate burns	Burns 2001, 233 - 239
6 Holland *et al* INCLUDED	Laser Doppler Imaging	Laser Doppler Imaging and Clinical examination	Paediatric burns	Burns 2002, 28, 11 – 17
7 Niazi *et al* INCLUDED	Laser Doppler Imaging	Laser Doppler Imaging, Clinical assessment and Histology	Burns	Burns 1997, 19(6) 485 – 489
8 La Hei *et al* INCLUDED	Laser Doppler Imaging	Laser Doppler Imaging and clinical outcome scarring	Burns	Burns 2006, 32, 550 - 553
9 Monstrey *et al* 1 INCLUDED	Laser Doppler Imaging	Laser Doppler Imaging and healing wound	Burns	Burns, in press
10 Baker *et al* INCLUDED	Statistical analysis of Monstrey et al 1	Laser Doppler Imaging and healing wound	Burns	BMC Med Res Meth 2009, 9:11.
11 Jeng *et al* INCLUDED	Laser Doppler Imaging	Laser Doppler Imaging and Clinical assessment	Burns	Burns 2003, 29, 665 - 670
12 Bargues *et al*	Laser Doppler Imaging	Laser Doppler Imaging and	Burns	EBA 2007

Excluded		Clinical score		Poster BP7
13 Banwell *et al* Excluded	Laser Doppler Imaging	Laser Doppler Imaging, Clinical assessment and Histology	Burns	2nd Annual meeting EC SAPS
14 Banwell *et al* Excluded	Laser Doppler Imaging	Laser Doppler Imaging and Clinical assessment	Burns	British Trauma Society poster
15 Holland *et al* Excluded	Laser Doppler Imaging	Laser Doppler Imaging and Clinical Assessment	Paediatric burns	ANZBA 2001 poster
16 Jeng *et al* Excluded	Laser Doppler Imaging	Laser Doppler Imaging and Clinical assessment	Burns	ABA 2001 poster S72
17 La Hei *et al* Excluded	Laser Doppler Imaging	Laser Doppler Imaging and outcome	Paediatric burns	ANZBA 2002 poster
18 Monstrey *et al* 2 Excluded	Laser Doppler Imaging	Laser Doppler Imaging and healing wound or biopsy	Burns	9th EBA 2001 No.97 poster
19 Monstrey *et al* 3 Excluded	Laser Doppler Imaging	Laser Doppler Imaging and clinical assessment	Burns	12th ISBI 2004 No.143 poster
20 Pape *et al* Excluded	Laser Doppler Imaging	Laser Doppler Imaging and Clinical assessment	Burns	BBA 1998
21 Spence *et al* Excluded	Laser Doppler Imaging	Laser Doppler Imaging, Clinical assessment and outcome	Burns	27th Mid Atlantic Burn Congress 2004 presentation

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

Bargues *et al* (2007)

Available as a poster only. They concluded that Laser Doppler Imaging seemed more accurate and reliable than clinical assessment even using a comprehensive score, and that Laser Doppler based surgical indications were that it could help to avoid overgrafting and was valuable for burn depth diagnosis.

This work has not been peer reviewed or published and has insufficient data available to asses the decision problem.

Banwell *et al* (1998)

Available as an abstract only. The study confirmed that Laser Doppler is a valuable tool for the measurement of burn depth and has a high predictive power at 48 hours regarding the need for surgery. It was also concluded that Laser Doppler Imaging is a rapid non-contract method of assessing large areas with varying burn depth and can be used to provide an accurate surgical map of the burn wound.

This work has not been peer reviewed or published and has insufficient data available to asses the decision problem

Banwell *et al* (1998)

Available as a poster only. The study confirmed that Laser Doppler is a valuable tool for the measurement of burn depth and has a high predictive power at 48 hours regarding the need for surgery. It was also concluded that Laser Doppler Imaging is a rapid non-contract method of assessing large areas with varying burn depth and can be used to provide an accurate surgical map of the burn wound.

This work has not been peer reviewed or published and has insufficient data available to asses the decision problem

Holland *et al* (2001)

Available as an abstract only. They concluded that Laser Doppler Imaging appears to accurately and reliably predict burn wound outcome in children.

This work has not been peer reviewed or published and has insufficient data available to asses the decision problem

Jeng *et al* (2001)

Available as an abstract only. The authors concluded that Laser Doppler Imaging allowed for earlier, objective determination of need to operate. Concurrence with clinical judgement in this blended study was excellent. Laser Doppler Imaging should be seen as an effective aid to clinical judgement when contemplating excision of burns with intermediate depth.

This work has not been peer reviewed or published and has insufficient data available to asses the decision problem.

La Hei *et al* (2002)

Available as an abstract only. The authors concluded accurate predictions of burn wound out come can be made via the standard information generated by the Laser Doppler Imaging.

This work has not been peer reviewed or published and has insufficient data available to asses the decision problem.

Monstrey *et al* (2001)

Presented here as an abstract from a conference. The authors concluded that Laser Doppler Imaging is not reliable during the acute phase of a burn wound. However, between days 3 and 5 the accuracy of burn depth could be substantially improved with Laser Doppler Imaging scanning: 93.3% - 96.6% versus 61% - 67% by clinical evaluation only. It is concluded from this study that Laser Doppler Imaging is a useful tool in determining the most appropriate and cost-effective treatment of dermal burn wounds.

Full publication was later published in a peer reviewed journal (Hoeksema et al 2009 and is included). This abstract is excluded from further discussion.

Monstrey *et al* (2004)

Presented and available as an abstract only. This study concluded that Laser Doppler Imaging has become an essential tool to predict whether a better functional or aesthetic outcome can be obtained by early surgery or conservative therapy.

This work has not been peer reviewed or published and has insufficient data available to asses the decision problem.

Pape *et al* (1998)

Presented here as an abstract from a conference. The authors state that the audit performed by them concluded that Laser Doppler Imaging is a very useful tool for the assessment of burn wound depth and the planning of treatment.

This was later published as a full paper in a peer reviewed journal (Pape et al 2000). This abstract is therefore excluded from further discussion.

Spence *et al* (2004)

Presented as an abstract from a conference presentation only. This study concluded that Laser Doppler Imaging is the favourable performance in facilitating burn depth assessment. As a result of this study Laser Doppler Imaging has become a routine clinical tool in their own burn centre, helping to make clinical decisions on mid dermal and otherwise intermediate depth burn wounds. The statistical analyses of data from this study have been published in a peer reviewed journal (Baker et al 2009) and 2 further publications have been submitted for publication (accepted with minor corrections).

5.3 Summary of methodology of relevant studies

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

Methods

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

Table B3 Comparative summary of methodology of the studies

Study no. (acronym)	**Hoeksema 2009**	**Mill *et al* (2009)**
Location	Department of Plastic Surgery, Gent University Hospital, Gent, Belgium	Royal Children's Hospital, University of Queensland, Australia
Design	Non-randomised cohort	Observational clinical Study
Duration of study	12 months	Unknown: A total of 48 patients with 85 burns were included
Method of randomisation (if applicable)	n/a	n/a
Method of blinding (care provider, patient and outcome assessor) (if applicable)	Clinical evaluation performed by 2 observers blinded to the Laser Doppler Images.	None
Intervention(s) (n =) and comparator(s) (n =)	Interventions = Laser Doppler Imaging Comparator = Biopsy and Clinical assessment	Interventions = Laser Doppler Imaging Comparator = Time to re-epithelisation (days)
Primary outcomes (including scoring methods and timings of assessments)	Compare changing accuracies of LDI and clinical judgement during the important early days post burn. Depth determined by biopsy for surgically treated wounds. Conservatively treated wounds – if complete healing needed less than 21 days, it was considered superficial. If healing needed more than 21 days it was considered deep dermal.	1. Healing, time to re-epithelisation (in days) 2. Laser Doppler Imaging scan colours dark blue, light blue, green, yellow, pink/red.
Secondary outcomes (including scoring methods and timings of assessments)	N/A	Scar management = number of wounds requiring active scar management.
Duration of follow-up	To healing or grafting (whichever was first)	Until scar management was assessed.

Study no. (acronym)	**Brown *et al* (1998)**	**Kim *et al* (2010)**
Location	Biomedical Sciences Department, Salisbury District Hospital, Salisbury, UK	Children's Hospital Burns research Institute and Burns Unit, New South Wales severe burn injury service, The children's hospital at Westmead, NSW, Australia
Design	Pilot Study	A prospective, non-randomised cohort study
Duration of study	N/A	19 months
Method of randomisation (if applicable)	N/A	None
Method of blinding (care provider, patient and outcome assessor) (if applicable)	N/A	N/a
Intervention(s) (n =) and comparator(s) (n =)	Laser Doppler Imaging and Histology	Laser Doppler Imaging and Clinical assessment
Primary outcomes (including scoring methods and timings of assessments)	Histology	Decision for surgical intervention, timing of operative intervention.
Secondary outcomes (including scoring methods and timings of assessments)	N/A	Microbiological culture swabs
Duration of follow-up	7 days	Time to decision making.

Study no. (acronym)	**Pape *et al* (2001)**	**Holland *et al* (2002)**
Location	Royal Victoria Infirmary, Newcastle Upon Tyne, UK	Division of Surgery, The Children's Hospital at Westmead, Royal Alexandra Hospital for Children, Sydney, Australia
Design	Audit, Prospective	Observational pilot study
Duration of study	6 months	10 months
Method of randomisation (if applicable)	n/a	n/a
Method of blinding (care provider, patient and outcome assessor) (if applicable)	n/a	1st Author performed and interpreted Laser Doppler Imaging scans whilst blinded to clinical assessment. Medical, and nursing staff, caring for patient were blind to Laser Doppler Imaging scans.
Intervention(s) (n =) and comparator(s) (n =)	Intervention – Laser Doppler Imaging Comparator – Clinical assessment and biopsy	Intervention – Laser Doppler Imaging Comparator – Healing time in days
Primary outcomes (including scoring methods and timings of assessments)	Time to healing within 21 days. Biopsy – Histological classification of burn depth. Laser Doppler Imaging – High= superficial dermal burn, Low = deep dermal burn.	Healing by day 12, or after day 12.
Secondary outcomes (including scoring methods and timings of assessments)	None	Moderate degrees of movement on scan accuracy
Duration of follow-up	6 weeks after date of injury	12 days

Study no. (acronym)	**Niazi *et al* (1993)**	**La Hei *et al* (2006)**
Location	Newcastle General Hospital, Newcastle Upon Tyne, UK	Burns Unit, The Children's Hospital at Westmead, University of Sydney, NSW, Australia
Design	Pilot study	Blinded audit
Duration of study	13 patients out of 347 were included during June 1990 – February 1992.	6 months
Method of randomisation (if applicable)	n/a	n/a
Method of blinding (care provider, patient and outcome assessor) (if applicable)	Unknown	Both reporters 'blinded', never visualising the burn wound or having direct patient contact
Intervention(s) (n =) and comparator(s) (n =)	Interventions – Laser Doppler Imaging Comparator – Clinical assessment and Histology	Interventions – Laser Doppler Imaging Comparator – Clinical assessment
Primary outcomes (including scoring methods and timings of assessments)	Healing within 21 days – A = healed with stable epithelium B = healed with unstable epithelium C = remains unhealed D = grafted and healed E = grafted. No take of grafts F = grafted. Partial take of grafts. Histology and clinical assessment – Epidermal, superficial dermal, deep dermal, full thickness.	Prediction of burn wound outcome
Secondary outcomes (including scoring methods and timings of assessments)	None	n/a
Duration of follow-up	21 days	To complete epithelialisation of burn wound.

