NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Medical technologies guidance

Assessment report summary

Ambulight PDT for the treatment of non-melanoma skin cancer

This assessment report summary has been written by technical analysts at NICE. It summarises the evidence that has been evaluated by the External Assessment Centre and highlights key issues and uncertainties. It should be read in conjunction with the Manufacturer's Submission and with the full Assessment Report, The summary formed part of the information received by the Medical Technologies Advisory Committee when it formulated its recommendations on the technology.

This report also contains:

Appendix A: Sources of evidence

Appendix B: Comments from professional bodies

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Appendix D: Manufacturer's comments on the assessment report and the External Assessment Centre's responses

1 The technology

The purpose of the Ambulight PDT device is to deliver ambulatory photodynamic therapy to treat non-melanoma skin cancer.

The Ambulight PDT comprises a small single-use light-emitting device (containing its own red light source generated by a diffuser and a series of light-emitting diodes), which is connected by a lead to a pocket-sized battery.

This light-emitting device sticks to the skin using a disposable plaster, 3 cm in diameter, worn directly over the treatment site. The battery can be carried in a pocket, attached to a belt or worn around the neck.

The light source generated by the device emits the same dose and wavelength of light as existing photodynamic therapy light sources, but the intensity is reduced and administered over a longer period of time. The light source emits a peak wavelength of 640 nm and a full-width half-maximum (FWHM) of 20 nm. The irradiance of light emitted is 7 mM/cm^2 and a total light dose of 75 J/cm^2 is delivered directly to the treatment site over a period of 3 hours.

Before delivery of the photodynamic therapy treatment, a photosensitising pro-drug is topically applied to the treatment site for 3 hours and is absorbed and metabolised to the active photosensitiser. This photosensitiser is activated by the red light source (illumination).

Two treatments with the Ambulight PDT (with separate devices) are needed to complete a course; with each treatment lasting 6 hours (3 hours for drug absorption and 3 hours of controlled photodynamic therapy delivery). These two treatments, as with conventional photodynamic therapy, are carried out between 1 week and 1 month apart.

The device is worn for the full 6 hours. It is programmed so that the light source does not turn itself on until 3 hours after the battery pack is switched on to allow for the drug absorption. A flashing light indicates when treatment is complete; the device switches itself off and can be removed by the patient.

Unlike current photodynamic therapy using large static light sources, the Ambulight PDT can be administered in a community setting including in the patient’s home. This avoids the need for a hospital appointment, reduces the need for travel and in some cases allows patients to continue with their normal daily activities.

It is claimed that the lower irradiance of the Ambulight PDT reduces the pain that patient's experience compared with conventional photodynamic therapy light sources.

2 Proposed use of the technology

2.1 Disease or condition

The Ambulight PDT is intended for use by people who have non-melanoma skin cancer.

2.2 Patient group

Non-melanoma skin cancers are the most common cancers in the UK and are most common in older age groups. The number of new diagnoses in the UK is estimated at 100,000 cases each year.

The target group for treatment with this device is people with pre-malignant and malignant non-melanoma skin cancer tumours, with single lesions less than 2.4 cm in diameter. This includes people with basal cell carcinomas, actinic keratosis and Bowen's disease.

The target group does not include people with invasive squamous cell carcinomas.

2.3 Current management

After initial presentation in primary care, a patient with a non-melanoma skin cancer lesion is usually referred to secondary care for confirmation of the diagnosis.

Current management of non-melanoma skin cancer in secondary care (specifically those lesions intended for treatment with the Ambulight PDT) might include standard hospital-based photodynamic therapy, topical chemotherapy, topical immunomodulators, surgical excision, curettage, cryotherapy or radiotherapy. Alternatively a clinician may decide not to offer treatment.

Conventional photodynamic therapy is offered in some primary care clinics.

2.4 Proposed management with new technology

The Ambulight PDT could enable photodynamic therapy to be delivered in a community setting. For some patient's, such as those with reduced mobility, there is the potential for the photodynamic therapy to be administered in their home. This could reduce the demand on hospital outpatient and inpatient services as well as improving accessibility to treatment and potentially reducing waiting times.

2.5 Equality and diversity issues

No equality and diversity issues were identified.

3 Issues for consideration by the Committee

In summary, the evidence included in the submission showed that treatment with the Ambulight PDT can reduce the pain that patient's experience compared with conventional photodynamic therapy and demonstrated efficacy in treating non-melanoma skin cancer.

The volume price of the Ambulight PDT, as presented in the cost model, is £166.

From the economic evidence submitted, it is not possible to draw firm conclusions on the cost savings associated with the use of the Ambulight PDT in primary care. The cost analysis submitted showed the potential for delivery of photodynamic therapy using the Ambulight PDT in primary care to be cost saving or cost neutral. The use of the Ambulight PDT removes the need for staff to administer illumination, room hire for the illumination period and the use of anaesthesia.

