# NCCHTA

# 23 February 2009

# CRD TAR team, HTA TAR Project (08/55/01): Final Protocol

## Introduction

In its role as part of the CRD/CHE Technology Appraisal Review team, CRD was approached by the HTA programme, on behalf of the National Cancer Director, to undertake a project looking at photodynamic therapy in five areas (Barrett's oesophagus, head and neck cancer, lung cancer, oesophageal cancer, and skin cancer). The scope of the project was subsequently expanded to include an additional two cancer sites (bile duct, brain) at the request of the Scottish Government Health Directorates. No economic component was requested and so attention has been restricted to clinical effectiveness and safety.

## 1. Title of the project:

Photodynamic therapy (PDT) in the treatment of Barrett's oesophagus and cancers of the bile duct, brain, head and neck, lung, oesophagus and skin.

## 2. Name of TAR team and project 'lead'

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## 3. Plain English Summary

Photodynamic therapy (PDT) uses laser, or other light sources, combined with a light sensitive drug (known as a photosensitising agent) to destroy diseased tissue. Photosensitising agents may be given in the form of creams applied to the skin or may be taken internally as a drink, or by injection. A period of time varying from a few minutes up to 4 days is required for the optimum uptake of the drug in cancers after which light is shone on to the cancerous area. The light may be shone directly onto the skin or delivered to an internal cancer site via a flexible tube (endoscope) into organs like the gullet and lungs and with optical fibres inserted through needles into solid organs, like deep in the neck. Normal tissue is affected as well as cancerous areas, but there is no effect in areas not exposed to the treatment light and most treated areas heal remarkably well with little scarring. PDT is usually used alongside other treatments such as surgery, radiotherapy or chemotherapy and can sometimes be used for locally recurrent cancer when conventional treatments fail. Increasingly, it is being used as an initial treatment for some early cancers. PDT is usually a minimally invasive procedure with a short recovery time. The effects are apparent within a few days; treatment can be repeated if necessary and can sometimes be delivered to areas that are inaccessible to

conventional surgery (particularly in patients who are unfit for major surgery). It does not appear to have any life-threatening side effects although residual drug in the skin can leave patients sensitive to bright indoor or outdoor light. With some of the photosensitising drugs, this can persist for a number of weeks.

The aim of this research is to systematically review the relevant evidence pertaining to the effectiveness and safety of PDT for the following conditions: Barrett's Oesophagus (a pre-cancerous condition) and cancers of the bile duct, brain, head and neck, lung, oesophagus and skin.

## 4. Decision problem

### Background

Photodynamic therapy (PDT) is used for a number of indications, but this protocol will focus on its use in the treatment of certain cancers and the pre-cancerous condition of Barrett's Oesophagus.

PDT is the use of photosensitising agents in combination with a high-frequency light source such as a laser to destroy cancer cells.[1] In PDT, photosensitising agents are administered either as topical creams or internally as a drink, tablet or injection and the cancerous cells preferentially absorb the agent. A period, varying from a few minutes up to 4 days, is required for the absorption to take place, following which light is shone onto the cancerous area. The photo-chemical reaction results in the local release of toxic, singlet oxygen and therefore destruction of the cancerous tissue.[2]

Various visible light sources have been used in PDT, the exact spectrum of light chosen varies including 'red', 'blue' and 'green' depending on the scatter and effective depth required.[3] The light may be directed onto the skin, or delivered to an internal cancer site via an endoscope (flexible tube), or a number of needles and optic fibres.

The most common side effect of PDT is photosensitisation of the patient's skin. The area treated (if a skin cancer) will usually be sensitive to bright light (natural of artificial) initially, but more residual systemic photosensitisation occurs for 1-3 months following treatment.[4]

Generally PDT is proposed as an adjunctive treatment alongside surgery, radiotherapy or chemotherapy as appropriate. Trials have tended to focus on patients who have not responded to usual treatment, but more ongoing research is now assessing the effectiveness of PDT as a first-line intervention. Some of the potential advantages of PDT include speedy effects, preservation of non-diseased tissue, and limited and non-life threatening side effects.[5] Additionally, PDT offers the ability to treat large areas of diseased tissues (subject to light penetration), the potential to combine with other treatments and the ability to treat areas not reachable with surgery. PDT may be used as a curative or palliative treatment option and is usually delivered in an out-patient setting as a single treatment episode or repeated episodes.