Study no. (acronym)	**Monstrey *et al* (In press)**	**Baker *et al* (2009)**
Location	Gent, Belgium; Baltimore, USA; Washington, USA; Nottingham, UK; Newcastle upon Tyne, UK.	Salford, UK; Gent, Belgium; Baltimore, USA; Washington, USA; Nottingham, UK; Newcastle upon Tyne, UK.
Design	Multi-centre observational study	Statistical analysis of a multi-centre observational study
Duration of study	1 year	n/a
Method of randomisation (if applicable)	Not applicable	n/a
Method of blinding (care provider, patient and outcome assessor) (if applicable)	Treatment blinded to LDI scans where LDI not in routine use. LDI scan assessors blinded to clinical outcome.	n/a
Intervention(s) (n =) and comparator(s) (n =)	Intervention, LDI (n = 433); comparator, wound healing (n = 433).	n/a
Primary outcomes (including scoring methods and timings of assessments)	Wound healing at 14 and 21 days and 5-point scoring of accuracy and usefulness of LDI images	Accuracy of LDI prediction of wound healing at 14 and 21 days.
Secondary outcomes (including scoring methods and timings of assessments)	Influence of other parameters on LDI prediction of wound healing at 14 and 21 days	Influence of other parameters on LDI prediction of wound healing at 14 and 21 days
Duration of follow-up	21 days, earlier if grafted.	n/a

Study no. (acronym)	**Jeng *et al* (2003)**	
Location	Washington, USA;	
Design	Blinded trial	
Duration of study	Not known	
Method of randomisation (if applicable)	N/A	
Method of blinding (care provider, patient and outcome assessor) (if applicable)	Surgeon blinded to LDI scans prior to decision for surgery	
Intervention(s) (n =) and comparator(s) (n =)	Intervention, LDI (n=41); comparators, healing (n=20), biopsy (n=21).	
Primary outcomes (including scoring methods and timings of assessments)	Accuracy of decision to operate.	
Secondary outcomes (including scoring methods and timings of assessments)	N/A	
Duration of follow-up	Until healing or surgery	

Participants

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

Table B4 Eligibility criteria in the studies

Study no. (acronym)	Inclusion criteria	Exclusion criteria
Hoeksema *et al* (2009)	Admitted and adequately resuscitated Dermal burn wound Not obviously Full thickness or superficial 4 years or older and TBSA 2% or more	Have concomitant illness such as psychiatric disease, diabetes and other known vascular problems No informed consent
Mill *et al* (2009)	Children presenting at Stuart Pegg Paediatric burn centre Parents consented to study From 0 – 190 hours after burn injury Outpatients and inpatients	Any patients not fitting the inclusion criteria
Brown *et al* (1998)	Female, white pigs (body weight 22-28kg)	None other than the above
Kim *et al* (2010)	Patients who under went a skin grafting procedure for a burn wound at a single institution between June 2006 and December 2007	Presentation 5 days or more after date of injury Those requiring escharotomy Patients unable to be transported to the Laser Doppler Imaging room Patients with periorbital facial burns that could not be adequately shielded
Pape *et al* (2001)	Those burns in which the differentiation between superficial dermal and deep dermal involvement could not be made on observational grounds alone	Those not in the inclusion group
Holland *et al* (2002)	Children presenting within 72 hours of burn injury Parents consented	Those not presenting within 72 hours of burn injury No consent Patients with multi system trauma
Niazi *et al* (1993)	Less than 12% TBSA Burns sustained within 24 hours of admission Clinically doubtful burn depth or deep dermal burns as assessed at the time of admission Patients admitted at the 1st half of the week Signed consent	All children Patients with associated trauma Patients presenting with burns more than 24 hours old

La Hei *et al* (2006)	All inpatients and outpatients who presented within 3 days of injury between march 2002 and August 2002 had a Laser Doppler scan performed	Patients with facial burns in which the eyes could not be satisfactorily screened Patients with multi-system trauma
Monstrey *et al*, in press	Acute burn, treatment as inpatient or outpatient, patient or parent able to give informed consent	Patient unable to keep still or likely to become distressed during LDI scan; facial burns (if eyes cannot be protected from laser beam); burns more than 5 days old at presentation; patients who, in the opinion of the clinician would be exposed to excessive risk of infection or discomfort as a result of being scanned
Baker *et al* (2009)	Acute burn, treatment as inpatient or outpatient, patient or parent able to give informed consent	Patient unable to keep still or likely to become distressed during LDI scan; facial burns (if eyes cannot be protected from laser beam); burns more than 5 days old at presentation; patients who, in the opinion of the clinician would be exposed to excessive risk of infection or discomfort as a result of being scanned
Jeng *et al*, (2003)	Acute burns of indeterminate depth; informed consent from patient or next of kin.	Patients unable to keep still long enough for an adequate LDI to be obtained, patients susceptible to extra risk of infection or discomfort as a result of being imaged, patients with burns to the face who could not be protected from laser exposure to the eyes, patients whose injury occurred more than 48 h prior to consideration for enrolment, and patients with obviously superficial or obviously full thickness burns.
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee		

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

Of the 11 relevant studies 10 were performed on human subjects with intermediate depth burn wounds, and 1(Brown *et al*) used a pig model.

3 studies included adults only and, 4 studies included children only and 3 studies included both adults and children. The studies were not gender specific with the exception of Brown *et al* who used only female pigs.

All studies included both inpatients and out patients presenting with intermediate or indeterminate burn injury.

In the animal study conducted by Brown *et al*, female white pigs with a body weight of 22-28kg were used. In these cases burns were not accidental but were vesicant burns specifically inflicted to assess the use of Laser Doppler Imaging for burn assessment.

Outcomes

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

Table B5 Primary and secondary outcomes of the studies

Study no. (acronym)	Primary outcome(s) and measures	Reliability/validity / current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
Hoeksema *et al* (2009)	Depth determined by biopsy (surgically treated wounds) Healing by 21 days (conservatively treated wounds)	Reliable measurement as once considered gold standard in burn depth assessment. However, due to invasive nature of the procedure and heterogeneity of burn wound injuries this method is no longer practiced clinically. Commonly recognised amongst burn surgeons that complete re-epithelisation prior to day 21, considered as a 'healed wound' so is deemed valid and reliable.	n/a	n/a
Mill *et al* (2009)	Healing time in days, to re-epithelisation Laser Doppler Imaging scan colours	Commonly recognised amongst burn surgeons that complete re-epithelisation prior to day 21, considered as a 'healed wound' so is deemed valid and reliable. The scan colours used in this study are no longer valid as the software has been updated since the date of this study and is no longer clinically used. At the time of this	Scar management i.e. number of wounds requiring active scan management	Unreliable due to lack of supporting evidence, not used in clinical practice.

		study the palette used was valid and up to date, therefore this study is deemed reliable and valid		
Brown *et al* (1998)	Histology	Reliable measurement as once considered gold standard in burn depth assessment. However, due to invasive nature of the procedure and heterogenic nature of burn wound injuries this method is no longer practiced clinically.	n/a	n/a
Kim *et al* (2010)	Decision for surgical intervention – time between burn and operative intervention with Laser Doppler Imaging and without	There was significant reduction in time to grafting decision in Laser Doppler Imaging group. Laser Doppler Imaging is currently used clinically to determine need for surgery.	Microbiology culture swabs	Reliable and valid for wound infection detection and widely used in clinical practice
Pape *et al* (2001)	Time to healing days Biopsy, Histology classification of burn depth Laser Doppler Imaging perfusion: high = superficial dermal low = deep dermal	Commonly recognised amongst burn surgeons that complete re-epithelisation prior to day 21, considered as a 'healed wound' so is deemed valid and reliable. Reliable measurement as once considered gold standard in burn depth assessment. However, due to invasiveness of the	n/a	n/a

		procedure and heterogenic nature of burn wound injuries this method is no longer practiced clinically. Laser Doppler Imaging is reliable, valid and is currently widely used to determine wound healing potential in terms of days to healing.		
Holland *et al* (2002)	Healing by day 12, or after day 12	Commonly recognised by burn surgeons that complete re-epithelialisation by day 12 would be indicative of a superficial dermal burn wound.	n/a	n/a
Niazi *et al* (1993)	Healing by 21 days. Histology. Clinical assessment	Commonly recognised amongst burn surgeons that complete re-epithelisation prior to day 21, considered as a 'healed wound' so is deemed valid and reliable. Biopsy results deemed a reliable measurement as once considered gold standard in burn depth assessment. However, due to invasiveness of the procedure and heterogenic nature of burn wound injuries this method is no longer	n/a	n/a

		practiced clinically. Currently standard practice in burn assessment. Reliability and validity are questionable: clinical assessment is frequently quoted as between 60-78% accuracy.(see section 7 appendix B)		
La Hei *et al* (2006)	Prediction of time to heal by clinical assessment <14 days or >14 days. Prediction of time to heal Laser Doppler Imaging <14 days or >14 days.	Commonly recognised amongst burn surgeons that complete re-epithelisation prior to day 21, considered as a 'healed wound' so is deemed valid and reliable. Laser Doppler Imaging is reliable, valid and is currently widely used to determine wound healing potential in terms of days to healing.	n/a	n/a
Monstrey *et al,* in press	Accuracy and usefulness of complete LDI images with matching clinical photographs (5-point scale) Accuracy of healing potential prediction compared to actual healing	5-point scales are commonly used but entry is subjective so are of moderate reliability. All rules for LDI interpretation and confounding factors are defined therefore this study is highly valid. Complete epithelialisation is a reliable and valid	Assessment of the importance of patient age, burn cause and site, %TBSA and other parameters to determine the healing potential.	Standard statistical techniques were used therefore considered reliable and valid

	(from clinical notes and photos)	assessment of healing.		
Baker *et al* (2009)	Accuracy of LDI prediction of healing time independent of other parameters	Standard statistical techniques were used therefore considered reliable and valid	Influence of gender and high %TBSA	Objective statistical analysis, high validity.
Jeng *et al*, (2003)	To compare LDI with clinical judgment for determining need to operate. Biopsy assessment of wound grafted. Healing time.	A limitation of the study was that healing potential was inferred from biopsies that confirm depth at one point. Complete epithelialisation is a reliable and valid assessment of healing.	N/A	N/A

Statistical analysis and definition of study groups

5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew. The following table provides a suggested format for presenting the statistical analyses in the studies when there is more than one study.