3.1 Main issues

- The clinical evidence presented on the Ambulight PDT is limited. The Committee should be aware that this is a new device and the

manufacturer is carrying out extensive postmarket surveillance to increase the evidence base. It is important to remember when reading the submission, that this technology does not claim to be more efficacious that conventional photodynamic therapy. It claims to be equivalent and the claims of benefit focus on the reduction in pain experienced during treatment and the ambulatory nature of the device which increases convenience of treatment for the patient.

- The manufacturer claims that the Ambulight PDT has the potential for use in both primary and secondary care settings and that the greatest benefits to healthcare providers and patients are offered within the primary care setting. The effects of this have not been studied in NHS practice because of the early stage of product development.

- It was suggested in the manufacturer's submission that the Ambulight PDT is not suitable for the treatment of lesions > 1.5 cm diameter because of the size of the device (2 cm diameter).

- It is not possible to draw firm conclusions on whether the methods of costing service provision with the Ambulight PDT and conventional photodynamic therapy in the manufacturer's submission are comparable. However, the GP and overhead costs used in the economic models for the delivery of photodynamic therapy with the Ambulight PDT are based on actual models of service provision in the NHS.

- Four models of service delivery in primary care with the Ambulight PDT were submitted for the cost analysis. It is not clear whether all these models of service delivery are currently used in the NHS and if they are equally as effective in providing treatment with the Ambulight PDT.

- The volume price of the Ambulight PDT, as presented in the cost model, was £166. The average selling price of the Ambulight PDT was stated as £200 in the submission, with a price range of £180–250. The

External Assessment Centre considered that it may have been more appropriate to use the average selling price, because the volume price could result in an underestimation of service provision costs.

- The Ambulight PDT can be used with either methyl aminolevulinate (Metvix) or 5-aminolevulinic acid photosensitiser; the manufacturer submitted data on the use of the Ambulight PDT with both pharmaceuticals. The active ingredient of the photosentisier can influence treatment efficacy, but the comparative effectiveness of methyl aminolevulinate and 5-aminolevulinic acid was not considered an issue by the NICE team.

- The cost model submitted by the manufacturer used an expected annual incidence of non-melanoma skin cancer in the UK of 100,000 cases and using statistics from Ninewells Hospital Dundee, estimated that 60% of patients would be suitable for photodynamic therapy. Of these, approximately 40% would have lesions of a suitable size and location suitable for photodynamic therapy using the Ambulight PDT. This translates to 24,000 patients that might be eligible for treatment with the Ambulight PDT. It is possible that this figure is too high but because of inaccuracies in reporting methods it is difficult to determine the number of photodynamic therapy treatments that take place in the UK each year. The fact that some patients receive no treatment for non-melanoma skin cancer was considered in this estimate by the manufacturer.

- The cost model submitted by the manufacturer does not address the cost consequences of how a patient's health state is changed compared with existing photodynamic therapy treatments. The focus is on the change to the way in which photodynamic therapy services are implemented.

3.2 Other issues

- The Committee should consider that the use of Ambulight PDT might require additional staff training for accurate diagnosis and treatment delivery, and for infrastructure to be set up within primary care settings.

- As specified in the scope issued by NICE and based on the Committee selection and routing considerations, the submission focused on patients with basal cell carcinomas, actinic keratosis or Bowen's disease. This is in line with the manufacturer's instructions for use. The Committee can develop recommendations only within the issued scope and not for use in other forms of non-melanoma skin cancer such as invasive squamous cell carcinoma.

- No subgroup analysis was presented to demonstrate the effectiveness of the Ambulight PDT in people with smaller lesions, different body size, multiple lesions or differential between different types of lesion in comparison with other techniques as outlined in the scope issued by NICE.

- The External Assessment Centre was unclear if all relevant literature had been captured by the search strategy used in the manufacturer's submission. The NICE team noted this but believe all relevant literature to be included.

- The 'instructions for use' protocol for methyl aminolevulinate states that the pharmaceutical cream should be removed from the treated area after 3 hours, before the light source is applied. This is different to the protocol for the Ambulight PDT because methyl aminolevulinate is left on the skin for the duration of treatment (6 hours). No adverse events relating to the extended cream application time were identified in the manufacturer's submission or External Assessment Centre report. From the evidence presented, it is unlikely that a cream application time of 6 hours will raise significant safety concerns.

- There is some evidence to suggest that pain experienced during photodynamic therapy may be influenced by the type of non-melanoma skin cancer lesion. The evidence on the Ambulight PDT is too premature to address this so there is insufficient direct evidence to be confident of its efficacy for the treatment of each tumour type.

- The Committee should be aware that there is published 'normal arrangements'NICE guidance on 'Photodynamic therapy for non-melanoma skin tumours' (NICE interventional procedures guidance 155). Other NICE guidance has also been published in this area: 'Improving outcomes for people with skin tumours including melanoma (update): the management of low-risk basal cell carcinomas in the community' and 'Improving outcomes for people with skin tumours including melanoma (NICE cancer service guidance CSGSTIM 2006 and 2010) .

