



University of Dundee

British Association of Dermatologists and British Photodermatology Group guidelines for topical photodynamic therapy 2018

Wong, Terence; Morton, C. A.; Collier, Nick; Haylett, Ann K.; Ibbotson, Sally; McKenna, K. E.

Published in:
British Journal of Dermatology

DOI:
[10.1111/bjd.17309](https://doi.org/10.1111/bjd.17309)

Publication date:
2018

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Wong, T., Morton, C. A., Collier, N., Haylett, A. K., Ibbotson, S., McKenna, K. E., ... Exton, L. S. (2018). British Association of Dermatologists and British Photodermatology Group guidelines for topical photodynamic therapy 2018. *British Journal of Dermatology*. <https://doi.org/10.1111/bjd.17309>

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

British Association of Dermatologists and British Photodermatology Group guidelines for topical photodynamic therapy (PDT) 2018

T. H. Wong¹, C.A. Morton¹, N. Collier², A. Haylett², S. Ibbotson³, K.E. McKenna⁴, R. Mallipeddi⁵, H. Moseley³, D.C. Seukeran⁶, L.E. Rhodes², K.A. Ward⁷, M.F. Mohd Mustapa⁸, L.S. Exton⁸

¹Stirling Community Hospital, Stirling FK8 2AU, U.K.

²Photobiology Unit, Dermatology Centre, University of Manchester & Salford Royal NHS Foundation Trust, Manchester M6 8HD, U.K.

³Photobiology Unit, Department of Dermatology, University of Dundee, Ninewells Hospital & Medical School, Dundee DD1 9SY, U.K.

⁴Department of Dermatology, Belfast City Hospital, Belfast BT9 7AB, U.K.

⁵St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London SE1 9RT, U.K.

⁶The James Cook University Hospital, Middleborough TS4 3BW, U.K.

⁷Cannock Chase Hospital, Cannock WS11 5XY, U.K.

⁸British Association of Dermatologists, Willan House, 4 Fitzroy Square, London, W1T 5HQ, U.K.

Corresponding author: Terence H. Wong, terence.wong@nhs.net, guidelines@bad.org.uk

**These guidelines were first produced by the British Photodermatology Group in 2002
Reviewed and updated jointly by the British Association of Dermatology and the
British Photodermatology Group 2008, 2018**

Key words: GRADE, systematic review, 5-aminolaevulinic acid, methyl aminolaevulinate, dermatology, guidelines, non-melanoma skin cancer, protoporphyrin IX, topical photodynamic therapy.



NICE has accredited the process used by the British Association of Dermatologists to produce clinical guidelines. The renewed accreditation is valid until 31 May 2021 and applies to guidance produced using the process described in Updated guidance for writing a British Association of Dermatologists clinical guidance – the adoption of the GRADE methodology 2016. The original accreditation term began on 12 May 2010. More information on accreditation can be viewed at www.nice.org.uk/accreditation

1.0 PURPOSE AND SCOPE

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations for the use of topical photodynamic therapy (PDT). The document aims to:

- offer an appraisal of all relevant literature up to April 2018, focusing on any key developments
- address important, practical clinical questions relating to the primary guideline objective.
- provide guideline recommendations and if appropriate research recommendations

The guideline is presented as a detailed review with highlighted recommendations for practical use in primary care and in the clinic, in addition to an updated Patient Information Leaflet (PIL; available on the BAD website, www.bad.org.uk/leaflets).

1.1 Exclusions

The guideline does not cover systemically administered PDT or PDT as a treatment option for genital warts and anal intraepithelial neoplasia as these are out of the remit of Dermatology for this guideline

2.0 METHODOLOGY

This set of guidelines has been developed using the BAD's recommended methodology¹ with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument [www.agreetrust.org]² and the Grading of Recommendations Assessment, Development and Evaluation (GRADE).³ Recommendations were developed for implementation in the UK National Health Service (NHS).

The guideline development group (GDG), which consisted of consultant dermatologists (later joined by a trainee dermatologist), a consultant physicist, a photobiology technologist, a patient and a technical team (consisting of a guideline research fellow and project manager providing methodological and technical support), established several clinical questions pertinent to the scope of the guideline and a set of outcome measures of importance to patients, ranked according to the GRADE methodology,⁴ (see section 3.1.1 & 3.2).

A systematic literature search of PubMed, MEDLINE, EMBASE, Cochrane and AMED databases was conducted to identify key articles for PDT from 1st January 2007 up to April 2018; search terms and strategies are detailed in the supplementary information (Appendix L). Additional references relevant to the topic were also isolated from citations in reviewed literature and the previous versions of the guidelines. Evidence from included studies was graded according to the GRADE system (high, moderate, low or very low quality). Recommendations are based on evidence drawn from systematic reviews of the literature pertaining to the clinical questions identified; the summary of findings with forest plots (Appendix B), GRADE evidence profiles indicating the quality of evidence (Appendix E), tables Linking the Evidence To the Recommendations (LETR) (Appendix D), PRISMA flow diagram (Appendix I) and list of excluded studies (Appendix J) are detailed in the supplementary

information and a separate systematic review for BCC.⁵ The strength of recommendation is expressed by the wording and symbols as shown in Table 1.

Strength	Wording	Symbols	Definition
Strong recommendation <i>for</i> the use of an intervention	“Offer” (<i>or similar, e.g.</i> “Use”, “Provide”, “Take”, “Investigate”, <i>etc.</i>)	↑↑	Benefits of the intervention outweigh the risks; most patients would choose the intervention whilst only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policy makers, it would be a useful performance indicator.
Weak recommendation <i>for</i> the use of an intervention	“Consider”	↑	Risks and benefits of the intervention are finely balanced; most patients would choose the intervention but many would not; clinicians would need to consider the pros and cons for the patient in the context of the evidence; for policy makers, it would be a poor performance indicator where variability in practice is expected.
No recommendation		⊖	Insufficient evidence to support any recommendation.
Strong recommendation <i>against</i> the use of an intervention	“Do not offer”	↓↓	Risks of the intervention outweigh the benefits; most patients would <i>not</i> choose the intervention whilst only a small proportion would; for clinicians, most of their patients would <i>not</i> receive the intervention.

Table 1: Strength of recommendation ratings

3.0 INTRODUCTION

3.1 Topical photodynamic therapy in non-melanoma skin cancers and precancerous lesions

Topical PDT has been approved in over 18 countries worldwide for use in at least one NMSC indication.