Table B6 Summary of statistical analyses in studies

Study no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Hoeksema *et al* (2009)	Accuracy of early burn depth assessment by Laser Doppler Imaging on different days post-burn	Mann-Whitney U test A P valve of less 0.005 was considered significant	N = 40 Laser Doppler Imaging accuracy was significantly higher than clinical accuracy on day 3 ($p<0.001$) and day 5 ($p=0.005$)	None reported
Mill *et al* (2009)	Laser Doppler Imaging was compared to wound outcomes in children's burns to determine if the technology could be used to predict these outcomes	Mini tab software package was used. Logistic multiple regressions performed (binary or nominal regressions with the logit link function) Chi-square and exact fishers test were conducted where execution of logistics regression was not possible. Significance level was set at 5%.	N = 48	None reported
Brown *et al* (1998)	Can laser Doppler imaging be used as an aid in clinical management decision making in the treatment of vesicant burns	None stated	N=8	None stated.

Kim *et al* (2010)	To determine whether there was evidence that Laser Doppler Imaging in Paediatric patients led to earlier decision making of the need for operative intervention to ensure optimal burn wound healing.	Statistical analysis was performed using V10.0 software. Bivariate analyses were conducted to examine the associations among Laser Doppler Imaging scanning, other variables and time to surgery decision. Continuous variables either independent students t-tests or one way analysis of variance (one way ANOVA) were used for comparisons of means. For categorical data pear sans X^2 tests were applied. A significant level of 5% was used for all test of hypothesis.	N = 196 patients divided into 2 groups: those who underwent Laser Doppler Imaging and those who were only clinically assessed. There was no significant association confounding variables including age, gender, burn mechanism %TBSA and positive wound culture. There were logistical factors limiting the number of patients being scanned and Laser Doppler Imaging was achieved on slightly less than half of these patients (49%). There was a significant association between earlier decision for surgical interventions and those patients	None reported

			having Laser Doppler Imaging (p=0.01) A similar trend was noted between the 2 groups in relation to the ultimate of operative intervention with Laser Doppler Imaging patients having surgery an average 3 days earlier than those patients not scanned (p=0.004)	
Pape *et al* (2001)	To compare the accuracy of clinical assessment and laser Doppler imaging assessment of intermediate depth burns.	In group A, clinical review 21 days after injury showed that 41 (95%) had healed. Only 2 burns showed evidence of incomplete epithelialisation which were confirmed by microbiology as infected. Comparing clinical judgement with the measurement technique, the clinician correctly diagnosed burn depth in 30 cases and over estimated the depths in 13 cases (30%). In these cases, unnecessary	N=48. Patients were divided into 2 groups according to Laser Doppler Imaging assessment of burn depth: Group A related to superficial burns which were expected to heal within 21 days. Group b related to deeper burns requiring surgery.	In their audit, 4 additional burns were assigned to group A on the basis of their Laser Doppler Imaging scan in which the clinician decided to break the protocol. These burns had been diagnosed as deep on clinical grounds. The histology reports indicated that 2 were superficial and 2 were deep.

		surgery would have been performed. In group B, 25 burns showed low perfusion on Laser Doppler Imaging and were treated surgically. There was 100% agreement between Laser Doppler Imaging image and histology in all 25 burns. However, when clinical assessment of burn depth was compared with histology there was only agreement in 21 of the burns (84%). By using Laser Doppler Imaging, the accuracy of burn depth assessment was found to be 97% compared with 70% by clinical assessment.		
Holland *et al* (2002)	Assess the ability of Laser Doppler Imaging to evaluate burn depth in children.	Laser Doppler images were interpreted by 1st author and assessment of depth obtained based on flux perfusion units. This was compared to subsequent wound outcome. Any wound that had not healed by day 12 was regarded as deep partial or full	N=58. 1 patient excluded due to excessive movement for the Laser Doppler Imaging scans to be interpreted. Study showed that clinical examination correctly determined 66% of these patients with	No reported withdrawals.

		thickness. No statistics available.	deep partial or full thickness burns compared to 90% with the Laser Doppler Imaging (71% specificity compared with 96% with Laser Doppler Imaging). Thus, Laser Doppler Imaging correctly predicted wound outcome in 9 out of 10 children.	
Niazi *et al* (1993)	To evaluate whether the Laser Doppler Imager is a valuable adjunct in burn depth assessment compared with clinical judgement and histological assessment.	Correlation of clinical assessment with histological review and scan resulted were evaluated. No specific statistics available.	N = 13. The LDI scans were compared with clinical judgement which were then both compared with the histology reports. In 18% of the burns assessed clinically, the histology reports showed them to be deeper, I.E they were clinically under diagnosed. When Laser Doppler Imaging scans were	None Listed

			compared with histology reports it was found that there was a consistently accurate correlation in all areas – deep and superficial.	
La Hei *et al* (2006)	To assess whether burn wound outcome in paediatric population can be predicted by LDI in the absence of any direct clinical assessment.	Predictions as to the depth of the burns and time to healing were made based on Laser Doppler Imaging P.U and actual income. 97% of predictions were correct with just 4 areas of deep burn incorrectly predicted to heal within 14 days. The sensitivity and specificity of Laser Doppler Imaging was 0.97 and 1.0 respectively. No other statistics available.	50 scans were performed on 31 patients generating 100 reports. These were then reported on by both the 2nd and 3rd author without any direct patient contact.	None reported.

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

No subgroups identified

Participant flow

Where applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomized, and allocated to

each treatment. Provide details of, and the rationale for, patients who were lost to follow-up or withdrew from the study.

See table B6.

5.4 Critical appraisal of relevant studies

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

None of the studies in table B2 have been previously critically appraised, so we will offer our appraisal of each.

Hoeksema *et al* (2009)

This paper was written by a group from the leading specialist burns unit in Gent, Belgium. The lead consultant, Professor Monstrey, also co-author of the paper, is the president of the Royal Belgian Society for Plastic, Reconstructive and Aesthetic Surgery. He is head of the leading burn centre at Gent, Belgium They are also extremely experienced and competent users of the moorLDI2-BI in this field so can be regarded as valuable and reliable authors. Their institution publishes numerous papers and under go continuous research in the field of burns.

Both adults and children were recruited so the results are not limited to age. In this specific study 40 patients were prospectively evaluated which appeared to be an adequate sample size in relation to the hypothesis – comparing and evaluating Laser Doppler Imaging (LDI) and clinical assessment. Clinical assessment was performed by two observers experienced in burn care who

were blinded to the LDI images which limits any opportunity for bias, and can therefore be deemed as reliable.

Accuracies were assessed by comparison with outcome: healing times longer than 21 days were considered to be equivalent to a biopsy finding of a deep dermal wound, which is entirely appropriate as this practice is commonly adopted amongst burn surgeons. Although biopsies are no longer common practice, they were once considered to be the ‘gold standard’ in diagnosis. Clinical assessments were judged to be accurate if they agreed with the healing period or biopsy findings. Their study fulfilled their aims and showed that LDI was more reliable than clinical evaluation alone, which is directly relevant to our decision problem and comparator.

This not a UK based study, but this is not relevant as there is no standard practice in relation to the clinical assessment of burns as it remains entirely subjective according to each clinician. It therefore has no impact not having been carried out in a UK based NHS hospital.

This is the first study that has been carried out looking at accuracies of LDI on different days post burn, so we have nothing to compare it to. Based on the results of this study, the authors recommend that all burns of intermediate depth should be analysed with a combination of LDI and clinical evaluation. They conclude that this combination has shown to be more accurate than either technique alone in the appropriate early management of the burn wound by avoiding unnecessary surgery and thus reducing mortality, hospital stay and costs.

Mill *et al* (2009)

The burns team at Brisbane Royal Children’s Hospital is led by Professor Roy Kimble, a prolific author on burns research with many years experience in the use of LDI.

The study compared LDI images with wound outcomes in 85 burns in 48 children. Laser Doppler Imaging scans were obtained within 186 hours post burn and did not influence burn treatment. Burn outcome and scar

management was found to be significantly related ($p < 0.001$). LDI flux levels were defined but objective (biopsy) confirmation of wounds grafted was not stated for all cases. In wounds that were not grafted, reepithelialisation was significantly related to LDI level ($p<0.003$).

This study lends support to the use of LDI for prediction of healing time but it has some limitations regarding objectivity and as stated by the authors the surgeons were not blinded to the LDI scan and this may have introduced bias to the resulting clinical judgement and course of treatment.

Brown *et al* (1998)

This paper is very different from the other studies appraised in this section, as it assesses LDI in animal burns not human. The group investigated whether LDI could be used as an aid in clinical judgement decision making in the treatment of vesicant burns. They compared the LDI images with histological results which as previously mentioned was considered the gold standard for burn depth assessment, though not widely used in present day practice. As this relates directly to our decision problem, it was deemed as relevant and thus included.

The results of this study are limited as only 8 pigs were used and validity of these results questionable as the pathophysiology of the skin of the pigs does differ from that of humans. However, the bias introduced by this is reduced as a result of the animal chosen (the white pig). It is widely accepted in the Burn Research community that the skin structure is similar to humans and the pig is often selected for animal experimentation. In addition it would be unacceptable to inflict vesicant wounds on humans.

Very little statistical data is reported and the LDI software used in this study is now out of date. The study does however demonstrate that laser Doppler imaging represents a simple, reproducible and non-invasive means of assessing simple changes in tissue perfusion and hence tissue viability in developing and vesicant burns.

The authors conclude that in conjunction with clinical assessment, LDI would be a useful investigative tool which may influence the clinical management for the early treatment of vesicant skin burns.

Holland *et al* (2002)

A prospective clinical study was performed looking at the ability of LDI to evaluate burn depth in children compared to clinical assessment. The sample size was 58 and a clear inclusion and exclusion criteria was followed.

Most scanning was performed between 36-72 hours post burn which is outside the validated recommended time of 48hours to 5 days. The author does state that ideally the scans were performed at 48 hours but is none the less a limitation of the study. It could therefore be assumed that the results could have been more favourable had the scans been performed within the manufacturers recommended scan time. Clinical examination correctly determined 66% of patients between 36-72hours post injury compared to 90% with the LDI. In terms of specificity 71% of those patients not thought to have a deep burn on clinical examination healed within 12 days compared to 96% with LDI. They do however acknowledge that their decision to scan between 36-72 hours was based on data from an adult pilot study by Niazi (1993) which suggested that areas of superficial partial thickness burn may initially appear as low flux at 24 hours but subsequently improve. Perhaps more evidence is needed before such information can be validated, particularly as their study is looking at children. This is acknowledged by the authors.

The results however do suggest that LDI between 36-72 hours is an accurate tool in differentiating superficial and deep partial or full thickness burns in children, but it is advocated that further clinical studies should be performed. This study still provides important data regarding the use of LDI in burn wound assessment in children, and is directly relevant to the decision problem.

Kim *et al* 2010

This is another paper to come out of the children's hospital at Westmead, Sydney, Australia. Professor Holland was a co-author of this paper so again

can be deemed as reliable. They performed a prospective cohort study to determine whether there was evidence that LDI in paediatric patients led to earlier decision making of the need for operative intervention to ensure optical burn wound healing.

