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# BMJ Open

## PHOTodynamic versus white light-guided treatment of non-muscle invasive bladder cancer: A randomised trial of clinical and cost effectiveness

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3 Title page

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5 PHOTodynamic versus white light-guided treatment of non-  
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8 muscle invasive bladder cancer: A randomised trial of clinical  
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Key words:

- Bladder cancer
- Photodynamic diagnosis
- Quality of life
- Health economics
- Cost effectiveness
- Sample biorepository

The authors declare that they have no competing interests.

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For peer review only

## **Abstract**

**Introduction:** Bladder cancer is the most frequently occurring tumour of the urinary system. Ta, T1 tumours and carcinoma in situ (CIS) are grouped as non-muscle invasive bladder cancer (NMIBC), which can be effectively treated by transurethral resection of bladder tumour (TURBT). There are limitations to the visualisation of tumours with conventional TURBT using white light illumination within the bladder. Incomplete resections occur from the failure to identify satellite lesions or the full extent of the tumour leading to recurrence and potential risk of disease progression. To improve complete resection, photodynamic diagnosis (PDD) has been proposed as a method that can enhance tumour detection and guide resection. The objective of the current research is to determine whether PDD-guided TURBT is better than conventional white light surgery and whether it is cost-effective.

**Methods and Analysis:** PHOTO is a pragmatic multi-centre randomised controlled trial (open parallel group, non-masked, superiority trial) comparing the intervention of PDD-guided TURBT with standard white light resection in newly diagnosed intermediate and high risk NMIBC within the UK NHS setting. Clinical effectiveness is measured with time to recurrence. Cost-effectiveness is assessed within trial via the calculation of incremental cost per recurrence avoided and incremental cost per quality adjusted life per year (QALY) gained over three years, and over long term through a modelling exercise over patients' life time.

**Ethics and dissemination:** Formal ethics review was undertaken with a favourable opinion, in line with UK regulatory procedures (REC reference number: 14/NE/1062; Trial registration: ISRCTN84013636). If reductions in time to recurrence is associated with long term patient benefits the cost-effectiveness evaluation will provide further evidence to inform adoption of the technology. Findings will be

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3 shared in lay media such as patient and charity forums and will be presented at key  
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5 meetings and published in academic literature.  
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9 **Article Summary:**  
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13 Strengths and limitations of the PHOTO study include;  
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18 • the effectiveness of the photodynamic diagnosis (PDD) for the initial resection  
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20 of intermediate and high risk non-muscle invasive bladder cancer as part of  
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22 routine care will be demonstrated with a pragmatic clinical trial design,  
23  
24 • full-health economic evaluation will provide high quality evidence of the  
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26 burden of NMIBC for the NHS  
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28 • a well-characterised trial associated biorepository of longitudinal serially  
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30 collected tissue samples  
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## 1. Background

Bladder cancer is the most frequently occurring tumour of the urinary system [1]. Staging of bladder cancer is described using the Tumour, Node, Metastasis (TNM) system [2], for which an illustration is provided in Figure 1. Tumours confined to the epithelial lining (urothelium) are classified as stage Ta and those invading the lamina propria are classified as stage T1.

Ta and T1 tumours can be removed by transurethral resection (TURBT) that involves passing a cystoscope through the urethra into the bladder and resecting the tumour under direct visualisation. For therapeutic purposes Ta and T1 tumours are grouped together as non-muscle invasive bladder cancer (NMIBC). Grade (microscopic characteristics of the tumour cells) can be used to describe aggressiveness of cancers and are characterised as either low grade (relatively benign) or high grade (aggressive). NMIBC also include flat, high-grade tumours that are confined to the epithelium classified as carcinoma in situ (CIS).

Complete resection of the tumour with TURBT is essential to obtain good prognosis. It is thought that failure to identify satellite tumours or to appreciate the full extent of the tumours visualised during resection using conventional white light cystoscopy may be a factor in 20-40% of recurrent bladder tumours [3, 4]. Incomplete resection with TURBT is also associated with staging errors. In order to correct the staging errors associated with initial TURBT a second resection within 2-6 weeks is suggested for select group patients [5]. It has been postulated that development in cystoscopy imaging can improve resections and decrease the need for a second resection [6].

