Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Photobiomodulation for the prevention or treatment of oral mucositis in people receiving cancer treatment

1. Purpose of the Evidence Appraisal Report

This report aims to identify and summarise evidence that addresses the following question: What is the clinical and cost effectiveness of photobiomodulation to prevent or treat oral mucositis in people receiving cancer treatment?

Evidence Appraisal Reports are based on rapid systematic literature searches, with the aim of published evidence identifying the best clinical and economic evidence on health technologies. Researchers critically evaluate this evidence. The draft Evidence Appraisal Report is reviewed by experts and by Health Technology Wales multidisciplinary advisory groups before publication.

2. Health problem

Oral mucositis constitutes a common side effect of cancer treatment. It can develop after chemotherapy or radiotherapy for cancer treatment, or after conditioning chemotherapy before bone marrow transplantation (Lalla et al. 2021). It is characterised by damage to tissue and can be graded from signs and symptoms, usually occurring within 10 days. Signs and symptoms can range from minor discomfort to speech and language difficulties, ulceration, and death of skin tissue (Alvariño-Martín & Sarrión-Pérez 2014, Lalla et al. 2021). The frequency and severity of oral mucositis primarily depend on the type, dose, and duration of chemotherapy or radiotherapy administered (Alvariño-Martín & Sarrión-Pérez 2014). For example, myeloablative chemotherapy is associated with a 60% to 100% risk of oral mucositis (Rubenstein et al. 2004), while the combination of chemotherapy and radiotherapy is associated with a risk of nearly 100% (Rodríguez-Caballero et al. 2012, Alvariño-Martín & Sarrión-Pérez 2014). This applies to both children and adults undergoing these cancer treatments (Redman et al. 2022, Peng et al. 2020). People with head and neck cancer undergo radiotherapy five days a week over five to seven weeks continuously (Lalla et al. 2008), thus this population is significantly more likely to be affected by oral mucositis than those undergoing fewer sessions (Lalla et al. 2021).

There are several classifications and staging systems available for oral mucositis. For the purposes of this Evidence Appraisal Report, we use the World Health Organization (WHO) scale which classifies the severity of oral mucositis into four grades (1979) (Table 1).

Table 1. Oral mucositis classification – staging system: WHO (1979)

Grade	Clinical manifestations
0	No subjective or objective evidence of mucositis
I	Pain with or without erythema, without ulcers
II	Erythema and ulceration – the individual can swallow solids
III	Erythema and ulceration – the individual can swallow liquids, but not solids
IV	Erythema and ulceration – the individual cannot swallow liquids or solids

In Wales, experts reported that the WHO (1979) oral mucositis staging system is used alongside the Radiation Therapy Oncology Group (RTOG) grading system and Common Terminology Criteria for Adverse Events (CTCAE) v4 (Villa et al. 2021).

Treatment for oral mucositis is symptomatic, and includes:

- oral hygiene
- good hydration
- soft food diet
- avoiding tobacco and alcohol
- using ice
- using water-based moisturisers
- painkillers
- non-steroidal anti-inflammatory medicines (NICE 2018, Lalla et al. 2021).

Palifermin, which is a human keratinocyte growth factor, is occasionally used to prevent or treat oral mucositis (NICE 2018, Lalla et al. 2008). Antibiotics might be also used to treat infective complications (NICE 2018).

3. Health technology

Photobiomodulation is a non-invasive procedure aiming to treat or prevent oral mucositis by stimulating healing, decreasing inflammation, and increasing cellular metabolism (Lalla et al. 2021, NICE 2018). It involves the application of either low-level laser or light-emitting diode (LED) sources in the visible and near-infrared spectrum via a hand-held probe (Adnan et al. 2021, NICE 2018). The procedure can be delivered either outside or inside the mouth, or as a combination of both. If delivered outside the mouth, the hand-held probe is placed against or close to the individual's cheek. If delivered inside the mouth, the probe, approximately the size of a dental light-curing unit, is positioned inside the mouth (Adnan et al. 2021). Delivery of photobiomodulation therapy varies in terms of duration, wavelength, irradiation, and who delivers the treatment.

Low-level laser and LED systems differ in terms of light wavelength emission and delivery. Lasers generally have a very narrow bandwidth, while LED devices typically have bandwidth between 1 and 2 nanometres (Heiskanen & Hamblin 2018). Additionally low-level lasers have a pin-point focus, whilst LED systems emit light at a beam angle that causes the light to spread out and become weaker as it travels from the source (Heiskanen & Hamblin 2018). This means that low-level lasers have the potential to treat a smaller, more precise area, whilst LED systems can treat a much larger surface area at once (Heiskanen & Hamblin 2018). Additionally, manufacturers of

LED systems state that a skilled technician is not needed to administer the photobiomodulation session with these devices.

Including preparation, a photobiomodulation session lasts between 20 and 30 minutes. Frequency of sessions can vary, ranging from two to five times a week before or during the cancer treatment (NICE 2018). To date, there are several photobiomodulation devices, such as Twin Flex II or Evolution (MMOptics, Brazil), and THOR LX2 (THOR Photomedicine Ltd, UK), as well as the CareMin650 (Oncology Imaging Systems Ltd, UK).

4. Guidance and guidelines

The Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) has developed guidelines for the management of mucositis secondary to cancer therapy (Elad et al. 2020). The MASCC/ISOO guidelines recommend the use of photobiomodulation inside the mouth using low-level lasers for the prevention of oral mucositis in adults receiving radiotherapy to the head and neck (with or without chemotherapy), but that safety considerations specific to adults with oral cancer should be considered (Elad et al. 2020). The guidelines also recommend that the specific photobiomodulation therapy parameters of selected protocols should be followed for optimal therapy (Elad et al. 2020, Zadik et al. 2019).

In 2018, the National Institute for Health and Care Excellence (NICE) published interventional procedures guidance (IPG615) on the safety and efficacy of low-level laser therapy for preventing or treating oral mucositis caused by radiotherapy or chemotherapy. The IPG615 recommendations state that the existing evidence shows there are no major safety concerns, and that there is adequate evidence on the efficacy of photobiomodulation; therefore, this procedure can be used under standard arrangements for clinical governance, consent, and audit (NICE 2018). IPG615 also states that the procedure can be delivered in children; however, most of the evidence reviewed was from adults (NICE 2018). Additionally, HTW has been made aware that photobiomodulation is currently used in children and young people in one centre in England and Wales (Redman et al. 2022). Experts also identified additional UK-based centres that use photobiomodulation, such as the Leeds Teaching Hospitals NHS Trust, the Royal United Hospitals Bath NHS Foundation Trust, and the University Hospitals of Leicester NHS Trust. More detail on the centres using photobiomodulation across the UK is available in Section 7.

5. Clinical effectiveness

HTW searched for relevant evidence and identified a range of primary and secondary sources. We considered a recent systematic review and meta-analysis of randomised control trials (RCTs) on photobiomodulation for the prevention or treatment of oral mucositis for people (children and adults) undergoing cancer treatment as the highest priority evidence (Peng et al. 2020). We also identified six RCTs, comparing photobiomodulation versus sham or usual care for the prevention or treatment of oral mucositis for children or adults with cancer, published after the Peng et al. (2020) evidence search dates (Dantas et al. 2020, Karaman et al. 2022, Kauark-Fontes et al. 2022, Marin-Conde et al. 2019, Martins et al. 2021, Reyad et al. 2022). We also included one 41.3-month RCT follow-up study reporting long-term survival outcomes (Antunes et al. 2017) that had not been included in Peng et al. (2020). More detail on the evidence identification and selection process is available in Section 12.

Peng et al. (2020) conducted a systematic review and meta-analysis comparing the preventive and therapeutic effects of photobiomodulation for people who have developed, or might go on to

develop, oral mucositis during cancer treatment. The review included 29 RCTs comparing photobiomodulation with either control, sham or usual care, with 1,611 participants in total. One RCT reported stratified outcomes for two different cancer populations, thus Peng et al. (2020) treated this as two separate studies. Twenty-four RCTs delivered photobiomodulation for oral mucositis as a prevention, four RCTs used photobiomodulation as a therapeutic method, and two RCTs used photobiomodulation both as prevention and treatment. Additionally, all 29 RCTs included in Peng et al. (2020) involve photobiomodulation using low-level lasers. The authors performed a random effects model and reported pooled estimates for the relative risk (RR), weighted mean difference (WMD), or standardised mean difference (SMD) of each preventive and therapeutic outcome (dichotomous or continuous). The authors also undertook subgroup analyses for photobiomodulation stratified by age, underlying conditions, wavelength, energy density, and location of photobiomodulation irradiation. In addition, the I^2 test for heterogeneity was performed for each pooled estimate. Egger's test and funnel plots were used to analyse publication bias. Further details on the systematic review and its findings are summarised across Table 2 (characteristics) and Table 4 (outcomes).

The six RCTs published after the Peng et al. (2020) search dates compared photobiomodulation with either usual care, sham, or no treatment for oral mucositis during cancer treatment. The studies varied in terms of participant baseline characteristics, geographical location, outcomes reported and length of follow-up. Across all studies, most of the participants were male, and over 55 years old, and only two RCTs (Karaman et al. 2022, Reyad et al. 2022) involved children. Three RCTs involved photobiomodulation for oral mucositis as a preventive method (Dantas et al. 2020, Kauark-Fontes et al. 2022, Marin-Conde et al. 2019), while three RCTs involved photobiomodulation as a therapeutic method (Karaman et al. 2022, Martins et al. 2021, Reyad et al. 2022). Two RCTs performed photobiomodulation both inside and outside the mouth (Dantas et al. 2020, Karaman et al. 2022), three performed photobiomodulation inside the mouth only (Marin-Conde et al. 2019, Martins et al. 2021, Reyad et al. 2022) and one performed photobiomodulation outside the mouth only (Karaman et al. 2022). Most of these studies were conducted in Brazil. Additionally, four out of the six recent RCTs involved photobiomodulation using low-level laser (Dantas et al. 2020, Karaman et al. 2022, Marin-Conde et al. 2019, Martins et al. 2021), while only one recent RCT performed photobiomodulation via LED systems (Kauark-Fontes et al. 2022). In the remaining study, the type of photobiomodulation was not clearly defined (Reyad et al. 2022). The RCT follow-up evaluated the overall, disease-free, and progression-free survival of 94 adults receiving cancer treatment with or without photobiomodulation to prevent oral mucositis (Antunes et al. 2017). Most of the participants were male, over 53 years old, and received photobiomodulation inside the mouth using low-level lasers. This study was also conducted in Brazil. Details of the six additional RCTs, the RCT follow up, and their findings are reported and summarised across Table 3 (RCT characteristics), Table 4 (RCT follow-up characteristics) and Table 5 (outcomes). For RCTs reporting multiple endpoints, we include the outcome (Table 5) reported at final visit or follow-up of the treatment.

Table 2. Systematic review and meta-analysis: Peng et al. (2020)

Included studies	Inclusion criteria	Quality	Observation/notes
Number of studies: 29 RCTs **Total number of patients:** 1,611 **Publication year:** 2020 **Population mean age:** NR, but age ranged from 3 to 79 years **Population:** children (n = 10), adults (n = 15), and both (n = 5) **PBM usage:** prevention (n = 24), treatment (n = 4), and both (n = 2) **PBM system:** low-level lasers **Locations:** Brazil (n = 14), France (n = 2), Italy (n = 3), Iraq (n = 1), Iran (n = 1), India (n = 5), USA (n = 3), and Russia (n = 1)	**Review period:** until December 2018 **Review purpose:** to compare the preventive and therapeutic effects of photobiomodulation versus usual care, sham or no treatment for people who have developed, or might go on to develop, oral mucositis during cancer treatment. **Language limits:** only English **Included study designs:** RCTs **Included outcome measures:** Pooled effect of risk ratio for (1) overall incidence of severe oral mucositis (primary), (2) incidence of oral mucositis of any stage, (3) incidence of severe oral mucositis at the most anticipated periods, (4) overall mean grade of oral mucositis, (5) incidence of severe pain as defined by VAS scale, (5) overall mean VAS score, (6) number of people requesting analgesia, (7) number of unplanned radiotherapy interruption events due to the presence of oral mucositis.	**Tools:** The Jadad scale to assess the generation of randomisation, application of blinding, and reports of dropouts was used. The GRADE system was also used to evaluate the overall quality of the evidence covering the following aspects: (a) risk of bias, (b) imprecision, (c) inconsistency, (d) indirectness, and (e) publication bias. **Risk of bias:** Egger's test was used, and the analysis of publication bias was presented with a funnel plot. The result showed no significant publication bias.	One RCT stratified outcomes so was treated by the authors as two separate RCTs (therefore, 30 studies considered in total). Only two RCTs applied PBM irradiation outside of the mouth. Oral mucositis was evaluated using the WHO, RTOG, NCICTC and Tardieu scales. Severe oral mucositis was defined based on the following scores of each scale: 3 to 4 (WHO and RTOG scales), or 3 to 5 (NCICTC), or 2 to 3 (Tardieu scale). In studies that used multiple scales, the WHO scale was considered first, if applicable.

