NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Evaluation Pathway Programme assessment

Specification for manufacturer/sponsor submission of evidence

August 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.

Ambulight PDT.

1.2 What is the principal mechanism of action of the technology?

The Ambulight PDT device delivers the light dose required to activate a separate pharmaceutical, thereby allowing photodynamic therapy (PDT) to be delivered in an ambulatory fashion for the treatment of non melanoma skin cancer (NMSC).

1.3 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).

The Ambulight PDT device is CE marked Class 2a medical device and achieved this regulatory status in September 2009.

1.4 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).

It should be noted that Photodynamic Therapy (PDT) is the action of a pharmaceutical on NMSC lesions. The light sources used in this process activate this pharmaceutical. As the mechanism of action on the patient is entirely derived from the pharmaceutical it is natural that the principal regulatory and safety issues reside with the pharmaceutical rather than with the light sources.

The Ambulight PDT differs from the other light sources used in PDT in the fact that it is ambulatory, discussions from a regulatory/safety perspective have therefore focussed on the ambulatory side of the treatment and not on the pharmaceutical cream.

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

The Ambulight PDT is indicated for use in the treatment of superficial basal cell carcinoma (sBCC), Bowen's disease and Aktinic Keratoses (AK) in combination with a photosensitising cream such as methyl aminolevulinate (Metvix) or 5-aminolevunic acid (5-ALA) to deliver photodynamic therapy to the treatment area.

1.6 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.

Ambulight PDT is currently being used by a number of Key Opinion Leaders in the UK and across Europe. They are assessing a number of aspects of the device including the introduction of an ambulatory aspect to PDT. They are also investigating the patient's pain tolerability of ambulatory PDT vs.

traditional static lamp PDT therapy during the treatment of sBBC, Bowens and AKs using both Metvix and 5-ALA. In the next 12 months Ambicare anticipates that at least 3 papers will be published reporting the findings of these investigations. It is anticipated that at least 100 patients will be included in these. Further details of these are included in Section B.

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

Ambulight PDT is currently available in UK.

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

Ambulight PDT is CE marked therefore it has regulatory approval in all EU countries and where EU approval is recognised.

1.9 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)	£250
Average selling price	£200
Range of selling prices	£180 - 250
Consumables (if applicable) Per consumable: name, list price, average/range selling price, frequency	n/a – single use device
Service/maintenance cost and frequency (if applicable)	n/a – single use device
Anticipated life span of technology	n/a – single use device
Average length of use per treatment	6 hours
Average frequency of use	Once
Average cost per treatment	£200 plus 1 primary care 15 minute consultation.

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

The Ambulight PDT does not change the PDT treatment itself, however it would allow PDT treatments to be delivered at the point of need and diagnosis, in the community, at a time and place suitable to both the patient and the HCP.

This is in contrast to current protocol where treatment is dictated by the location and availability of large expensive static lamps mainly within secondary care. Flexibility in treatment is also reduced due to the resource required to deliver the service within this setting.

The Ambulight PDT may reduce the number of outpatient visits and / or hospitalisations for patients with NMSC requiring PDT as well as improve accessibility to treatment and reduce waiting times.

1.11 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.

1.12 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.

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

None.

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

No.

2 Context

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

The technology is designed to treat pre-malignant and malignant NMSC tumours, single lesions less than 2.4 cm in diameter. This includes patients with Basal Cell Carcinomas (BCC), Actinic Keratosis (AK) and Bowen's Disease (BD).

The diseases affect the skin and are associated with certain genetic factors and exposure to sunlight. Although basal cell carcinoma rarely metastasizes, it grows locally with invasion and destruction of local tissues. The cancer can impinge on vital structures like nerves and result in loss of sensation or loss of function or rarely death.

The target group does not include patients with Squamous Cell Carcinomas (SCC). The recommended choice of target lesion types is dictated by the PDT pharmaceutical (Metvix or 5-ALA) rather than the light delivery source, Ambulight PDT device.

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.

There are a reported ~ 100,000 new NMSC patients diagnosed each year. The number of lesions each patient presents with is not recorded but will be at least one per patient so this equates to a minimum of NMSC lesions (the number could be much higher as the options patients present with could be more than one lesion at any given time). Based on statistics from Ninewells Hospital and other existing PDT clinics, of these 100k lesions 60% would be suitable for PDT treatment. Of those suitable for PDT treatment ~ 40% have lesions of a size and location suitable for Ambulight PDT. So this equates to

~ 24k patients per annum in the UK. The incidence of NMSC is doubling every ten years so in 5 years time this would equate to ~ 36k patients.