PDT is a fairly well accepted treatment in clinical practice for some types of skin cancer,[6] although there appears to be a lack of good quality systematic reviews. As a treatment for other forms of cancer it has yet to be fully explored, although NICE have issued a number of Interventional Procedure guidance documents which make recommendations about whether the treatment is safe enough and works well enough for routine use.[7-12]

Photochemotherapy or PUVA uses ultra-violet light and acts via an alternative mode of action to PDT,[13] it is more commonly used to treat psoriasis or dermatitis. Extracorporeal photochemotherapy or extracorporeal photopheresis (ECP) is used to treat T-cell lymphomas. ECP involves extracting blood from the cancer patient, adding a sensitiser to the blood and then administering UVA light to selectively destroy cancerous cells. The treated blood is then returned to the patient. PUVA and ECP will not be considered in this project.

**Objectives**

The aim of this project is to systematically review the clinical effectiveness and safety of photodynamic therapy in the treatment of Barrett's oesophagus and the following cancers: bile duct, brain, head and neck, lung, oesophageal and skin. This will inform decisions about the role of PDT in clinical practice and also the need for further research.

**Scope of the technology assessment**

Full details of the populations, intervention and comparators, outcomes and study designs which will enable us to address the decision problem are given below. Published and unpublished studies from any country and reported in any language will be eligible for inclusion provided they meet the following inclusion criteria:

**Population:** The eligible population will include people with specified pre-cancerous conditions or primary cancer in the following sites.

Bile
- Biliary tract
- extrahepatic cholangiocarcinoma (usually adenocarcinoma)
- perihilar cholangiocarcinoma
- distal cholangiocarcinoma
- gall bladder
- ampulla

- Brain
  - Gliomas (astrocytoma, ependymoma, oligodendroglioma or mixed glioma)
  - any of the rarer brain cancer types
- Head and neck
  - Laryngeal cancer
  - Hypopharyngeal cancer

  - Oropharyngeal cancer
  - Oral cavity cancer
- Lung
  - small cell, non-small cell lung cancer (squamous cell carcinoma, adenocarcinoma, large cell carcinoma)

- Oesophagus
  - Barrett's oesophagus (a pre-cursor to cancer)
  - squamous cell carcinoma, adenocarcinoma or undifferentiated cancer of the oesophagus
- Skin
  - Non-melanoma skin cancers (basal cell carcinoma (superficial and nodular), squamous cell carcinoma, Merkel cell carcinoma, Kaposi's sarcoma, T cell lymphoma of skin or sarcoma)
  - Pre-cancerous conditions: Bowen's Disease, Actinic/solar keratosis

We do not anticipate identifying any trials dealing with paediatric patients as these cancers are extremely rare in such groups. Any data on children will be included and considered separately if appropriate.

**Intervention:** Photodynamic therapy (PDT) for both curative and palliative treatment. The specific interventional details will vary according to cancer site.

There are a number of variations possible in the application of PDT, for example the type of photosensitising agent, the method of light delivery, wavelength and duration of light used. We will not restrict our review according to the details of the PDT treatment, but will extract and report data on agent, light source, wattage, duration, number of treatment sessions and wavelength.

Photosensitising agents may include, for example:
- Topical application of Aminolaevulinic acid (ALA)
- Topically applied methyl aminolevulinate (MAL) (Metvix, PhotoCure)
- Systemically administered porfimer sodium (Photofrin)
- Systemically administered temporfin (Foscan)

Light sources delivering visible or near infra-red spectra of light may include for example:
- Lasers (pumped dye or semi-conductor diode)
- xenon arc/discharge lamps
- incandescent filament lamps
- solid-state light emitting diodes (LEDs).

**Comparators:** No restrictions will be placed in the inclusion criteria as to comparators. The relevant comparators will vary according to the cancer site, but are likely to include:

- surgery (e.g. surgical resection, surgical excision, curettage, salvage surgery)
- chemotherapy
- radiotherapy
- brachytherapy
- cryotherapy
- laser ablation
- stenting
- radiofrequency ablation (RFA).

Studies comparing differing application of PDT treatments (e.g. photosensitising agents; source, duration, or wavelength of light) will also be included.

**Outcomes:** The primary outcomes the review will focus on are listed below. These will be addressed individually by site, where appropriate, due to expected differences in the specific outcome measures. Outcomes will also reflect the curative or palliative nature of the intervention.

- Mortality
- Morbidity (symptom burden, symptom improvement, time to healing)
- Quality of Life (patient based outcomes such as cosmetic appearance, depression scores)
- Adverse events (e.g. photosensitivity of skin in general, ulceration of the underlying tissues, haemotypsis, scarring, carcinogenicity, oesophageal strictures, cardiac complications, nausea, inflammation, pain, constipation)
- Resource use (e.g. length of hospital stay)
- Return to normal activities

We will also extract data on recurrence and tumour response measures (such as tumour or lesion clearance or response) while bearing in mind the extent to which these outcomes relate to symptomatic morbidity and patient-perceived benefits.