4 The evidence

4.1 Summary of evidence of clinical benefit

The main clinical outcomes relevant to this technology are tumour response rates (including recurrence rates or need for additional treatment), pain during treatment and other complications or adverse events.

A total of 28 papers were included in the submission. Of these, two studies reported outcomes specific to the Ambulight PDT.

4.1.1 Tumour response rate

A pilot study by Attili et al. (2009) of 12 patients (8 patients with Bowen's disease and 4 patients with basal cell carcinomas) with a median lesion diameter of 1.1 cm (range 0.6–1.9 cm) were treated using a prototype of the Ambulight PDT device and 5-aminolevulinic acid. A complete response was reported in 75% (9/12) of patients at 6-month follow-up. At 12 months, 58% (7/12) of patients had complete tumour response (4 patients had peripheral

margin failure; 1 had residual nodular component). In all patients for whom treatment was unsuccessful, the lesion size was > 1.5 cm in diameter.

4.1.2 Pain

Pain is commonly reported by patients having photodynamic therapy. The submission described various techniques that have been developed to reduce pain during photodynamic therapy and presented studies that demonstrate that reduced irradiance is associated with reduced pain. Only those studies directly relevant to the Ambulight PDT are included in this summary.

In the pilot study of 12 patients, pain immediately after treatment was recorded using a numerical rating scale (1–10; higher score indicates worse pain). All 12 patients reported a pain score ≤ 2 (range 0–2). No patients required pain relief in the form of local anaesthesia or cool air treatment during therapy. One patient who reported excessive pain during previous photodynamic therapy commented on the lack of discomfort with the Ambulight PDT. These scores were compared retrospectively with those of 50 patients who had received conventional photodynamic therapy using an inorganic light-emitting diode static lamp source (dose 75 Jcm^{-2}). The static lamp cohort had a median numerical rating scale score of 6 (range 1–10). Eleven of these 50 patients needed local analgesia and all needed cool air treatment.

The submission presented unpublished clinical data from an ongoing study at Ninewells Hospital Dundee into the use of a light-emitting diode light source and methyl aminolevulinate cream. These data included 5 patients with single lesions treated using the Ambulight PDT and 11 patients with multiple lesions whose lesions were treated with different photodynamic therapy treatments (at least one lesion site was treated with Ambulight PDT, other sites were treated using conventional photodynamic therapy or different light-emitting diode sources). Pain immediately after treatment was recorded on a visual analogue scale (1–10; higher score indicates worse pain). For single lesions treated using the Ambulight PDT the pain score ranged from 1.5 to 7, with the second

treatment often being more painful than the first. For patients with multiple lesions treated using the Ambulight PDT the pain scores ranged from 0 to 7.5 and for multiple lesions treated with other photodynamic therapy, pain scores ranged from 1.5 to 10.

4.1.3 Overview of safety of photodynamic therapy

The scope issued by NICE requested that the manufacturer include data on adverse events reported by users of the device.

The submission stated that the Ambulight PDT is a light source for activating the photochemical reaction of a drug within the skin and that light at the wavelength and irradiance of the Ambulight PDT is not considered hazardous.

The safety outcomes presented in the submission relate to the safety of the drug after it is activated by a light source. These included localised erythema, urticaria, blistering and crusting of the skin, pigmentary changes and scarring, erosive pustular dermatosis of the scalp, and contact dermatitis. None of these outcomes have been observed with use of the Ambulight PDT.

4.1.4 Photodynamic therapy at lower irradiance

The submission presented evidence to support the use of photodynamic therapy at lower irradiance using conventional fixed light sources. The External Assessment Centre concluded from the studies presented that reduced irradiance was at least as effective as higher irradiance.

A non-randomised study by Langmack et al. (2001) reported on 22 patients with superficial basal cell carcinoma treated by a light source at a low irradiance of 7 mW/cm^2. Among these patients, tumour response rate was 84% after 12 months. The authors considered that this response was comparable with other photodynamic therapy studies using higher irradiances.

Wiegell et al. (2008) compared two photodynamic therapy treatment areas in 29 patients with actinic keratosis. The mean effective light dose was 37 J/cm^2 for light-emitting diode compared with 43.2 J/cm^2 (range 11.7–65.9 J/cm^2) for

'daylight treatment'. At 3 months, no significant differences were reported between the percentage reductions in actinic keratosis lesion size, with a reduction of 71% in the light-emitting diode area compared with 79% in the daylight area. In this study photodynamic therapy using daylight was found to be as effective as conventional photodynamic therapy using a light-emitting diode.

4.1.5 Comparison of light source

The submission stated that irradiation for photodynamic therapy is nearly always carried out using a red light source and described a wide range of fixed light sources that have been used in photodynamic therapy with similar lesion clearance rates achieved.

The scope issued by NICE highlighted a static lamp as the most relevant comparator for the submission. The External Assessment Centre agreed with the manufacturer that the measurements of peak wavelengths and FWHM are similar for the Ambulight PDT and Aktilite static lamp (640 nm [FWHM 25 nm] and 635 nm [FWHM 18 nm]).