Currently, three prodrugs are licensed for use in topical PDT, a formulation of 5-aminolaevulinic acid (ALA), Levulan® (DUSA Pharmaceuticals, Wilmington, MA, U.S.A.) for actinic keratosis (AK), and an esterified formulation, methyl aminolaevulinate (MAL), Metvix® (PhotoCure ASA, Oslo, Norway and Galderma, Paris, France) for AK, SCC *in situ*, and superficial and nodular basal cell carcinoma (BCC). A nanoemulsion (nc-ALA), Ameluz® (Biofrontera AG, Leverkusen, Germany) is licensed for PDT in combination with red light for the treatment of mild and moderate AK. The licensed indications are for the treatment of non-

hyperkeratotic AK, SCC *in situ* and superficial BCC (and in certain thin, nodular BCC) in adults. The nc-ALA (Ameluz®) is also recently licensed for treatment of superficial and/or nodular BCC unsuitable for surgical treatment due to possible treatment-related morbidity and/or poor cosmetic outcome in adults.

Daylight PDT for AK is a recent indication. Metvix® is licensed for PDT in combination with daylight and is being increasingly used as a light source in the treatment of AK.

3.1.1 Place in the treatment pathway

Topical PDT is used in selected patients after considering the appropriateness, clinical efficacy, other modalities of treatment, patient age, lesion site, histology, cosmesis and patient choice.

To address these issues the GDG has asked the following question in relation to the use of topical PDT in the treatment of non-melanoma skin cancer (NMSC) (See supplementary information Appendix A for full review protocol):

Review Question 1:

In adults with a non-melanoma skin cancer (NMSC) and pre-cancerous lesions,* what are the clinical effectiveness/efficacy, safety and tolerability of photodynamic therapy (MAL-PDT, ALA-PDT) compared with cryotherapy, curettage, surgical excision, topicals, laser therapy, placebo, no treatment, each other or in combination treatment

*Including actinic keratosis (AK), SCC *in situ* (Bowen's disease), basal cell carcinoma (BCC) (superficial, nodular and other), squamous cell carcinoma (SCC), skin cancer prophylaxis, cutaneous T-cell lymphoma (CTCL), intraepithelial neoplasia of the external genitalia (PIN, VIN & extragenital), extramammary Paget's disease, hyperkeratosis in organ transplant patients

3.2 Topical photodynamic therapy for infectious and inflammatory dermatoses

Topical PDT has also been used in the treatment of a number of inflammatory conditions on an unlicensed basis.

To address these issues the GDG has asked the following question in relation to the use of topical PDT in the treatment of inflammatory conditions with the following criteria (case series with patient number size ≥ 4 will be included) (See supplementary information Appendix A for full review protocol):

Review Question 2:

In adults with certain infectious and inflammatory dermatoses,† what are the clinical effectiveness/efficacy, safety and tolerability of photodynamic therapy (MAL-PDT, ALA-PDT) compared with standard treatment modalities, including topical therapies, systemic therapies, UVB phototherapy, control or each other

†Including acne, actinic cheilitis, disseminated superficial actinic porokeratosis, alopecia areata, angiofibroma, cutaneous leishmaniasis, Darier's disease, erythrasma, folliculitis,

fungal infections, Granuloma annulare, hypertrophic scars, keratoacanthoma, lichenoid dermatoses, molluscum contagiosum, morphea & localised scleroderma, interdigital mycoses, necrobiosis lipoidica, perioral dermatitis, photorejuvenation, porokeratosis, psoriasis, radiodermatitis, rosacea, sebaceous hyperplasia, viral warts, vulval lichen sclerosus, vulvodynia, wound healing, Zoon's balanitis.

Outcomes

The GDG also established a set of outcome measures of importance to patients (treatment) for each review question, which were agreed by the patient representative, ranked according to the GRADE methodology,⁴ data on which are extracted from included studies (See Appendix F). Outcomes ranked 7, 8 and 9 are critical for decision-making; those ranked 4, 5 and 6 are important but not critical for decision making:

NMSC and pre-cancerous lesions

Clearance of treated disease* (3 months initial lesion clearance)	(9)
Sustained clearance of treated disease* (1 year)	(9)
Sustained clearance of treated disease* (2 years SCC in situ; 5 years BCC)	(9)
Recurrence rate (> 1 year)	(8)
Severe pain (leading to break in treatment/use of local analgesia)	(8)
Cosmetic outcome	(6)
Treatment tolerability – low or manageable pain	(5)
Other adverse effects – pigmentation, etc.	(4)

Infectious and inflammatory dermatoses

Improvement of inflammatory/infectious dermatosis [†] (3 months)	(9)
Recurrence rate (only for infectious dermatosis) (6 months)	(8)
Severe pain (leading to break in treatment/use of local analgesia)	(8)
Cosmetic outcome	(6)
Treatment tolerability – low or manageable pain	(5)
Other adverse effects – pigmentation, etc.	(4)
Treatment associated down-time (photorejuvenation)	(3)
Quality of Life (QoL) after treatment (acne)	(3)

4.0 SUMMARY OF RECOMMENDATIONS

The following recommendations and ratings were agreed upon unanimously by the core members of the GDG and patient representative. For further information on the wording used for recommendations and strength of recommendation ratings see section 2. The evidence for recommendations is based on the studies as listed (See Appendices B, C, D, E & F for detail and discussion of the evidence). GDG recommendations relating to referral pathways are based on discussion and clinical experience, as evidence-based details are not available at the time of writing. The GDG is aware of the lack of high-quality evidence for some of these recommendations, therefore strong recommendations with an asterisk (*) are based on available evidence, as well as consensus and specialist experience. Good practice point

(GPP) recommendations are derived from informal consensus. Please note that recommendations made in this guideline may only partly overlap with formal licensed indications for the use of topical PDT in skin, hair and nail disorders.

The clinical efficacy and appropriateness of other treatment modalities should also be considered, taking into account lesion site, histology, cosmesis, patient age and patient choice.

All the recommendations listed below apply where service provision makes them practically possible to do so.