**Study Designs:** In the evaluation of effectiveness and safety of clinical procedures randomised controlled trials (RCTs) are normally seen as providing a ‘gold standard’ of evidence which is less prone to bias. However such trials are unlikely to have been conducted in large numbers in the cancer sites under investigation. Hence there will be a need to consider other types of evidence. The particular study design inclusion criteria will depend on the cancer site as shown below:

- Skin: we anticipate sufficient randomised controlled trials (RCTs) and therefore will restrict our attention to these.
- All other sites and Barrett’s Oesophagus: given the paucity of RCTs identified in our initial scoping searches we will consider experimental studies with a control group (e.g. quasi-randomised trials) in addition to RCTs.

Alongside the systematic review we will conduct a scoping review of the observational studies in each cancer site. The extent to which we extract data from these studies will depend on the cancer site. For example in skin cancer we anticipate a sufficient number of trials on which to base results. Therefore we are likely to restrict our scoping of the observational studies to the number and nature of these studies. In cancer sites where we find few or no trials we will extract further data on the observational studies to provide a current picture of the evidence.

Animal models, preclinical and biological studies, narrative reviews, editorials, opinions and reports containing no outcome data will be excluded from the reviews.

## 5. Methods for synthesis of evidence of clinical effectiveness

The methods outlined in this protocol have been informed by a rapid evaluation of the existing literature, based on the results of a previous scoping report[14] and a sample from a recent search of the electronic databases MEDLINE, CINAHL and EMBASE. We will undertake a series of systematic reviews (by cancer site) following the principles recommended in CRD Report 4[15] and the QUOROM statement[16] (or forthcoming PRISMA statement if available). The following sections give an overview of the systematic review process.

### Search strategy

A comprehensive search strategy will be developed to ensure all relevant sources of data are located. The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field including manufacturers of photosensitising agents
- Scrutiny of bibliographies of included studies and existing reviews

Electronic databases: Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL), Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (NHS EED), MEDLINE (including MEDLINE In Process), EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PASCAL, and Latin American & Caribbean Health Sciences Literature (LILACS).

Searches will not be restricted by language or study design. A draft search strategy can be found in the Appendix.

### Inclusion and exclusion strategy

Two reviewers will independently screen all titles and abstracts. Full paper manuscripts that may be relevant will be obtained where possible and the relevance of each study assessed independently by two reviewers according to the inclusion criteria described in the previous section. Discrepancies will

be resolved by discussion, or by referral to a third reviewer when necessary. Studies that do not fulfil all of the criteria will be excluded with documented reasons for their exclusion.

**Data extraction strategy**
Data will be extracted independently by one reviewer, using a standardised data extraction form, and checked by another. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. If time constraints allow, attempts will be made to contact authors for missing data. Data from multiple publications of the same study will be extracted and reported as a single study. Extraction will include data on: study details (e.g. study identifier, author, year, country, setting, number of participants, and duration of follow up), patient characteristics (e.g. age, gender, cancer site and stage), intervention (full details of photosensitising agent with dosage, light source, wavelength, spectrum and method of delivery), comparison (type of comparison with full details of delivery methods), study quality, and outcomes relating to effectiveness and safety as specified above.

**Quality assessment strategy**
The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. The quality of RCTs will be assessed using standard checklists adapted as necessary to incorporate topic-specific quality issues. Consideration of the quality will include the following factors: method of randomisation, allocation concealment, blinding of outcome assessors, numbers of participants randomised, excluded and lost to follow up, methods for handling missing data and appropriateness of statistical analysis.

The quality of study designs other than RCTs will be assessed using checklists appropriate to the study design and will highlight any potential sources of bias.

**Methods of analysis/synthesis**
Data extracted from the studies will be tabulated and discussed in a narrative review. The results of the quality assessment will be tabulated, and where possible, the effect of study quality on effectiveness data and the findings of the review will be discussed.

Where appropriate, meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses. Meta-analysis will be carried out using fixed and random effects models using appropriate software. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the $\chi^2$ test for homogeneity and the $I^2$ statistic. If the evidence allows, meta-analysis will be carried out on subgroups including types of photosensitising agent.

Recommendations for further research may also be made as a result of gaps in the evidence base.

## 6. Methods for synthesising evidence of cost-effectiveness

Not applicable. No economic component was requested and so attention has been restricted to clinical effectiveness and safety.