The study is well laid out and all aims clearly stated and achieved. Patients included in the study were divided into 2 groups: those having a LDI scan and those assessed clinically only. The sample size was the largest in our studies included (n=196) therefore the results gained can be treated as accurate and reliable. LDI scans were performed between day 2 and 5 post injury, which is entirely as recommended and clinical evaluation was performed by a paediatric burns surgeon in conjunction with nursing and allied health personnel. This may be more reliable than the clinical evaluation methods in other papers as it involves more than one person. It is assumed that their subjective opinions would therefore be more accurate than one person alone.

Results and statistics were analysed appropriately allowing quantitative data to be produced. All variables listed clearly, and to investigate the possibility of bias, the authors compared each one between the LDI group and non-LDI group. No significant association was seen. The study shows that in paediatric burns, there was a significant reduction in time to decision making for operative intervention in the LDI group compared with the non – LDI group that was assessed on clinical grounds alone. This also equated to earlier surgery and definitive care. The author suggests that this would translate to potential financial savings, with a reduction in the costs associated with additional dressings and other medical interventions in those patients whose decision on the need for operative intervention was delayed. This supports the previous adult study by Jeng *et al* (2003) on the benefits of LDI in accurately deciding the need for earlier operation in paediatric burn population.

As acknowledged by the authors, there were several limitations to this study. All data used was reviewed retrospectively.

This paper is extremely valid to our decision problem and demonstrates the LDI as useful in reducing overall treatment cost particularly in respect to operating theatre time.

Pape *et al* (2001)

Mrs Pape is head of burns and Medical Director of the Skin Clinic at Newcastle Upon Tyne, UK. The burns department at Newcastle has nearly 20 years experience of using LDI for burn assessment, probably more than anywhere in the world.

The audit was a prospective study comparing clinical and LDI assessment of 76 intermediate depth burns (term defined) in 48 patients. Patients were divided into two groups – with high or low LDI perfusion. Of the 43 with high perfusion 41 healed within 21 days (95%) and the 2 non-healed were found to be infected (microbiology exam). Of the 25 burns with low perfusion all were found to be deep or subdermal by histology.

The authors concluded correct treatment was made in 97% if cases using protocol that included LDI and that correct treatment would have been made in only 70% of cases by clinical assessment.

Clinical assessment, according to numerous publications is suggested to be between 65-75% accurate. Please refer to Appendix B Accuracy of Clinical Assessment of Burn Wounds.

A limitation of this study was that high and low LDI levels were not defined. Another limitation was that healing was used for one group and biopsy measurements were used for the other group; this is a necessary and practical study design for patient investigations.

Niazi *et al* (1993)

This earlier paper also addresses the decision problem by evaluating the LDI's ability to assess burn depth by measuring the blood flow. The study was performed at the regional burns unit, Newcastle Upon Tyne, UK, which aside

from being a dedicated specialist centre, has been a champion in LDI research in burns for many years.

This was a pilot study with only 13 patients, which could limit the reliability of the results, please refer to appendix B. Although this is an early paper the LDI results of this study can be deemed as reliable as scan results were evaluated in correlation with clinical judgement and histological review, which as previously stated, was considered the 'gold standard' in burn assessment and would have been at the time of the study. As before the accuracy of clinical assessment is subjective, but none the less is standard practice. High and low LDI values are not defined.

The results are laid out clearly and explained well concluding that their study showed there was a consistent correlation between the LDI scans and histology results in all areas. Minimal statistical information is available.

La Hei *et al* (2006)

The study was carried out by the burns unit at the children's hospital at Westmead, Sydney, the 2nd author Professor Holland is a well respected and highly regarded in the field of paediatric burns.

In this paper the authors set out to asses the validity of independent blinded reporting of the LDI prediction of burn wound outcome in children without any direct patient access.

Although their sample size was smaller (n=31) it seems entirely appropriate for their study design. Both reporters were 'blinded' never visualising the burn wound or seeing the patient. Further bias was avoided by all scans being performed by the 1st author, not the reporters, as scan operators unavoidably visualise the burn wound.

They concluded that accurate prediction of the burn wound outcome could be made via the standard information generated by LDI and appeared more reliable than clinical prediction. Overall the reported predictions from assessing the LDI scans were 97% correct. Only 4 areas of deep burn were

incorrectly predicted to heal within 14 days. No superficial burns were reported as deep. The sensitivity and specificity of LDI was 0.97 and 1.0 respectively.

The mean time for scanning was documented by the author as 54 hours, which is within the recommended manufacturers scanning time of 48hours – 5 days. It does state that some scans were performed earlier than this, which is a limitation of the study.

Another possible limitation of the study was that one of the reporters had less experience of LDI, which is noted in the paper, had an impact on their overall accuracy. Over a 6 month period it had risen from 83% -96% by the end of the study.

The well planned study does demonstrate at least in children the ability of LDI to greatly assist in predicting burn wound outcome.

Monstrey *et al* (2010) (in press)

Professor Monstrey, as previously stated is a highly regarded and well respected surgeon in the field of burns.

The paper describes various methods validating the LDI burn palette derived by Pape *et al* (2010) (in press). The methods of analysis were based on areas identified as healed or not healed at 14 days or 21 days. The study included 139 patients 433 wounds (adults and children). Statistical analyses are presented showing LDI accuracies greater than 90% and factors confound LDI or scanning or image interpretation are given acknowledging the essential input of the clinician in this process. No new comparison with clinical assessment accuracy is presented. The limitations of comparison with biopsy results are also described. The independence of LDI – assisted prediction of wound healing from age, burn source, burn site, %TBSA and other parameters is also presented (based on a more in depth study by Baker *et al,* 2009).

This is a well planned study with good statistical analysis.

Baker *et al* (2009)

Professor Baker is an academic statistician at Salford University Centre for Operational Research and Applied Statistics. Professor Baker has extensive experience in the analysis of Clinical and other data. This paper described an in-depth statistical analysis of data from the study of Monstrey *et al* (in press): 1. Analysis of average LDI blood flow values (n=299) and the influence of other parameters to predict healing time analysis of the accuracy LDI image interpretation using the moorLDI palette for predicting healing time (n=433). 2. An extended analysis of the influence of %TBSA on accuracy of LDI prediction.

Results found were 1. With statistical modelling healing time was predicted with 92% accuracy with LDI and gender included 90.9% with gender excluded (no other parameters influenced accuracy). 2. At a mean %TBSA of 40% LDI accuracy would be 86%, significantly higher than clinical assessments.

This study is based on objective statistical analysis techniques with high construct validity.

Jeng *et al* (2003)

Dr Jeng is a past president of the American Burn Association and heads a well respected burn centre in Washington, USA. The study included 23 patients with 41 wounds assessed by LDI and clinically (with clinical assessors blinded to Laser Doppler Imaging images). Accuracy of LDI was assessed by comparison with whole burn healing time or biopsy if treated surgically. LDI scans were performed mostly on day 1 post burn (i.e. earlier than currently recommended by the Manufacturer) and 2 days earlier than clinical assessment. The LDI analysis was based on average flux values of the whole burn wound. The analysis is completely inappropriate because it included areas of high flux and low flux (above and below 250 pu) within the area analysed rather than assess them separately. Biopsy confirmation of wound depth was obtained for 21 wounds clinical assessment of these wounds was correct in 15 (71%) of wounds. LDI medium flux accurately predicted need for exclusion in all cases (7/7). In 18 of 41 cases the surgeon

decided to treat surgically but LDI indicated that these wounds would heal. Case review determined that the surgeon over estimated burn depth in 10 out of 18 cases (55%). The other 8 cases had high medium LDI flux values but in each case ‘a predominant area of 3rd degree burn with surrounding hyperaemia was noted’. The inappropriate LDI analysis was acknowledged by the authors.

Limitations of this study include the method of LDI analysis and no description was given of how case review determined overestimation of burn depth (biopsy assumed).

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

The studies included in the critical appraisal are centred around the use of a medical device for diagnostic purposes and not as a ‘treatment’ method for a specified condition and do not include randomised controlled trials. Systematic reviews and meta-analyses are also unavailable.

As a result the standard quality assessment instrument (as detailed in systematic reviews) CRD ‘s guidance for undertaking reviews in healthcare (www.york.ac.uk/inst/crds) are not completely relevant. As a result the suggested format for the quality assessment has been modified to include areas of studies which introduce potential bias to the studies and therefore effect overall quality of the study.
In preparation of this table reference has been made to the Cochrane handbook. Section 13.5 ‘assessing risk/bias in non-randomised studies’.
The table of results is provided in section 7.3 appendix 3.

5.5 Results of the relevant studies

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

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

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

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

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

This is not applicable for the technology being evaluated. It is not a treatment method. It is medical device used for diagnostic purposes to aid clinical judgment time to healing of burn wounds.

5.6 Meta-analysis and evidence synthesis

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

5.6.1 Describe the technique used for meta-analysis and/or evidence synthesis, the steps undertaken and results of the analysis including methodology. For example, when direct comparative evidence is not available, indirect treatment comparison methods can be used. The following descriptions should be included if indirect or mixed treatment comparisons are undertaken.

- Identification, selection, methodology and quality assessment of relevant studies
- Summary of the studies used to conduct the indirect comparison. For the selected studies, provide a summary of the data used in the analysis.
- Indirect/mixed treatment comparison methodology.
- Results of the analysis.
- The statistical assessment of heterogeneity and any sensitivity analyses

No meta-analyses have been conducted.

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

Accuracy of moorLDI Assessment of Burn Wounds

The accuracy of moorLDI assessment of burn wounds has been assessed with a variety of criteria, including accuracy to predict healing within 14 days or 21 days and by comparison with histological assessment of burn depth (biopsy). The day on which the LDI assessment is made will affect the accuracy; in most studies this is normally performed within the first few days post burn (PB). A further confounding factor is the burns included in each

study: most exclude cases that are considered obvious (very superficial dermal and definite full thickness). The table below summarises the accuracy of LDI assessments within the limitations described.

Reference	Verification	Number of burns	Accuracy
Hoeksema *et al* 2009	Healing or biopsy	40	96%
Pape *et al*, 2001	Healing	76	97%
Holland *et al*, 2002	biopsy; healing (deep/full; sup partial thick.)	29; 28	90%; 96%
Niazi *et al*, 1993	Punch biopsy	17	100%
La Hei, 2006	healing	50	97%
Monstrey *et a*l, in press	Healing	433	96%
Baker *et a*l, 2009	Healing and biopsy	299	91%
Jeng *et al*, 2003	Healing and biopsy	41	100%*

* based on LDI image review following authors' acknowledgement that their numerical assessment was not appropriate.

There are 2 included studies relating to earlier surgical decisions with use of moorLDI.

Reference	Verification	Number of patients	Days earlier
Kim *et al* 2010	Comparison of groups scanned/not scanned	196	3
Jeng *et al*, 2003	Day of clinical decision compare day of LDI scan	23	2

5.7 Adverse events

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

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

No specific studies of safety. The measurement of blood flow in the burn wound is non-contact. Only trained personnel are permitted to operate the instrument.

5.7.2 Please provide details of all important adverse events. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

No adverse events have ever been reported.

Table B7 Adverse events across patient groups

N/A as no adverse events have been reported.