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3 Recurrence and stage progression to muscle invasive (T2-T4) or metastatic  
4 cancer is more likely to occur in those with high-grade tumours with concomitant  
5 CIS. CIS in particular can be easily missed using conventional white light guided  
6 resection [6].  
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10  
11 Surveillance of NMIBC is carried out with cystoscopy to detect recurrence early  
12 and allow treatment before progression. Clinical guidelines tailor follow up protocols  
13 according to the risk groups (low, intermediate and high) developed using clinical and  
14 histological parameters [7]. Advised follow-up of low risk is at three months and if  
15 negative the next cystoscopy is scheduled for nine months later and then yearly for  
16 five years. Patients with high-risk tumours have cystoscopy and urine cytology at  
17 three months. If negative, it is repeated every three months for two years, then every  
18 six months until five years, and annually thereafter [5]. The intensity of cystoscopic  
19 follow up for patients with intermediate risk is not clearly defined, for which a follow-  
20 up scheme in-between those described for low and high risk and is adapted according  
21 to personal and subjective factors [5].  
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### 39 1.1. Photodynamic diagnosis of NMIBC:

40 As an attempt to improve resection rates, photodynamic diagnosis (PDD) has  
41 been developed to enhance tumour detection and guide resection. Meta-analyses and  
42 systematic reviews of PDD guided treatment of NMIBC have shown efficacy in  
43 tumour detection and reduction in residual tumour compared with white light  
44 cystoscopy alone. These findings translate into reduced recurrence rates [6, 8].  
45  
46 However, these trials were efficacy studies and the systematic review called for a  
47 pragmatic study to allow better interpretation of possible benefit into daily clinical  
48 practice.  
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## 1.2. Health economics of NMIBC:

NMIBC is one of the most costly cancers to manage on a per patient basis because of its high prevalence, high recurrence rate, need for adjuvant treatments and the requirement for long-term cystoscopic surveillance. The total cost of treatment and 5-year follow-up of patients with NMIBC diagnosed in the United Kingdom has increased from £73 million to £213 million from 2001 to 2012 (inflation corrected) [9, 10]. From a patient perspective, there often are considerable anxieties about recurrences, transurethral resection and progression, requiring additional therapies with potential mortality and long-term morbidity (e.g. radical surgery). Transurethral resection itself is associated with reduced quality of life, including both mental and physical health domains; although these effects are usually transient [11]. Substantial effects on health related quality of life (HRQoL) are most likely to come from adjuvant intravesical treatments and radical or palliative treatments for progression [12]. The cost-effectiveness of NMIBC treatment strategies has not been widely studied.

## 1.3. NMIBC biomarkers and clinical impact:

To date, existing non-invasive commercial biomarkers (primarily urinary) are not embedded in routine clinical practice due to poor sensitivity, specificity and lack of evidence. Several research bodies have recognized the lack of clinically useful biomarkers for bladder cancer. “Fit for purpose” sample resources accessible to high-throughput ‘omic’ technologies will afford the greatest opportunity to generate translational hypotheses and ensure clinical validity and utility of putative candidate markers/signatures [13, 14]. Robust, ‘future-proof’, longitudinal serial sample

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3 archives providing critical insights of the natural history of bladder cancer correlated  
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5 with clinical detail for retrospective translational biomarker discovery, are lacking.  
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#### 8 9 1.4. Current research objectives:

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11 More efficient management strategies to reduce NMIBC recurrence and hence  
12  
13 decrease both the burden to patients and costs are urgently needed. PDD-guided initial  
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15 TURBT has been identified as a technique that can help achieve these aims. The  
16  
17 objective of the current research (PHOTO trial) is to determine whether  
18  
19 photodynamic surgery guided by a fluorescent tumour marker is better than  
20  
21 conventional white light surgery in the cystoscopic treatment of people with  
22  
23 intermediate and high risk cancers confined to the bladder lining and whether its  
24  
25 implementation is cost-effective. The trial includes a full assessment of the costs of  
26  
27 patient management through the care pathway. Individual patient data from this trial  
28  
29 will be used for subsequent mathematical modelling studies to investigate safe  
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31 monitoring frequency. The Photodynamic versus white light-guided treatment of non-  
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33 muscle invasive bladder cancer trial has the following research objectives:  
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##### 36 37 i. Primary objectives:

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39 Clinical effectiveness: To compare time to recurrence for each of the two treatment  
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41 strategies, with a principal point of interest at 3 years.  
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44 Cost-effectiveness: To evaluate cost-effectiveness as measured by the incremental  
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46 cost per recurrence avoided and the cost-utility as measured by the incremental cost  
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48 per quality-adjusted life year (QALY) gained at three years and over patients' life  
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50 time.  
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##### 52 53 ii. Secondary objectives:

- 54  
55 a. To measure relative rates of disease progression at three years.  
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- 3 b. To measure relative harms and safety.
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- 5 c. Patient lifetime HRQoL and cancer-specific survival.
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- 7 iii. Additional objectives:
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- 9 a. To model the safest and most cost-effective cystoscopic follow-up surveillance
- 10 schedule;
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- 12
- 13 b. To evaluate the learning curve for the procedure and account for its effects on
- 14 outcomes of both PDD-guided and standard white light resections;
- 15
- 16 c. To establish a well-characterised cohort of serial samples from patients with
- 17 intermediate and high-risk NMIBC including clinical data, urine, blood and
- 18 tumour specimens for separately funded translational research.
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## 26 **2. Methods & Design**

### 27 2.1. Study design

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31 PHOTO is a multi-centre randomised open parallel group non-masked superiority

32 trial comparing the intervention of PDD guided bladder tumour resection with

33 standard white light resection in patients with newly diagnosed intermediate and high

34 risk NMIBC. Apart from initial treatment, both groups will receive standard care,

35 including single dose intravesical mitomycin C within 24 hours of initial resection,

36 surveillance according to risk-adjusted schedules and adjuvant therapy as indicated by

37 current practice guidelines. The target number of patients to be recruited is 533 with a

38 trial specific follow-up of at least 36 months for each individual. The outline of the

39 study protocol is shown in Figure 2.

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## 2.2. Intervention

The interventions being compared within PHOTO trial are:

- i. Photo dynamic diagnosis (PDD) guided trans-urethral resection (TURBT) (experimental group) vs;
- ii. Standard white light TURBT (control group)

All participants, unless there are clinical contra-indications, receive intravesical mitomycin C (40 mg in 40 ml saline), ideally within 6 hours following TURBT but otherwise within the inpatient setting before discharge.

### 2.2.1. Technique of photodynamic diagnosis

PDD requires preliminary instillation of the photosensitiser hexaminolevulinate (85 mg in 50 ml of phosphate buffered saline) into the participant's bladder through a urethral catheter. Participants are asked not to pass urine for at least one hour after insertion. Following operating theatre preparation according to local standard procedures and under appropriate anaesthesia, participants undergo TURBT of their bladder tumour under blue light (wavelength 380-450 nm) illumination of the bladder. The equipment required includes a specialised light source, cystoscope, light cables and cameras. When using PDD, normal bladder epithelium appears blue whilst red areas should be considered suspicious and should be resected.

### 2.2.2. Technique of standard white light cystoscopy

The control group does not have any preliminary photosensitiser instillation and undergo standard tumour localisation and resection under white light (wavelength 400-800 nm) illumination of the bladder.

### 2.3. Participants

In the PHOTO trial adult patients with a suspected new diagnosis of intermediate or high risk NMIBC are studied. Participants are identified prior to initial resection based on results of preliminary visual assessment via cystoscopy or imaging performed as part of standard evaluation for suspected urinary tract malignancy.

Patients with the following criteria are included in the PHOTO trial:

- Adult men and women aged  $\geq 16$  years.
- First suspected diagnosis of bladder cancer.
- Visual/ultrasound/Computerized tomography (CT) diagnosis of intermediate/high risk NMIBC.
- White light visual appearances of intermediate or high risk disease ( $\geq 3$ cm OR two or more tumours OR flat velvety erythematous changes alerting a clinical suspicion of CIS).