4.1.6 Cream application time

The methyl aminolevulinate protocol differs to the Ambulight PDT protocol in a number of ways. Most significantly is that the cream is left on the skin for longer than the 3-hour absorption period when used with the Ambulight PDT. The Ambulight PDT protocol requires the photosensitising cream to remain on the treatment area during the 3-hour illumination period.

The External Assessment Centre reported that of the seven studies that were presented in the submission to demonstrate the effects of increased cream application time, no adverse events were reported. There were no reports of reduced treatment efficacy from studies with application times longer than 3 hours.

Braathen et al. (2009) reported on 112 patients with 384 actinic keratosis lesions treated with conventional photodynamic therapy. Methyl

aminolevulinate cream application times of 1 hour and 3 hours were used and recurrence rates at 12 months were 19% and 17% respectively (significance not stated). Ibbotson et al. (2006) investigated application times ranging from 1 to 6 hours in 21 patients and reported no significant difference in the time to reach maximum photoactive porphyrin PPIX fluorescence. The submission concluded that there is no evidence to suggest that adverse events are more common with longer cream application times.

4.2 Summary of economic evidence

4.2.1 Model structure

The analysis submitted by the manufacturer evaluated the costs and savings from the potential change to service configuration that the Ambulight PDT will have, compared with the existing NHS service of conventional photodynamic therapy using a static lamp in secondary care. The analysis did not include any cost consequences associated with treatment efficacy or adverse events. The submission used a narrow range of costs. This was justified in the submission by the manufacturer's assumption that treatment using the Ambulight PDT provided in primary care and conventional hospital-based photodynamic therapy are clinically equivalent.

The cost analysis assumed that patients had already been diagnosed with non-melanoma skin cancer. It represents the operating costs of the Ambulight PDT therapy and conventional hospital-based photodynamic therapy for a complete treatment cycle, which consists of two treatments, 1 week apart.

Four clinical scenarios for a GP with special interest in dermatology were used for the comparison with conventional hospital-based photodynamic therapy:

- operating in their own practice
- operating in a specialist centre
- operating in an outpatient clinic in secondary care
- nurse hybrid service model.

The costs of three of these scenarios for service delivery were calculated using the Cancer Service guidance on skin cancer (NICE cancer service guidance CSGSTIM; for details of costs see section 4.2.2). The 'GP with special interest nurse hybrid service' model refers to nurses delivering treatment in the patient's home. No overheads or GP costs are required for this model of service delivery.

The cost analysis did not consider any impact on staff costs for additional training and support for patients who are using the Ambulight PDT. Training and support may be required by patients because the Ambulight PDT is used while the patient continues with daily activities, outside a clinical setting.

4.2.2 Costs

The costs compared in the cost analysis submitted by the manufacturer were equipment and consumable costs, staff and overhead costs, and hospital transport costs. It was stated in the submission that the costs that should be considered in the analysis of photodynamic therapy are:

- light source, consumables and ongoing maintenance
- pharmaceutical
- lesion preparation
- patient transportation
- patient management as a day case
- dressings during and following treatment
- healthcare professional time
- room required during treatment

The cost of providing conventional photodynamic therapy in secondary care was estimated by calculating the cost for each resource required to provide the service. The costs for conventional photodynamic therapy from the manufacturer's submission are presented in table 1. Clinician and nurse time were estimated by a clinical expert and the price of cream represents the price for methyl aminolevulinate.

Table 1. Costs for conventional photodynamic therapy

Cost description	Cost
Ambulance to hospital/clinic	£58.00
Lesion assessment (clinician)	£35.20
Room hire – lesion preparation	£100.00
Communication/education of patient (nurse)	£27.00
Lesion debridement (nurse)	£27.00
Cream application (nurse)	£9.00
Cream	£177.57
Illumination of lesion (nurse)	£45.00
Room hire – lesion illumination	£100.00
Consumables (curette, gloves, dressings)	£10.00
Lamp	£53.00
Anaesthesia (including clinician form filling time)	£100.00
Ambulance home	£58.00
Total	**£799.77**

Included in the costs for treatment with the Ambulight PDT were costs calculated in the cancer service guidance supporting document 'Improving outcomes for people with skin tumours including melanoma: Analysis of the potential economic impact of the guidance'. The analysis carried out for the cancer service guidance produced indicative costs for providing services in the community by GPs with special interest in dermatology:

- operating in their own practice
- operating in a specialist centre
- operating in an outpatient clinic in secondary care.

The accounting models in the manufacturer's submission represent the cancer service guidance models of how each of these services can be commissioned.

The accounting models in the cancer service guidance analysis provide different estimates for the staff and overhead costs. GP and overhead costs were calculated per patient and not per treatment so it was assumed by the manufacturer that the per patient related cost included two treatments of

photodynamic therapy. The costs of staff and overheads per patient varied significantly.