Preparation prior to PDT

R1 (GPP) Explain the potential benefits and harms of topical PDT therapy to the patient and provide a BAD Patient Information Leaflet (PIL; www.bad.org.uk/leaflets) for PDT before choosing the treatment

R2 (GPP) Refer to the appropriate summaries of product characteristics (SPCs) on the electronic Medicines Compendium (eMC) when administering PDT as there are different preparation and administration procedures for each licenced indication

Basal cell carcinoma (BCC)

R3 (↑↑) Offer* topical PDT as a treatment option to people with superficial BCC, particularly for poorly healing or cosmetically sensitive skin sites, multiple lesions and large area lesions

R4 (↑) Consider topical PDT to people with thin (<2mm) nodular BCC in situations where other treatments are not practical or contraindicated (see R6)

R5 (↑↑) Offer a further cycle of PDT to residual lesions where the BCC have shown a good response to the preceding treatment

R6 (↓↓) Do not offer topical PDT as a standard treatment for nodular BCC at high-risk sites

R7 (GPP) Use red light and not that of a shorter wavelength (blue or green light; nor daylight) for enhanced penetration for BCC

Squamous cell carcinoma *in situ* (SCC *in situ*; Bowen's disease)

R8 (↑↑) Offer PDT as a treatment option to people with SCC *in situ* (Bowen's disease), particularly for poorly healing or cosmetically sensitive skin sites, multiple lesions and large area lesions

Actinic keratosis (AK)

R9 (↑↑) Offer topical PDT as a treatment option to people with AK, particularly for cosmetically sensitive skin sites, multiple lesions and large area lesions

R10 (↑↑) Offer a further cycle of topical PDT to residual lesions where the AK lesions have shown a good response to the preceding treatment

R11 (↑) Consider daylight PDT as a treatment option for people with mild (slightly palpable AK, more easily felt than seen; Olsen Grade I) or moderate (moderately thick AK, easily felt; Olsen Grade II) AK lesions where pain is likely to be an issue, particularly for confluent areas on the face or scalp

R12 (↑) Consider combining topical PDT with other treatment modalities if feasible (e.g. imiquimod or pre-treatment with ablative fractional laser) for people with thick (very thick or obvious AK; Olsen Grade III) AK lesions

Squamous cell carcinoma (SCC)

R13 (↑) Consider PDT as a treatment option for microinvasive SCC if surgery is contraindicated

R14 (↓↓) Do not offer PDT as a treatment option for invasive SCC

Skin cancer prophylaxis

R15 (↑) Consider field-PDT as prophylaxis to reduce the emergence of new lesions in people with AKs / NMSC, including those with organ transplantation

Vulval intraepithelial neoplasia (VIN)

R16 (↑) Consider PDT as a treatment option for VIN lesions which are:

- uni-focal
- non-pigmented
- without associated HPV infection
- and with lower grades of dysplasia

Erythroplasia of Queyrat (EQ)

R17 (↑) Consider PDT as a treatment option for EQ, bearing in mind that pain may be a limiting factor

Cutaneous T-cell lymphoma (CTCL)

R18 (↑) Consider PDT as a treatment option for CTCL particularly for early-stage disease, few localized lesions and challenging sites such as skin folds

Extramammary Paget's disease (EMPD)

R19 (↑) Consider PDT as a treatment option for EMPD for thin or small lesions:

- where Paget cell infiltrate is less dense
- or when there is limited adnexal involvement

R20 (↑) Consider PDT as a treatment option for EMPD either before or after surgery

R21 (↑) Consider CO₂ laser prior to PDT as a treatment option for EMPD

Acne

R22 (↑) Consider PDT as a treatment option for acne where standard treatments are ineffective or contraindicated

Antimicrobial – cutaneous leishmaniasis, fungal infections, viral warts

R23 (↑) Consider conventional PDT as a treatment option for cutaneous leishmaniasis, particularly in cosmetically sensitive skin sites

R24 (↑) Consider daylight PDT as a treatment option for cutaneous leishmaniasis, bearing in mind that many treatments may be required

R25 (↑) Consider PDT as a treatment option for recalcitrant viral warts

R26 (↓↓) Do not offer* PDT as a treatment option for fungal infections

Psoriasis

R27(↓↓) Do not offer* PDT as a treatment option for psoriasis

Actinic cheilitis

R28 (↑) Consider PDT as a treatment option for actinic cheilitis

Insufficient evidence to support any recommendation

(⊖) Currently there is insufficient evidence to support any recommendation for the following: alopecia areata, angiofibroma, Darier's disease, folliculitis, granuloma annulare, hypertrophic scars, keratoacanthoma, lichenoid dermatoses, necrobiosis lipoidica, morphea & localised scleroderma, perioral dermatitis, photorejuvenation, porokeratosis, radiodermatitis, rosacea, sebaceous hyperplasia, vulval lichen sclerosus, vulvodynia, wound healing and Zoon's balanitis.

List of key future research recommendations (FRRs)

FRR1 Comparison of topical therapies with PDT for superficial/thin nodular BCC:

- where there is residual BCC at 3 months after first cycle of PDT
- to include detailed assessment of post-treatment events and tolerability assessed both cumulatively over time and in intensity (including pain, irritation), and patient treatment preference

FRR2 Potential for combination therapy including PDT to optimise sustained response rates in BCC

FRR3 Comparison of PDT in combination with other therapies for large lesions or lesions unresponsive to monotherapy in BCC

FRR4 Comparison of conventional versus fractionated PDT in BCC

FRR5 Comparison of efficacy of conventional vs. daylight PDT for AK in an RCT

- stratified by Olsen Grade of AK lesion, complete response and recurrence rates
- at sites other than the scalp, treatment of individual AK lesion(s) versus treatment of field area

FRR6 Comparison of cost effectiveness of conventional vs. daylight PDT in AK, with consideration of complete response and recurrence rates

FRR7 What is the efficacy and safety of daylight PDT in SCC *in situ* (Bowen's disease)?

FRR8 Comparison of PDT with curettage + cautery in SCC *in situ* (Bowen's disease)

FRR9 Comparison of PDT in combination with other therapies for large lesions or lesions unresponsive to monotherapy in SCC *in situ* (Bowen's disease)

FRR10 Further study of the efficacy and safety of PDT for superficial microinvasive SCC where surgery is contraindicated

FRR11 Potential for combination therapy including PDT to achieve sustained high response rates in microinvasive SCC when surgery is contraindicated

FRR12 Need for RCT data to assess the efficacy of PDT for VIN, EQ, AIN, CTCL and EMPD.

FRR13 What measures can be used to limit pain in patients with genital lesions treated with PDT?

FRR14 Improved modelling of light transmission, photosensitiser distribution and tumour shape and location to enable more accurate prediction of outcome

FRR15 Need for larger well-designed randomized, controlled, adequately powered studies of full face studies rather than split-face studies for acne, with a longer follow-up required to determine period of remission and if sustained.

FRR16 Need for well-designed randomized, controlled, adequately powered studies with a longer follow-up and ideally histological confirmation of clinical findings for photorejuvenation.