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.

Improving outcomes for people with skin tumours including melanoma relating to the management of low risk basal cell carcinomas in the community. Cancer service guidance CSGSTIM. Issued Feb 2006.

Review in progress: Draft guidance currently available on NICE website for final fact check - See Improving Outcomes for People with Skin Tumours including Melanoma relating to the management of low risk basal cell carcinomas (BCCs) in the community.

Photodynamic therapy for non-melanoma skin tumours Interventional procedures guidance. Interventional procedures guidance IPG155. Issued Feb 2006.

Final recommendations:

1.1 Current evidence suggests that there are no major safety concerns associated with photodynamic therapy for non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions).

1.2 Evidence of efficacy of this procedure for the treatment of basal cell carcinoma, Bowen's disease and actinic (solar) keratosis is adequate to support its use for these conditions, provided that the normal arrangements are in place for consent, audit and clinical governance.

1.3 Evidence is limited on the efficacy of this procedure for the treatment of invasive squamous cell carcinoma. Recurrence rates are high and there is a risk of metastasis. Clinicians should ensure that patients understand these risks and that retreatment may be necessary. In addition, use of the Institute's Information for the public is recommended (available from www.nice.org.uk/IPGxxxpublicinfo).

Providing public information to prevent skin cancer. Public health guidance. Due Jan 2011

Resources and environmental changes to prevent skin cancer. Public health guidance. Due Jan 2011

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.

Conventional PDT Pathway:

Patient presents to primary care and is then referred to secondary care for diagnosis. The patent presents to secondary care. At the secondary care first visit the lesion is diagnosed and identified if suitable for conventional PDT, the patient is then booked in the central PDT clinic x weeks later. X weeks later the patient presents to the secondary care PDT clinic as a day outpatient and undergoes conventional PDT, this treatment involves initial application of the photosensitizing cream, a minimum 3 hour wait for the cream to activate followed by the light therapy being applied, essentially 1 full days treatment. The patient is then discharged. 1 week to 1 month later the patient presents to the secondary care PDT clinic again as a day outpatient and undergoes the second conventional PDT treatment, as above. The patient is then discharged. The patient then returns for a clearance examination on either single or multiple visits as outlined in the regional protocol. In total the patient has 1 primary care visit and a minimum of 4 secondary care visits.

Ambulight PDT Pathway:

Patient presents to primary care. At the first visit the lesions is diagnosed and identified as suitable for Ambulight PDT. The lesion has the photosensitising cream applied and the first Ambulight PDT treatment applied at same time. The patient is discharged. The patient presents back to

primary care 1week to 1 month later for second Ambulight PDT treatment. The patient is discharged. The patient returns to primary care for clearance examination. In total the patient has 3 primary care visits.

For elderly or infirm patients the Ambulight PDT treatment could be done in their home.

Note: There are already ~ 200 plus GPs with Specialist Interest (GPwSI) in dermatology who are affiliated with secondary care dermatology units. These GPwSI would already be trained in accurate diagnosis in NMSC.

If the diagnosis is maintained in secondary care there is still the opportunity to deliver the actual Ambulight PDT treatment in primary care, avoiding the patient having two additional journeys to the hospital as a day outpatient.

A secondary care remote diagnosis platform is already in place in many trusts and this would be expanded to ensure accurate diagnosis and appropriate treatment, further reducing costs and creating a patient centric service.

It is also worth noting that cutting out healthy tissue misdiagnosed as a NMSC could lead to greater secondary infections and scarring than using Ambulight PDT on healthy skin i.e. Ambulight PDT has the potential to do less harm in the case of misdiagnosis than other treatments

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

The main issues with current conventional PDT are: (i) limited access to service (few centres) and low patient throughput (ii) pain and inconvenience for patient (iii) overhead of a secondary care delivery mechanism and (iv) burden of conventional PDT treatment on patients lives. PDT is a treatment that best practice indicates should be given to patients with suitable lesions as an option to other treatment methods such as surgery. Many patients are not offered or elect not to take up PDT, despite the cosmetic benefits, due to the inconvenience and limited access. A number of dermatologists can only offer PDT as a tertiary service. There is also considerable anecdotal evidence that

patients are reluctant to undergo PDT a second time having experienced the pain involved in the first treatment.