For conventional photodynamic therapy using lamps, each photodynamic therapy treatment visit is a two-stage process. In the first stage, the lesion is prepared and cream applied. The second stage of the process is the illumination which starts after a 3-hour wait for the cream to be absorbed in to the skin. The manufacturers cost model does not account for separate illumination costs because the cream and light source are applied at the same time when using the Ambulight PDT. The manufacturer's cost model does not account for anaesthesia costs for the Ambulight PDT. Conventional photodynamic therapy is painful and patients need anaesthesia. It is claimed by the manufacturer that treatment using the Ambulight PDT is less painful than using a conventional photodynamic therapy lamp and therefore anaesthesia is not needed.

Table 2 shows the cost model submitted by the manufacturer for providing photodynamic therapy using the Ambulight PDT by a GP with a specialist interest in dermatology operating in their own practice.

Table 2. Costs for GP with special interest in dermatology operating in their own practice

Cost description	Accounting model A	Accounting model B
Ambulance to hospital/clinic	£58.00	£58.00
GP time	£100.00	£23.04 (*inc. overheads*)
Overheads	£600.00	
Cream	£177.57	£177.57
Consumables (curette, gloves, dressings)	£10.00	£10.00
Lamp	£332.00	£332.00
Ambulance home	£58.00	£58.00
Total	£1,335.57	£658.61

Table 3 shows the cost model submitted for providing photodynamic therapy using the Ambulight PDT by a GP with a specialist interest in dermatology operating in a specialist centre.

Table 3. Costs for GP with special interest in dermatology operating in a specialist centre

	Accounting model			
Cost Description	**A**	**B**	**C**	**D**
Ambulance to hospital/clinic	£58.00	£58.00	£58.00	£58.00
GP time and overheads	£470.00	£123.67	£43.41	£27.73
Cream	£177.57	£177.57	£177.57	£177.57
Consumables (curette, gloves, dressings)	£10.00	£10.00	£10.00	£10.00
Lamp t	£332.00	£332.00	£332.00	£332.00
Ambulance home	£58.00	£58.00	£58.00	£58.00
Total	£1,105.57	£759.24	£678.98	£663.30

Table 4 shows the cost model submitted for providing photodynamic therapy using the Ambulight PDT by a GP with a specialist interest in dermatology operating in secondary care.

Table 4. Costs for GP with special interest in dermatology operating in secondary care

Cost description	**Accounting model E**	**Accounting model F**
Ambulance to hospital/clinic	£58.00	£58.00
GP time and overheads	£42.85	£16.85
Cream	£177.57	£177.57
Consumables (curette, gloves, dressings)	£10.00	£10.00
Lamp	£332.00	£332.00
Ambulance home	£58.00	£58.00
Total	£678.42	£652.42

The costs for the cream, consumables and travel are equivalent for treatment using the Ambulight PDT and conventional photodynamic therapy. Equipment, staff and overhead costs differ for the two treatment types. The methods used to calculate the staff and overhead costs associated with the Ambulight PDT and conventional photodynamic therapy were different, so these costs might not be comparable. It is not possible to conclude whether the cost differences between the use of the Ambulight PDT and conventional photodynamic therapy are because of the different service delivered using the Ambulight PDT or the method of calculating costs.

A nurse hybrid service using the Ambulight PDT was also modelled. This was not a model of service delivery addressed in the cancer service guidance. In this scenario a nurse provided treatment using the Ambulight PDT in a patient's home after diagnosis by a GP with specialist interest in dermatology (table 5).

Table 5. Costs for GP with special interest in dermatology nurse hybrid service model

Cost description	Cost
Transport for nurse	£58.00
Nurse time	£27.00
Cream	£177.57
Consumables (curette, gloves, dressings)	£10.00
Lamp	£332.00
Total	£604.57

The model submitted by the manufacturer does not include the costs associated with the assessment of the lesion by a GP. Costs incurred during assessment would depend on whether it takes place in the patient's home or at a surgery. Additional costs to be considered could be GP time, patient or GP transport and overheads.

4.2.3 Additional analysis

The External Assessment Centre undertook additional work to confirm the values used for some of the main costs in the analysis submitted by the manufacturer.

The cost of methyl aminolevulinate in the submission was considered low at £177.57 for two treatments and an alternative value of £234.91 was calculated by the External Assessment Centre. The External Assessment Centre also evaluated using 5-aminolevulinic acid instead of methyl aminolevulinate at a cost of £46.67 for two photodynamic therapy treatment sessions. These alternative costs do not affect the overall cost difference between conventional photodynamic therapy and treatment using the Ambulight PDT because the quantity used with each method of photodynamic therapy is the same and therefore the total cost of the pharmaceutical will be the same.

The External Assessment Centre considered the cost of lesion assessment by the clinician in conventional photodynamic therapy and the lamp costs in conventional photodynamic therapy to be low. These factors had overestimated the cost of conventional photodynamic therapy in the submission.

The average selling price of the Ambulight PDT was stated as £200 in the submission, with a price range of £180–250. In the cost models, a volume price of £166 was used. The External Assessment Centre considered that it might have been more appropriate to use the average selling price, as the volume price could result in an underestimation of service provision cost with the Ambulight PDT.