System organ/ class/adverse events	Time period 1			Time period 2 etc.		
	Intervention % of patients (n = x)	**Comparator % of patients (n = x)**	**Relative risk (95% CI)**	**Intervention % of patients (n = x)**	**Comparator % of patients (n = x)**	**Relative risk (95% CI)**
Class 1 (for example, nervous system disorders)						
Adverse event 1						
Adverse event 2						
Class 2 (for example, vascular disorders)						
Adverse event 3						
Adverse event 4						
CI, confidence interval Adapted from European Public Assessment Reports published by the European Medicines Agency						

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

It is a non-contact method of imaging blood flow in a burn wound using a low power (less than 2mW) visible red laser beam. Only trained personnel are permitted to operate the instrument. Eye protection is provided for the patient.

5.8 Interpretation of clinical evidence

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

The principal findings are that the moorLDI2-BI aids the prediction of time to healing of a burn wound. The instrument used in combination with clinical judgement enables earlier and more accurate predictions compared to un-aided clinical judgement. On average, hospital bed days per patient are typically reduced by 2 to 3 days and operations are avoided for some patients. There are no adverse affects from having a burn wound imaged using the moorLDI2-BI.

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

The strength of the clinical based evidence is that studies done at burn centres in the UK and worldwide consistently find that there is a significant improvement in the accuracy of prediction of time to healing of a mixed depth (intermediate) burn wound. Accurate predictions are done up to 5 days earlier than may be possible using un-aided clinical judgment. These studies done with the moorLDI2-BI have covered a 14 year period and include an MHRA registered multi-centre clinical investigation.

The limitations are that scanning and the interpretation of images requires knowledge of a number of confounding factors. For example patient movement during scanning, wound infection, undebrided wounds imaged etc. Confounding factors are described in the User Guide and knowledge of these factors is required during competence based training.

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

The decision problem requires an answer to the question does the use of the moorLDI2-BI in a burn centre aid the clinician in predicting the time to healing of a burn wound. The published evidence and expert opinion that is on record supports the use of the moorLDI2-BI as a clinical aid. Examples of published statements of support are as follows:-

‘Very superficial and very deep burns are relatively easy to diagnose clinically. In reality many burns are of mixed and/or intermediate depth. These are much more difficult to assess clinically.

The findings of the clinical trial established that use of the moorLDI, in combination with clinical assessment, accurately predicted wound healing in 95% of all cases. This compares with approximately 65% accuracy for clinical assessment alone found in previous studies.

We strongly believe that use of the moorLDI allows early and accurate prediction of burn healing potential and ensures that patients receive the most appropriate and cost effective treatment for their burns. ‘

Professor Stan Monstrey Mr Henk Hoeksema; University Hospital Ghent, Belgium

Dr Robert Spence; Johns Hopkins Bayview Medical Center, Baltimore, USA

Dr James Jeng; Washington Hospital Center, Washington, DC, USA

Dr David Wilson; City Hospital, Nottingham, UK

Mrs Sarah Pape. Royal Victoria Infirmary, Newcastle upon Tyne, UK

‘Based on the results of this study we recommend that ideally, all burns of intermediate depth should be analyzed with a combination of both LDI scanning and clinical evaluation. This combination of diagnostic techniques has shown to be more accurate than either technique alone in ensuring early appropriate management of the burn wound by avoiding unnecessary surgery and therefore reducing mortality, hospital stay and costs.’

Henk Hoeksema *, Karlien Van de Sijpe, Thiery Tondu, Moustapha Hamdi,

Koenraad Van Landuyt, Phillip Blondeel, Stan Monstrey

Department of Plastic Surgery, Gent University Hospital, De Pintelaan 185, B-9000 Gent, Belgium

Laser Doppler Imaging (LDI) has been used in our Burns Unit since 1991. It is now part of the routine assessment of all burns. Patients are scanned with the moorLDI at 48 hours or on admission, if this is later than 48 hours after burning. We have been able to improve the accuracy of assessment of burn depth from 65% to 96%. This ensures that our patients receive the most appropriate and cost-effective treatment of their burns.

Sarah A. Pape, FRCSEd(Plast), Consultant Plastic Surgeon,Director, Burns Unit Newcastle upon Tyne

LDI in children appears to be extremely accurate in predicting burn wound outcome in children, with a sensitivity and specificity of 0.97 and 1.0, respectively, when performed within 3 days of the burn injury. This accuracy appeared independent of examination of the burn wound. Although optimal patient management would seem most likely to occur by combining clinical and LDI assessments of burn wounds, burns surgeons should be guided by LDI data.

E.R. La Hei a,b, A.J.A. Holland a,b,c,*, H.C.O. Martin a,b

a Burns Unit, The Children’s Hospital at Westmead, The University of Sydney, New South Wales, NSW, Australia

b The Children’s Hospital at Westmead Burns Research Institute, The Children’s Hospital at Westmead,

The University of Sydney, New South Wales, NSW, Australia

c The Department of Academic Surgery, The Children's Hospital at Westmead,

The University of Sydney, New South Wales, NSW, Australia

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

Studies were conducted as part of normal clinical patient assessment. Scans, which typically take 2 minutes, were done at the time of routine dressing change days 2 to 5 post burn. Generally one scan only was needed for each separate area of burn.

All patients admitted to hospital with a burn wound judged to be of intermediate character would be scanned in a burn centre that had an instrument and a trained operator available.

6 Analysis of Cost

6.1 Published cost-effectiveness and cost evaluations

Identification of studies

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

A search of the NHS EED database was carried out using the terms Laser Doppler Imaging and burn. Please refer to section 7.6 appendix 6 for search strategies used. No relevant studies were found.

Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

No relevant studies were identified.

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

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

No relevant studies were identified.

6.2 De novo cost analysis

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

As no previous cost studies or economic evaluations relating to the use of laser Doppler imaging in burns patients were identified a de novo cost analysis was conducted to assess the cost impact of the introduction of the technology.

Patients

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

Patients admitted to specialist hospital burn centres who are clinically assessed to have, or possibly have, one or more intermediate burns.

Model structure

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

As a result of a lack of data no formal model structure has been considered. The main benefits of LDI are earlier and more precise diagnosis allowing appropriate treatment decisions. Therefore the savings generated by reduced length of hospital stay and fewer operations have been calculated per patient.

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

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

It should be noted that the main benefits of laser Doppler imaging in terms of resource savings are expected to be during the initial period of hospitalisation and therefore extrapolation of results beyond this period was not deemed necessary.

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

Not applicable, please see response to 6.2.3.

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

Not applicable, please see response to 6.2.3.

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

Not applicable, please see response to 6.2.3.

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

Table B8 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Period of hospitalisation	Benefits of technology are during the hospitalisation period	
NHS, National Health Service; PSS, Personal Social Services.			

Technology

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

The intervention is implemented as per its CE marking.

6.2.9 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

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

The moorLDI2-BI is a diagnostic device and therefore treatment continuation rules do not need to be considered.

6.3 Clinical parameters and variables

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

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

As stated previously evidence no formal model structure has been considered as a result of a lack of relevant cost analysis studies. The moorLDI2-BI allows for earlier and more accurate diagnosis, allowing appropriate treatment. Therefore best estimates of the reduced length of hospital stay and the reduced number of operations have been included to calculate cost savings during the hospitalisation period.

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

As no formal model structure has been considered there are no health states to transition between and therefore transition probabilities were not required.

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

Not applicable, please see response to 6.3.2.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what

sources of evidence were used, and what other evidence is there to support it?

As the de novo cost analysis focuses purely on reduced hospital stay and reduced operations no clinical outcomes have been taken into account and therefore no link between intermediate and final outcomes was necessary.

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

- the criteria for selecting the experts

  Consultant burn surgeons and burn treatment coordinators experienced in the use of LDI for burn wound assessment.
- the number of experts approached

  14
- the number of experts who participated

  8
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought

None of the experts declared a conflict of interest; however 2 of the experts contacted were part of a study that established the colour coding (palette) used for easier interpretation of moorLDI images and its validation. Two other experts are part of a new study to assess a new type of LDI imager. No personal payments have been made to any of the experts.

- the background information provided and its consistency with the totality of the evidence provided in the submission

  The background information is recorded in the sensitivity analysis spreadsheet included with this submission. The data includes percentage of patients admitted who are scanned, and typical OR duration and information on costs.
- the method(s) used to collect and collate the opinions.

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

Various methods were used to collect the data including questionnaires, e-mails, telephone calls and face to face meetings. All data presented and assumptions made have come from reliable and experienced Consultant Plastic Surgeons or members of their burn care team

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

Uncertainty is addressed in the sensitivity analysis.

Summary of selected values

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

Table B9 Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Age	Adult or Child	40% children 60% adults	Patient characteristics section 5.3.4
Number of patients admitted with intermediate burns	Percentage of total admitted to hospitals with specialist burn centres. Typical 75%	75% of 10,000 patients admitted	Study results section 5.5
Day beds saved	Typical 2	2 to 3	Cost Analysis Spread sheet
Cost of standard day bed in a burn unit for adult	Typical £378	£320 to £772	Cost Analysis Spread sheet
Cost of standard day bed in a burn unit for child	Typical £794	£320 to £794	Cost Analysis Spread sheet
Length of operating theatre time in hours and minutes	Typical 60 minutes	45 minutes to 4hours	Cost Analysis Spread sheet
Cost of operation per minute	Typical £76	£50 to £83	Cost Analysis Spread sheet
Percentage of patients scanned who avoid operation	Typical 17%	10% to 30%	Cost Analysis Spread sheet
Number of moorLDIs system	Typical 28	25-64	UK Burn centres list
MoorLDI system leasing cost	Typical £22,000	n/a	Moor Instruments price list
moorLDI system purchasing cost	Typical £50,000	n/a	Moor Instruments price list
MoorLDI system annual servicing cost	Typical £8,000	n/a	Moor Instruments price list
Nurse operation time (minutes)	Typical 60	30-90 min	Consultations with users
Nurse cost hour rate	Typical £45	n/a	Unit cost of health and social care
Clinician Interpretation time (minutes)	Typical 15	5-30 min	Consultations with users

Clinicaian cost hour rate	Typical £170	n/a	Unit cost of health and social care 2009
Registrar cost hour rate	Typical £61	n/a	Unit cost of health and social care 2009
Administration cost	Typical £15	n/a	Unit cost of health and social care 2009
Cost to NHS staff time spent training	Typical £2,680	n/a	Fixed cost for NHS staff training: 2 days (16 hours) for 1 clinician, 2 registrars and 3 nurses every 2 years

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

No extrapolation has been conducted as the benefits, in terms of cost savings, are assumed to be during the hospitalisation period.

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

- A significant percentage of the patients admitted will have intermediate burns
- Approximately 40% of these patients will be children
- On average 2 bed days are saved per patient scanned
- Approximately 15% of patients scanned will avoid an unnecessary graft
- Approximately 1 hour of operating theatre time is saved for these 15%
- Costs are for lease or purchase (plus service contract) of the instrument plus instrument operating time and image interpretation and hospital administration.

These assumptions have been justified throughout the submission and are further justified in the cost analysis spreadsheet text.