OR

Suspicion of papillary bladder tumour  $\geq 3$ cm based on ultrasound or CT scanning (without hydronephrosis).

- Written informed consent for participation prior to any study specific procedures.
- Willing to comply with the following life style guidelines:
  - Female participants must be surgically sterile or be post-menopausal, or must agree to use effective contraception after joining the study and for 7 days after treatment. Female participants must not breast feed for 7 days after treatment.

- Male participants must be surgically sterile or must agree to use effective contraception after joining the study and for 7 days after treatment.
- Effective contraception is defined as two forms of contraception, including one barrier method.

Exclusion criteria applied in the PHOTO trial are:

- Visual evidence of low risk NMIBC (solitary tumour < 3cm).
- Visual evidence of MIBC on preliminary cystoscopy, i.e. non-papillary or sessile mass (attached directly by its base without a stalk).
- Imaging evidence of MIBC – CT/USS (this includes the presence of hydronephrosis, which may be present despite clear imaging of MIBC in the bladder).
- Upper tract (kidney or ureteric) tumours on imaging.
- Any other malignancy in the past 2 years (except: non-melanomatous skin cancer cured by excision, adequately treated carcinoma in situ of the cervix, DCIS/LCIS of the breast or prostate cancer in patients who have a life expectancy of >5 years upon trial entry).
- Evidence of metastases.
- Porphyria or known hypersensitivity to porphyrins.
- Known pregnancy (based on history and without formal testing, in keeping with day-to-day NHS practice of PDD use).
- Any other conditions that in the Principal Investigator's opinion would contraindicate protocol treatment.
- Unable to provide informed consent.



- Unable or unwilling to complete follow-up schedule (including HRQoL questionnaires).

#### 2.4. Informed consent-ethics approval

Favourable ethical opinion for this research was provided by the Newcastle & North Tyneside 2 ethics committee (REC reference number: 14/NE/1062) in July 2014. The study complies with the Helsinki Declaration and the principles of Good Clinical Practice (GCP).

Potential participants are identified mainly through rapid access haematuria clinics at participating sites. An eligibility checklist is completed by the local Principal Investigator (or delegate) to assess fulfilment of the entry criteria for all patients considered for the study. Information from the diagnostic cystoscopy is used to assess eligibility.

All potentially eligible patients are provided with an information sheet to explain why they have been approached and the nature of the study. Eligible patients are asked to provide written informed consent for the study only after they have had sufficient time to consider the trial and had the opportunity to have any further questions addressed.

#### 2.5. Recruitment and randomisation

Eligible patients are centrally randomised using either the secure web-based or the 24-hour Interactive Voice Response randomisation system at the Centre for Healthcare Randomised Trials (CHaRT) in Aberdeen, using minimisation by centre and gender, to allocate participants 1:1 to the control and experimental groups. The

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3 minimisation algorithm incorporates a random element in order to prevent  
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5 deterministic treatment allocation.  
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## 8 9 2.6. Outcome measures 10

### 11 12 13 2.6.1. Primary outcome measures

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15 Clinical effectiveness: Time to recurrence is measured as time from randomisation to  
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17 first recurrence.  
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20 Cost effectiveness: A health economic model will be developed to calculate  
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22 incremental cost per recurrence avoided and incremental cost per QALY gained over  
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24 three years.  
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### 28 29 2.6.2. Secondary outcome measures

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31 Clinical effectiveness:

- 32  
33 • Adverse events and complications up to 3 months from initial or second TURBT  
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35 are captured and will be included in analysis.  
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38 • HRQOL is captured for each participant at baseline (prior to knowledge of  
39  
40 treatment allocation), following surgery and at 3, 6, 12, 18, 24 and 36 months  
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42 after randomisation.  
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- 44  
45 • Disease progression is captured within the trial time. Patient life time projections  
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47 will be made by using the trial data at baseline and supplementing as necessary  
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49 from other published data.  
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- 51  
52 • Overall survival and bladder cancer specific survival will be compared between  
53  
54 the two treatment arms. Minimum follow-up of the last included patient will be 3  
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56 years and maximum expected follow-up is 66 months.  
57