It is not possible to draw firm conclusions about whether the methods of costing the services with the Ambulight PDT and conventional photodynamic therapy are comparable. To provide an insight into the impact that the different treatment procedure for the Ambulight PDT can have on costs in comparison with conventional photodynamic therapy, an additional analysis was carried out by the External Assessment Centre using the bottom up approach and unit costs for conventional photodynamic therapy. The difference in costs after removing the cost of anaesthesia and the staff and overhead costs for illumination was calculated.

4.2.4 Results

The cost difference between photodynamic therapy using the Ambulight PDT and conventional photodynamic therapy ranged from a cost saving of £195.20 to a cost increase of £535.80 depending on which method of service delivery using the Ambulight PDT was used and the accounting model used for the analysis. From the analyses undertaken in the submission it is difficult to determine the proportion of the cost difference attributable to the use of the Ambulight PDT and the difference in costing methods.

From additional analyses carried out by the External Assessment Centre, the impact of not needing anaesthesia or the resource for illumination attributable to the use of the Ambulight PDT in secondary care, together with an increased equipment cost was associated with a cost increase of £44.00. However, this is not an accurate analysis of the costs attributable to treatment using the Ambulight PDT.

5 Ongoing research

Postmarket surveillance is ongoing.

6 Authors

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NICE Evaluation Pathway Programme for Medical Technologies

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Appendix A: Sources of evidence considered in the preparation of the assessment report summary

A Colechin E, Sims A, Reay C, Bousfield D, Allen J, Regional Medical Physics department, Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust. *Ambulight photodynamic therapy.* November 2010

B Submissions from the following manufacturer/sponsors: Ambicare Health

C Related NICE guidance:

- Improving outcomes for people with skin tumours including melanoma (update): the management of low-risk basal cell carcinomas in the community. Cancer service guidance CSGSTIM (2010).
- Improving outcomes for people with skin tumours including melanoma. Cancer service guidance CSGSTIM (2006)
- Photodynamic therapy for non-melanoma skin tumours Interventional procedures guidance. Interventional procedures guidance 155 (2006) Available from www.nice.org.uk/IPG155
- Providing public information to prevent skin cancer. Public health guidance (publication expected January 2011)
- Resources and environmental changes to prevent skin cancer. Public health guidance (publication expected January 2011)

D Additional references:

1. Attili SK, McNeill LA, Camacho-Lopez M et al. (2009) An open pilot study of ambulatory photodynamic therapy using a wearable low-irradiance organic light-emitting diode source in the treatment of nonmelanoma skin cancer. Br J Dermatol, 161:170–3.
2. Braathen LR, Paredes BE, Saksela O et al. (2009) Short incubation with methyl aminolevulinate for photodynamic therapy of actinic keratoses. J Eur Acad Dermatol Venereol, 23:550–5.

3. Ibbotson SH, Jong C, Lesar A et al. (2006) Characteristics of 5-aminolaevulinic acid-induced protoporphyrin IX fluorescence in human skin in vivo. Photodermatol Photoimmunol Photomed, 22:105–10

4. Langmack K, Mehta R, Twyman P, Norris P. (2001) Topical photodynamic therapy at low fluence rates - theory and practice. J Photochem Photobiol B, 60:37–43.

5. Wiegell SR, Haedersdal M, Philipsen PA, et al. (2008) Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses; a randomized, controlled, single-blinded study. Br J Dermatol, 158:740–6.

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their specialist society, Royal College or professional body. The advice received is their individual opinion and does not represent the view of the society.

For this device expert advice was also sought from clinicians who are using the device within manufacturer-funded trials.

Expert advice was received from Paul Norris, Consultant Dermatologist (British Association of Dermatologists); Sally Ibbotson, Photobiology Honorary Consultant Dermatologist (British Association of Dermatologists/British Photodermatology Group); Alison Layton (British Association of Dermatologists), Victoria Goulden, Consultant Dermatologist (British Association of Dermatologists/British Photobiology group) and Christopher Harland, General Dermatologist (British Association of Dermatologists).

Two Expert Advisers expressed a desire to use this technology but it is not currently available to them. Two Advisers had used this technology.

Two Expert Advisers considered this technology to be a significant modification of existing technologies with real potential for different outcomes and impact. Three Expert Advisers considered this technology to be a minor variation in existing technologies with little potential for different outcomes and impact.

The Expert Advisers considered this technology to be most useful in patients with single lesion non-melanoma skin cancer or dysplasia. These patients might be unable to use conventional photodynamic therapy because of difficulties in attending hospital or intolerance of pain. One Adviser considered this technology to have a use in the elderly or infirm who may have difficulty in attending hospitals.

One Adviser considered intolerance of conventional photodynamic therapy because of pain to be uncommon. A different Adviser expressed the opinion that is it not yet clear whether this technology is as effective in treating non-melanoma skin cancer as current treatment methods; this adviser stated that the type of lesions for which this device might be useful tend to be very low-risk, so ‘no treatment’ might be a better treatment option in some patients.