FRR17 Need for larger well-designed randomized, controlled, adequately powered studies comparing conventional PDT with topical paromomycin / cryotherapy / placebo for cutaneous leishmaniasis

FRR18 Need for larger well-designed randomized, controlled, adequately powered studies comparing daylight PDT with topical paromomycin / cryotherapy / placebo for cutaneous leishmaniasis

FRR19 Need for well-designed randomized, controlled, adequately powered studies comparing PDT with conventional treatments for vitiligo

5.0 PHOTSENSITIZING AGENTS

PDT is commonly performed using the prodrugs aminolaevulinic acid (ALA) and its methyl ester, methyl aminolaevulinic acid (MAL). MAL is demethylated by intracellular esterases, and ALA is metabolised by the haem biosynthetic pathway, leading to accumulation of the photosensitiser protoporphyrin IX (PpIX). The PpIX has several absorption peaks, with the 632 nm (red light) peak being utilised most frequently for irradiation, in treatment of a range of skin lesions including BCC and BD, whilst the 410 nm (blue light) peak is also utilised for more superficial lesions, i.e. AK.

The prodrugs are relatively selectively concentrated in the target lesion. ALA is hydrophilic and addition of the methyl group produces the more lipophilic MAL, with the aim to enhance tissue penetration.⁶ Studies comparing ALA and MAL in AK and inflammatory acne report higher PpIX levels but less selectivity for the target tissue with ALA, and less pain with MAL-PDT, although similar treatment efficacy of ALA- and MAL-PDT is seen.⁶ Both ALA- and MAL-PDT are effective in BD and BCC, with less pain reported in MAL-PDT.⁷

PDT with MAL (Metvix®) is performed according to its license, a treatment cycle comprising 1 PDT treatment in AK, and 2 PDT treatments with a one-week interval in BD and in nodular and superficial BCC, and light exposure 3 hours after pro-drug application. A second PDT cycle is usually performed at 3 months in incompletely responding lesions. In contrast, a range of different ALA formulations and ALA-light exposure intervals have been used. A self-adhesive ALA patch has been licensed for use in mild AK.⁸ A gel formulation of ALA with nanoemulsion, nc-ALA (BF-200 ALA, Ameluz®) which enhances ALA stability and skin penetration, has shown higher complete lesion clearance than MAL-PDT in thin-moderate thickness AK.⁹ The nc-ALA is also recently licensed for the treatment of superficial and nodular BCC.

Further approaches to enhance skin target cell delivery of prodrugs/photosensitisers include the use of liposomal delivery.^{10,11} With liposomal ALA, a low (0.5%) ALA concentration reduces phototoxic effects in acne.¹² Levels of PpIX have been potentiated by adjuvant treatment with ferrochelatase inhibitors¹³ differentiating agents, including low-dose methotrexate and vitamin D,¹⁴ and heat.¹⁵ Higher PpIX levels are also seen with ALA after skin surface disruption, e.g. by pretreatment with fractional laser.¹⁶

Attempts have also been made to perform topical PDT using exogenous photosensitisers, particularly to pursue the advantage of using chemicals with longer activation wavelength, and hence potentially PDT with deeper tissue effect. This includes exploratory studies of the use of silicon phthalocyanine (Pc4), peak absorption 675 nm, which was safe and tolerable in a dose-escalation study in NMSC and CTCL¹⁷ and meso-tetra(hydroxyphenyl)chlorin (mTHPC), peak absorption 652 nm.¹⁰ A Phase IIa randomised controlled trial of PDT with topical application of cationic photosensitizer PPA904 [3,7-bis(N,N-dibutylamino)phenothiazin-5-ium bromide] versus placebo in chronic leg ulcers demonstrated significant reduction in bacterial load with a trend towards wound healing.¹⁸

6.0 PHOTODYNAMIC DIAGNOSIS (PDD)

Photodynamic diagnosis (PDD) employs the non-invasive detection plus/minus quantification of photosensitiser fluorescence; when performed, this is usually prior to treatment with PDT or another modality. Topical prodrugs ALA and MAL have been utilised, with PpIX fluorescence used both in therapy and diagnosis.¹⁹

The simplest method involves the illumination of a porphyrin-enriched tumour by Wood's lamp (long wavelength ultraviolet-A) revealing a brick-red fluorescence. However, this is a crude technique and relevance to clinical practice is undefined. The fluorescence can also be quantitatively measured assessed through use of CCD camera systems coupled digital imaging.²⁰

In addition to wide field optical imaging, technological approaches include surface point measurements (e.g. fluorescence spectroscopy), which allow assessment of superficial tissues. Multimodal techniques are in development, combining fluorescence with technologies such as ultrasound or optical coherence tomography (OCT) or confocal microscopy, allowing greater depth assessment.¹⁹

There is particular interest in applying PDD to delineate lesional margins,²¹ with human studies indicating high predictive value, e.g. in MAL-PDD of BCC.^{22,23} Assessment of PpIX levels and kinetics can also be applied in a range of situations including evaluation of prodrugs, impact of adjunctive agents and prediction of clinical clearance.²⁴ In future, PDD could enable tailoring of treatment regimens to optimise patient outcomes.

7.0 LIGHT SOURCES AND DOSIMETRY

A light source is required that will deliver the necessary irradiance within the absorption band of the photosensitizer at sufficient depth to destroy the target tissue while causing minimal damage to surrounding healthy tissue.^{25,26} The most common light sources used for PDT of skin lesions are laser diodes, filtered lamps or light emitting diodes (LEDs). LEDs have the advantage of a narrow spectral emission with minimal cost and are virtually maintenance-free. These all emit light centred around 630 nm. Fluorescent lamps with an emission spectrum between 400 and 450 nm are also used for PDT of AK. There are numerous publications describing the use of other light sources including dye lasers and intense pulsed lights (IPLs).²⁷⁻³² In the case of MAL-PDT standard procedures involve the use of LEDs.^{6,33} (See supplementary information: Appendix M for further detail and spectra.)