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

Conventional hospital based PDT.

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

Adverse reactions in PDT are related to the pharmaceutical prescribed and not to the light source. For a list of these adverse reactions please refer to the SPC (specific product characteristics) associated with the pharmaceuticals.

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 Ambulight is a device that is flexible in its use and hence can be used in both primary and secondary care settings. The use of the device in a primary setting offers the greatest benefits to the HPC and the patients. As such the main resource use would be GPs and primary care nursing resource. The location of care would be the GPs surgery. After diagnosis each Ambulight PDT treatment would require a 15 minute appointment with either the GP or health practice nurse.

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).

The additional costs to the Ambulight PDT device are the pharmaceutical but this would be the same as for conventional PDT. Ambulight PDT has the potential to reduce administration and hospital planning costs, hospital transport costs and clinical overhead.

Currently patients PDT procedure codes are classed as day case outpatient treatments. Reimbursement rates vary regionally but these are between £500 - £1000 per patient treatment. Ambulight PDT would allow the code to be reduced to a primary care 15 minute consultation with a nurse specialist.

Transportation and care costs need also to be considered for elderly or less competent patients for current PDT therapy around static lamps in secondary or tertiary care. These costs could be substantially reduced or removed with Ambulight PDT treatment in the community.

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.

n/a

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)?

n/a

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

n/a

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 NMSC or dysplasia (ie. Superficial basal cell carcinoma, actinic keratosis or Bowen's disease and excluding those with SCC), single lesion. Lesions should be < 2.4 cm in diameter		
Intervention	Ambulight PDT with Metvix pharmaceutical Ambulight PDT with 5-ALA pharmaceutical		
Comparator(s)	Conventional hospital based PDT The Aktilite CL128 lamp No treatment *Comparators should present data using Metvix and 5-ALA agents where possible.*		
Outcomes	Tumour response rates to include recurrence rates or need for re-treatment or additional treatment), pain during treatment, quality of life parameters, device failure, other complications or adverse effects	Pain during treatment, quality of life parameters, device failure.	It should be noted that Photodynamic Therapy (PDT) is the action of a pharmaceutical on NMSC lesions. The light sources used in this process activate this pharmaceutical. As the mechanism of action on the patient is entirely derived from the pharmaceutical the efficacy of the treatment is dependent on the pharmaceutical and not on the light that simply activates the drug. The Ambulight is therefore slightly different to most devices in that it is a combination product.

			The instructions relating to the pharmaceutical specify the exact type and dose of light required for the treatment. The Ambulight, as with all other lights on the market fully meets these requirements. There is therefore no need to question the efficacy of the Ambulight over other light sources. In fact the recent NICE summary on PDT (document 31364) systematically analysed clinical papers relating to PDT. In this no mention was made of the influence of different light sources although there were at least 3 light sources used in the different papers. None of the papers themselves make any distinction between the light sources. In the wider clinical community, the variation of light sources is not seen as a significant factor in influencing efficacy. (British Journal of Dermatology 2008 159, pp1245–1266 in particular P1247)

Cost analysis	Comparative cost analysis of Ambulight PDT with Metvix and the relevant comparator for the treatment of NMSC: conventional hospital based Metvix PDT. Cost analysis should account for initial delivery costs including equipment, pharmaceuticals and staff costs during set up and monitoring, hospital and clinic care, staff training, long-term disease management, adverse events including repeat or additional treatments and pharmaceutical costs. Cost savings from reduced demand on outpatient and inpatient services should also be included in the analysis. A sensitivity analysis for the use of 5-ALA would be useful.		
Subgroups to be considered	For NMSC lesion types (BCC, AK and BD), consider whether there is any evidence of differential benefit between these types of lesion in comparison with other techniques. The role of Ambulight PDT in treating multiple lesions. Patients with smaller lesions: consider whether Ambulight PDT is more effective with reduced lesion size. Consider whether body size may affect effectiveness of Ambulight PDT.		
Special considerations, including issues related to equity or equality	No special considerations were identified at scoping stage.		

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.

Ambicare has based its strategy on identifying clinical data in two parts; the first of these is a rationale explaining why the Ambulight device is equivalent to the existing light sources on the market. This rationale systematically evaluates any differences between the Ambulight and these devices and uses this to identify the areas requiring clinical evaluation. This rationale is included in the attached appendix compiled by Ambicare.