Abbreviations
GRADE: Grading of Recommendations Assessment, Development, and Evaluation; NCICTC: National Cancer Institute Common Terminology Criteria; NR: not reported; PBM: photobiomodulation; RCT: randomised control trial; RTOG: Radiation Therapy Oncology Group; VAS: Visual Analogue Scale; WHO: World Health Organization.

Table 3. Randomised control trials published after the Peng et al. (2020): designs and characteristics

Reference	Study design	Participants	Intervention and comparator	Relevant outcomes	Additional notes / Comments on applicability
Dantas et al. (2020)	RCT Single centre (Salvador, Brazil) **Enrolment period:** February 2016 and December 2017 **Follow-up:** 24 days **PBM use:** prevention **PBM system**: low-level lasers	n = 54 **Inclusion criteria:** • Adults with malignant neoplasm in the head and neck region who had not started treatment • 18 years old and above • If receiving chemotherapy, only people receiving cytotoxic drugs were included. **Exclusion criteria:** • Adults with systemic disease that could impact tissue repair (for example diabetes and autoimmune diseases) • Adults scheduled for fewer than 24 radiotherapy sessions. **Age (mean ± SD):** 55.9 years (PBM) and 57.9 years (control), SD NR **Sex:** 76.7% male (PBM) and 92.3% male (control)	**Intervention:** Outside and inside of the mouth use of the InGaAlP diode laser, Twin Flex (MMOptics, São Carlos, Brazil), with a maximum output power of 86.7 mW, active tip area of 0.1256 cm^2, and continuous wavelength of 660 nm. The dosimetry used in each application was 2 J for 3 seconds, hence totalling 56 J. A total of 28 equidistant points of laser application were delineated. The PBM operator was not reported. **Comparator:** Simulation of laser application inside and outside of the mouth, but without light emission.	• Frequency of OM (day 1, 6, 12, 18, and 24) • median VAS score of pain (day 1, 6, 12, 18, and 24)	The first photobiomodulation session was conducted in the first day of radiotherapy, and the following sessions were performed every other day every week, immediately before the administration of each fraction.
Karaman et al. (2022)	RCT Single centre (Van, Turkey) **Enrolment period:** June 2019 and December 2019 **Follow-up:** 11 days **PBM use:** treatment	n = 40 **Inclusion criteria:** • Children with leukaemia who underwent chemotherapy • 3 to 18 years old. **Exclusion criteria:** NR **Age:** median 9.1 years (PBM) and median 8.9 years (control), IQR NR **Sex:** 45% male (PBM) and 30% male (control)	**Intervention:** Outside and inside of the mouth use of the CHEESE, GIGAA Laser (Wuhan Gigaa Optronics Technology Co. Ltd, China), with output power 150 mW, spot size 1 cm^2 and wavelength of 830 nm. The dosimetry used in each application was 4.5 J/cm^2. The PBM application was delivered by one dentist.	• Grade of OM (WHO) (day 1, 2, 3, 4, 6, 7, 11) • VAS score of pain (day 1, 2, 3, 4, 6, 7, 11) • Average VAS score of pain (day 1, 2, 3, 4, 6, 7, 11)	The WHO scale and VAS score has been performed by a paediatric haematologist and a paediatrician.

Reference	Study design	Participants	Intervention and comparator	Relevant outcomes	Additional notes / Comments on applicability
	PBM system: low-level lasers	**WHO OM scale 0 to I:** 55% (PBM) and 55% (control) **WHO OM scale II:** 40% (PBM) and 35% (control) **WHO OM scale III:** 5% (PBM) and 10% (control) **WHO OM scale IV:** None	**Comparator:** Oral hygiene training alone involving counselling sessions on oral hygiene techniques to both children and their parents.		

Kauark-Fontes et al. (2022)	Double-blinded, prospective RCT
	
	Single centre (São Paulo, Brazil)
	
	Enrolment period: June 2019 and November 2020
	
	Follow-up: 1 year
	
	PBM use: prevention
	
	PBM system: LED
		n = 55
		
		Inclusion criteria:
		• Adults with OOPSCC (Stage III or IV)
		• 18 years and above
		• Adults treated with curative radiotherapy (5 sessions per week) as a single modality or in association with chemotherapy.
		
		Exclusion criteria:
		• Adults who had distant metastasis and previously received radiotherapy to the head and neck
		• Adults scheduled to receive palliative radiotherapy.
		
		Age (mean ± SD): 59.5 ± 8.1 years (PBM) and 62.1 ± 8.7 years (control)
		
		Sex: 79.3% male (PBM) and 84.6% male (control)
			Intervention: Outside the mouth use of THOR (THOR Photomedicine Ltd, UK) with total output power of 1,390 mW, 63 mm of active area diameter and wavelength composed of 34 × 660 nm (red; 10 mW) and 35 × 850 nm (near-infrared; 30 mW). The dosimetry used in each application was an average of 44.6 mW/cm^2. The probe was applied for 60 seconds at 5 treatment sites. The PBM application was performed by 2 dentists.
			
			Comparator: Simulation of PBM application outside the mouth with an inactivated probe, following the same model and daily applications as the PBM group.
				• Occurrence of OM (week 1, 2, 3, 4, 5, 6, and 7)
				• Incidence of severe OM (week 1, 2, 3, 4, 5, 6, and 7)
				• Mean VAS score of pain
				• Health service utilisation
				  ○ Anti-inflammatory prescription
				• QoL, measured using the UW-QOL v4 questionnaire with the following domains:
				  ○ General
				  ○ Physical
				  ○ Social-emotional
				• Overall survival (12-month follow up)
					The QoL questionnaires were performed at the first and last day of radiotherapy.
					
					UW-QOL included 12 objective questions on specific variables. Scores are made on a scale of 0 to 100, with 100 representing the best possible condition.

Reference	Study design	Participants	Intervention and comparator	Relevant outcomes	Additional notes / Comments on applicability

Marin-Conde et al. (2019)	Experimental, prospective, double-blinded RCT
	
	Single centre (Seville, Spain)
	
	Enrolment period: 2013 and 2015
	
	Follow-up: 12th visit
	
	PBM use: prevention and treatment
	
	PBM system: low-level lasers
		n = 26
		
		Inclusion criteria:
		• Adults with OOPSCC
		• 18 years and above
		• Adults treated with combined curative radiotherapy for 7 weeks and chemotherapy on the 1st, 22nd and 43rd irradiation days
		• Adults presenting an ECOG stage of 0 to 1.
		
		Exclusion criteria:
		• Adults with HIV, diabetes, or an autoimmune disease
		• Adults with a hypersensitivity or allergy to one of the components of the RCT.
		
		Age: average 61.01 ± 9.22 years (PBM) and 60.13 ± 10.77 years (control)
		
		Sex: 100% male (PBM) and 60% male (control)
			Intervention: Inside the mouth use of BIOLASE laser (BIOLASE, Inc, Irvine, USA) with power of 0.5 W, 0.036 cm^2 of beam diameter, and wavelength of 940 nm. The dosimetry used in each application was of 0.5 J/s. The PBM application was performed by a doctor.
			
			Comparator: Simulation of PBM inside the mouth with the device turned off, following the same model procedures as the PBM group.
				• Occurrence of OM (RTOG/EORTC) (week 1, 2, 3, 4 ,5, 6, and 7)
				• Health service utilisation
				  ○ Application or use of medication
				• Adverse events
				  ○ Infectious complications
				  ○ Treatment tolerance
					The PBM group included only males. Overall, the sex distribution resulted in statistically significant differences between male and female participants in both groups ($p < 0.05$).

Martins et al. (2021)	Double-blinded RCT
	
	Single centre (Goiânia, Brazil)
	
	Enrolment period: July 2017 and June 2019
	
	Follow-up: 30 days
	
	PBM use: treatment
		n = 48
		
		Inclusion criteria:
		• Adults with OOPSCC
		• 18 years and above
		• Adults who are indicated for conventional radiotherapy, associated or not with chemotherapy
		• Adults without history of previous radiotherapy in the region of interest or previous chemotherapy.
		
		Exclusion criteria:
		• Adults with major infections (for example sepsis, pneumonia, tooth infections),
			Intervention: Inside the mouth use of the Twin Flex Evolution laser (MMOptics, São Carlos, Brazil) with an output power of 25 mW, a spot size of 0.04 cm^2, and a continuous wavelength of 660 nm (red). The exposure duration was 10 seconds. POCP for daily monitoring of oral conditions and instructions about oral care by the dental team was also provided. The PBM application was performed by a dentist.	• Severity of OM (WHO) (day 0, 7, 14, 21, 30)
				• Adverse events
				• Oral health-related QoL
				  ○ OHIP-14
				  ○ PROMS Scale
					They translated, adapted, validated, and simplified the form of the Brazilian version of OHIP-14. This questionnaire contained 14 questions answered on a 5-point ordinal scale and divided into 7 sub-scales.
					
					They also used a translated version of PROMS which included 10 questions

Reference	Study design	Participants	Intervention and comparator	Relevant outcomes	Additional notes / Comments on applicability
	PBM system: low-level lasers	neoplasms or infections of the salivary glands, Sjögren syndrome, lymphoma, or melanoma. **Age (mean ± SD):** 59.75 ±11.69 years **Sex:** 85.4% male **WHO OM scale 0 to I:** 10.4% **WHO OM scale II:** 68.8% **WHO OM scale III:** 16.7% **WHO OM scale IV:** None	**Comparator:** Simulation of laser application inside the mouth, but without light emission.		regarding OM symptoms.
Reyad et al. (2022)	Parallel RCT Single centre (Alexandria, Egypt) **Enrolment period:** October 2020 and November 2021 **Follow-up:** 14th visit **PBM use:** treatment **PBM system**: low-level lasers	**n** = 44 **Inclusion criteria:** • Children with leukaemia • Between 2 and 14 years old • Children who are diagnosed with OM (WHO scale) receiving chemotherapy. **Exclusion criteria:** • Children who have received radiotherapy in the previous 2 weeks • Children with any oral lesions other than mucositis or trismus • Children with any known systemic disease that could impact tissue repair (for example diabetes and autoimmune diseases).	**Intervention:** Inside the mouth use of Simpler laser (Doctor Smile, Italy) in addition to usual care. The laser had power of 1.5 W for 30 seconds, wavelength of 980 nm and energy density of 4.5 J/cm^2 by a non-contacting continuous mode. The PBM operator was not reported. **Comparator:** Usual care, including antifungal and agent, topical anaesthetics and anti-inflammatory agents, topical analgesic gel, and sodium bicarbonate	• Occurrence of OM (WHO) (day 1, 5, 10, 14) • VAS score of pain (day 1, 5, 10, 14) • Adverse events	Before chemotherapy, all children admitted to the hospital were educated about basic oral hygiene, dietary lifestyle, and medications that could help reduce the probability of experiencing severe OM. All children were also instructed to perform tooth brushing using a specific silicone brush. In addition, all parents and carers were given these

Reference	Study design	Participants	Intervention and comparator	Relevant outcomes	Additional notes / Comments on applicability
		Age (mean ± SD): 7.41 ± 2.48 years (PBM) and 7.68 ± 2.89 years (control) **Sex:** 50% male (PBM) and 45.5% male (control) **WHO OM scale 0 to I:** 4.5% (PBM) and 22.7% (control) **WHO OM scale II:** 63.3% (PBM) and 72.7% (control) **WHO OM scale III:** 22.7% (PBM) and 4.5% (control) **WHO OM scale IV:** 9.1% (PBM) and 0% (control)	mouthwash 3 times a day for a week)		instructions in a printed brochure.

Abbreviations
ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range; LED, light-emitting diode; NR: not reported; OHIP-14: Oral Health Impact Profile-14; OM: oral mucositis; OOPSCC: oral and oropharynx squamous cell carcinoma; PBM: photobiomodulation; POCP: Preventive Oral Care Program; PROMS: Patient-Reported Oral Mucositis Symptom; RCT: randomised control trial; QoL: quality of life, RTOG/EORTC: Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scale for oral mucositis; SD: standard deviation; UW-QOL v4: University of Washington Quality of Life Questionnaire; VAS: Visual Analogue Scale; WHO: World Health Organization.