Only a few clinical comparative studies have been carried out using different light sources. Narrow-band LEDs appeared more efficacious than broad-band LEDs in one study³⁴ but other studies failed to find a significant difference when different light sources were used.³⁵⁻³⁷ There is evidence to support a fractionated treatment regime in which a dark interval is introduced between two light fractions.^{38,39} Also, pre-treatment using a fractional laser may enhance penetration of the pro-drug.^{16,40,41}

Traditionally, PDT has been a hospital-based treatment using relatively bulky light sources. Developments are underway to facilitate easier delivery of the treatment. These include so-called ambulatory PDT using a lightweight portable LED device^{42,43} and light-diffusing

textiles.⁴⁴ Another novel way to deliver PDT outside the hospital is to use daylight as the light source.⁴⁵⁻⁴⁷

Commercial PDT light sources are supplied with no evidence of traceability to national measurement standards to validate indicated delivered dose.⁴⁸ In one case, the dose fell to just over a third at a distance of only 2 cm from the central area.

It is important to know what is the effective dose being delivered to the target cells.^{49,50} Factors such as photobleaching can increase the treatment depth and use of Monte Carlo (MC) models provide an insight into generation of singlet oxygen within the tumour.^{26,51-55} MC simulations predict a 72% increase in depth of tumour necrosis for a wavelength of 630 nm compared to 405 nm.⁵⁵ MC modelling also showed that the effective treatment depth increased from 2.0 mm to 2.7 mm for a light dose of 37.5 J/cm² and 75 J/cm², respectively, and increased further to 3.3 mm for 150 J/cm², largely due to photobleaching.⁵³

8.0 PROTOCOLS FOR DELIVERY OF PHOTODYNAMIC THERAPY

A successful PDT outcome requires the optimisation of applying the appropriate prodrug/drug/photosensitizer, light parameters and oxygen thereby achieving the mechanism of action intended. The resultant photodynamic reaction at the target cell produces the therapeutic result. PDT utilises the higher selectivity of the photosensitizer for the target tissue compared to healthy tissue. The topically applied photosensitizer prodrugs are converted intracellularly to active photosensitizers, principally PpIX. Reactive oxygen species, i.e. singlet oxygen produced by the photodynamic reaction, cause programmed cell death, i.e. apoptosis, and necrosis of target cells, and can also modify cellular processes via molecular events. In addition to direct effects of PDT on lesional tissue, indirect effects can occur both through dermal vascular events and via the host inflammatory and immune responses.⁵⁶

The various regimes of PDT delivery with multiple different combinations are aimed to optimise the therapeutic response.

The following recommended protocols refer to the two prodrugs that are currently licensed for use in the UK: methyl aminolaevulinate (MAL) Metvix® for non-hyperkeratotic AKs, SCC *in situ* and superficial BCCs, and BF-200 ALA (Ameluz®) nc-ALA which is the only ALA approved in UK licensed for AKs on face and scalp, recently also licensed for BCC.

Variation of administration of PDT protocols between studies may contribute to limitations in the ability to compare studies.

Lesion preparation is a routinely performed aspect of delivering topical PDT regardless of which product is being used. The gentle removal of crusts and scale with scalpel/curette is commonly performed without causing pain and not requiring local anaesthesia. The treatment area could be degreased with 70% isopropyl alcohol (especially for Ameluz®). Other additional preparation techniques or combination treatment approach reported include microneedling, skin vapourization with CO₂ laser or ablative fractional resurfacing.⁵⁷⁻⁶¹

A layer of prodrug cream approximately 1 mm thick is applied via spatula to the lesion and the surrounding 5-10 mm of skin.

Treatment sites are covered with light-occlusive dressings as full exposure to ambient light during the incubation period potentially increases activation of PpIX superficially (bleaching), thereby reducing deeper prodrug/photosensitiser penetration before photoactivation. Occlusion is standard practice for conventional PDT using MAL and nc-ALA.

After the incubation time of 3 hours, the dressing is removed with the remnant cream or gel wiped off with 0.9% saline solution. This is followed by illumination using red-light spectrum 570-670 nm achieving a dose of 75 J/cm², or narrow spectrum 635 nm LED lamp light with a distance from skin to lamp of 5-8 cm achieving a dose of 37 J/cm² with intensity approximately 50-80 mW/cm².

The regime for AK is one treatment, whereas for BCC and SCC *in situ* is two treatments 7 days apart. Protocols used in other indications are discussed with each indication.

Daylight PDT is performed by the application of an organic sunscreen initially,⁶² followed by lesion preparation 15 minutes later, then MAL to the treatment area without occlusion. After 30 minutes' application, patients are exposed to daylight for 1.5-2 hours when treating AK.^{46,63} Location, weather and the availability of daylight could be limitations.

9.0 ADVERSE EFFECTS

The most apparent acute adverse effect of topical PDT is pain. Historically, with high irradiance regimens, this was a limiting factor for the effective delivery of PDT in some instances. PDT-induced pain appears to have neurogenic and inflammatory components. Predictive factors for PDT-induced pain have been investigated but many studies have multiple confounding influences. Overall, it appears that treatment of larger lesions or areas, particularly if there is field change photodamage, and those on the head and neck, are associated with the likelihood of higher levels of pain than smaller lesions or fields on non-head and neck sites. Methods of pain relief such as topical analgesics and anaesthetics, cold air and pausing irradiation have little or limited impact on minimising pain experienced, although nerve blockade may be more effective. The introduction of PDT with lower irradiance regimens, e.g. daylight PDT, has markedly improved both the ability to deliver to a large area and the tolerability of the treatment. Indeed, with current usage and appropriate selection of PDT treatment regimens, pain appears no longer to be a major limiting factor for most patients receiving PDT.

The inflammation induced during topical PDT is an expected effect rather than an adverse effect, manifesting as erythema, oedema and even frank urticaria in some patients. Hyper- or hypo-pigmentation are also uncommon occurrences, which may last for weeks to months after treatment. Scarring is a rare event and excellent cosmetic outcome is a considerable advantage of PDT in comparison with other treatments such as cryotherapy.

Rarely, contact sensitisation to the prodrugs used in topical PDT may occur and this should be considered particularly for patients who have received treatment to large areas and in multiple sessions, such as those with extensive field change and actinic keratoses, including patients receiving daylight PDT. Vigilance is required with respect to patients developing unusually severe reactions or dermatitic responses after PDT; patch testing should be carried out if indicated. Other medium-term to chronic adverse effects of PDT are rare. Whilst there

are isolated reports of invasive SCC and melanoma developing at sites treated by PDT, these are in patients with otherwise pre-malignant skin changes and any causal association with PDT is unproven.⁶⁴ Although there is no convincing evidence of a carcinogenic risk of PDT, vigilance is recommended. Details and references of the adverse effects of topical PDT are included in a separate review.⁶⁵

10.0 RECOMMENDED AUDIT POINTS

In the last 20 consecutive patients treated with PDT is there evidence of:

1. Clearance rates of at least 75% of AK, SCC *in situ* and superficial BCC lesions (including daylight PDT for individual AK lesions or field areas):
 - a. at 3 months after the last treatment
 - b. at 12 months after the last treatment (SCC *in situ* and superficial BCC only)
2. An effective pain management protocol for patients treated for individual AK, SCC *in situ* or BCC lesions who experience severe pain requiring interruption of treatment or local anaesthesia.
3. Patient feedback on their:
 - a. satisfaction with cosmetic outcome at 1 year (poor, moderate, good or excellent)
 - b. satisfaction with PDT therapy in general (very satisfied, satisfied, dissatisfied, or very dissatisfied)
 - c. preferred therapy, *if* they had received alternative therapies for the same/similar lesion previously.
4. Initial clearance rates (3 months) of indications for which PDT use is not licenced.