The second part of the strategy is identifying which papers are suitable for inclusion in the review. This strategy is summarised on P24 of the attached appendix.

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.

The inclusion and exclusion criteria used in this evaluation are included on P25 of the attached appendix.

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

The number of papers included and excluded in the search are included on p25 of the attached appendix.

Complete list of relevant studies (RCTs and non-RCTs)

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.

A summary of the relevant studies is included on P25-28 of the attached appendix.

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.

The ONLY criteria for rejecting papers for inclusion in the attached appendix were the ones laid out in the MED-DEV guidance 2.7.1 (section 4.3.1 d) on the basis of either; clinical, technical or biological aspects.

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.

The methods used in the studies are included on P19, 20, 25-28 of the attached appendix.

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.

The participants and their eligibility are described on P19, 21, 24 of the attached appendix.

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

The patient characteristics are included on P19, 24 of the attached appendix.

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.

The outcomes of the studies are listed on P21 & 24, 25-28 of the attached appendix.

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.

The hypotheses under consideration in this clinical evaluation are considered on P24 & 25 of the attached appendix.

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.

There were no subgroup analyses made.

Participant flow

Where applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who were lost to follow-up or withdrew from the study.

The number of patients that were included in the study and their flow through the study are described on P19, 21, 24.

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.

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).

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.

Section 5.5 is included in the attached appendix.

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-analysis has been performed as part of this review

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.

N/a

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.

The studies relating to safety are included on P8, 9, 10 of the attached appendix.

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 been reported for the Ambulight PDT to date. PDT is a combination therapy, a summary of the adverse events relating to PDT in general is included on P8-9 for completeness.

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

It should be noted that the Ambulight PDT product is a light source for use in a combination therapy and that it activates the photochemical reaction of a separate drug within the skin. Light at this wavelength and irradiance is not considered hazardous. Further the aim of the review by NICE is to review the Ambulight device and not PDT in general.

Use of the device and any associated risks relating to the device have been addressed in the development phase and have been considered fully through an extensive risk analysis process. The protocol relating to

use of the Ambulight does not raise any further significant safety issues. The risk analysis relating to the device and its use are available upon request.

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 principle findings from the clinical evidence are summarized on P28 & 29 of the attached appendix.

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

A summary of the strengths and limitations of the clinical evidence is included on P22, 23, 25-28.

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.

It should be noted that the two presented studies either; used the Ambulight, or an early prototype of the Ambulight, so are directly relevant to the decision problem. A discussion of the relevance of the other clinical data is included on P25-28 of the attached appendix.

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.

In both of the sets of clinical data that were presented in the attached appendix, the patients were identified through routine referrals at Ninewells hospital in Dundee. As such the choice of patients was identical to the clinical practice at Ninewells. In the first study, the ambulatory nature of the device was restricted so that although patients could move around they were restricted to the dermatology department.

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.

Using EMBASE, EconLIT, NHS EED and Medline databases (1996 – 2010), a search was conducted (photodynamic AND cost) AND (Photodynamic AND economic) which revealed 253 titles. From this, publications were excluded from this analysis due to not being relevant to the decision problem only. The main reason for exclusion was for publications not relevant to PDT of the skin, i.e. PDT of the eye, bladder etc. From this 13 publications were identified as being relevant to the decision problem.

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.

See tab 'Table B1' on the attached Spreadsheet.

Table B1 Summary list of all evaluations involving costs

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	Costs (currency) (intervention, comparator)	QALYs (intervention, comparator) (when referred to in the study)	ICER (per QALY gained) (if applicable)
Study 1							
Study 2							
Etc.							
ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s)							

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.

All of the papers revealed in the systematic search provide costs for PDT in secondary care in comparison to alternative therapies. The Ambulight PDT is an ambulatory device that affects the way in which PDT services are implemented and consequently what they cost. Performing a quality assessment analysis of the papers relating to PDT will not add to the accuracy of costing of how Ambulight PDT affects PDT service implementation. This section has therefore not been completed.

6.2 De novo cost analysis

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

[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.

The Ambulight PDT device is unique in the area of PDT in that it is the first truly ambulatory device. This means that the device can be used within the NHS differently to conventional static lamps, and this difference has a knock on effect on PDT treatment economics. There is a certain amount of data that already exists that accounts for typical PDT treatments but there is none that accounts for ambulatory PDT. As such a de novo cost analysis is justified as there is no data to account for the effect of an ambulatory device.