Table 4. RCT follow-up on survival outcomes (Antunes et al. 2017): designs and characteristics

Reference	Study Design	Participants	Intervention and Comparator	Relevant outcomes	Additional notes / Comments on applicability
Antunes et al. (2017)	RCT follow-up Single centre (Rio de Janeiro, Brazil) **Enrolment period:** July 2007 to December 2015 **Follow-up:** median 41.3 months (IQR 0.7 to 101.9) **PBM use:** prevention **PBM system**: low-level lasers	n = 94 **Inclusion criteria:** • Adults with OOPSCC • 18 years old and above • Eligible for combined radiotherapy and chemotherapy. **Exclusion criteria:** • Adults receiving medication for the prevention and treatment of OM • Adults not able to comply with the treatment procedure • Adults performing the oral hygiene protocol. **Age (mean ± SD):** 53.6 ± 6.9 years (PBM) and 55.7 ± 8.6 years (control) **Sex:** 89.4% male (PBM) and 85.1% male (control)	**Intervention:** Inside the mouth use of the InGaAlP diode, Twin Flex (MMOptics, São Carlos, Brazil), with a maximum output power of 100 mW, a spot size of 0.24 cm^2, and continuous wavelength of 660 nm. The application time per point was 10 seconds and the total application time was 12 minutes. The PBM application was performed by 2 dentists. **Comparator:** Simulation of laser application inside the mouth, but without light emission.	• Overall survival • Disease-free survival • Progression-free survival	

Abbreviations
IQR: interquartile range; OOPSCC: oral and oropharynx squamous cell carcinoma; PBM: photobiomodulation; RCT: randomised control trial; SD: standard deviation.

5.1 Overall incidence of severe oral mucositis

In the systematic review and meta-analysis, 22 out of 29 RCTs reported that photobiomodulation reduced the risk of severe oral mucositis when used as a preventative therapy (RR 0.40; 95% CI 0.28 to 0.57; p < 0.01) (Peng et al. 2020).

Peng et al. 2020 also performed several subgroup analyses, stratifying by underlying condition, age group and other photobiomodulation delivery parameters, such as wavelength, energy density, location of irradiation and treatment schedule. When stratifying by age, all groups shows a reduction of severe oral mucositis (adults: RR 0.27; 95% CI 0.15 to 0.49; p = 0.04; children: RR 0.59; 95% CI 0.36 to 0.97; p < 0.01; all: RR 0.31; 95% CI 0.11 to 0.83; p = 0.26). Regarding the stratification by wavelength, authors reported that photobiomodulation performed with either red and infrared lasers showed a lower risk of severe oral mucositis compared with the control group (red: RR 0.36; 95% CI 0.23 to 0.56; p < 0.01; infrared: RR 0.56; 95% CI 0.37 to 0.84; p < 0.01), but combined laser treatment did not. When stratifying by energy density, low (4 J/cm^2 or lower) or high (over 4 J/cm^2) energy density lasers both had a lower risk of severe oral mucositis compared with the control group (low: RR 0.33; 95% CI 0.18 to 0.60; p < 0.01; high: RR 0.41; 95% CI 0.27 to 0.63; p < 0.01). Stratification by location of photobiomodulation irradiation showed that photobiomodulation performed inside the mouth also showed a lower risk of severe oral mucositis when compared with the control group (RR 0.37; 95% CI 0.28 to 0.48; p < 0.01), but photobiomodulation performed inside the mouth did not (RR 1.19; 95% CI 0.8 to 1.78; p = 0.39).

Kauark-Fontes et al. (2022) reported the overall incidence of oral mucositis in the photobiomodulation and control group during different periods. During Week 1, there were no incident cases of oral mucositis in the photobiomodulation group compared with the sham group in which the oral mucositis incidence was 19% (p = 0.014). In Week 2, the oral mucositis incidence was 55% for the photobiomodulation group compared with 85% for the control group (p = 0.009). During Week 3, the oral mucositis incidence of the sham group was 100% (p = 0.161), while similar results were noted at Week 6 for the photobiomodulation group (p = 0.911) (Kauark-Fontes et al. 2022). During Week 7, the oral mucositis incidence was 100% for both the photobiomodulation and sham group (p = 0.469).

Martins et al. (2021) reported the severity of oral mucositis using the WHO and National Cancer Institute (NCI) scales. Based on the WHO scale, they reported that photobiomodulation reduced the severity of oral mucositis compared with the control group (RR 0.55; 95% CI 0.30 to 1.01; p = 0.045). Based on the NCI scale, they reported that photobiomodulation reduced the severity of oral mucositis compared with the control group (RR 0.59; 95% CI 0.36 to 0.98; p = 0.038).

5.2 Incidence of oral mucositis of any grade

In Peng et al. (2020), 15 out of the 30 RCTS reported that preventative photobiomodulation can reduce the incidence of oral mucositis of any grade by 8.9% (RR 0.90; 95% CI 0.81 to 1.00; p = 0.06).

Dantas et al. (2020) reported that the incidence of grade 0 to 1 oral mucositis was 76.77% in the photobiomodulation group and 75.93% in the control group, while incidence of grade 2 oral mucositis was 16.12% and 12.78% in the photobiomodulation group and control group respectively. Reported incidence of grade 3 oral mucositis was 7.11% and 8.27% in the photobiomodulation group and control group, respectively. Grade 4 oral mucositis was observed only in people in the control group (3.02%). Dantas et al. (2020) reported no statistically significant difference between the groups regarding the development of oral mucositis (p > 0.05).

Marin-Conde et al. (2019) reported that the grade of oral mucositis on the fifth week of cancer treatment showed statistically significant differences between the photobiomodulation group

(72.7%, grade 0) and the control group (20.0%, grade 0; 40% grade 2) ($p < 0.01$). During the seventh and eighth week, Marin-Conde et al. (2019) reported no grade 3 oral mucositis in the photobiomodulation group, while they reported 33.3% (seventh week) and 46.2% (eighth week) of people in the control group presented confluent mucositis.

Reyad et al. (2022) reported that there was a significant reduction of oral mucositis (any stage) between the photobiomodulation group (median 1.00, interquartile range [IQR] 1.00) and control group (median 2.00, IQR 1.00) at day 14 ($p = 0.003$). At earlier timepoints, Reyad et al. (2022) reported no statistically significant effects on the reduction of oral mucositis (any stage) between the photobiomodulation (day five: median 2.00, IQR 1.00; day 10: median 2.00, IQR 1.00) and the control (day five: median 2.00, IQR 1.00; day 10: median 2.00, IQR 1.00) group ($p = 0.16$; $p = 0.56$ respectively).

5.3 Incidence of severe oral mucositis at the most anticipated periods

In Peng et al. (2020), nine out of the 30 RCTs reported on the incidence of severe of oral mucositis at the most anticipated periods (RR 0.35; 95% CI 0.18 to 0.70; $p < 0.01$).

Dantas et al. (2020) reported that both groups showed a statistically significant increase in the severity of oral mucositis with an increasing number of radiotherapy sessions. In the photobiomodulation group, they found statistically significant differences between the first and 12th session, first and 18th session, first and 24th session, sixth and 12th session, sixth and 18th session, and sixth and 24th session ($p < 0.001$). In the control group, Dantas et al. (2020) reported differences between more time points, including the first and 12th session, first and 18th session, first and 24th session, sixth and 12th session, sixth and 18th session, sixth and 24th session, and 12th and 24th session ($p < 0.001$). Generally, Dantas et al. (2020) reported that the early development of oral mucositis was observed by the 12th radiation session, with an incidence peak during the 18th and 24th sessions. They also reported that both groups had no statistically significant differences between them regarding the oral mucositis development ($p > 0.05$) (Dantas et al. 2020).

Kauark-Fontes et al. (2022) reported that the incidence of severe oral mucositis was higher in the sham group during all examination periods; however, during the last week of radiotherapy the photobiomodulation group showed an incidence of 52% for oral mucositis grade 3 compared with 41% for the sham group ($p = 0.469$).

5.4 Incidence of mean grade of oral mucositis

In the systematic review and meta-analysis, nine studies reported that the incidence of mean grade of oral mucositis in the photobiomodulation group ranged from 0.36 to 2.18, while in the control group the incidence of mean grade of oral mucositis ranged from 0.58 to 3.33. Peng et al. (2020) also reported that the pooled SMD estimate was −1.23 (95% CI −1.67 to −0.77; $p < 0.01$).

Karaman et al. (2022) did not report on mean grade but did report the grade of oral mucositis on the first, second, fourth, and 11th days of the treatment. They did not show a significant difference between the photobiomodulation group and control group at any of the timepoints.

5.5 Visual analogue scale (VAS) score

In Peng et al. (2020), six out of 30 studies reported that there was no significant difference between photobiomodulation and control for incidence of severe pain, defined as a VAS score

greater than seven (RR 0.38; 95% CI 0.13 to 1.06; p = 0.06). Six studies reported that the overall mean of VAS score was lower for the photobiomodulation group (SMD −3.97; 95% CI −6.42 to −1.52; p < 0.01).

Karaman et al. (2022) reported that the VAS score for the photobiomodulation group was statistically significantly lower compared with the control group at all examinations starting from the first treatment day (p < 0.0001).

Dantas et al. (2020) reported that both groups showed a statistically significant increase of oral cavity-related pain as the study period progressed and more radiotherapy sessions were received. Both groups had similar results in all five examination periods, with no statistically significant differences between them (p > 0.05).

Kauark-Fontes et al. (2022) reported that the lower mean VAS score was observed in the photobiomodulation group, while the highest mean VAS score was 2.8 during the fifth radiotherapy week for both groups. They also found a moderate VAS score (3 to 7) in the sham group during the sixth (3.3) and seventh (4.5) week, representing the highest mean level of VAS score in the sham group. Kauark-Fontes et al. (2022) also reported a statistically significant difference during the seventh week with a lower VAS of 2.1 for the photobiomodulation group compared with 4.5 for the sham group (p = 0.009).

Reyad et al. (2022) also reported on mean VAS score of oral mucositis at different timepoints during the two-week study period. At day five, they found no statistically significant differences in the mean VAS score of oral mucositis between the photobiomodulation group (3.14 ± standard deviation [SD] 3.17) and the control group (3.23 ± 2.20; p = 0.29). Reyad et al. (2022) reported a statistically significant reduction of oral mucositis in the photobiomodulation group compared to the control group at day 10 (1.45 ± 1.26 versus 3.82 ± 2.44, respectively; p < 0.001) and day 14 (1.27 ± 1.08 versus 4.27 ± 2.71, respectively; p < 0.01).

5.6 Number of people with severe oral mucositis after seven days of photobiomodulation

In the systematic review and meta-analysis, only three out of 30 studies reported the severity of oral mucositis after the seventh day of receiving photobiomodulation as treatment. Peng et al. (2020) reported that the number of people with severe oral mucositis decreased after the seventh day receiving therapeutic photobiomodulation compared with usual or sham (RR 0.37; 95% CI 0.10 to 1.36; p = 0.03).

5.7 Duration of severe oral mucositis

In Peng et al. (2020), three studies reported that the duration of severe oral mucositis was reduced when receiving photobiomodulation compared with usual care or sham treatment (WMD −5.81 days; 95% CI −9.34 to −2.28; p < 0.01).

5.8 Survival

The systematic review and meta-analysis did not report any outcomes on survival (Peng et al. 2020).

Out of the six recent RCTs, only Kauark-Fontes et al. (2022) reported on overall survival outcomes, while the RCT follow up reported on long-term overall, disease-free, and progression-free survival outcomes (Antunes et al. 2017).

5.8.1 Overall survival

Kauark-Fontes et al. (2022) reported outcomes on overall survival during a mean 12-month follow-up. They found non-statistical significance on overall survival between the photobiomodulation group (74.0%) and control group (68.7%) (HR 0.88; 95% CI 0.21 to 3.65; p = 0.889).

Antunes et al. (2017) also reported long-term outcomes on overall survival during a median 41.3 months (IQR 0.7 to 101.9) follow-up. They reported a higher overall survival in the photobiomodulation group (57.4%) compared with the control group (40.4%) (HR 1.64; 95% CI 0.92 to 2.91; p = 0.90).

5.8.2 Disease-free survival

Antunes et al. (2017) reported that the disease-free survival was higher in the photobiomodulation group (65.9%) compared with the control group (58.9%) (HR 1.19; 95% CI 0.55 to 2.57; p = 0.659).

5.8.3 Progression-free survival

Antunes et al. (2017) also reported that progression-free survival was statistically significantly higher in the photobiomodulation group (61.7%) compared with the control group (40.4%) (HR 1.93; 95% CI 1.07 to 3.5; p = 0.030).

5.9 Adverse events

Peng et al. (2020) reported that none of the studies reported adverse events after preventive or therapeutic photobiomodulation. Similarly, the Karaman et al. (2022), Kauark-Fontes et al. (2022), Martins et al. (2021) and Reyad et al. (2022) RCTs reported no adverse reactions to preventive or therapeutic photobiomodulation. However, Marin-Conde et al. (2019) reported a statistically significant difference in the incidence of adverse events between the photobiomodulation and control group, with 13 people in total displaying infectious complications in the oral cavity; of these, two people were in the photobiomodulation and 11 people were in the control group (p < 0.01).