The Expert Advisers listed additional patient benefits to include less pain, less travelling and ability to treat at home, and improved cosmetic outcomes compared with surgery.

Likely benefits to the healthcare system were listed by the Expert Advisers as the potential for a reduced number of hospital visits, reduction in staff time involved and reduced usage of hospital-based irradiation devices.

Appendix C: Comments from patient organisations

NICE's Patient and Public Involvement Programme contacted the following patient organisations:

Skcin - Karen Clifford Skin Cancer Charity

British Skin Foundation

Cancer Equality

Cancer52

CANCERactive

CancerHelp UK

Helen Rollason Heal Cancer Charity

Macmillan Cancer Support

Rarer Cancers Forum

Skin Care Campaign

Tenovus The Cancer Charity

Patient commentary was received from the Skin Care Campaign.

With regards to the specific questions asked:

1. ***Information about any aspects of current management of non-melanoma skin cancer which might be improved by patients or carers having access to or using Ambulight PDT***

"Currently patients need to use a lot of time in attending for conventional large, hospital based light treatment - Ambulight would allow patients to apply and use the light therapy at their convenience and this would particularly be useful if people did not want to take time off work. This is a real issue for

people who require many treatments due to recurrence of BCCs e.g.: Gorlin's Syndrome.

Where clinically appropriate, all PDT can offer an alternative to scarring surgical treatment."

2. ***Information about possible disadvantages of Ambulight PDT for patients and/or carers.***

   No response received.

3. ***Identifiable sub groups of patients (for example, those protected by equalities legislation):***

a. for whom Ambulight PDT would provide increased benefit,

b. for whom Ambulight PDT would address an unmet need, or

c. who would be disadvantaged by Ambulight PDT being unavailable

"Many immunocompromised people and others with Gorlin's syndrome etc are plagued by recurrent BCCs - any treatment that enhances their quality of life is invaluable."

4. ***Identifiable sub groups of patients (for example, those protected by equalities legislation) for whom Ambulight PDT would not be appropriate***

No response received.

5. ***Potential impact for patients and carers if Ambulight PDT is not adopted by the NHS***

   "For the reasons outlined above patients with BCCs would need costly hospital based treatment. Ambulatory PDT is a real enhancement to the quality of care patients can be offered."

6. Any other information specific to Ambulight PDT about which patients and/or carers might have particular insights.

"Patients who have experienced Ambulight say that it is less painful than conventional large light treatment and much less painful than surgery."

Appendix D: Manufacturer comments and External Assessment Centre responses

The tables below summarise factual inaccuracies identified by the manufacturer in the assessment report and their proposed amendments. The final column contains a response from the External Assessment Centre.

Factual check received by NICE 24 November 2010

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment
Ambicare finds no factual inaccuracies in the final External Assessment Centre (EAC) Report as issued to us on 19/11/2010		

Factual Check received by NICE 27 October 2010 (External Assessment Centre report subsequently revised)

Issue 1 Section 2.2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
We found no evidence that PDT is currently used in the primary care setting. Current practice seems to be that PDT is exclusively delivered in secondary care.	The manufacturer claimed that the Ambulight could be used in primary or secondary care, and that use in primary care offered the greatest benefit to healthcare providers and patients.	Conventional PDT is available in selected primary care clinics e.g. OneLife Centre in Middlesbrough and Ambulight has already been successfully trialled in primary care. The Ambulight could be used in primary or secondary care.	Section 2.2 now states that the Ambulight can be used in primary and secondary care. It has also been noted that the Ambulight has been trialled in primary care.

Issue 2 Section 3.3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Critique: In the cost analysis, conventional hospital-based PDT was used as a comparator using methyl aminolaevulinate (generic name for Metvix) as the agent. The use of 5-ALA was not considered.	The manufacturer's cost analysis was in line with the agreed scope	5-ALA does not have a licence in the UK for use in PDT therefore a cost could not readily be derived. From a clinical comparison 5-ALA has been used with PDT in trials therefore it was possible to use as comparator from this perspective.	Section 3.3 now states that Metvix and ALA were considered in the analysis of clinical effectiveness. NICE's scope asked for ALA to be considered in the sensitivity analysis of the costs. Four of the cited papers for cost effectiveness gave a cost for treatment with ALA-PDT (Clayton *et al* 2006, Ramrakam-Jones and Herd 2003, Gold 2008 and Morton *et al* 2002). For Metvix, the manufacturer estimated costs from studies including some conducted outside the UK.

Issue 3 **Section 1.4.2**

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The submission did not address all of the points raised in the scope issued by NICE, in particular those relating to outcomes (i.e. device failure and quality of life parameters) and sensitivity analysis	NICE had been informed and agreed with the manufacturer that due to unavailability of data it would not be possible to address all of the points raised in the scope and the manufacturer should not be penalised for this.	Communication and agreement with NICE by email and telephone during the appraisal and submission stages.	The EAC were unaware of this communication. Section 4.1.4 now notes that NICE and the manufacturer agreed that the outcomes of quality of life and device failure did not need to be addressed prior to submission.