6.4 Resource identification, measurement and valuation

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

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

The costing of the non elective treatment for burn requiring hospitalisation is illustrated by the study by Hemington-Gorse et al (2009) and formally under

several HRG codes (see table ?, National Schedule of Reference Costs Year : '2008-09' - NHS Trusts Non-Elective Inpatient (Long Stay) HRG Data)

Currency Code	Currency Description	Activity	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	No. of Bed Days	Average LOS - Days
JB01A	Major Burn, Third degree or more than 19% TBSA or Affecting Multiple Body Regions with Significant Graft	163	£15,287	£4,693	£21,596	3,254	19.96
JB01B	Major Burn, third degree or more than 19% TBSA or Affecting Multiple Body Regions, transferred in 2 days or less	38	£1,284	£623	£1,450	85	2.24
JB01C	Major Burn, third degree or more than 19% TBSA or Affecting Multiple Body Regions without Significant Graft	64	£4,636	£2,049	£6,456	722	11.28
JB11A	Other Burn with Multiple Significant Graft Procedures with Major CC	34	£21,684	£16,344	£20,926	1,207	35.50
JB11B	Other Burn with Multiple Significant Graft Procedures without Major CC	27	£13,400	£8,520	£16,083	487	18.04
JB12A	Other Burn with One Significant Graft Procedure with Major CC	189	£13,211	£9,523	£16,005	3,418	18.08
JB12B	Other Burn with One Significant Graft Procedure without Major CC	446	£6,435	£4,744	£8,510	3,519	7.89
JB13A	Other Burn with Other Procedure with Major CC	151	£7,063	£3,995	£9,033	1,572	10.41
JB13B	Other Burn with Other Procedure without Major CC	455	£2,823	£2,345	£3,054	1,486	3.27
JB21A	Other Burn without Other Procedure with Major CC	478	£3,692	£1,801	£4,638	4,182	8.75
JB21B	Other Burn without Other Procedure without Major CC	1,321	£1,796	£1,100	£2,673	3,754	2.84

These codes stratify by type of burn (major or other) type of procedure (significant graft, multiple significant grafts or other procedure), and complications (with or without). These are all the codes relating to the non elective treatment of patients requiring hospitalisation

Each of the inpatient HRG codes included refers to burn wound(s) that will or might require surgery to all or significant parts of the burn wound(s). In each of these groups a decision must be made to treat all or part of a wound surgically: a major burn of third degree (full thickness, JB01A -C) will normally be associated with adjacent parts of the wound that are intermediate, therefore LDI can help to determine the area that needs to be grafted and hence duration of surgery. Some major burns greater than 19%TBSA, without parts that are 3rd degree, can benefit from LDI by a reduction in graft area or a finding that surgery is not required. For burns considered less serious (JB13A – JB21B), there is the potential to underestimate healing time with need for surgery and/or scar management not recognised until later; LDI can help to

avoid surgical delay and reduce healing time and length of stay. Cases classified as intermediate HRG codes (JB11A – 12B) can benefit by an LDI finding that surgery is not required (and consequent change of HRG for some cases) or a reduction in the number of areas grafted or a reduction in graft size; i.e. avoidance of surgery or a reduction in its duration.

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

The weighted average of the cost of a standard bed has been used in the cost analysis. Also the average length of stay in days is found to be approximately 7-8 days. It is not straight forward to extract the costs of grafting procedures from the NHS reference costs as these costs will include dressing costs etc.

Resource identification, measurement and valuation studies

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

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

	Griffiths *et al*, 2006	Hemington-Gorse *et al*, 2009	International Burn injury Database Report, May 2008
Country of study	UK	UK	UK
Date of study	1.12.02 – 30.11.03	Financial 2005 -2006	1986 - 2007
Applicability to UK clinical practice	Applicable to UK clinical practice	Applicable to UK clinical practice	Applicable to UK clinical practice
Cost valuations used in study	Hospital bed (total stay), Theatre visits, Dressings, Medication. NHS HRG costs used.	Hospital bed day costs for adults and children; operation costs per minute, dressing costs, NHS HRG costs. (costs in euros 2006).	No costs evaluated
Technology costs	N/A	N/A	N/A

See Section 7.9 Appendix 9 for details of search strategy.

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

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought

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

- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method(s) used to collect and collate the opinions.

The uncertainty around these values should be addressed in the sensitivity analysis.
Refer to section 6.3.5

Intervention and comparators' costs

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

Table B10 Unit costs associated with the technology in the economic model

Number of moorLDIs system	Typical 28	25-64	UK Burn centres list
MoorLDI system leasing cost	Typical £22,000	n/a	Moor Instruments price list
moorLDI system purchasing cost	Typical £50,000	n/a	Moor Instruments price list
MoorLDI system annual servicing cost	Typical £8,000	n/a	Moor Instruments price list
Nurse operation time (minutes)	Typical 60	30-90 min	Consultations with users
Nurse cost hour rate	Typical £45	n/a	Unit cost of health and social care
Clinician Interpretation time (minutes)	Typical 15	5-30 min	Consultations with users
Clinicaian cost hour rate	Typical £170	n/a	Unit cost of health and social care 2009
Registrar cost hour rate	Typical £61	n/a	Unit cost of health and social care 2009
Administration cost	Typical £15	n/a	Unit cost of health and social care 2009
Cost to NHS staff time spent training	Typical £2,680	n/a	Fixed cost for NHS staff training: 2 days (16 hours) for 1 clinician, 2 registrars and 3 nurses every 2 years

Health-state costs

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

As previously stated the submission does not include a formal model and has no health states. Instead the de novo cost analysis focuses on the cost savings by reduced length of admission and less operations. Both of these were requested as outcomes in the NICE scoping document. The costs of hospital stay and of skin graft procedures are shown in the table below:

Table B11 List of health states and associated costs in the economic model

Cost of standard day bed in a burn unit for adult	Typical £378	£320 to £772	Cost Analysis Spread sheet
Cost of standard day bed in a burn unit for child	Typical £794	£320 to £794	Cost Analysis Spread sheet
Length of operating theatre time in hours and minutes	Typical 60 minutes	45 minutes to 4hours	Cost Analysis Spread sheet
Cost of operation per minute	Typical £76	£50 to £83	Cost Analysis Spread sheet

Adverse-event costs

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

As stated in section 5.7, no adverse events have been reported and therefore no account needs to be taken of any adverse event costs.

Miscellaneous costs

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

No other costs have been considered. As previously stated the impact of LDI is expect to be on the resource use of the initial hospitalisation period which have been reflected in the de novo cost analysis.

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

Further savings with use of moorLDI.

1 – scars: It is common practice to give prophylactic anti-scar therapy when wounds have healed. This normally consists of pressure with or without application of silicones. For a wound that is grafted, there will normally be the added expense of fitting pressure garments and 8 to 12 follow-up appointments lasting up to 30minutes each. This will be an unnecessary expense for a wound where surgery could have been avoided for a wound that could heal with conservative treatment within about 16 days. On the other hand, where surgery is required but the decision to graft is delayed, healing will be later and the duration of anti-scar therapy would be extended.

2 - dermal substitutes: Another area where moorLDI can have an impact on cost savings is under investigation at several burn centres: to determine the optimum time for grafting deep or full thickness burn wounds covered with

dermal substitute (e.g. Integra). At present the silicon sheet that covers the Integra is removed at 21 days post surgery and a skin graft applied. However in many patients this time could be reduced if moorLDI indicates earlier adequate vascular in-growth into the dermal substitute. Conversely, if moorLDI indicates poor vascular in-growth, grafting can be delayed to avoid poor 'take' and need for later re-grafting. In each case length of stay can be reduced by several days.

6.5 Sensitivity analysis

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

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

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

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

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

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

As no formal model has been used in this analysis it is not possible to investigate the uncertainty around structural assumptions.

6.5.2 Was deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How variables were varied and what was the rationale for this? Where relevant, the distributions and their sources should be clearly stated. If any parameters or variables listed in section 6.2.7 were omitted from sensitivity analysis, please provide the rationale.

As there is no formal model it has not been possible to conduct a probabilistic sensitivity analysis. However, it has been possible to conduct deterministic sensitivity analyses as well as threshold analyses examining to what level a parameter must change before LDI is cost neutral.

6.6 Results

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

- Costs.
- Disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A tabulation of the mean cost results.
- Results of the sensitivity analysis

Clinical outcomes from the model

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

Table B12 Summary of model results compared with clinical data

Outcome	Clinical study result	Model result
Progression-free survival	C_1	R_1
Post-progression survival	C_2	R_2
Overall survival	C_{1+2}	R_{1+2}
Adverse event 1	C_3…	$R_{3...}$
Etc.	…	…

This section is not applicable. As previously stated, our de novo cost analysis focuses solely on the reduced resource use associated with LDI and does not include a model reflecting clinical outcomes.

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

Table B13 Summary of costs by health state

Health state	**Cost intervention (X)**	**Cost comparator (Y)**	**Increment**	**Absolute increment**	**% absolute increment**
Health state 1 (HS1)	X_{HS1}	Y_{HS1}	$X_{HS1} – Y_{HS1}$	$\|X_{HS1} – Y_{HS1}\|$	$\|X_{HS1} – Y_{HS1}\|$/ (Total absolute increment)
HS2	X_{HS2}	Y_{HS2}	$X_{HS2} – Y_{HS2}$	$\|X_{HS2} – Y_{HS2}\|$	$\|X_{HS2} – Y_{HS2}\|$/ (Total absolute increment)
…	…	…		…	…
Adverse event 1 (AE1)	X_{AE1}	Y_{AE1}	$X_{AE1} – Y_{AE1}$	$\|X_{AE1} – Y_{AE1}\|$	$\|X_{AE1} – Y_{AE1}\|$/ (Total absolute increment)
AE2	X_{AE2}	Y_{AE2}	$X_{AE2} – Y_{AE2}$	$\|X_{AE2} – Y_{AE2}\|$	$\|X_{AE2} – Y_{AE2}\|$/ (Total absolute increment)
Total	**X_{Total}**	**Y_{Total}**	**$X_{Total} – Y_{Total}$**	**Total absolute increment**	**100%**
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table B14 Summary of costs by category of cost

Item	**Cost intervention (X)**	**Cost comparator (Y)**	**Increment**	**Absolute increment**	**% absolute increment**
Technology cost	£22,000 annual lease fee per system	Zero. The instrument is used to aid clinical judgement.	£22,000	£22,000	100%)
Man power costs per patient: Training,	£2,680	Zero	£2,680	£2,680|	100%
System operation per patient and image	£65	Zero	£65	£65	100%

interpretation costs,					
Administration cost	£15	Zero	£15	£15	100%
Total	**£24,760**	**Zero**	**£24,760**	**£24,760**	**100%**

Base-case analysis

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

Table B15 Base-case results

Technology	Total costs (£)

There are no other technologies in clinical use to make a comparison. The comparison is between clinical judgement alone with clinical judgement plus LDI.