5.10 Health service utilisation

The systematic review and meta-analysis did not report any health service utilisation outcomes (Peng et al. 2020).

Out of the six recent RCTs, only two reported on the application or use of medication during the study period (Kauark-Fontes et al. 2022, Martins et al. 2021).

5.10.1 Application or use of medication during study period

Kauark-Fontes et al. (2022) reported on anti-inflammatory prescriptions received in both groups during the treatment period. They found that the numbers of anti-inflammatory prescriptions were higher in the sham group compared with the photobiomodulation group, but the difference was not always significant. The maximum number of prescriptions was observed for both groups during Week Four of the cancer treatment, with the higher percentage for the sham group (34.6%) compared with the photobiomodulation group (20.7%; p = 0.5879). At Week Five, anti-inflammatory prescription rates were 30.8% for the sham group and 6.9% for the photobiomodulation group (p = 0.0346).

Marin-Conde et al. (2019) found no statistically significant differences between the photobiomodulation and control groups regarding the application or usage of medication throughout the study period, which included analgesic and anti-inflammatory medications (p > 0.05).

5.11 Patient-reported outcomes

The systematic review and meta-analysis did not report any patient-reported outcomes (Peng et al. 2020).

Out of the six recent RCTs, only two reported on quality of life (QoL) outcomes using different questionnaires and assessments (Kauark-Fontes et al. 2022, Martins et al. 2021).

5.11.1 Quality of life

Kauark-Fontes et al. (2022) utilised the University of Washington Quality of Life Questionnaire (UW-QOL v4) validated for the Portuguese version before (day one) and during the last day (day 35) of cancer treatment. The UW-QoL questionnaire gives a score ranging from 0 to 100 for each of the 12 domains (i.e. max score of 1,200), with 100 representing best possible quality of life. Authors reported outcomes on general, physical, and social-emotional QoL. In both the photobiomodulation group and the sham group, general QoL and physical QoL scores had significantly decreased between day 1 and day 35 (p < 0.0001). The general UW-QOL scores at day one and day 35 for the photobiomodulation group were 910 and 687, respectively, while for the sham group they were 868 and 607, respectively. When observing between-group differences, Kauark-Fontes et al. (2022) reported similar scores between the photobiomodulation and sham groups at day 1 of treatment, for general, physical and social-emotional QoL. At day 35, although scores had decreased in both groups overall, the photobiomodulation group had significant higher scores for general QoL (687 versus 607; p = 0.0390). Similar results were seen in the social-emotional QoL scores (408 with photobiomodulation versus 348 with sham; p = 0.0034). This trend was observed in the physical QoL scores, but the difference was not significant (279 with photobiomodulation and 258 with sham; p = 0.1330).

Martins et al. (2021) translated, adapted, validated, and simplified the form of the Brazilian version of Oral Health Impact Profile-14 (OHIP-14) and provided an overall QoL score for both photobiomodulation and control group. In the photobiomodulation group, significant differences were observed at the 7th, 14th, and 21st cancer treatment sessions compared with baseline, while in the control group a reduction in QoL during cancer treatment was reported at the 14th, 21st, and 30th cancer treatment sessions compared with baseline. The QoL score was worse in the control group compared with the photobiomodulation group at the 21st (p = 0.029) and 30th (p = 0.006) cancer treatment sessions.

Table 5. Photobiomodulation compared with usual or sham or no treatment: outcomes

Outcome	Evidence source	Number of participants	Study period / Follow up	Absolute effect	Relative effect
Overall incidence of severe oral mucositis					
Prevention	Peng et al. (2020)	22 RCTs, 1,190 participants	NR	-30.9% (95% CI -37 to -22.1) Favours PBM	RR 0.40 (95% CI 0.28 to 0.57) p < 0.01 Favours PBM
Prevention (NCI scale)	Kauark-Fontes et al. (2022)	1 RCT, 1 RCT, 55 participants	Week 7	PBM: 52% Control: 41% p = 0.469 Favours neither	NR
Treatment (WHO scale)	Martins et al. (2021)	1 RCT, 48 participants	30 days	NR	RR 0.55 (95% CI 0.30 to 1.01) p = 0.045 Favours PBM
Treatment (NCI scale)	Martins et al. (2021)	1 RCT, 48 participants	30 days	NR	RR 0.59 (95% CI 0.36 to 0.98) p = 0.038 Favours PBM
Incidence of oral mucositis of any stage					
Prevention	Peng et al. (2020)	15 RCTs, 900 participants	NR	-8.9% (95% CI -16.9 to -0) Favours PBM	RR 0.90 (95% CI 0.81 to 1.00) p = 0.06 Favours PBM
Prevention, grade 0 to 1	Dantas et al. (2020)	1 RCT, 56 participants	24 days	PBM: 76.77% Control: 75.93% p > 0.05 Favours neither	NR

Outcome	Evidence source	Number of participants	Study period / Follow up	Absolute effect	Relative effect
Incidence of oral mucositis of any stage					
Prevention, grade 2	Dantas et al. (2020)	1 RCT, 56 participants	24 days	PBM: 16.12% Control: 12.78% p > 0.05 Favours neither	NR
Prevention, grade 3	Dantas et al. (2020)	1 RCT, 56 participants	24 days	PBM: 7.11% Control: 8.27% p > 0.05 Favours neither	NR
Prevention, grade 4	Dantas et al. (2020)	1 RCT, 56 participants	24 days	PBM: 0% Control: 3.02% p > 0.05 Favours control	NR
Prevention and treatment, grade 0	Marin-Conde et al. (2019)	1 RCT, 26 participants	Day 12	PBM: 80% Control: 0% p < 0.05 Favours PBM	NR
Treatment, grade 0 to 4	Reyad et al. (2022)	1 RCT, 44 participants	Day 14	Median (IQR) PBM: 1.00 (1.00) Control: 2.00 (1.00) (**p = 0.03**) Favours PBM	NR
Incidence of severe oral mucositis at the most anticipated periods					
Prevention	Peng et al. (2020)	9 RCTs, 737 participants	NR	-35.4% (95% CI -37 to -22.1) Favours PBM	RR 0.35 (95% CI 0.18 to 0.70) p < 0.01 Favours PBM
Prevention (WHO scale)	Dantas et al. (2020)	1 RCT, 56 participants	24 days	Median (IQR) PBM: 0.5 (0 to 2) Control: 1.5 (0 to 3) (**p = 0.131**) Favours neither	NR

Outcome	Evidence source	Number of participants	Study period / Follow up	Absolute effect	Relative effect
Incidence of severe oral mucositis at the most anticipated periods					
Prevention	Kauark-Fontes et al. (2022)	1 RCT, 55 participants	Week 7	PBM: 52% Control: 41% p = 0.469 Favours neither	NR
Mean grade of oral mucositis					
Prevention, incidence	Peng et al. (2020)	9 RCTs, 602 participants	NR	SMD -1.23 (95% CI -1.67 to -0.77) p < 0.01 Favours PBM	NR
Prevention, grade type	Karaman et al. (2022)	1 RCT, 40 participants	Day 11	PBM: NR Control: NR Favours neither	NR
Incidence of severe pain (VAS < 7)					
Prevention	Peng et al. (2020)	6 RCTs, 319 participants	NR	-35.4% (95% CI -49.7 to -3.4) Favours PBM	RR 0.38 (95% CI 0.13 to 1.06) p = 0.06 Favours PBM
VAS score					
Prevention	Karaman et al. (2022)	1 RCT, 40 participants	Day 11	PBM: 1.5 Control: 5.6 p < 0.001 Favours PBM	
Prevention	Peng et al. (2020)	4 RCTs, 143 participants	NR	SMD -3.87 (95% CI -6.42 to -1.52) Favours PBM	NR
Prevention	Dantas et al. (2020)	1 RCT, 56 participants	24 days	Median (IQR) PBM: 4.0 (0.00 to 8.0) Control: 3.5 (0.0 to 8.0) p = 0.722 Favours neither	NR

Outcome	Evidence source	Number of participants	Study period / Follow up	Absolute effect	Relative effect
VAS score					
Prevention	Kauark-Fontes et al. (2022)	1 RCT, 55 participants	Week 7	PBM: 2.1 Control: 4.5 p = 0.009 Favours PBM	NR
Treatment	Reyad et al. (2022)	1 RCT, 44 participants	Day 14	Mean ± SD PBM: 1.27 ± 1.08 Control: 4.27 ± 2.71 p < 0.001 Favours PBM	NR
Number of people with severe oral mucositis after 7-day PBM therapy					
Treatment	Peng et al. (2020)	3 RCTs, 243 participants	7-days	-19.9% (95% CI -25.6 to 10.2) Favours PBM	RR 0.37 (95% CI 0.10 to 1.36) (**p = 0.14**) Favours PBM
Duration of severe oral mucositis					
Treatment	Peng et al. (2020)	3 RCTs, 352 participants	NR	WMD -5.81 (days) (95% CI -9.34 to -2.28) p < 0.01 Favours PBM	NR
Overall survival					
Prevention	Kauark-Fontes et al. (2022)	1 RCT, 55 participants	12 months	PBM: 74% Control: 68.7% p = 0.889 Favours PBM	HR 0.88 (95% CI 0.21 to 3.65) p = 0.889 Favours PBM
Prevention (follow-up)	Antunes et al. (2017)	1 RCT, 94 participants	median 41.3 (IQR 0.7 to 101.9) months	PBM: 57.4% Control: 40.4% p = 0.90 Favours PBM	HR 1.64 (95% CI 0.92 to 2.91) p = 0.90 Favours PBM

Outcome	Evidence source	Number of participants	Study period / Follow up	Absolute effect	Relative effect
Disease-free survival					
Prevention (follow-up)	Antunes et al. (2017)	1 RCT, 94 participants	median 41.3 (IQR 0.7 to 101.9) months	PBM: 65.9% Control: 58.6% p = 0.659 Favours PBM	HR 1.19 (95% CI 0.55 to 2.57) p = 0.659 Favours PBM
Progression-free survival					
Prevention (follow-up)	Antunes et al. (2017)	1 RCT, 94 participants	median 41.3 (IQR **0.7 to 101.9)** months	PBM: 61.7% Control: 40.4% p = 0.030 Favours PBM	HR 1.93 (95% CI 1.07 to 3.5) p = 0.030 Favours PBM
Adverse events					
Prevention	Peng et al. (2020)	22 RCTs, 1,190 participants	NR	PBM: 0/593 Control: 0/597 Favours neither	NR
Treatment	Peng et al. (2020)	3 RCTs, 592 participants	NR	PBM: 0/296 Control: 0/296 Favours neither	NR
Prevention	Karaman et al. (2022)	1 RCT, 40 participants	Day 11	PBM: 0/20 Control: 0/20 Favours neither	NR
Prevention	Kauark-Fontes et al. (2022)	1 RCT, 55 participants	Week 7	PBM: 0/29 Control: 0/26 Favours neither	NR
Prevention and treatment	Marin-Conde et al. (2019)	1 RCT, 26 participants	Day 12	PBM: 2/11 Control: 11/15 p < 0.01 Favours PBM	NR
Treatment	Martins et al. (2021)	1 RCT, 48 participants	30 days	PBM: 0/25 Control: 0/23 Favours neither	NR

Outcome	Evidence source	Number of participants	Study period / Follow up	Absolute effect	Relative effect
Adverse events					
Treatment	Reyad et al. (2022)	1 RCT, 44 participants	14 days	PBM: 0/22 Control: 0/22 Favours neither	NR
Application and/or use of medication during study period					
Prevention	Kauark-Fontes et al. (2022)	1 RCT, 55 participants	Week 5	PBM: 6.9% Control: 30.7% p = 0.0346 Favours control	NR
Prevention and treatment	Marin-Conde et al. (2019)	1 RCT, 26 participants	Day 12	PBM: NR Control: NR p > 0.05 Favours neither	NR
Quality of life					
Prevention, general UW-QOL (day 1)	Kauark-Fontes et al. (2022)	1 RCT, 55 participants	Week 7	PBM: 910 Control: 868 p = 0.5275 Favours neither	NR
Prevention, general UW-QOL (day 35)	Kauark-Fontes et al. (2022)	1 RCT, 55 participants	Week 7	PBM: 687 Control: 607 p = 0.0390 Favours PBM	NR
Prevention, physical UW-QOL (day 35)	Kauark-Fontes et al. (2022)	1 RCT, 55 participants	Week 7	PBM: 279 Control: 258 p = 0.1330 Favours PBM	NR
Prevention, social-emotional UW-QOL (day 35)	Kauark-Fontes et al. (2022)	1 RCT, 55 participants	Week 7	PBM: 408 Control: 348 p = 0.0034 Favours PBM	NR

Outcome	Evidence source	Number of participants	Study period / Follow up	Absolute effect	Relative effect
Quality of life					
Treatment, OHIP-14	Martins et al. (2021)	1 RCT, 48 participants	30 days	Median (IQR) PBM: 3.78 (**1.97** to **7.59)** Control: 9.76 **(4.63** to **16.45**) p = 0.006 Favours PBM	NR
Treatment, PROMS Scale	Martins et al. (2021)	1 RCT, 48 participants	30 days	Median (IQR) PBM: 24 (**10** to **39.25**) Control: 38.8 (**13** to **58)** p = 0.065 Favours PBM	NR

Abbreviations
CI: confidence interval; HR: hazard ratio; IQR: interquartile range; NCI: National Cancer Institute; NR: not reported; OHIP-14: Oral Health Impact Profile-14; PBM: photobiomodulation, PROMS: Patient-Reported Oral Mucositis Symptom; QoL: quality of life, UW-QOL v4: University of Washington Quality of Life Questionnaire, RCT: randomised control trial, RR: relative risk, SD: standard deviation; SMD: standardised mean difference; VAS: Visual Analogue Scale; WHO: World Health Organization; WMD: weighted mean difference.