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2  
3 Cost effectiveness:

- 4 • Estimation of the incremental cost per recurrence avoided using the economic  
5 model over the patients' lifetime.
  - 6 • Estimation of the incremental cost per QALY gained using the economic  
7 model over the patients' lifetime.
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### 16 2.6.3. Additional outcomes measures

17 Schedules for follow-up: Using data from within the trial and, if appropriate,  
18 from other relevant sources, the risk of recurrence at each interval surveillance  
19 cystoscopy will be described to then model the most safe and efficient surveillance  
20 follow-up schedule.  
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26 The effect of PDD guided resection experience (learning curve) on clinical  
27 effectiveness: A subgroup analysis comparing outcomes from PDD-experienced and  
28 PDD-naïve surgeons (determined at baseline) will be conducted. Also for PDD-naïve  
29 surgeons an assessment of learning curve will be undertaken by comparing increasing  
30 experience and recurrence, in both PDD and WL resections.  
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### 40 2.7. Tracking and monitoring adverse events

41 Direct surgically related post-operative events occurring within 30 days following  
42 the first TURBT or second TURBT if required will be assessed using The Clavien  
43 Dindo classification for surgical complications. Events occurring up to 3 months after  
44 TURBT (second TURBT if required) will be assessed and recorded using the  
45 National Cancer Institute Common Terminology Criteria for Adverse Events  
46 (CTCAE) v4.0 framework (<http://ctep.cancer.gov/>) [15].  
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## 2.8. Trial assessment and measures

PHOTO trial schedule of assessment and investigations are summarised in Table 1. Routine attendances for diagnosis and staging of new bladder cancers are used to establish eligibility, which includes obtaining the medical history. Eligible patients who consent for the trial are administered HRQoL questionnaires prior to primary TURBT and prior to discharge.

Time to recurrence will be measured from the day of randomisation to the day of subsequent biopsy with pathologically proven recurrence. Data will be collected from the following routine visits; 3, 6, 9, 12, 18, 24 and 36 months post initial TURBT (or second TURBT if required). Associated costs and changes in HRQoL will be measured. These will be collected by postal questionnaires sent directly to participants at 3, 6, 12, 18, 24 & 36 months post randomisation.

Disease progression will be assessed using results of further resection or imaging during follow-up. Progression will be defined as increase of stage into MIBC or development of nodal or metastatic disease. In addition, patients showing failure to respond to intravesical treatment (e.g. BCG failure) will also be captured.

The relative changes in HRQoL resulting from the physical and psychological benefit together with any harms associated with each strategy and with subsequent necessary cancer treatment will be measured using the generic EQ-5D-3L questionnaire, cancer specific EORTC-QLQ-C30 and disease-specific EORTC QLQ-NMIBC24 questionnaire completed by the participant.

Effect of PDD guided resection experience on clinical effectiveness: All recruiting surgeons will complete a learning curve questionnaire to elicit their white light and PDD resection experience prior to any recruitment. The subsequent accruing

experience of each surgeon will be captured on case report forms. Early recurrence (12 weeks) will be used as a proxy of incomplete resection.

Table 1, Schedule of investigations/assessments in PHOTO trial

Visit/Assessment	Pre-randomisation screening	Pre-treatment	TURBT	Prior to discharge	Surveillance										Annually thereafter	At first disease recurrence/progression	
					Second TURBT (as clinically indicated)	3 months post treatment	6 months post treatment	9 months post treatment	12 months post treatment	18 months post treatment	24 months post treatment	36 months post treatment					
Visual diagnosis of IR/HR NMIBC	X																
Medical history	X																
HRQoL questionnaire <sup>1</sup>		X		X	X	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>		
TURBT according to treatment allocation with post treatment MMC instillation			X														
Second TURBT, if required, according to treatment allocation					X												
Assessment of adverse events (CTCAE & Clavien Dindo)						X											
Cystoscopy						X	X	X	X	X	X	X	X	X			
Histological confirmation of recurrence/ progression																	X
Collection of FFPE tissue <sup>3</sup>			X														X
Urine sample collection <sup>3</sup>		X				X				X		X	X				X
Blood sample collection <sup>3</sup>		X				X				X		X	X				X