Sensitivity analyses

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

The detailed sensitivity analysis results are recorded in the cost analysis spreadsheet attached. **Cost Analysis LDI.xls**

6.6.5 Please present the results of PSA.

PSA was not conducted as it was not considered appropriate for the model used. See response 6.5.2

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

The basic structure of the cost analysis (bed days saved and operations avoided) has been established over a 17 year period involving clinical research (published) and clinical evaluation studies. The different scenarios resulting from considering the percentage of patients with intermediate burns and the percentage of these scanned have been analysed in the cost analysis.

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

If it's assumed that 10,000 patients are admitted to the 28 specialist burn centres and the percentage of patient's scanned range from 10% - 100%, it is found that a range of savings per patient are from £1,076 - £4,596. The breakeven point for each burn centre identified is at 14 patients scanned. See **Cost Analysis LDI.xls**

6.6.8 What are the key drivers of the cost results?

The key driver is the number of patients scanned. This is determined by the availability of the technology in the burn centre, trained staff and the provision of hospital resources and funds to allow routine use of the instrument for burn wound assessment.

6.7 Validation

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

The model is based on savings arising from bed days saved and operations avoided. The validation has been done over a period of more than 10 years by a number of burn surgeons who have published their results showing that clinical judgement aided by LDI blood flow imaging saves bed days and reduces the number of operations required.

6.8 Subgroup analysis

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

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

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

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

No sub groups identified.

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

6.8.3 Please describe how the statistical analysis was undertaken.

See 6.8.1

6.8.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.6.3 (Base-case analysis).

See 6.8.1

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

See 6.8.1

6.9 Interpretation of economic evidence

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

The economic data available, cost of bed days, cost of operations, cost of personel, have been used in the sensitivity analysis.

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

Yes

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

The main strength is that the basis for the cost analysis, bed saved and operations avoided have been established by clinical research and evaluation. The main weaknesses are the uncertainty concerning the total number of patients that can potentially benefit from the technology. A further weakness is being able to establish, with a high degree of confidence, the bed days and theatre costs.

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

We need to establish the confidence limits for the data used to enable probabliistic data analysis to be used.

Appendices

Appendix A Bibliography

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Appendix B Accuracy of Clinical Assessment of Burn Wounds

Accuracy of Clinical Assessment of Burn Wounds

The accuracy of clinical assessment of burn wounds has been assessed with a variety of criteria, including accuracy to predict healing within 14 days or 21 days and by comparison with histological assessment of burn depth (biopsy). The day on which the clinical assessment is made will affect the accuracy; in many studies this information is not recorded but it is normally performed within the first few days post burn (PB). A further confounding factor is the burns included in each study: most exclude cases that are considered obvious (very superficial dermal and definite full thickness). The table below summarises the accuracy of clinical assessments within the limitations described.

Reference	Comparison	Number of burns	Accuracy
Gursu , 1978	Punch biopsy, 2° burns	19	67%
Hlava et al, 1983	Healing within 3 weeks	N/A	50%
Alsbjorn et al, 1984	Punch biopsy	60	75%
Niazi et al, 1993	Punch biopsy	17	65%
Yeong et al, 1996	Healing within 14 days	152	70%
Pape et al, 2001	Healing	76	70%
Hoeksema, 2009	Healing (assessments on 1, 3, 5 days PB)	40	62%

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6.10 Appendix 1

6.10.1 IFU, scientific discussion or drafts.

6.11 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

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

- PubMed – this database includes 20 million citations for biomedical literature from Medline, life science Journals and online books.
- The Cochrane Library
- ScienceDirect
- BioMed Central
- Medline
- Burns Journal - website journal search facility
- CINHAL Journal search facility
- OVID including Medline (R) In-Process
- Embase – this was not searched as we do not have a Company subscription with this database

6.11.2 The date on which the search was conducted.

The search has been conducted on a regular monthly basis, with the last search conducted on August 2nd 2010

6.11.3 The date span of the search.

The date span of searches was from 1970-Present in order to include references for Burn Assessment using standard clinical techniques. For Burn Assessment specifically using the Moor Instruments laser Doppler system the date span of literature searches was 1990-Present.

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

Keywords searched	
Laser AND Doppler AND imaging AND burn$1 OR thermal	Boolean
Burn$1 AND depth AND laser AND Doppler	Boolean
Burn$1 AND diagnosis AND laser AND Doppler	Boolean
Burn$1 AND assessment	Boolean
LDI AND burn$1	Boolean
Burn$1 AND laser AND Doppler	Boolean
Laser AND Doppler AND Burn	Boolean
Laser AND burn$1 AND scan OR imag$1	Boolean

i.e. $1 – Boolean truncation to identify references with “burn” or “burns” but will exclude burning for example

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

Searches were also completed for competitors’ websites – Perimed in particular. At present the system produced by the competitor does not have CE Marking or FDA 510K for burn assessment and has not been proven to be useful/accurate for Burn Assessment. However, searches are performed regularly for research literature regarding Competitor equipment and to ensure any comparative studies, with the moorLDI2-BI and Perimed systems, performed by them would be identified by Moor Instruments.

Searches are also performed on a regular basis to identify material published and/or presented at Conferences. Searches for such material include attending conferences, searching Specific Society websites (including, but not limited to, the British Burn Association, European Burn Association, Australia New Zealand Burn Association etc) and their associated Publications including Abstract/Meeting Proceedings.

6.11.6 The inclusion and exclusion criteria.

Inclusion and exclusion criteria are given in the following table:

Inclusion criteria	Population – Burn Injuries, adult and paediatric population, both male and female Interventions – Laser Doppler Imaging of burn wounds with CE Marked 510K FDA Equipment. Moor Instruments equipment, moorLDI systems Outcomes – any of the following: time to healing, scarring, length of stay, cost reduction, time to surgery, treatment decision, burn depth by biopsy Study design – audits, clinical studies, pilot studies, observational studies, cohort study, statistical studies Language restrictions – English Level of results available – fully published articles in the press and papers submitted for publication (i.e. *In Press*)
Exclusion criteria	Population – Non-burn injuries Interventions – non-use of Laser Doppler Imaging, use of Laser Doppler Imagers without CE marking/510K FDA. Outcomes – Other than those listed above Study design – None Language restrictions – Languages other than English Level of results available – unpublished audits and posters

6.11.7 The data abstraction strategy.

A minimum of two Moor Instruments Employees (of JR, RG, AW) reviewed the title and abstract of each article identified in the literature search detailed in the previous sections to determine if the article has met the inclusion criteria detailed in Section 7.2.6. Disagreements over the inclusion and/or exclusion of specific literature were resolved by repeated review and discussion by the Employees responsible for the data abstraction.

Articles for which it was deemed were requiring full text review – in this case this included all publications (whether published or In Press) considered for inclusion in this study, where available to us, were abstracted by one of the Employees, and then all abstracted data were verified by a second Employee and checked against a Bibliography for conformation. Throughout the abstraction process, the investigators maintained an active dialog regarding specific

articles and reviewed questions regarding data abstraction to maintain a consensus approach among abstractors.

A complete bibliography was maintained detailing Abstracts, Full Publications, Posters, *In Press* Publications and any other references identified on record. Thus enabling those responsible for data abstraction to confirm and double-check all required Abstracts and publications had been obtained.