## 7. Expertise in this TAR team

The Technology Assessment Review team at the University of York is drawn from two specialist centres: the Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE). CRD undertakes reviews of research about the effects of interventions used in health and social care (www.york.ac.uk/inst/crd). CHE undertakes research and training in all areas of health economics (www.york.ac.uk/inst/che). Recent TARs undertaken include treatments for bipolar disorder, catheter ablation for atrial fibrillation, stapled haemorrhoidopexy, endovascular stents for abdominal aortic aneurysms and continuous positive airway pressure for sleep apnoea. From 1995 to 2004 CRD was involved in the production of site specific National Guidance for Cancer and has recently undertaken a programme of work funded by Cancer Research UK to inform the Cancer Reform Strategy.

### Team members

Alison Eastwood will take overall responsibility for management of the project. She has over 15 years experience in health services research, over 10 of which is in the field of systematic reviews and with a particular interest in the field of cancer. She has been responsible for CRD's role in the production of site-specific national cancer service guidance, work to support the National Cancer Research Network and more recently work to inform the Cancer Reform Strategy.

Debra Fayter will take day to day responsibility for the project and be involved in all stages of the review from inclusion of studies to writing the final report. She is an experienced systematic reviewer who has conducted reviews in a wide range of fields including surgical procedures and cancer.

Morag Heirs will be involved in all stages of the review from inclusion of studies to writing the final report. New to CRD, she brings two years experience in systematic reviews and related methodology from her work in Health Sciences. She has recently produced a systematic review for the Cochrane Collaboration.

Mark Corbett will be involved in all stages of the review, from inclusion of studies, to writing the final report. He has recently been involved in a systematic review of drugs for influenza, and for the previous ten years worked on conducting large, randomised cardiovascular trials.

Dave Fox is an Information Specialist who will design the search strategy, carry out the database searches, order papers and manage references. He has much experience of supporting health reviews, including a recent NICE MTA.

**Clinical Advisors**

The clinical advisors will provide clinical input to the project, comment on the protocol and various drafts of the final report, and contribute to the discussion section of the report.

Roger Ackroyd is consultant surgeon to the Sheffield Teaching Hospitals NHS Trust. He is an upper gastrointestinal surgeon with a clinical and research interest in PDT. He wrote his thesis on the use of ALA-induced PDT in the treatment of dysplastic Barrett's oesophagus and has supervised a number of PDT-related MD and PhD theses. His clinical and research interests centre around the use of PDT in the treatment of Barrett's oesophagus/early oesophageal cancer and in the palliation of advanced inoperable oesophageal cancer.

David de Berker has 20 years of clinical experience in Dermatology, with training in 4 Dermatology units in the UK and Australia. He spent 13 years as a consultant Dermatologist with a specialist interest in skin cancer and pre-malignant skin disease. He is lead author for British Association of Dermatologists national guidelines on the management of actinic keratoses and contributor to the NICE Improvement of Outcomes Guidance for skin cancer, 2006. He is Chair of the South West Cancer Intelligence Service expert tumour panel on skin cancer, representative of the South West Public Health Observatory task force for Cancer, Skin Cancer lead for the University Hospitals Bristol Foundation Trust. He is an expert reviewer for the Advertising Standards Authority and for 5 peer reviewed journals. David is the author of over 100 peer reviewed articles and multiple books and chapters.

Steve Bown has been involved in translational research on PDT for 25 years. It is one of the major interests of the National Medical Laser Centre (NMLC). His work has been to bring together scientists and clinicians to understand the biology of PDT and identify when it might be of clinical value, then to take forward promising applications into clinical trials in a range of organs for treating cancer, pre-cancer and a range of other diseases. He is a Trustee of the charity "KILLING Cancer", whose aims are to raise the public profile of PDT and to raise funds for PDT research. Until very recently, he was a director of the IPA (International Photodynamic Association), a professional organisation that organises a world congress on PDT every 2 years.