Footnotes

1. EORTC QLQ-C30 & NMIBC24, EQ-5D-3L
2. Questionnaire sent by-post directly to participant
3. If patient consented to participation in PHOTO-T (as this is archived pathology the tissue may be requested at an interval from the diagnostic resection/recurrence).

## 2.9. Sample size

We aim to detect an absolute reduction in recurrence at three years of 12%; from 40% (under the conservative assumption that all the patients recruited are intermediate risk patients with a probability of recurrence of 0.4 at 3 years) to 28% (similar effect sizes of photodynamic therapy are reported in both intermediate and high risk groups) this will be equivalent to a relative reduction of 30%.

Recruitment of 533 participants (214 recurrences) will detect a hazard ratio of 0.64 between experimental and control strategies and provide, using the log-rank test, 90% power at a 2-sided 5% significance level. This calculation assumes 2.5 years incremental recruitment, a minimum of three years follow-up and a 6.4% follow-up attrition at end of year three. To achieve this we plan to use 30 secondary care sites that would expect to see approximately 4,590 new bladder cancers diagnoses over 2.5 years, from which we will exclude patients with MIBC (20%) and, from the remaining NMIBCs, exclude low risk disease (50%). Furthermore, we predict only 30% of these patients will be recruited based on willingness to participate or missed opportunities for recruitment.

## 2.10 Health economics analysis

A within trial cost-effectiveness analysis will be conducted to calculate incremental cost per recurrence avoided and incremental cost per QALY gained over three years. Data on costs, recurrence and QALYs for each participant will be recorded in the trial and used to estimate mean cost, recurrence and QALYs for each intervention group. As the time horizon of the trial is three years these data will be discounted at 3.5% [16]. The cost, recurrence avoided and QALY data will then be

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3 used to estimate incremental costs, recurrence avoided and QALYs and incremental  
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5 cost per recurrence avoided and incremental costs per QALY.  
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9 An economic model will be developed to estimate relative rates of cost-  
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11 effectiveness and cost-utility, at three years (to mirror the within trial analysis) and  
12  
13 over a patient lifetime time horizon. An NHS perspective will be taken for the cost  
14  
15 calculations. The model takes the form of a Markov state transition model that  
16  
17 describes the consequences of different diagnosis and treatment strategies in terms of  
18  
19 clinical and cost outcomes [6]. The rates of recurrence and progression recorded with  
20  
21 the 3-year follow-up of the trial will be used to model short-term recurrence and  
22  
23 progression rates. Further data required for the model relates to the transition and  
24  
25 other probabilities of events beyond the 3 year follow-up, including the risk of  
26  
27 recurrence and progression, probabilities of receiving different types of intervention  
28  
29 should progression or recurrences occur, and risks of mortality (both from bladder  
30  
31 cancer and other causes), will be sought through a structured systematic review of  
32  
33 long-term outcomes of treatments of bladder cancer. The model will be used to  
34  
35 produce estimates of costs, QALYs, recurrence rates and survival. Both costs and  
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37 outcomes will be discounted at 3.5% in the base case analyses. Cost-effectiveness will  
38  
39 be reported as incremental cost per QALY gained and incremental cost per recurrence  
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41 avoided (at both 3 years and over the patient's lifetime). These data will be presented  
42  
43 as point estimates and bootstrapping techniques will be used to estimate the statistical  
44  
45 imprecision surrounding them. The results of this stochastic analysis will be presented  
46  
47 as cost and QALY plots and as cost-effectiveness acceptability curves. Further  
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49 deterministic sensitivity analyses will be conducted to explore other forms of  
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51 uncertainty e.g. surrounding the choice of discount rate or around the unit costs of  
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3 equipment. The model will be probabilistic and distributions will be attached to all  
4 parameters, the shape and type of distribution will depend upon the data available and  
5 recommendations for good practice in modelling [17].  
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#### 9 2.10. Patient and Public Involvement