6.12 Appendix 3: Quality assessment of RCT(s) and non-RCT(s) (section 5.4)

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

Hoeksema et al		
What is the accuracy of early burn depth assessment by Laser Doppler Imaging on different days post burn?	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Study type – cohort, observational, case studies.	Prospective evaluation and comparison study	Not clear: this study type can introduce bias
Is the sample size adequate for the study?	N=40, No power calculations or sample size analyses were provided in the methodology of this study	Unclear
Selection criteria for subjects?	Insufficient detail is provided in the methodology with regards to patient selection	Yes
Appropriateness of study design to study question	The study has been designed to address the study question.	No
Were participants/care providers/outcome assessors blind to Laser Doppler Imaging images? If not, how could this effect the risk of bias?	All care givers, clinical assessors and observers were unaware of Laser Doppler Imaging results. Burn wounds were managed according to clinical assessment only.	No
Were there unexpected drop outs/exclusions during the study which were inadequately explained?	No patients withdrew or were excluded but in some cases patients were not scanned on all details. Reasons were provided.	No
Are the choice of outcome measures appropriate to the study question?	All outcome measures were specific to the study question.	No
Were appropriate statistical analyses presented?	Yes, statistical analysis has been provided.	No
Quality of intervention with Laser Doppler Imaging – is scan timing appropriate?	Yes, Laser Doppler Imaging was performed on 5 days.	No
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Mill et al		
Can Laser Doppler Imaging be used to predict burn wound outcomes in a paediatric population?	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Study type – cohort, observational, case studies.	Case series, subject to bias of an observational study.	Yes
Is the sample size adequate for the study?	N=48, No details or power analyses provided on subject selection.	Yes
Selection criteria for subjects?	Insufficient details provided.	Unclear
Appropriateness of study design to study question	Study design was appropriate – based on paediatric population and appropriate measures of outcome.	No
Were participants/care providers/outcome assessors blind to Laser Doppler Imaging images? If not, how could this effect the risk of bias?	Surgeons not blind to Laser Doppler Imaging, authors state this may include bias	Yes
Were there unexpected drop outs/exclusions during the study which were inadequately explained?	It appears 4 patient's results have not been included and these are unexplained.	Yes
Are the choice of outcome measures appropriate to the study question?	Outcome measures entirely appropriate and relevant to study questions and results address initial aim.	No
Were appropriate statistical analyses presented?	All results documented clearly in tables and graphs, minitab statistics package used and significant logical regression statistics.	Not clear due to exclusion of 4 patients.
Quality of intervention with Laser Doppler Imaging – is scan timing appropriate?	Scanning time earlier than recommended by manufacturer but was entirely appropriate for the study question.	No.
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Brown et al		
Can Laser Doppler Imaging be used as an aid in clinical management decision making in the treatment of vesicant burns?	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Study type – cohort, observational, case studies.	Pilot study – animals	Yes (observational study can introduce bias)
Is the sample size adequate for the study?	N=8 Very small sample size but appropriate for a pilot study	No
Selection criteria for subjects?	Yes, for the purpose of this study	No
Appropriateness of study design to study question	No in the fact the study questions does not mention use of pigs as a subject but suggests 'human' involvement by mentioning clinical management: use of vesicant agents and skin burns.	No
Were participants/care providers/outcome assessors blind to Laser Doppler Imaging images? If not, how could this effect the risk of bias?	n/a	n/a
Were there unexpected drop outs/exclusions during the study which were inadequately explained?	No	No
Are the choice of outcome measures appropriate to the study question?	Yes, biopsies were taken (gold standard)	No
Were appropriate statistical analyses presented?	n/a	n/a
Quality of intervention with Laser Doppler Imaging – is scan timing appropriate?	n/a	n/a
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Kim et al		
Is there evidence that Laser Doppler Imaging in paediatric patients leads to earlier decision making of the need for operative intervention to ensure optimal burn wound healing?	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Study type – cohort, observational, case studies.	Non-randomised cohort study	Not clear – observational study subject to bias
Is the sample size adequate for the study?	Yes a large sample size was used (196)	No
Selection criteria for subjects?	Yes, selection criteria and exclusion criteria provided in full detail and sufficient not to introduce bias due to patient selection	No
Appropriateness of study design to study question	Completely appropriate design of study to answer the study question	No
Were participants/care providers/outcome assessors blind to Laser Doppler Imaging images? If not, how could this effect the risk of bias?	No – treating surgeon viewed Laser Doppler Imaging in order to decide on need of operative intervention	No
Were there unexpected drop outs/exclusions during the study which were inadequately explained?	No unexplained exclusions/drop outs	No
Are the choice of outcome measures appropriate to the study question?	Yes all outcome measures are appropriate	No
Were appropriate statistical analyses presented?	Yes, appropriate statistical analyses presented including one-way ANOVA, student t-test. Pearsons X2 were applied to categorical data	No
Quality of intervention with Laser Doppler Imaging – is scan timing appropriate?	Scan timing was described as recommended by the manufacturer	No
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Pape et al		
How accurate is Laser Doppler Imaging assessment of intermediate depth burns compared to clinical assessment?	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Study type – cohort, observational, case studies.	Prospective audit	No
Is the sample size adequate for the study?	N=48 for a 6 month audit the sample size appears adequate	No
Selection criteria for subjects?	The author describes the audit of patients admitted with intermediate burns. Assuming these were all patients during the 6 month period. No bias was introduced	No
Appropriateness of study design to study question	Study design was very appropriate to the study question.	No
Were participants/care providers/outcome assessors blind to Laser Doppler Imaging images? If not, how could this effect the risk of bias?	Clinical assessment was performed and documented prior to Laser Doppler Imaging assessment.	No
Were there unexpected drop outs/exclusions during the study which were inadequately explained?	No	No
Are the choice of outcome measures appropriate to the study question?	Yes all appropriate	No
Were appropriate statistical analyses presented?	No statistical analyses was presented	Yes
Quality of intervention with Laser Doppler Imaging – is scan timing appropriate?	Yes all scans performed 48-72 hours post burn within manufacturers guidelines	No
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Holland et al		
What is the ability of Laser Doppler Imaging in evaluating burn depth in children	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Study type – cohort, observational, case studies.	Observational pilot study	Yes as per observational studies
Is the sample size adequate for the study?	N=58, sufficient population size for pilot study	No
Selection criteria for subjects?	Selection criteria clearly detailed and were appropriate for study design and question	No
Appropriateness of study design to study question	Study design was appropriate to the study question	No
Were participants/care providers/outcome assessors blind to Laser Doppler Imaging images? If not, how could this effect the risk of bias?	Blind: Medical and nursing staff caring for the patients were unaware of results of Laser Doppler Imaging scans	No
Were there unexpected drop outs/exclusions during the study which were inadequately explained?	No reported withdrawals or exclusion	No
Are the choice of outcome measures appropriate to the study question?	Outcome measures described are appropriate	No
Were appropriate statistical analyses presented?	Sensitivity and specificity of both Laser Doppler Imaging and clinical assessments have been compared, this is sufficient to answer the study question	No
Quality of intervention with Laser Doppler Imaging – is scan timing appropriate?	Patients were scanned between 36 and 72 hours post burn, within the manufacturers recommended scan time	No
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Niazi et al		
Is the new Laser Doppler scanner a valuable adjunct in burn depth assessment?	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Study type – cohort, observational, case studies.	Pilot study	Yes, within limits of an observational – type study not controlled trial.
Is the sample size adequate for the study?	N=13, small sample size but considered adequate for pilot study no power analyses provided	No
Selection criteria for subjects?	Not adequately detailed	Yes
Appropriateness of study design to study question	Study design was entirely appropriate at the time of the pilot study	No
Were participants/care providers/outcome assessors blind to Laser Doppler Imaging images? If not, how could this effect the risk of bias?	No blinding according to methodology	Yes
Were there unexpected drop outs/exclusions during the study which were inadequately explained?	No – no exclusions or drop outs without inadequate explanation	No
Are the choice of outcome measures appropriate to the study question?	Yes all were appropriate to the study question	No
Were appropriate statistical analyses presented?	No statistical analyses detailed, but tables sufficiently indicate results for small data sample	Unclear
Quality of intervention with Laser Doppler Imaging – is scan timing appropriate?	Patients were scanned at 24, 48 and 72 hours appropriate for this study question.	No
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

La Hei		
Can burn wound outcome, in a paediatric population be predicted by Laser Doppler Imaging in the absence of any direct clinical assessment?	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Study type – cohort, observational, case studies.	Blinded audit	Yes
Is the sample size adequate for the study?	N=31 patients, 50 scans. Small sample size not adequate to answer study question	Yes
Selection criteria for subjects?	Yes sufficient details of this selection criteria have been provided	No
Appropriateness of study design to study question	Study design was appropriate considering the study question	No
Were participants/care providers/outcome assessors blind to Laser Doppler Imaging images? If not, how could this effect the risk of bias?	Reporters were blinded	No
Were there unexpected drop outs/exclusions during the study which were inadequately explained?	None	No
Are the choice of outcome measures appropriate to the study question?	Yes, outcome measures detailed were appropriate to the study question	No
Were appropriate statistical analyses presented?	Sensitivity and specificity reported but no other statistical data available	No
Quality of intervention with Laser Doppler Imaging – is scan timing appropriate?	Scans not all performed during the manufacturers recommended times.	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

6.13 Appendix 4: Search strategy for section 5.9 (Adverse events)

The following information should be provided.

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

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

The specific databases searched were:

- MedLine
- PubMed
- ScienceDirect
- Medline In-Process (via OVID)
- Note that EMBASE and EconLIT were not searched as we do not have Company subscriptions with these databases

6.13.2 The date on which the search was conducted.

01/09/2010

6.13.3 The date span of the search.

As no adverse events have ever been reported or found, a one off search was conducted on date above.

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

Search words used:

- moorLDI AND burn AND adverse AND events
- laser doppler imaging AND adverse AND events
- laser Doppler imaging AND burn AND complications

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

N/A

6.13.6 The inclusion and exclusion criteria.

N/A

6.13.7 The data abstraction strategy.

N/A

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

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

N/A

6.15 Appendix 6: Search strategy for cost-effectiveness and cost studies (section 6.1)

The following information should be provided.

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

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

- A search of the NHS EED (via CRD Database search engine) database was carried out. Note that EMBASE and EconLIT were not searched as we do not have Company subscriptions with these databases.

6.15.2 The date on which the search was conducted.

01/09/2010

6.15.3 The date span of the search.

Searches are carried out on a monthly basis up to 01/9/2010

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

Search words used:

- Burn AND cost
- Burn treatment AND cost
- Burn AND economics
- moorLDI AND burn AND cost

- laser Doppler imaging AND cost AND burn
- laser Doppler imaging AND economic AND burn

laser Doppler imaging AND financial study AND burn

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

N/A

6.16 Appendix 7: Quality assessment of cost-effectiveness and cost studies (section 6.1)

N/A as no studies found

	Study name	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?		
2. Was the economic importance of the research question stated?		
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?		
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?		
5. Were the alternatives being compared clearly described?		
6. Was the form of economic evaluation stated?		
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?		
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?		

9. Were details of the design and results of the effectiveness study given (if based on a single study)?		
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?		
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?		
12. Were the methods used to value health states and other benefits stated?		
13. Were the details of the subjects from whom valuations were obtained given?		
14. Were productivity changes (if included) reported separately?		
15. Was the relevance of productivity changes to the study question discussed?		
16. Were quantities of resources reported separately from their unit cost?		
17. Were the methods for the estimation of quantities and unit costs described?		
18. Were currency and price data recorded?		
19. Were details of price adjustments for inflation or currency conversion given?		
20. Were details of any model used given?		
21. Was there a justification for the choice of model used and the key parameters on which it was based?		
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?		
23. Was the discount rate stated?		
24. Was the choice of rate justified?		

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

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

The following information should be provided.

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

- Medline
- Embase

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

Covered by previous searches

6.17.2 The date on which the search was conducted.

01/09/2010

6.17.3 The date span of the search.

Monthly up to date above

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

As per previous searches

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

N/A

6.17.6 The inclusion and exclusion criteria.

As per previous searches

6.17.7 The data abstraction strategy.

As per previous searches

6.18 Appendix 9: Resource identification, measurement and valuation (section 6.4)

The following information should be provided.

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

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

The specific databases searched were:

- MedLine
- NHS EED (via CRD Database search engine)
- PubMed
- ScienceDirect
- Medline In-Process (via OVID)
- Note that EMBASE and EconLIT were not searched as we do not have Company subscriptions with these databases

6.18.2 The date on which the search was conducted.

Searches are conducted on a regular (monthly) basis with the last search performed on 20th August.

6.18.3 The date span of the search.

1990 – Present to include all Moor Instruments LDI's in use for Burn imaging.

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

Search words used:

- Burn AND cost
- Burn treatment AND cost
- Burn AND economics
- moorLDI AND burn AND cost
- laser Doppler imaging AND cost AND burn
- laser Doppler imaging AND economic AND burn
- laser Doppler imaging AND financial study AND burn

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

No additional searches performed

6.18.6 The inclusion and exclusion criteria.

Inclusion criteria	Population – Cost/economic studies related to the use of the moorLDI2-BI for burn assessment in UK or European Hospitals Interventions – Laser Doppler Imaging of burn wounds with CE Marked 510K FDA Equipment. Moor Instruments equipment, moorLDI systems Outcomes – cost analysis, economic analysis, cost savings Study design – Economic or cost studies Language restrictions – English Level of results available – fully published articles in peer reviewed journals, in the press and papers submitted for publication (i.e. *In Press*)
Exclusion criteria	Population – Studies using the moorLDI2-BI for burn assessment where they do not include any cost or economic evaluation or are outside of the UK or European area Interventions – non-use of Laser Doppler Imaging, use of Laser Doppler Imagers without CE marking/510K FDA for use in burn assessment Outcomes – Other than those listed above Study design – None Language restrictions – Languages other than English Level of results available – unpublished audits and posters

6.18.7 The data abstraction strategy.

A minimum of two Moor Instruments Employees (of JR, RG, AW) reviewed the title and abstract of each article identified in the literature search detailed in the previous sections to determine if the article has met the inclusion criteria detailed in Section 7.9.6. Disagreements over the inclusion and/or exclusion of specific literature were resolved by repeated review and discussion by the Employees responsible for the data abstraction.

Articles for which it was deemed were requiring full text review – in this case this included all publications (whether published or In Press) considered for inclusion in this study, where available to us, were abstracted by one of the Employees, and then all abstracted data were verified by a second Employee and checked against a Bibliography for conformation. Throughout the abstraction process, the investigators maintained an active dialog regarding specific articles and reviewed questions regarding data abstraction to maintain a consensus approach among abstractors.

A complete bibliography was maintained detailing all reference articles identified on record. Thus enabling those responsible for data abstraction to confirm and double-check all required Abstracts and publications had been obtained.

7 Related procedures for evidence submission

7.1 Cost models

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

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

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

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

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

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

7.2 Disclosure of information

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

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

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

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

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

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

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

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

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

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

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

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

7.3 Equity and equality

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

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

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

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