5.12 Ongoing studies

We identified 10 ongoing RCTs during the search. Of the ongoing RCTs, seven were recruiting, one had completed recruitment, one was due to start recruiting, and one held an unknown status. Details of the ongoing RCTs and their primary and secondary outcomes are reported and summarised in Appendix 4 (Table A4-1).

6. Economic evidence

6.1 Economic evidence review

The search identified 1,075 published papers. Following a title and abstract and then full paper sift, no health economic studies were deemed relevant. As such, no health economic studies have been included in this Evidence Appraisal Report. Of the eight publications that were identified by their title and abstract, four were excluded because they dealt with the wrong indication and four were considered not applicable because of their setting.

Antunes et al. (2016), Bezinelli et al. (2014), Campos et al. (2020) and Lopes Martins et al. (2021) were undertaken within the healthcare setting of Brazil. While these studies were excluded because they had limited applicability, a brief narrative summary is provided below as the studies may offer useful information and insight regarding the delivery of photobiomodulation.

Antunes et al. (2016) undertakes a cost-effectiveness analysis of low-level light therapy in cancer patients receiving concurrent chemoradiation. Oral mucositis was assessed according to whether it was grade 3 or higher, and a cost per grade 3 to 4 oral mucositis avoided was estimated at (US) $4,961 at 2013 prices, equivalent to GBP £3,698 in 2021 prices. Calculation to 2021 GBP £ follows an exchange rate transfer, using historic rates (XE.com 2022) and an inflation adjustment (Bank of England 2022), all subsequent figures are adjusted following the same approach. In addition to potential health outcomes of oral mucositis, the analysis provides a list of resources associated with the delivery of photobiomodulation, which may be used in micro-costing to inform health economic analysis.

Campos et al. (2020) undertook a systematic review and meta-analysis, followed by a cost-effectiveness analysis. The meta-analysis suggests that photobiomodulation is associated with an RR of 0.36 of developing oral mucositis grade 3 or higher compared with standard care. A cost of (US) $ 1,273 (£1,143 in 2021 prices) was estimated for the photobiomodulation treatment at 2019 prices. The prevalence of oral mucositis grade 3 or higher was approximately 69% across the studies included in the Campos et al. (2020) systematic review. The RR for the photobiomodulation group multiplied by the baseline prevalence offers a 0.25 rate for oral mucositis grade 3 or higher in the intervention group. The resulting cost per oral mucositis grade 3 or higher case avoided would be approximately (US) $2,893 (£2,371 in 2021 prices).

Lopes Martins et al. (2021) undertook a cost-effectiveness analysis alongside an RCT of photobiomodulation for the prevention of radiotherapy-induced oral mucositis. The analysis considered the costs of emergency service visits, nasoenteral tubes, opioids, non-steroidal anti-inflammatory medicines, corticosteroids, electrolyte replacement and general hospitalisation. Within-trial healthcare resource use was recorded for both groups over the six-week duration (n = 48). The photobiomodulation group incurred (US) $905 (£742 in 2021 prices) with intervention-specific costs contributing (US) $900 (£738 in 2021 prices). Resource use was higher in the control group, with a total per patient cost of (US) $48 (£39 in 2021 prices). The incremental cost increase associated with the use of photobiomodulation was (US) $ 857 (£702 in 2021 prices) and the cost to avoid one case of severe (grade 3 or higher) oral mucositis (based on the WHO oral mucositis scale) was (US) $2,963 (£2,428 in 2021 prices).

Bezinelli et al. (2014) assessed the cost effectiveness of laser photobiomodulation in hematopoietic stem cell transplantation. The clinical data were gathered from 167 individuals, with 91 receiving laser photobiomodulation and 76 receiving standard care. The prevalence of severe oral mucositis was far higher in the control group with an RR of 16.8 (95% CI −5.8 to 48.9). The cost analysis found laser photobiomodulation to be cost saving for both autologous and allogeneic transplantation. The cost savings associated with laser photobiomodulation were driven by a reduction in hospitalisation time and lower levels of prescription medication. The conclusions of the cost comparison are limited because of the baseline imbalance between the groups; ~89% of the control group underwent the relatively cheaper autologous transplantation compared with ~68% of the intervention group.

Collectively, the excluded cost effectiveness analyses reflect a value proposition for photobiomodulation which is situated in the north-eastern quadrant of the cost-effectiveness plane. Photobiomodulation is associated with a relative increase in healthcare costs and is more effective than standard care. The cost to avoid one case of severe (grade 3 or higher) oral mucositis ranged between (US) $2,963 (£2,428 in 2021 prices) and (US) $4,961 (£4,065 in 2021 prices).

6.2 HTW economic analysis

In the absence of existing health economic evidence, HTW developed a health economic analysis to address the cost effectiveness of photobiomodulation compared with standard care in the prevention of oral mucositis in people receiving radiotherapy to treat head and neck cancers. The analysis focuses on head and neck cancers as most evidence identified considers this indication for the intervention.

6.2.1 Cost of intervention

The costing approach takes a limited UK NHS and personal social services (PSS) perspective with a base cost year of 2021 GBP (£). The following strategy is constructed to reflect a plausible approach for the delivery of photobiomodulation within NHS Wales. Photobiomodulation can be offered as a prophylactic treatment for oral mucositis alongside radiotherapy or chemoradiotherapy. Whilst there is variation in the number of radiotherapy fractions delivered in the treatment of head and neck cancers, according to the recent radiotherapy dose fractionation guidelines a common number is 30 (RCR 2019). This analysis assumes photobiomodulation is delivered alongside each fraction. A duration of 20 minutes was assumed for the delivery of photobiomodulation per session in the base case, this is based on the recent interventional procedures guidance IPG615 (NICE 2018) which reports a duration between 20 and 30 minutes.

Details referring to the medical professional delivering the intervention are often not reported within the literature. An exception to this is Antunes et al. (2016), where photobiomodulation was delivered by two dentists in a Brazilian healthcare setting. Consultation with experts has informed the base case approach and an assumption was made that a specialist nurse (band 6) could deliver laser photobiomodulation in the NHS Wales setting. The delivery approach and costs are detailed below in Table 6. A hospital-based band 6 nurse costs £55 per hour according to the Personal Social Services Research Unit (PSSRU) (Curtis & Burns 2021). The staffing time includes direct staff wages, salary oncosts, staffing overheads, and capital overheads.

Table 6. Cost of intervention.

Healthcare resource	Cost information	Cost per patient
Band 6 nurse	20 minutes * 30 sessions	£550
Photobiomodulation device	5 years, 8 sessions a weekday. 10,400 session total	£28
Consumables	£1 for a lollipop sleeve	£30
Training and servicing	£1,470 a year	£4
Total cost per patient		£612

Capital expense devices are assumed to have a working life of five years with costs amortised over this duration. The initial purchase cost of the Thor laser was offered by experts at £9,630. Machine capacity is conservatively estimated at eight sessions per weekday, offering an effective lifetime usage of 10,400 or £0.93 per session, £27.78 per patient. The delivery of photobiomodulation includes consumable items; expert feedback has highlighted the use of a lollipop sleeve which is replaced prior to each use, costing £1 each.

Non-variable costs such as maintenance and training are needed, for the base case two healthcare professionals per device are assumed to be trained each year. The need for training each year reflects a position of staff turnover, repeat training and scheduling considerations. Experts have identified that laser photobiomodulation requires a single day of training which is offered at between £299 and £399, so a midpoint of £349 is used in this analysis. Training attendance for the healthcare professional is estimated according to wages plus salary oncosts for a band 6 hospital-based nurse, totalling £46,007 per annum. The PSSRU states 41.9 work weeks per year, resulting in a day cost of £220. Total training per year costs £1,138. Maintenance contracts were reported by experts to cost £235 +VAT and shipping. £282 for the servicing contract with a nominal fee of £50 for shipping would offer a yearly servicing cost of £332; this is needed to maintain the five-year warranty. The total non-variable costs equate to £1,470 per year, a per session cost of £0.14 and £4.24 per treatment series.

6.2.2 Cost effectiveness analysis

Cost effectiveness analyses offer a ratio between the costs and a natural disease unit. The primary outcome from Peng et al. (2020) is relative reduction in severe oral mucositis and the reported meta-analysis estimate is an RR of 0.40 (95% CI 0.28 to 0.57). No baseline prevalence is offered; however, a pooled average prevalence for the control group can be calculated. The systematic review studies included 597 people in the standard care arm; of these, 306 experienced severe oral mucositis, equating to a prevalence level of 0.51. The RR for photobiomodulation of 0.40 (95% CI 0.28 to 0.57) results in a treatment effect of 0.204 (95% CI 0.143 to 0.291). For simplicity, a cohort of 1,000 patients is modelled. The combination of the reduction in severe oral mucositis and cost of delivery offers a cost per avoided case of £2,000. As standard care is focused on oral hygiene and painkillers there is no additional cost applied for severe oral mucositis. Details are reported in Table 7.

Table 7. Cost effectiveness analysis

n = 1,000	Photobiomodulation	Standard care	Incremental
Severe oral mucositis	204 (95% CI 143 to 291)	510	306 (95% CI 367 to 219)
Cost	£612,019	-	£612,019
Cost per case avoided			£2,000

6.2.3 Cost utility analysis

Building on the cost effectiveness analysis by applying a quality-adjusted life-years (QALYs) benefit for each avoided case of severe oral mucositis offers us an opportunity to develop an estimated incremental cost effectiveness ratio (ICER) for the therapeutic delivery of laser photobiomodulation to avoid severe oral mucositis.

Brodin et al. (2021) report a quality-of-life decrement associated with severe oral mucositis. The QALYs lost due to severe oral mucositis are estimated at 0.06. Detail regarding how this QALY estimate is calculated is offered in Brodin et al. (2019). Brodin et al. (2019) assesses the influence of a range of adverse events associated with cancer therapy. The study uses regression analysis, where the dependant variable is the quality of life for the cohort experiencing cancer, and the independent variables are demographics and cancer-specific factors. Severe oral mucositis is included in the analysis as a binary variable; the coefficient associated with this variable reflects the influence oral mucositis has on quality of life. A 55-day duration factor is used to estimate the QALY impact of severe oral mucositis. The ICER for laser photobiomodulation is £33,334 per QALY; the calculation is offered in Table 8 below.

Table 8. Cost utility analysis

Cost per case avoided	Utility increase from avoided case	ICER
£2,000	0.06	£33,334

6.2.4 Sensitivity analysis - LED photobiomodulation

The weight of evidence assessing the clinical effectiveness of photobiomodulation is based on low-level laser therapy. However, there has been a movement towards the use of LED photobiomodulation in recent years. LED photobiomodulation has three key economic benefits over laser: a shorter delivery time, an easier process which allows for a broader range of healthcare professionals to undertake the procedure, and a shorter training period.

Following the same micro-costing structure that was used for laser photobiomodulation, the cost of delivering 30 sessions of LED photobiomodulation is offered in Table 9 below. Due to the relative simplicity of the LED device compared with the low-level laser, experts have suggested that patients may be able to self-administer the photobiomodulation; this would require clinical supervision for safety and to ensure hygiene. Due to the required presence of an NHS staff member, either to administer or monitor the process, a band 3 clinical support worker is costed for the session duration.