Issue 4 **Section 4.1.1**

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The literature review in the submission covers the effectiveness of low irradiance and the effect of prolonged cream application, reporting clearance and/or recurrence rates for some of the included studies. However, the review did not give consideration to the general effectiveness of PDT compared with other treatments for NMSC. The manufacturer does address this later (section 4), when they state that the effectiveness of PDT has already been established and presented by NICE in the intervention guidance [6]	The literature review in the submission covers the effectiveness of low irradiance and the effect of prolonged cream application, reporting clearance and/or recurrence rates for some of the included studies. The manufacturer demonstrated (in section 4) the effectiveness of PDT has already been established and presented by NICE in the intervention guidance [6].	To say the review did not give consideration to the general effectiveness of PDT compared with other treatments for NMSC is factually incorrect if it was addressed in section 4.	Section 4.1.1 has been revised and additional material provided in section 4.1.4, which makes it clear that the general effectiveness of PDT in treating NMSC is recognised.

Issue 5 **Section 4.1.1**

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The review lacks consideration of patient compliance. The Ambulight differs from other methods of PDT by requiring patient interaction with the device. Once the device is fitted in a clinic and the patient leaves, there is a risk that they could remove the device before the treatment	The review lacks consideration of patient compliance. However both conventional and ambulatory PDT involve periods without supervision therefore similar risks of compliance exist with both treatment methods. Evidence of improved compliance is an important consideration as	Conventional PDT treatment takes place over a 4 hour period and supervision is not always possible throughout this time period. Patients often leave the clinic for around 3 hours to return for the light based element of the treatment and compliance to treatment protocol is	The EAC recognise that patient compliance was outside the scope of the submission. Reference to patient compliance has been removed from section 4.1.1. Consideration of patient compliance has been added to section 7.3, 'Implications for

is completed, potentially increasing costs as additional treatment could be required. Compliance is an important consideration as approximately 80% of NMSCs occur in people aged 60 years and over [2].	approximately 80% of NMSCs occur in people aged 60 years and over [2] and this should be investigated in a comparative trial when larger patient numbers are being treated with the Ambulight in a real world setting.	as valid here as it is for the Ambulight. Both methods of delivering PDT require patient interaction albeit in different ways. The comment appears to be assumptive and opinion derived and does not balance compliance evidence of other treatments of NMSC. e.g. Tolerability from conventional PDT where patients have been reported to move away from the light to avoid pain Senior patients may also have issues with compliance to a topical chemotherapy regime three times per day for 60 days	guidance and research', using the form of words suggested by the manufacturer.

Issue 6 **Section 7.3**

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The analysis should compare the Ambulight with other treatments for NMSC, as evidence suggests that patients with some forms of NMSC are more frequently managed using other treatment methods. If the Ambulight is more appropriate for primary care use, then this should also be taken into account when identifying other suitable comparators.	A study at a later date to analyse how the Ambulight compares to other treatments for NMSC would be useful to identify further patient benefits and cost savings. This was out with the scope requested and agreed for this submission.	Suitable comparators were agreed within the scope and it was not suggested that the submission should go beyond the scope. If this evidence was required it could have been included in the scope.	The EAC have accepted the proposed amendment (section 7.3).

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Hospital episode statistics (HES) reported 35,774 treatments for NMSC in England during 2008-09 with PDT used in 4,125 of these [3]. These data are not complete and do not include Scotland or Wales, but it indicates how few patients are currently treated using PDT.	Due to inaccuracy in reporting methods and possible miscoding it is not possible to determine the numbers of PDT treatments in the UK each year. A clear coding system for PDT used to treat NMSC could be developed to clarify this situation.	The NHS Information Centre, Hospital Episode Statistics for England. Outpatient statistics, 2008-09 states clearly in line 23 that 89.7% of HES codes were recorded as X99.7 not known. The codes used to establish 4125 as the number of PDT treatment were *S07.1 Photodynamic therapy of skin of whole body 335* *S07.8 Other specified photodynamic therapy of skin 411* *S07.9 Unspecified photodynamic therapy of skin 3,379* However the following codes could also be counted *S09.3 Photodestruction of lesion of skin of head or neck NEC 1,339* *S09.8 Other specified photodestruction of lesion of skin 3,897* *S09.9 Unspecified photodestruction of lesion of skin 11,890* The above additions are not exhaustive and many other ambiguous codes exist within the coding system. If all codes were included which could possibly be PDT treatments it could be assumed that the data would still only represent 89.7% of the cases. Reference [3] is inaccurate and should not be used to assess the market or included	The EAC have removed the reference to the HES data from the report. In section 2.1 we now state that ‘due to inaccuracy in reporting methods it is not possible to determine the number of PDT treatments in the UK each year’ and in section 7.3 we suggest that further work is needed ‘to establish the sensitivity and specificity of coding practices with respect to clinical practice’ for PDT.

		in the report.	