Patients

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

Patients with NMSC or dysplasia (ie. Superficial basal cell carcinoma, actinic keratosis or Bowen's disease and excluding those with SCC), single lesion. Lesions should be < 2.4 cm in diameter.

Model structure

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

The model is a linear assessment of cost and as such is not suited to a diagrammatical representation.

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

The clinical pathway for PDT treatment was chosen as this is the way in which the Ambulight PDT will be used. This pathway also reflects the latest NICE guidelines whereby NMSC treatments should be carried out by clinicians in the community.

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

The Ambulight PDT works in exactly the same way as any other PDT lamps on the market or in use on the NHS today. The de novo model does not look at health states rather it looks at the impact on the NHS of

the costs involved with using the Ambulight in comparison to the existing light sources. The Ambulight PDT affects the way in which PDT services are implemented not the efficacy of PDT or the health state of the patient.

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.

The de novo model does not look at how the patient's condition is changed when compared to existing PDT lamps, it looks at the way in which PDT services are implemented.

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.

Please refer to the tab 'Table B2' on the attached spreadsheet.

Table B2 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon			
Cycle length			
Half-cycle correction			
Discount of 3.5% for costs			
Perspective (NHS/PSS)			
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 interventions and comparators are as their 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.

A clinical continuation rule has not been assumed for the Ambulight PDT device (but would be the same as conventional PDT).

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.

Given the clinical efficacy equivalence of the Ambulight PDT to existing light sources, no clinical efficacy data was included in the model. The model only evaluates the impact on the NHS of the costs involved with using the Ambulight in comparison to the existing light sources. The Ambulight PDT affects the way in which PDT services are implemented not the clinical efficacy of PDT. The clinical data was only used to determine costs in the model. Where this was the case, the range of values was determined and an average calculated.

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.

Transition probabilities were not calculated from the clinical data.

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.

N/a

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?

No, intermediate outcome measures were not linked to final outcomes.

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
- 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
- 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.

The clinical expert was chosen for their in depth, long term knowledge of PDT.

One expert was approached and participated.

The clinical expert was a founder of Ambicare.

A clinical expert was used only to determine; the flow of patients through a PDT clinic, and to determine the timings of the treatment. These individual elements were then costed using the supplied clinical data. The clinical expert had no input into the cost calculations.

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

[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.

cross-references to other parts of the submission. Please present in a table, as suggested below.

See Attached Spreadsheet for Table B3.

Table B3 Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Age	A years	x to y (normal)	Patient characteristics section 5.3.4
Overall survival	B months	x to y (Weibull)	Study results section 5.5
Etc.	…	…	…
CI, confidence interval			

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 but we anticipate these would be the same as convention PDT (or improved over conventional PDT)

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

See Table B3 in attached spreadsheet.

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 current costing is very ambiguous within the NHS for photodynamic therapy. PDT is not only used to treat NMSC but is also used to treat systemic cancers, therefore the actual costs versus the reimbursement and PBR costs could be quite disparate.

The following PBR costs are currently applied to the delivery of a PDT service and various bundles of these are used in different variations depending on the individual location where the treatment is being provided.

Code	National PBR Tarrif
JC05A	Minor Skin Procedures Category 3 with Major CC
JC05B	Minor Skin Procedures Category 3 with Intermediate CC
JC05C	Minor Skin Procedures Category 3 without CC
JC06A	Minor Skin Procedures Category 2 with Major CC
JC06B	Minor Skin Procedures Category 2 with Intermediate CC
JC06C	Minor Skin Procedures Category 2 without CC
JC07Z	Minor Skin Procedures Category 1
JC14Z	Skin Therapies level 2
JC15Z	Skin Therapies level 3
JC16Z	Skin Therapies level 4
JC17Z	Skin Therapies level 5
JC27Z	Nursing Procedures & Dressings 1
JC29Z	Phototherapy
JC32Z	Photochemotherapy
JD04A	Minor Skin disorders Category 3 with Major CC
JD04B	Minor Skin disorders Category 3 with Intermediate CC
JD04C	Minor Skin disorders Category 3 without CC
JD05A	Minor Skin disorders Category 2 with Major CC
JD05B	Minor Skin disorders Category 2 with Intermediate CC
JD05C	Minor Skin disorders Category 2 without CC

JD06A	Minor Skin disorders Category 1 with CC
JD06B	Minor Skin disorders Category 1 without CC
190	Anaesthetics
191	Pain Management

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

NHS tariffs and costs are not currently relevant for PDT. Given the wide range of cancers that can be treated with the therapy a clear relevant code would be an improved method to include all of the costs associated with delivering the service.