The PSSRU does not report an hourly cost for band 3 staff; however, following the same costing approach as used for hospital staff and applying the health visitors wage with the addition of oncosts, an hourly cost can be estimated. The mean wage for a band 3 is £20,699, with oncosts accounting for approximately a third of salary, an additional £6,900 is added to yearly costs, offering a total of £27,599 according to the PSSRU 2021 (Curtis & Burns 2021). Management, admin, and estate staff costs are applied according to a smoothed straight line extrapolation

technique offering a value of £6,234. Overheads are applied using the same approach as management, administration, and estate staff costs and total £9,046. Capital overheads are matched to those of a band 4 hospital-based nurse at £1,658. The total yearly cost for a band 3 clinical support staff is estimated at £44,537. The average hours worked a year are 1,575 which offers an hourly cost of £28.28. The delivery of LED photobiomodulation has been reported by experts to take between five and seven minutes, a time of six minutes is therefore used for the cost estimates.

The cost of the LED photobiomodulation device has been reported by experts to be £17,100, offering a per session cost of £1.64 and a per patient cost of £49.33. Consumables are included in the analysis at the same rate as laser photobiomodulation, which is a £1 sleeve per use. Training for LED photobiomodulation was reported by the manufacturer to be free, can be undertaken remotely and should take approximately an hour. The same training coverage model as used for the laser photobiomodulation, two staff members per year, would equate to a yearly cost of £56.55 (£28.28*2). Maintenance and servicing costs are included at the same level as offered in Table 6. The overall cost of delivering 30 sessions of LED photobiomodulation is estimated at £165.

Table 9. Cost of LED photobiomodulation.

Healthcare resource	Duration/frequency	Cost
Band 3 clinical support worker	6 minutes * 30 sessions	£85
Photobiomodulation device	5 years, 8 sessions per weekday. 10,400 session total	£49
Consumables	£1 per lollipop sleeve	£30
Training and servicing	£1,470 per year	£1
Total cost per patient		£165

Using the assumption that LED photobiomodulation is clinically equivalent to laser-based photobiomodulation, the cost per case avoided is estimated as £540, and the ICER is £9,002. The validity of this assumption of clinical equivalence is unclear, as this Evidence Appraisal Report did not look for evidence comparing LED- and laser-based photobiomodulation. It should also be noted that most of the clinical effectiveness evidence identified evaluated laser photobiomodulation, and only one study was identified that compared LED-based photobiomodulation with standard care. Therefore, the clinical effectiveness of LED photobiomodulation is less certain.

6.2.5 Threshold analysis

The lack of existing UK health economic analyses considering laser photobiomodulation necessitated the use of micro-costed estimates in this analysis. These estimates have been informed by experts but there is still inherent uncertainty. To better understand the relationship between clinical effectiveness and cost effectiveness a threshold analysis based on a willingness to pay of £20,000 per QALY is undertaken. The clinical evidence suggested a 30.6% avoided severe oral mucositis rate with a QALY of 0.06 per event. To be cost effective, the threshold photobiomodulation delivery cost per patient treated would need to be £367 (down from £612 in the base case).

6.2.6 Two-way deterministic sensitivity analysis

The main cost driver for the delivery of laser photobiomodulation is staff time; however, there is uncertainty surrounding the appropriate grade of healthcare professional needed to administer the intervention and the duration of delivery The base case details were informed by experts; however, there were ranges offered and a general acknowledgement that the figures may vary. To characterise the impact that the base case assumptions have on the overall cost effectiveness of laser photobiomodulation, varying levels of healthcare professional band and a range of durations are applied with the resulting ICER being reported. Table 10 reports the range of ICERs resulting from changes to healthcare banding and duration. ICERs are highlighted in red when not cost effective with a gradient to green when cost effective. Band 2 hourly costs are estimated following the same method as used for band 3 healthcare support workers above.

Table 10. Two-way sensitivity: staffing band and procedure duration.

	Duration of procedure (minutes)					
	6	12	20	30	45	60
Band 2	£7,048	£10,718	£15,611	£21,728	£30,902	£40,077
Band 3	£7,999	£12,620	£18,781	£26,483	£38,035	£49,587
Band 4	£8,770	£14,162	£21,352	£30,339	£43,819	£57,300
Band 5	£10,567	£17,757	£27,343	£39,326	£57,300	£75,273
Band 6	£12,365	£21,352	£33,334	£48,313	£70,780	£93,247
Band 7	£14,162	£24,947	£39,326	£57,300	£84,260	£111,221

6.2.7 Alternative device

The selection of the device included in this analysis is based on the technology predominant within the literature; however, there are a range of alternatives available. An alternative photobiomodulation delivery system is CareMin650, this is priced at ~£9,000 with consumables costing £2,600 for 150 sessions. Using the same approach as above, the CareMin650 device would cost £0.86 (£9,000 for 10,400 sessions) with consumables for each session costing £17.33 (£2,600 for 150), giving a total cost of £545.80 per patient ([£0.86+£17.33] *30). With the addition of healthcare professionals, a comparative training and servicing structure as the base case, the per patient total is £1,101.

6.3 Limitations

The cost utility analysis has a range of limitations. The uncertainties can be broadly grouped into three categories: input uncertainties, scope, and longevity. The limitation of the analysis with regard to input uncertainty is that many of the inputs are based on expert opinion due to a lack of appropriate evidence reported in the literature. Some of the cost inputs for wages were calculated estimates which may not be an accurate representation of true values. The analysis is limited by the available evidence; the scope of the analysis focuses on the short-term impact and only on the immediate health condition. The costs of managing severe oral mucositis were not included in the analysis. There may also be complications associated with severe oral mucositis which are not captured by the analysis, such as the discontinuation of cancer treatment. The literature focuses on the relative prevalence of severe oral mucositis, and this

approach is adopted in the economic evaluation. The relative incidence of each grade of oral mucositis is not considered. It is noted that the overall prevalence of any grade of oral mucositis is reduced with the use of laser photobiomodulation; however, not accounting for these changes may limit the applicability of the evaluation.

7. Organisational issues

Drawing on the evidence included in this rapid review, the delivery of photobiomodulation sessions varies due to a wide range of parameters, including the photobiomodulation's wavelength, power, energy density, duration, and location of irradiation (outside or inside the mouth), all of which may impact on its effectiveness and safety.

Experts also highlighted the importance of distinguishing between low-level laser and LED systems, since they have different impacts on clinical pathways, risks, costing and organisational issues. For instance, they reported that low-level lasers carry safety issues and further training needs, or additional considerations such as suitable rooms for safe laser treatment.

Based on the above, experts highlighted the significant need for future research to identify the optimal photobiomodulation delivery protocol.

Photobiomodulation can also be delivered by trained dentists or doctors. However, there is limited evidence on the training level, structure and duration needed to deliver preventive or therapeutic photobiomodulation in people receiving cancer treatment. CareMin650 is a new photobiomodulation device that can be operated by nursing staff or held in place by the patients themselves, but it is unclear if the nursing staff and the patients receive specific training to deliver the sessions successfully. Experts' views on the level of skills and training needed to deliver photobiomodulation varied. Most of the experts considered that experienced dentists, dental therapists, or dental nurses are the most appropriate professionals to deliver photobiomodulation. However, some supported that photobiomodulation could be delivered either by professionals with less clinical experience, such as health support workers, nurses, or the patients themselves. It is important to note that the latter justification was on photobiomodulation using LED systems only.

Experts highlighted to HTW several centres using photobiomodulation devices across the UK, including both low-level laser and LED systems. They reported that centres using lasers were located in Sheffield and Glasgow Children's Hospital, while centres using the THOR LED systems were the South Tyneside and Sunderland NHS Foundation Trust, the Leeds Teaching Hospitals NHS Trust (paediatrics), the University Hospitals Dorset NHS Foundation Trust, the Kendal Lymphology Centre, Nottingham University Hospitals NHS Trust, the Royal United Hospitals Bath NHS Foundation Trust, the Newcastle upon Tyne Hospitals NHS Foundation Trust (paediatrics), the Christie NHS Foundation Trust, Royal Devon and Exeter NHS Foundation Trust, the Gloucestershire Hospitals NHS Foundation Trust (Hereford), the Gloucestershire Hospitals NHS Foundation Trust (Cheltenham), the University Hospitals of Leicester NHS Trust, and the St George's University Hospitals NHS Foundation Trust (lymphoedema).

8. Patient issues

We did not identify any studies on patient issues and patient experience through our literature search.

HTW received a patient submission from The Swallows Head and Neck Cancer Group on the impacts of oral mucositis associated with cancer treatment and the potential impacts of photobiomodulation to treat or prevent oral mucositis. The submission can be read in full in Appendix 5.

In summary, their submission states that:

- Oral mucositis is a horrendous, debilitating condition.
- The condition can have a major impact on mental health and wellbeing, with some feeling suicidal.
- Photobiomodulation is clearly working for patients (and not just for oral mucositis).
- Photobiomodulation is quick and easy to use, reduces ulceration, reduces pain, and has an enormous positive impact on quality of life for patients, and also therefore care givers.
- Current usual care practices for oral mucositis treatment are managed *'poorly and seen as ineffective'*, involving mouthwashes and pain relief medication, and often having unpleasant side effects.
- Photobiomodulation made people feel empowered as a result of being able to self-administer and increased their confidence.

HTW also collaborated with the North Wales Cancer Patient Forum (NWCPF) to present the views, experiences, perspectives, and opinions of people with oral mucositis due to cancer treatment. A questionnaire on oral mucositis due to cancer treatment was co-produced by HTW and NWCPF. The questionnaire asked participants to report on their experiences and views of oral mucositis due to cancer treatment and photobiomodulation. A total of five responses were received.

This section summarises the five responses to the following three questions posed in the questionnaire:

1) Have you experienced any of the above symptoms after having treatment for cancer and can you tell us what this was like, how it made you feel, how it impacted your daily life, and anything else you'd like to tell us about?
2) How did your doctor recommend you manage your symptoms and how effective was this? How did this make you feel?
3) If you were offer photobiomodulation, how likely would you be to try this? Would anything put you off trying it?

8.1 Responses on oral mucositis due to cancer treatment

In response to the first question asked, those questioned reported that they have experienced one or more of the oral mucositis signs and symptoms listed, including: (1) red, shiny, or swollen mouth and gums, (2) blood in the mouth, (3) sores in the mouth, including on the gums or tongue, (4) soreness or pain in the mouth or throat, (5) trouble with swallowing or talking, and (6) feeling of dryness, mild to severe burning, or pain when eating food.

Specifically, some people described oral mucositis as a 'red hot poker […] thrust down my throat' and 'too painful to continue eating or even drinking'. Others noted they stopped treatment to enable sores to heal. People also experienced weight loss due to radiotherapy treatment ('lost over 3 stone in weight owing to the radiotherapy treatment'), while others shared experiences of pain due to radiotherapy that led them to 'almost stop the [cancer] treatment'. One of the most challenging oral mucositis symptoms was related with food consumption and swallowing.

People used several lifestyle-change strategies to reduce those symptoms, such as 'avoid spicy foods, and drink lots of cold water […] and cold yoghurt type drinks'. Some people also mentioned the use of percutaneous endoscopic gastrostomy (PEG) feeding tube insertion in combination with oral hygiene regimen strategies, while others used artificial saliva products 'which helped a little but wasn't very pleasant in itself'. Most people had been informed prior to cancer treatment of potential side effects, including oral mucositis.

' […] I had to avoid spicy foods, and drink lots of cold water, which helped. The skin on the inside of my cheeks was very sore. I found that cold yoghurt type drinks helped tremendously'

'The dryness was the first thing I noticed and I woke up each morning with a dry mouth and throat.'

'Sadly, I experienced all listed symptoms. However, the burning was NOT by any means 'mild' it was severe, like having a red hot poker […] thrust down my throat - I could not eat anything except swallow a few drops of ice cold water.'

8.2 Responses on photobiomodulation

In response to the second question asked, some of the respondents reported that they have received several different recommendations and support to manage oral mucositis symptoms due to cancer treatment, while others did not receive any recommendations. Recommendations by medical professionals (such as oncologists, health allied professionals, GPs) included the use of specific pain relief, anti-inflammatory mouthwashes and soft food diet. Some people mentioned that the preventive use of these mouthwashes 'from about day seven to ten seems to extend the time before ulcers start'. People also mentioned that they discovered themselves 'through trial and error' which food types worked best for them. Additionally, some people used 'thickened feeds', 'artificial saliva' and water-based moisturisers and 'eventually […] PEG feeding tubes'. Some people experienced 'good support throughout both in primary care and with the specialist team', while others expressed feelings of being 'helpless and totally reliant on their limited advice', since 'the doctors appeared to have no comprehension of the pain patients suffer'.

'The only thing that really seems to help the individual ulcers is [brand name of mouth ulcer pastilles] over the counter remedy.'

'A person from the Health team advised that I should avoid spicy foods, I then discovered through trial and error the sort of foods that worked best for me.'

'I used artificial saliva, thickened feeds, oral gel, oral rinses, but eventually had to commence PEG feeding. Each step was discussed, and I had good support throughout both in primary care and with the specialist team.'

'No recommendations but they are not really a problem.'