The audit recommendation of 20 cases per department is to reduce variation in the results, and allow benchmarking between different units. However, departments unable to achieve this recommendation may choose to audit all cases seen in the preceding 12 months.

11.0 STAKEHOLDER INVOLVEMENT AND PEER REVIEW

The draft document and supporting information was made available to the BAD membership, the British Photodermatology Group (BPG), British Dermatological Nursing Group (BDNG), Primary Care Dermatological Society (PCDS) and the Gorlin Syndrome Group for comments, which were actively considered by the GDG. Following further review, the finalized version was sent for peer-review by the Clinical Standards Unit of the BAD, made up of the Therapy & Guidelines Sub-committee (T&G), prior to submission for publication.

12.0 LIMITATIONS OF THE GUIDELINE

This document has been prepared on behalf of the BAD and is based on the best data available when the document was prepared. It is recognised that under certain conditions it may be necessary to deviate from the guidelines and that the results of future studies may require some of the recommendations herein to be changed. Additionally, it is acknowledged

that limited cost-effectiveness data in the context of UK healthcare setting may impact on the availability of a given therapy within the NHS, despite evidence of efficacy. Failure to adhere to these guidelines should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence.

13.0 PLANS FOR GUIDELINE REVISION

The proposed revision date for this set of recommendations is scheduled for 2023; where necessary, important interim changes will be updated on the BAD website.

SUPPORTING INFORMATION

Additional supporting information including the study selection PRISMA flow diagram, summary of findings with forest plots, GRADE evidence profiles indicating the quality of evidence, clinical evidence summary, summary of included studies, narrative findings for within-patient studies and non-comparative studies, LETR, list of excluded studies and search strategy may be found in the online version of this article.

ACKNOWLEDGEMENTS

We are very grateful to patient representative Eric Lockyear for his input in formulating the clinical questions, ranking of the outcomes, the patient values and preferences section of the LETR, examining the evidence and reviewing the subsequent draft guideline, as well as all those who commented on the draft during the consultation period.

Footnote:

This is an updated guideline prepared for the British Association of Dermatologists (BAD) Clinical Standards Unit, which includes the Therapy & Guidelines Sub-committee Members of the Clinical Standards Unit that have been involved are: PM McHenry [Chairman T&G], TA Leslie, S Wakelin, RYP Hunasehally, M Cork, GA Johnston, FS Worsnop, P Rakvit, A Salim, B McDonald, SL Chua, D Buckley, G Petrof, N Callachand [British National Formulary], T Flavell [British Dermatological Nursing Group], AA Salad [BAD Scientific Administrator], LS Exton [BAD Guideline Research Fellow], MF Mohd Mustapa [BAD Clinical Standards Manager].

CONFLICTS OF INTEREST

CAM: (1) Invited speaker – Galderma, Biofrontera/Spirit (specific), Astellas, Almirall, LEO Pharma – non-specific; (2) Advisory board - Spirit/Biofrontera - specific, Almirall, Astellas, LEO Pharma – non-specific; (3) Investigator participating in a study sponsored by Biofrontera - specific; HM: Runs a UKAS Laboratory calibrating UV meters for phototherapy - specific; SI: (1) Invited speaker – Galderma, Spirit healthcare - specific- specific; (2) Investigator participating in Biofrontera-sponsored study - specific; LR: (1) Travel expenses prior to 2013 – Galderma - specific; (2) nurse support for PDT on 2-3 occasions prior to 2013 – Galderma - specific; DS: (1) Sponsorship to attend EADV meeting – Galderma (non-specific); (2) Advisory board – Galderma - non-specific; KAW; Sponsorship to attend 2014 Euro PDT meeting – Galderma – specific