Colin Hopper is Head of the Unit of Oral and Maxillofacial Surgery at the Eastman Dental Institute and Hospital. He is a Senior Research Fellow at the National Medical Laser Centre London. He is also Honorary Consultant at:- St Mary's Hospital, London The Royal Free Hospital, London The Whittington Hospital, London The Great Ormond Street Hospital for Children, London The Royal National Throat Nose and Ear Hospital, London. Since 1991 Mr Hopper has been working in the National Medical Centre. In this position he has led a variety of research projects on the use of photodynamic therapy in the treatment of oral squamous cell carcinoma. Other related areas of research are fluorescence diagnostics (optical techniques for tissue interrogation) and the use of PDT in the treatment of non-malignant conditions such as neurofibromatosis

Professor Andrew Kaye is the Head of the Department of Neurosurgery at the Royal Melbourne Hospital, and Director of The Melbourne Comprehensive Cancer Centre. His main clinical interest involves neuro-oncology and cerebrovascular disease. In 1992 he was awarded the John Mitchell Crouch Fellowship by the Royal Australasian College of Surgeons, and in 1997 was appointed the Sir Arthur Sims Commonwealth Travelling Professor. In 2003 the American Association of Neurological Surgeons honoured him with the Ronald Bittner Award for contributions to the treatment of brain tumours and in 2006 the Paul Bucy Award for his contribution to neurosurgery education. He was awarded the Commonwealth of Australia Centenary Medal in 2003 and Order of Australia in 2004. In 2004 he presented the Sir John Eccles Lecture at the Australian Neuroscience Society. He is the foundation Editor-in-Chief of the Journal of Clinical Neuroscience. He has authored and co-authored over 150 journal articles and book chapters, as well as five books including being the co-author of “Brain Tumours”, a text recognised as being the definitive work on the subject.

Dr Robert Milroy is a consultant in respiratory medicine with a special interest in lung cancer. He was a founder member of the BTS Lung Cancer group and is a chairman of the Lung Cancer forum. He has researched extensively in the field of lung cancer and is the author of over 50 publications.

Stephen Pereira is Senior Lecturer in Hepatology & Gastroenterology at University College London and Honorary Consultant at UCL Hospitals NHS Foundation Trust, with translational and clinical research interests in PDT for pancreatic and biliary tract cancer. He is a specialist advisor for NICE interventional procedures and cancer topic selection consideration panels.

In addition, we are in contact with Professor Herwig Kostron of the Department of Neurosurgery at the Medical University in Innsbruck. We will also make contact with other experts in the field where we require additional information on site specific issues.

**Patient Perspective**

We hope to obtain patient input on the experience of photodynamic therapy to inform the review. In addition, if appropriate a patient representative will be asked to comment on the review and the final report. We are in contact with the director of the organisation Killing Cancer (David Longman).

## 8. Competing interests

Stephen Pereira has previous unrestricted educational grants from Axcan Pharma and QLT Inc. He is currently chief investigator for a randomised phase II/III study of porfimer sodium PDT for biliary tract cancer.

Steve Bown is involved in translational research on PDT and is a Trustee of the charity "KILLING Cancer", whose aims are to raise the public profile of PDT and to raise funds for PDT research. Until very recently, he was a director of the IPA (International Photodynamic Association), but he has no

personal financial interest in any of the pharmaceutical or instrument companies involved in developing PDT.

## 9. Timetable/milestones

| Milestone | Deadline |
|---|---|
| Team submit draft protocol to NCCHTA | September 2008 |
| Expected date of comments on draft protocol to Team | October 2008 |
| Literature searching | November 2008 (with ongoing current awareness searches) |
| Team submit revised/finalised protocol to NCCHTA | December 2008 |
| Relevance and inclusion assessment | December 2008 |
| Data extraction and quality assessment | April 30 2009 |
| Analysis and synthesis | June 30 2009 |
| Submission of report to HTA | July 31 2009 |

## 10. Appendix: Draft search strategy

The following is the strategy to be used in MEDLINE. The basic strategy will be adapted as necessary for other databases.

Database: Ovid MEDLINE(R)
Search Strategy:
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1 photochemotherapy/
2 photosensitizing agents/
3 ((photodynamic or (photo adj dynamic)) adj2 therap$).tw.
4 PDT.tw.
5 (photosensitise$ or photosensitize$ or photosensiti?ing or photochemotherapy or (photo adj chemotherapy)).tw.
6 ((photoradiation or (photo adj radiation)) adj2 therap$).tw.
7 PRT.tw.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 exp neoplasms/
10 (cancer$ or neoplas$ or oncolog$ or tumour$ or tumor$ or lump or lumps).tw.
11 (sarcoma$ or malignan$ or carcinoma$ or growth$ or mass or masses or lesion$ or glioma$).tw.
12 (premalig$ or pre-malig$ or pre malig$ or cyst or cysts).tw.
13 (metastatic or metastases or metastasis or squamous cell$).tw.
14 "Barrett Esophagus"/
15 (barret$ adj (oesophagus or esophagus)).tw.
16 9 or 10 or 11 or 12 or 13 or 14 or 15
17 8 and 16
18 exp Animals/ not humans/
19 17 not 18

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