'Take paracetamol and rinse my mouth was the Dr's only advice and eat soft foods- if only! As I was unable to swallow I could not take anything. I trusted the Doctors entirely at the time - it made me feel helpless and totally reliant on their limited advice. It was not effective at all, I'll never know how I managed to survive the devastating treatment. The Doctors appeared to have no comprehension of the pain patients suffer.'

8.3 Patient preferences and decision making

In response to the third question asked, respondents who have experienced oral mucositis signs and symptoms due to cancer treatment reported that they would be interested to try therapeutic photobiomodulation as long as they are informed about any potential side effects:

'I would love to try this would just need to be informed of any potential side effects.'

'I would have to be reassured that the photobiomodulation wouldn't increase the risk of cancer coming back into the lymph nodes in my neck!!'

'If I had been offered the device yes, I would have used it. Nothing would have put me off trying the device.'

'I would have been happy to have tried anything to potentially help. However, my particular type of cancer and the localised treatment would have made the PEG still essential as a safety net.'

'I would most certainly want this photobiomodulation. Nothing could put me off trying it.'

9. Conclusions

The aim of this rapid review was to examine the clinical and cost effectiveness of photobiomodulation to prevent or treat oral mucositis for people who received cancer treatment. Evidence is available from a recent systematic review and meta-analysis and six RCTs, which have been published since this review, as well as one 41.3-month RCT follow-up study that was not included in the systematic review.

The evidence suggests that application of preventive photobiomodulation can reduce the overall risk of severe oral mucositis due to cancer treatment. Incidence of severe oral mucositis at the most anticipated time, overall mean grade of oral mucositis, and overall mean VAS score were found to be reduced substantially after preventive photobiomodulation. Regarding therapeutic photobiomodulation, it appears to have no substantial effect on the remission of severe oral mucositis, although it can reduce its duration. There was a lack of evidence on the effects of photobiomodulation on length of hospitalisation and nutrition, as the studies included in this rapid review evidence did not report on those outcomes.

Most of the evidence included focuses on photobiomodulation performed with low-level lasers. One RCT compared LED-based photobiomodulation with a control for the prevention of oral mucositis in adults, and reported no difference in incidence of severe oral mucositis between photobiomodulation and control, although pain was lower in the photobiomodulation group.

However, there is uncertainty around the evidence included due to the heterogeneity and variability across studies regarding the delivery of photobiomodulation sessions. Across all studies, the delivery of photobiomodulation varied due to a wide range of parameters: (1) indication (prevention or treatment), (2) location of irradiation inside or outside the mouth), (3) frequency (number of sessions), (4) technical photobiomodulation parameters (such as wavelength, energy density) and (5) operator. Thus, it is important to further explore the integration of photobiomodulation into the clinical pathway.

Based on the results of the risk of bias assessment and heterogeneity analysis performed by Peng et al. (2020), more well-designed multicentre RCTs in this area are needed. The uncertain influence of different photobiomodulation parameters indicates the need to determine the optimal setting and delivery for photobiomodulation in future studies. These gaps may be further

addressed by the 10 ongoing RCTs that are anticipated to report evidence on both preventive and therapeutic photobiomodulation for oral mucositis due to cancer treatment from 2023 and onwards.

The health economic literature found photobiomodulation to be cost incurring whilst offering a positive clinical effect compared with standard care. The de novo analysis identified laser photobiomodulation to be not cost effective with an ICER of £33,334. There is a high level of uncertainty surrounding the cost effectiveness analysis. LED photobiomodulation offers a more economical method of delivery compared with laser; however, there is insufficient clinical effectiveness evidence on the use of LED photobiomodulation for a cost effectiveness conclusion to be made.

10. Contributors

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The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

A range of clinical experts from the UK provided material and commented on a draft of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of HTW.

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PPI evidence was contributed by The Swallows Head and Neck Cancer Group and the North Wales Cancer Patient Forum.

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12. Evidence review methods

We searched for evidence that could be used to answer the review question: What is the clinical and cost effectiveness of photobiomodulation to prevent or treat oral mucositis in people receiving cancer treatment?

The criteria used to select evidence for the appraisal are outlined in the protocol in Appendix 1. These criteria were developed in agreement with the HTW Assessment Group and UK experts.

The systematic search followed HTW's standard rapid review methodology. A search was undertaken of MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), KSR Evidence, Cochrane Library, Scopus, the International Network of Agencies for Health Technology Assessment (INAHTA) HTA database, and Epistemonikos. Additionally, searches were conducted of key websites and clinical trials registries. The searches were conducted in April 2022, with an updated search of MEDLINE, Embase, CINAHL, KSR Evidence, Cochrane Library, Scopus and INAHTA HTA database run on 12 September 2022. Appendix 2 gives details of the search strategy used for MEDLINE. Search strategies for other databases are available on request.

After the search was conducted, it was clear that there were several systematic reviews, as well as primary studies, comparing photobiomodulation with usual care, placebo or sham, or no treatment for the prevention or treatment of oral mucositis for children or adults undergoing cancer treatment. In line with the priority of evidence outlined in the protocol (Appendix 1), we selected for inclusion the most recent systematic review and meta-analysis focusing on both populations as well as prevention and treatment of oral mucositis (Peng et al. 2020). We also included RCTs comparing photobiomodulation with sham or usual care for oral mucositis in people undergoing cancer treatment, published since the literature search of Peng et al. (2020). Due to the presence of higher priority evidence, observational and non-randomised studies were not included. Additionally, we included one 41.3-month RCT follow-up study reporting long-term survival outcomes that had not been included in Peng et al. (2020). Appendix 3 summarises the selection of articles for inclusion in the review. A single reviewer screened studies and extracted data from relevant sources. Where there was uncertainty around eligibility for inclusion, studies were discussed with a second reviewer. A formal quality assessment was not conducted but the strengths and weaknesses of evidence are considered throughout.

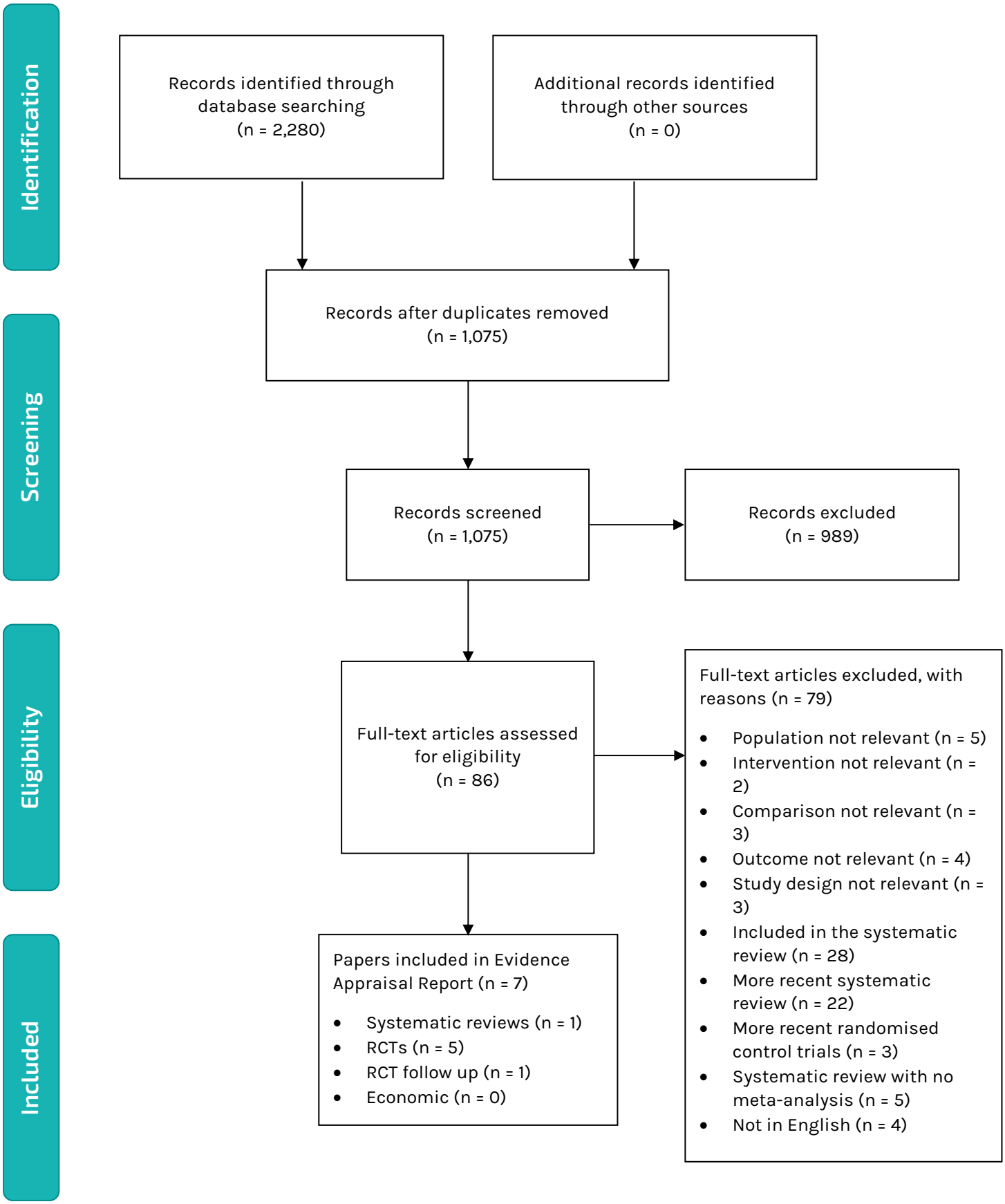
Appendix 1. Inclusion and exclusion criteria for evidence included in the review below

	Inclusion criteria	Exclusion criteria
Population	People with (or at risk of) oral mucositis	
Intervention	Photobiomodulation for oral mucositis, as either a prophylactic (preventive) or treatment, in addition to usual care.	Photobiomodulation to treat other conditions (for example radiation dermatitis).
Comparison/ Comparators	No treatment or placebo or sham treatment Usual care, which may include: • patient education and reinforcement of the importance of good oral and skin care • painkillers (for example paracetamol) • anti-inflammatory agents (for example benzydamine hydrochloride) • keratinocytes growth factors (for example palifermin) • antioxidants	
Outcome measures	• Incidence and severity of oral mucositis • Duration of oral mucositis (or duration of severe oral mucositis) • Severity reduction (for example reduction in oral mucositis scales or toxicity criteria) • Pain reduction (for example using a visual analogue scale) • Quality of life outcomes • Healthcare utilisation and economic outcomes (for example, intervention delivery, resource costs) • Safety outcomes (for example complications, adverse events)	
Study design	The following study types were prioritised, in the order listed: • Systematic reviews with or without meta-analysis • Randomised control trials • Non-randomised control trials • Single-arm trials We will only include evidence for 'lower priority' evidence where outcomes for each condition or symptom of interest are not reported by a 'higher priority' source or where 'lower priority' evidence relates to an intervention assessed to be of high potential. We will also search for economic evaluations or original research that can form the basis of an assessment of costs or cost comparison and for qualitative studies that provide information on patient or organisational issues.	
Search limits	No date limits apply	
Language limits	English language	
Sub-group analysis	Where evidence allows, we will report outcomes separately according to: • Evidence in children and/or adolescents, adults • Cancer subtypes • Photobiomodulation protocol (such as, differences in dose, wavelength)	

Appendix 2. MEDLINE search strategy

Ovid MEDLINE(R) ALL <1946 to April 19, 2022>		
Photobiomodulation & oral mucositis		
1	Stomatitis/	7006
2	((oral or mouth) adj2 mucosit*).tw,kf.	3030
3	(oromucosit* or oro-mucosit*).tw,kf.	5
4	stomatit*.tw,kf.	16023
5	Mucositis/	1789
6	mucosit*.tw,kf.	11094
7	((oral or mouth or mucos*) adj2 inflam*).tw,kf.	8710
8	or/1-7	37817
9	(photobiomodulation or photo-biomodulation or photobio-modulation or photo-bio-modulation).tw,kf.	2148
10	Low-Level Light Therapy/	6780
11	((low or soft or therapeutic) adj2 (level or power or intensity) adj2 (laser* or light* or photo*)).tw,kf.	7629
12	(LLLT or LEDT).tw,kf.	2129
13	((laser* or light* or photo*) adj2 (biostimulat* or bio-stimulat*)).tw,kf.	146
14	Laser Therapy/	39785
15	Phototherapy/	10673
16	((laser* or light* or photo*) adj3 (therap* or treatment* or irradiat* or intervent*)).tw,kf.	105706
17	or/9-16	142820
18	8 and 17	566
19	limit 18 to english language	526
Exclusions filter		
20	Letter/	1176991
21	Editorial/	602153
22	News/	212082
23	exp Historical Article/	408225
24	Anecdotes as Topic/	4746
25	Comment/	960120
26	Case Reports/	2263379
27	(letter or comment*).ti.	175901
28	or/20-27	4734333
29	Randomized Controlled Trial/ or random*.ti,ab.	1437523
30	28 not 29	4704148
31	exp Animals/ not Humans/	4996467
32	exp Animals, Laboratory/	939188
33	exp Animal Experimentation/	10147
34	exp Models, Animal/	627696
35	exp Rodentia/	3448316
36	(rat or rats or mouse or mice).ti.	1396796
37	or/30-36	10545046
Set combination		
38	19 not 37	419