REFERENCES

- 1 Mohd Mustapa MF, Exton LS, Bell HK *et al.* Updated guidance for writing a British Association of Dermatologists clinical guideline: the adoption of the GRADE methodology 2016. *Br J Dermatol* 2017; **176**:44-51.
- 2 Brouwers MC, Kho ME, Browman GP *et al.* AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010; **182**:E839-42.
- 3 GRADE. <http://www.gradeworkinggroup.org/> [Accessed 11th January 2018].
- 4 Guyatt GH, Oxman AD, Vist GE *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336**:924-6.
- 5 Collier NJ, Haylett A, Wong TH *et al.* Conventional and combination topical photodynamic therapy for basal cell carcinoma: systematic review and meta-analysis *Br J Dermatol* 2018:doi: 10.1111/bjd.16838. [Epub ahead of print]
- 6 Morton CA, McKenna KE, Rhodes LE *et al.* Guidelines for topical photodynamic therapy: update. *Br J Dermatol* 2008; **159**:1245-66.
- 7 Gaal M, Otrosinka S, Baltas E *et al.* Photodynamic therapy of non-melanoma skin cancer with methyl aminolaevulinate is associated with less pain than with aminolaevulinic acid. *Acta Derm Venereol* 2012; **92**:173-5.
- 8 Hauschild A, Stockfleth E, Popp G *et al.* Optimization of photodynamic therapy with a novel self-adhesive 5-aminolaevulinic acid patch: results of two randomized controlled phase III studies. *Br J Dermatol* 2009; **160**:1066-74.
- 9 Dirschka T, Radny P, Dominicus R *et al.* Efficacy and safety comparison of photodynamic therapy with BF-200 ALA versus Metvix® for the treatment of actinic keratosis: A prospective, randomized, placebo-controlled multinational, phase III study. *J Dtsch Dermatol Ges* 2011; **9**:196-7.
- 10 Bendsoe N, Persson L, Johansson A *et al.* Fluorescence monitoring of a topically applied liposomal Temoporfin formulation and photodynamic therapy of nonpigmented skin malignancies. *J Environ Pathol Toxicol Oncol* 2007; **26**:117-26.
- 11 Skupin-Mrugalska P, Piskorz J, Goslinski T *et al.* Current status of liposomal porphyrinoid photosensitizers. *Drug Discov Today* 2013; **18**:776-84.
- 12 An JS, Kim JE, Lee DH *et al.* 0.5% Liposome-encapsulated 5-aminolevulinic acid (ALA) photodynamic therapy for acne treatment. *J Cosmet Laser Ther* 2011; **13**:28-32.
- 13 Campbell SM, Morton CA, Alyahya R *et al.* Clinical investigation of the novel iron-chelating agent, CP94, to enhance topical photodynamic therapy of nodular basal cell carcinoma. *Br J Dermatol* 2008; **159**:387-93.
- 14 Anand S, Honari G, Hasan T *et al.* Low-dose methotrexate enhances aminolevulinate-based photodynamic therapy in skin carcinoma cells in vitro and in vivo. *Clin Cancer Res* 2009; **15**:3333-43.
- 15 Gerritsen MJ, Smits T, Kleinpenning MM *et al.* Pretreatment to enhance protoporphyrin IX accumulation in photodynamic therapy. *Dermatology* 2009; **218**:193-202.
- 16 Lim HK, Jeong KH, Kim NI *et al.* Nonablative fractional laser as a tool to facilitate skin penetration of 5-aminolevulinic acid with minimal skin disruption: a preliminary study. *Br J Dermatol* 2014; **170**:1336-40.
- 17 Baron ED, Malbasa CL, Santo-Domingo D *et al.* Silicon phthalocyanine (Pc 4) photodynamic therapy is a safe modality for cutaneous neoplasms: results of a phase 1 clinical trial. *Lasers Surg Med* 2010; **42**:728-35.
- 18 Morley S, Griffiths J, Philips G *et al.* Phase IIa randomized, placebo-controlled study of antimicrobial photodynamic therapy in bacterially colonized, chronic leg ulcers and diabetic foot ulcers: a new approach to antimicrobial therapy. *Br J Dermatol* 2013; **168**:617-24.

- 19 Rollakanti KR, Kanick SC, Davis SC *et al.* Techniques for fluorescence detection of protoporphyrin IX in skin cancers associated with photodynamic therapy. *Photonics Lasers Med* 2013; **2**:287-303.
- 20 Fritsch C, Lang K, Schulte KW *et al.* Fluorescence diagnosis and photodynamic therapy in dermatology: an overview. In: *Photodynamic therapy* (Patrice T, ed). Cambridge: Royal Society of Chemistry. 2003; 177-212.
- 21 Lee CY, Kim KH, Kim YH. The efficacy of photodynamic diagnosis in defining the lateral border between a tumor and a tumor-free area during Mohs micrographic surgery. *Dermatol Surg* 2010; **36**:1704-10.
- 22 Tierney E, Petersen J, Hanke CW. Photodynamic diagnosis of tumor margins using methyl aminolevulinate before Mohs micrographic surgery. *J Am Acad Dermatol* 2011; **64**:911-8.
- 23 Tyrrell J, Campbell SM, Curnow A. Monitoring the accumulation and dissipation of the photosensitizer protoporphyrin IX during standard dermatological methylaminolevulinate photodynamic therapy utilizing non-invasive fluorescence imaging and quantification. *Photodiagnosis Photodyn Ther* 2011; **8**:30-8.
- 24 Tyrrell JS, Campbell SM, Curnow A. The relationship between protoporphyrin IX photobleaching during real-time dermatological methylaminolevulinate photodynamic therapy (MAL-PDT) and subsequent clinical outcome. *Lasers Surg Med* 2010; **42**:613-9.
- 25 Brancaleon L, Moseley H. Laser and non-laser light sources for photodynamic therapy. *Lasers Med Sci* 2002; **17**:173-86.
- 26 Wilson BC, Patterson MS. The physics, biophysics and technology of photodynamic therapy. *Phys Med Biol* 2008; **53**:R61-R109.
- 27 Kennedy JC, Marcus SL, Pottier RH. Photodynamic therapy (PDT) and photodiagnosis (PD) using endogenous photosensitization induced by 5-aminolevulinic acid (ALA): mechanisms and clinical results. *J Clin Laser Med Surg* 1996; **14**:289-304.
- 28 Enk CD, Levi A. Low-irradiance red LED traffic lamps as light source in PDT for actinic keratoses. *Photodermatol Photoimmunol Photomed* 2012; **28**:332-4.
- 29 Fernández-Guarino M, Harto A, Jaén P. Pulsed dye laser does not seem as effective as red light in Basal cell carcinoma mal-pdt: a small pilot study. *J Skin Cancer* 2012; **2012**:396481.
- 30 Mizutani K, Akita Y, Yanagishita T *et al.* Comparison of the efficacy of ALA-PDT using an excimer-dye laser (630nm) and a metal-halide lamp (600 to 740nm) for treatment of Bowen's disease. *Photodermatol Photoimmunol Photomed* 2012; **28**:142-6.
- 31 Gold MH, Bradshaw VL, Boring MM *et al.* Split-face comparison of photodynamic therapy with 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone for photodamage. *Dermatol Surg* 2006; **32**:795-801.
- 32 Babilas P, Schreml S, Szeimies RM *et al.* Intense pulsed light (IPL): a review. *Lasers Surg Med* 2010; **42**:93-104.
- 33 Morton CA, Szeimies RM, Sidoroff A *et al.* European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications - actinic keratoses, Bowen's disease, basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2013; **27**:536-44.
- 34 Szeimies RM, Radny P, Sebastian M *et al.* Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a prospective, randomized, double-blind, placebo-controlled phase III study. *Br J Dermatol* 2010; **163**:386-94.
- 35 Clark C, Bryden A, Dawe R *et al.* Topical 5-aminolaevulinic acid photodynamic therapy for cutaneous lesions: outcome and comparison of light sources. *Photodermatol Photoimmunol Photomed* 2003; **19**:134-41.
- 36 Babilas P, Travník R, Werner A *et al.* Split-face-study using two different light sources for topical PDT of actinic keratoses: non-inferiority of the LED system. *J Dtsch Dermatol Ges* 2008; **6**:25-32.