The following costs should be included specifically for NMSC PDT.

- **The drug**
- **Lesion preparation**
- **Patient transportation**
- **Patient management as a day case outpatient**
- **Dressings during and following treatment**
- **Healthcare Professional time**
- **Cost of light source, consumables and ongoing maintenance**
- **Cost of room for treatment**

A specific code could also be developed for delivering static lamp PDT in primary or secondary care or an ambulatory service in both these settings since the cost of room hire, healthcare professional and patient

management would vary significantly depending on the location of the service and the choice of light source used to deliver it.

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.

Given the nature of the model that is included for the Ambulight PDT, the resource identification was included in the previous section. Please refer to question 6.1.1 for details on the search methodology.

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.

Given the nature of the model that is included for the Ambulight PDT, the resource identification was included in the previous section. Please refer to question 6.3.5 for details on clinical experts used.

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.

This data is included in the attached spreadsheet. The unit costs for the comparator are included on tab 'Comparator Costs' and the unit costs for the Ambulight are split into two areas. The first set of unit costs for the Ambulight are for primary care being administered by a GPSI, and the second set of costs are the Ambulight being administered by a nurse.

Table B4 Unit costs associated with the technology in the economic model

Items	Intervention (confidence interval)	Ref. in submission	Comparator 1 (confidence interval)	Ref. in submission	Etc.
Technology cost					
Mean cost of technology treatment					
Administration cost					
Monitoring cost					
Tests					
Etc.	…		…		…
Total					

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.

An analysis of the costs included for each health state has not been included in the model.

Table B5 List of health states and associated costs in the economic model

Health states	Items	Value	Reference in submission
Health state 1	Technology		
	Staff		
	Hospital costs		
	Etc.		
	Total		
Health state 2			
Etc.	…	…	…

Adverse-event costs

6.4.7 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.

The Ambulight PDT device just with all other existing PDT light sources activates a separate pharmaceutical. As such, the adverse events resulting from PDT are derived from the pharmaceutical and not the light sources. The adverse events are therefore exactly the same as the other light sources and as such an examination of the costs of the adverse events will be exactly the same.

Table B6 List of adverse events and summary of costs included in the economic model

Adverse events	Items	Value	Reference in submission
Adverse event 1	Technology		
	Staff		
	Hospital costs		
	Etc.		
	Total		
Adverse event 2	Technology		
	Staff		
Etc.	…	…	…

Miscellaneous costs

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

All costs are included in the model.

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

The Ambulight PDT device brings a number of QoL benefits to the relevant patient group. None of these QoL benefits have been included in the model. Early clinical results have demonstrated that a PDT treatment with the Ambulight PDT device is significantly less painful than with the existing lamps. The Ambulight also allows the treatment to occur in the community without the need for travel to a secondary care setting. Thus freeing up secondary care resource for other requirements.

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.

There has been no investigation into the uncertainty around the 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.

There has not been any deterministic and/or probabilistic sensitivity analysis undertaken. This is because the model is a simple linear combination of terms and variations in the input variables have a direct linear relationship with the outcome of the model.

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.

The model does not have any clinical outcomes but these will be the same as conventional PDT (or potentially improved over conventional PDT).

Table B7 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.	…	…

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

Health states were not analysed as part of the model and so the costs are not summarised here.

Table B8 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					

For Table B9 please refer to the attached spreadsheet.

Table B9 Summary of costs by category of cost

Item	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Technology cost	X_{tech}	Y_{tech}	$X_{tech} - Y_{tech}$	$\|X_{tech} - Y_{tech}\|$	$\|X_{tech} - Y_{tech}\|$/ (Total absolute increment)
Mean total treatment cost	X_{treat}	Y_{treat}	$X_{treat} - Y_{treat}$	$\|X_{treat} - Y_{treat}\|$	$\|X_{treat} - Y_{treat}\|$/ (Total absolute increment)
Administration cost	X_{admin}	Y_{admin}	$X_{admin} - Y_{admin}$	$\|X_{admin} - Y_{admin}\|$	$\|X_{admin} - Y_{admin}\|$/ (Total absolute increment)
Monitoring cost	X_{mon}	Y_{mon}	$X_{mon} - Y_{mon}$	$\|X_{mon} - Y_{mon}\|$	$\|X_{mon} - Y_{mon}\|$/ (Total absolute increment)
Tests	X_{tests}	Y_{tests}	$X_{tests} - Y_{tests}$	$\|X_{tests} - Y_{tests}\|$	$\|X_{tests} - Y_{tests}\|$/ (Total absolute increment)
Etc.	…	…	…	…	…
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

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 B10 Base-case results

Technology	Total costs (£)
Ambulight PDT	612.44
Aktilite in secondary care	748.91

Sensitivity analyses

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

No DSA was performed.