Appendix 3. PRISMA flow diagram outlining selection of papers for clinical and cost effectiveness



Appendix 4. Ongoing studies

Table A4-1. Ongoing studies: designs and characteristics

Study information	Status	Research question & outcome measures
Prevention of oral mucositis		
Registration: NCT03972527 **Country:** United States **Target recruitment:** 69 participants **Follow-up:** NR **Estimated primary completion date**: December 2023	Recruiting **Last updated:** February 2022	This RCT aims to compare preventive PBM with sham treatment for adults receiving cancer treatment. **Population**: adults receiving cancer treatment **Intervention**: PBM in addition to usual care **Comparator**: sham treatment **Primary outcome measure**: (1) incidence of severe oral mucositis (WHO) at the 6th week of cancer treatment **Secondary outcome measure:** 1) use of opioid analgesics between the 6th and 8th week in days, and (2) changes in overall QoL over the 6-week treatment period
Registration: NCT03983369 **Country:** France **Target recruitment:** 300 participants **Follow-up: NR** **Estimated primary completion date**: September 2021	Recruiting **Last updated:** February 2021	This RCT aims to compare preventive PBM with sham treatment for people receiving cancer treatment. **Population**: both children and adults receiving cancer treatment **Intervention**: K-Laser Cube 3 **Comparator**: sham treatment **Primary outcome measure:** (1) proportion of grade 3 to 4 of oral mucositis **Secondary outcome measure:** NR
Prevention of oral mucositis		
Registration: RBR-92md93 **Country:** Brazil **Target recruitment:** 132 participants **Follow-up:** NR **Estimated primary completion date**: NR	Recruiting **Last updated:** May 2022	This RCT aims to compare preventive PBM with sham treatment for adults receiving cancer treatment. **Population:** adults receiving cancer treatment **Intervention**: Laser DUO **Comparator:** sham treatment **Primary outcome measure:** (1) prevalence of oral mucositis **Secondary outcome measure:** (1) severity of oral mucositis (WHO), and (2) pain of oral mucositis (VAS score)

Study information	Status	Research question & outcome measures
Treatment of oral mucositis		
Registration: ChiCTR2000041531 **Country: China** **Target recruitment:** 160 participants **Follow-up:** NR **Estimated primary completion date**: December 2022	Recruiting **Last updated:** March 2021	This RCT aims to compare therapeutic PBM with sham treatment for adults with oral mucositis receiving cancer treatment. **Population**: adults with oral mucositis due to cancer treatment **Intervention**: low-level laser therapy **Comparator**: sham treatment **Primary outcome measure**: (1) overall severity of oral mucositis **Secondary outcome measure:** (1) overall patient experience, and (2) QoL endpoints
Treatment of oral mucositis		
Registration: IRCT20191107045357N2 **Country:** Iran **Target recruitment:** 58 participants **Follow-up:** NR **Estimated primary completion date**: NR	Pending **Last updated:** April 2022	This RCT aims to compare therapeutic PBM with sham treatment for adults with oral mucositis receiving cancer treatment. **Population**: adults with oral mucositis due to cancer treatment **Intervention**: low-level laser therapy **Comparator**: sham treatment **Primary outcome measure**: (1) severity of oral mucositis (OMAS) **Secondary outcome measure:** (1) pain of oral mucositis (VAS score)
Registration: ISRCTN14224600 **Country:** United Kingdom **Target recruitment:** 380 participants **Follow-up:** 14 months **Estimated primary completion date**: NR	Recruiting **Last updated:** April 2022	This RCT aims to compare therapeutic PBM with sham treatment for adults receiving cancer treatment. **Population**: adults with oral mucositis due to cancer treatment **Intervention**: low-level laser therapy in addition to usual care 3 times a week **Comparator**: sham treatment in addition to usual care 3 times a week **Primary outcome measure**: (1) clinical and (2) cost effectiveness (OMWQ-HN score) **Secondary outcome measure:** (1) QoL at baseline, 6th week, 4th month and 14th month, (2) use of opioid analgesics, (3) safety and adverse events, (4) patient survival, (5) quality-adjusted survival recurrence, (6) persistence of disease (14 months), (7) healthcare utilisation, (8) total costs of PBM and sham

Study information	Status	Research question & outcome measures
		treatment, (9) participant and family costs, (10) healthcare perspectives on delivering PBM, and (11) patient perspectives on receiving PBM
Treatment of oral mucositis		
Registration: NCT05452668 **Country:** Egypt **Target recruitment:** 51 participants **Follow-up:** 10 days **Estimated primary completion date**: December 2022	Not yet recruiting **Last updated:** July 2022	This RCT aims to compare therapeutic PBM with sham treatment for children with oral mucositis receiving cancer treatment. **Population**: children with oral mucositis due to cancer treatment **Intervention**: low-level laser therapy (red wavelength, 660 nm or infrared wavelength, 970 nm) in addition to usual care (that is, antifungal or antiviral and analgesics) **Comparator**: sham treatment in addition to usual care **Primary outcome measure**: (1) pain of oral mucositis (ChIMES) **Secondary outcome measure:** (1) severity of oral mucositis (NCI-CTCAE scale, version 5)
Registration: RBR-5h4y4n **Country:** Brazil **Target recruitment:** 50 participants **Follow-up:** NR **Estimated primary completion date**: NR	Recruiting **Last updated:** May 2022	This RCT aims to compare therapeutic PBM with sham treatment for adults receiving cancer treatment. **Population**: adults with oral mucositis due to cancer treatment **Intervention**: Twin Flex Evolution (MMOptics, Brazil) in addition to usual care **Comparator**: usual care **Primary outcome measure**: (1) costs due to severe levels of oral mucositis (WHO) calculated by opioid medications, use of probes, hospitalisation length and parenteral nutrition. **Secondary outcome measure:** (1) radiotherapy interventions
Registration: RBR-63nvsq6 **Country:** Brazil **Target recruitment:** 36 participants **Follow-up:** NR **Estimated primary completion date**: NR	Recruitment completed **Last updated:** August 2022	**Population**: adults with oral mucositis due to cancer treatment **Intervention**: low-level laser therapy **Comparator**: sham treatment **Primary outcome measure**: (1) reduction of size of oral mucositis **Secondary outcome measure:** (1) pain of oral mucositis (VAS score)

Study information	Status	Research question & outcome measures
Prevention and treatment of oral mucositis		
Registration: NCT01772706 **Country:** France **Target recruitment:** 97 participants **Follow-up:** 5 years **Estimated primary completion date**: March 2021	Unknown **Last updated:** January 2013	This RCT aims to compare preventive and therapeutic PBM with sham treatment for adults receiving cancer treatment. **Population**: adults receiving cancer treatment **Intervention**: low-level laser therapy **Comparator**: sham treatment **Primary outcome measure**: (1) efficacy of preventive and therapeutic PBM (7 weeks) **Secondary outcome measure:** (1) VAS score, (2) nutritional status, (3) treatment compliance, (4) laser tolerance, (5) QoL using QLQ-HN35 questionnaire, (6) overall survival (follow-up), and (7) disease-free survival (follow-up)

Abbreviations:
ChIMES: Children's International Mucositis Evaluation Scale; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NR: not reported; OMAS: Oral Motor Assessment Scale; OMWQ-HN: Oral Mucositis Weekly Questionnaire-Head and Neck Cancer; PBM: photobiomodulation; QoL: quality of life; QLQ-HN35: Quality of life - Head and Neck Cancer Module; VAS: Visual Analogue Scale; WHO: World Health Organization.

Appendix 5. The Swallows Head and Neck Cancer Group patient submission form

The health condition

1. Describe any sources you used to gather information for this submission

I have spoken with clinicians that are currently treating patients with PBM, and directly to some of the patients.

I have gathered the following testimonials:

- [clinician's testimonials 1-7 removed]
- *PBM Therapy….(I think treatment is a better word) I feel the machine on its own has helped me to have more movement in my jaw and slight softening so far in my neck may that continue to improve with more sessions. PBM Therapy is so simple to administer and very comfortable.*
- *Hi my baby is going through cancer treatment at the moment and is currently using the thor machine to help with mucusitis… we are really impressed with the results of the treatment as we can see a massive improvement in are son when it comes to easing the side effects*
- *Since starting the PMB treatment I have become more confident and I am now able to go out and socialise in public. This is due to an increase in my mouth opening and the ability to speak more clearly. I also have an improvement in the tightening of my neck and my lymphoedema has reduced. I can now move my neck more and I feel that overall my level of pain has decreased. The treatment has worked well along with the exercises. The machine is very easy to use and I have not noticed any side effects. I do it myself.*
- *The THOR treatment is certainly helping me, I believe in the following ways:*
    - *Less mucus build up*
    - *Decreased oral mucositis*
    - *Minimal sores on my inner cheeks*
    - *Possible new nerve and facial pawlsy recovery*

    It's been a great help, thank you!

2. What is the health condition and how does it affect the day-to-day lives of patients, their families, carers etc?

Oral mucositis is debilitating, a horrendous thing to live through.
The best way I can describe it is that it's like when you bite your lip and get a mouth ulcer, except it fills your entire mouth and is unrelenting. I could not eat or drink and was in constant agony.
As a result, I also couldn't sleep, so the knock-on effect on my general wellbeing was dreadful. I was irritable and difficult to be around so it had a massive effect on my family, with whom I also couldn't communicate properly because it was so painful to talk. It's not something I would wish on my worst enemy. It was a major contributory factor to me attempting to take my own life on two occasions during my treatment – I can't put it any plainer than that.
To think that other people may not have to suffer as I did, and we can see from the testimonials that the treatment really does work, is amazing. I do still suffer with recurrent mucositis but thankfully these episodes are infrequent and nothing like as severe as when I was being treated.

3. How is the health condition currently managed/treated?

Poorly! Mouthwashes are widely given but both myself and the patients I speak to get little to no benefit from them. Pain medication is given but this comes with its own unpleasant side effects, such as stomach issues and mental health issues.

4. What are the challenges associated with current practice and what does this mean for patients, their families, carers, etc?

Because the treatments are ineffective you still get all the problems, I outlined in question two.
One of the biggest problems with ineffective treatment is the lack of hope this gives to patients from a mental perspective, but more importantly, some patients even end up not being able to continue with treatment as it's just so unbearable to live with. And of those that do, plenty of them end up back in hospital because their inability to eat or drink means they become malnourished. It's torture.

The health technology or model of care and support

5. What difference did/could the health technology make to the lives of patients and what outcomes matter most to them, their families, etc?

As you can see from the patient and clinician testimonials, the difference is profound. I honestly cannot stress enough what a difference not experiencing mucositis makes to a patient's life (even if they don't necessarily realise it because they've not actually been through it!) Also, PBM is helping patients with all sorts of other issues, like skin problems and lymphoedema. There's a huge knock on for families as the patient requires significantly less care, and they can also continue to communicate properly. PBM is quick and easy to use so it doesn't have any impact on life in the way that painkillers can, for example, and as far as I'm aware there is nothing else out there at all that comes close to having such a positive effect. All the patients I speak to love it, and I think one of the reasons is worth noting. They seem to feel empowered about being given something to do for themselves. A lot of being a patient is doing what you're told, having needles stuck in you etc. With PBM, patients take hold of the probes and do everything for themselves, and I have definitely seen a positive psychological benefit to that aspect. I would say that the things that matter most to patients are being in less pain and being able to eat and drink – PBM seems to clearly achieve that.

6. Additional information you believe would be helpful for HTW to consider.

I am a Head & Neck Cancer Survivor and now run a charity dealing with supporting Head & Neck Cancer Patients dealing with mucositis. I know there is NICE guidance for the treatment and a lot of supporting clinical evidence.

7. Summarise the key points of your submission in up to five statements.

1) Oral mucositis is a horrendous, debilitating condition that I would not wish on my worst enemy
2) It is so horrific, that it was a major contributory factor in my attempting to take my own life on two occasions during treatment
3) PBM is clearly working for patients (and not just for oral mucositis)
4) PBM is quick and easy to use, reduces ulceration, reduces pain, and has an enormous positive impact on quality of life for patients, and also therefore care givers
5) To think that others may not need to suffer in the way that I have is remarkable