- 37 Mikolajewska P, Iani V, Juzeniene A *et al.* Topical aminolaevulinic acid- and aminolaevulinic acid methyl ester-based photodynamic therapy with red and violet light: influence of wavelength on pain and erythema. *Br J Dermatol* 2009; **161**:1173-9.
- 38 van der Veen N, van Leengoed HL, Star WM. In vivo fluorescence kinetics and photodynamic therapy using 5-aminolaevulinic acid-induced porphyrin: increased damage after multiple irradiations. *Br J Cancer* 1994; **70**:867-72.
- 39 de Haas ER, Kruijt B, Sterenberg HJ *et al.* Fractionated illumination significantly improves the response of superficial basal cell carcinoma to aminolevulinic acid photodynamic therapy. *J Invest Dermatol* 2006; **126**:2679-86.
- 40 Forster B, Klein A, Szeimies RM *et al.* Penetration enhancement of two topical 5-aminolaevulinic acid formulations for photodynamic therapy by erbium:YAG laser ablation of the stratum corneum: continuous versus fractional ablation. *Exp Dermatol* 2010; **19**:806-12.
- 41 Haak CS, Farinelli WA, Tam J *et al.* Fractional laser-assisted delivery of methyl aminolevulinate: Impact of laser channel depth and incubation time. *Lasers Surg Med* 2012; **44**:787-95.
- 42 Moseley H, Allen JW, Ibbotson S *et al.* Ambulatory photodynamic therapy: a new concept in delivering photodynamic therapy. *Br J Dermatol* 2006; **154**:747-50.
- 43 Attili SK, Lesar A, McNeill A *et al.* An open pilot study of ambulatory photodynamic therapy using a wearable low-irradiance organic light-emitting diode light source in the treatment of nonmelanoma skin cancer. *Br J Dermatol* 2009; **161**:170-3.
- 44 Cochrane C, Mordon SR, Lesage JC *et al.* New design of textile light diffusers for photodynamic therapy. *Mater Sci Eng C Mater Biol Appl* 2013; **33**:1170-5.
- 45 Wiegell SR, Haedersdal M, Eriksen P *et al.* Photodynamic therapy of actinic keratoses with 8% and 16% methyl aminolaevulinate and home-based daylight exposure: a double-blinded randomized clinical trial. *Br J Dermatol* 2009; **160**:1308-14.
- 46 Wiegell SR, Wulf HC, Szeimies RM *et al.* Daylight photodynamic therapy for actinic keratosis: an international consensus: International Society for Photodynamic Therapy in Dermatology. *J Eur Acad Dermatol Venereol* 2012; **26**:673-9.
- 47 Wiegell SR, Fabricius S, Heydenreich J *et al.* Weather conditions and daylight-mediated photodynamic therapy: protoporphyrin IX-weighted daylight doses measured in six geographical locations. *Br J Dermatol* 2013; **168**:186-91.
- 48 Moseley H. Light distribution and calibration of commercial PDT LED arrays. *Photochem Photobiol Sci* 2005; **4**:911-4.
- 49 Moseley H. Total effective fluence: A useful concept in photodynamic therapy. *Lasers Med Sci* 1996; **11**:139-43.
- 50 Sayre RM, Dowdy JC, Gottschalk RW. Comparative effectiveness of clinically used light sources for cutaneous protoporphyrin IX-based photodynamic therapy. *J Cosmet Laser Ther* 2011; **13**:63-8.
- 51 Mang TS. Dosimetric concepts for PDT. *Photodiagnosis Photodyn Ther* 2008; **5**:217-23.
- 52 Jacques SL, Joseph R, Gofstein G. How photobleaching affects dosimetry and fluorescence monitoring of PDT in turbid media. *Proc SPIE Int Soc Opt Eng* 1993; **1881**:168-79.
- 53 Valentine RM, Brown CT, Moseley H *et al.* Monte Carlo modeling of in vivo protoporphyrin IX fluorescence and singlet oxygen production during photodynamic therapy for patients presenting with superficial basal cell carcinomas. *J Biomed Opt* 2011; **16**:048002.
- 54 Valentine RM, Ibbotson SH, Wood K *et al.* Modelling fluorescence in clinical photodynamic therapy. *Photochem Photobiol Sci* 2013; **12**:203-13.
- 55 Valentine RM, Wood K, Brown CT *et al.* Monte Carlo simulations for optimal light delivery in photodynamic therapy of non-melanoma skin cancer. *Phys Med Biol* 2012; **57**:6327-45.
- 56 Ortel B, Shea CR, Calzavara-Pinton P. Molecular mechanisms of photodynamic therapy. *Front Biosci (Landmark Ed)* 2009; **14**:4157-72.

- 57 Kearney MC, Brown S, McCrudden MT *et al.* Potential of microneedles in enhancing delivery of photosensitising agents for photodynamic therapy. *Photodiagnosis Photodyn Ther* 2014; **11**:459-66.
- 58 Clementoni MT, MBR, Munavalli GS. Photodynamic photorejuvenation of the face with a combination of microneedling, red light, and broadband pulsed light. *Lasers Surg Med* 2010; **42**:150-9.
- 59 Whitaker IS, Shokrollahi K, James W *et al.* Combined CO(2) laser with photodynamic therapy for the treatment of nodular basal cell carcinomas. *Ann Plast Surg* 2007; **59**:484-8.
- 60 Togsverd-Bo K, Haak CS, Thaysen-Petersen D *et al.* Intensified photodynamic therapy of actinic keratoses with fractional CO2 laser: a randomized clinical trial. *Br J Dermatol* 2012; **166**:1262-9.
- 61 Nicolodelli G, Angarita DP, Inada NM *et al.* Effect of photodynamic therapy on the skin using the ultrashort laser ablation. *J Biophotonics* 2014; **7**:631-7.
- 62 Morton CA, Wulf HC, Szeimies RM *et al.* Practical approach to the use of daylight photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: a European consensus. *J Eur Acad Dermatol Venereol* 2015; **29**:1718-23.
- 63 Wiegell SR, Fabricius S, Gniadecka M *et al.* Daylight-mediated photodynamic therapy of moderate to thick actinic keratoses of the face and scalp: a randomized multicentre study. *Br J Dermatol* 2012; **166**:1327-32.
- 64 Gracia Cazaña T, Salazar N, Vera-Álvarez J *et al.* Comparative study of the clinical, histological, and biological characteristics of squamous cell carcinomas in areas previously treated with photodynamic therapy. *Eur J Dermatol* 2017; **27**:627-34.
- 65 Ibbotson S, Wong TH, Morton CA *et al.* The adverse effects of topical photosynamic therapy: a consensus review. *Br J Dermatol* 2018:Accepted.