6.6.5 Please present the results of PSA.

No PSA was performed.

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

No scenario analysis was performed.

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

No sensitivity analysis was performed.

6.6.8 What are the key drivers of the cost results?

The overhead of secondary care is being replaced by a smaller resource use in primary care setting.

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.

Contributing elements of the costing model were discussed with clinicians delivering PDT in a secondary care and GPSWs delivering dermatology services in primary care. The model is a simple linear

combination of terms, and where possible these values were determined from the published literature as outlined in this submission.

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 subgroup analysis was performed.

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

N/a

6.8.3 Please describe how the statistical analysis was undertaken.

N/a

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).

N/a

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.

N/a

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?

A key aspect of the model is ensuring that the comparator is accurately accounted for. In the model the comparator costs can be broken down into two parts; direct costs and indirect costs. The direct costs are £332

and this is broadly in agreement with the papers identified in the 'References' tab of the attached spreadsheet. What the model does in addition to this is look at the indirect costs of the treatment as a whole such as transport to hospital and room costs. This adds another £416 to the total cost of treatment and is not reflected in the literature. It should be noted that this value of £416 will also be significantly higher in certain locations due to MFF. Where possible all values in the model have been sourced from the literature.

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 of the analysis is the use of actual GPSI example costs taken from the NICE economic evaluation. Although there is a wide range of values for the treatment costs that stem from this, these are actual examples of real-life costs in a setting that is directly related to the Ambulight treatment setting.

The main weakness of the analysis was the inability to reliably source costs for; the room hire and the cost and administration of analgesia. These numbers were arrived at anecdotally. However the model is a simple linear combination of values so that the impact of varying this cost can be readily appreciated by making the appropriate modification to the spreadsheet.

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

An analysis of room costs and analgesia would enhance the results.

References

Please use a recognised referencing style, such as Harvard or Vancouver.

Please refer to the ‘References’ tab of the attached spreadsheet for full list of references used in this analysis.

7 Appendices

7.1 Appendix 1

7.1.1 IFU, scientific discussion or drafts.

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

The following information should be provided.

7.2.1 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.

Response

7.2.2 The date on which the search was conducted.

Response

7.2.3 The date span of the search.

Response

7.2.4 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).

Response

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

Response

7.2.6 The inclusion and exclusion criteria.

Response

7.2.7 The data abstraction strategy.

Response

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

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

Study ID or acronym		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?		
Was the concealment of treatment allocation adequate?		
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		
Is there any evidence to suggest that the authors measured more outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Response

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

The following information should be provided.

7.4.1 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.

Response

7.4.2 The date on which the search was conducted.

Response

7.4.3 The date span of the search.

Response

7.4.4 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).

Response

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

Response

7.4.6 The inclusion and exclusion criteria.

Response

7.4.7 The data abstraction strategy.

Response

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

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

Response

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

The following information should be provided.

7.6.1 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.

Response

7.6.2 The date on which the search was conducted.

Response

7.6.3 The date span of the search.

Response

7.6.4 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).

Response

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

Response

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

	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		

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

The following information should be provided.

7.8.1 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.

Response

7.8.2 The date on which the search was conducted.

Response

7.8.3 The date span of the search.

Response

7.8.4 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).

Response

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

Response

7.8.6 The inclusion and exclusion criteria.

Response

7.8.7 The data abstraction strategy.

Response

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

The following information should be provided.

7.9.1 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.

Response

7.9.2 The date on which the search was conducted.

Response

7.9.3 The date span of the search.

Response

7.9.4 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).

Response

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

Response

7.9.6 The inclusion and exclusion criteria.

Response

7.9.7 The data abstraction strategy.

Response

8 Related procedures for evidence submission

8.1 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.

8.2 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.

8.3 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).