10 Patient involvement was ensured at the early stages of protocol development and  
11 contributed to user-lead development of outcomes of value to patients in  
12 the design of the trial. Additionally, the patient journey of patient representatives was  
13 investigated through the diagnosis and treatment of bladder cancer, which includes an  
14 anonymised account impact on his quality of life. This helped understand the burden  
15 of the intervention on patients. A patient representative was involved as a co-  
16 investigator and member of the trial steering committee helping manage and analyse  
17 the implications of the research.  
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#### 28 2.11. PHOTO-Translational side study

29 PHOTO Translational (PHOTO-T) aims to establish a well-characterised trial  
30 associated biorepository of longitudinal serially collected tissue samples (blood, urine  
31 and FFPE). The collection of samples from PHOTO patients is optional with every  
32 PHOTO-T consented participant collecting a urine and blood sample at baseline (pre-  
33 treatment/TURBT) and 3, 12, 24 and 36 months treatment follow-up or at recurrence  
34 (whichever comes first, predicted at 70% for the highest risk group over a trial period  
35 of 3 years). A FFPE core at baseline (plus recurrence, if occurs) will also be collected  
36 (supplement).  
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### 50 3. Discussion

51 Bladder cancer is the most frequent urothelial cancer and the overall costs for  
52 treatment and follow-up remain higher than most other cancers [18]. Achieving  
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3 complete resection of NMIBC with TURBT is associated with lower recurrence rates  
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5 in follow-up. However, it is unclear if this translates into lower progression rates in  
6  
7 long-term follow-up. PDD guided initial TURBT is a technology that could improve  
8  
9 resection and ultimately reduce recurrence and the need for further treatments.  
10  
11 Studies on PDD have demonstrated the efficacy of the technology using strict study  
12  
13 entry requirements, for which translation into daily clinical practice is limited.  
14  
15 Therefore, in the PHOTO trial the effectiveness of the technology as part of routine  
16  
17 care will be demonstrated with a pragmatic clinical trial design.  
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20  
21 PHOTO trial includes measurement of HRQoL using EQ-5D at the time of  
22  
23 initial treatment and surveillance. The measurement of HRQoL around the time of the  
24  
25 cystoscopy and TURBT can be particularly dynamic due to an acute deterioration in  
26  
27 health score associated with the invasive procedure followed by a typical rapid  
28  
29 recovery [11, 19]. Therefore, a side study was developed, where patients are recruited  
30  
31 from the PHOTO trial to evaluate the acute deterioration in quality of life by  
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33 suspected diagnosis or TURBT around the time of resection. This side study will use  
34  
35 a time trade off exercise and the outcomes will supplement the calculation of QALYs  
36  
37 in the health economic model.  
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41 The high costs of bladder cancer to health care systems has usually been  
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43 obtained from weak data and the true costs are unclear. The pragmatic design of the  
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45 PHOTO trial alongside the robust data collection for a full-health economic  
46  
47 evaluation will provide high quality evidence of the burden of NMIBC for the NHS.  
48  
49 Moreover, it will also provide a cost effectiveness comparison of white light vs PDD-  
50  
51 guided initial TURBT resections.  
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54 Evidence suggests that 20 cases are required for PDD naïve surgeons to gain  
55  
56 competency the technology. This could act as a potential confounder on the clinical  
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3 outcomes measured and therefore will be accounted for during analysis. Moreover,  
4 the evidence is gained from small number studies and an evaluation of the learning  
5 curve of PDD will also be carried out.  
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9 The primary outcome of the study is time to recurrence measured from the day  
10 of randomisation to the day of subsequent biopsy with pathologically proven  
11 recurrence. If decrease in time to recurrence is associated with long term patient  
12 benefits the cost-effectiveness evaluation will provide further evidence for the NHS to  
13 decide on full adoption of the technology.  
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#### 4. List of abbreviations

CIS: Carcinoma in-situ

cm: centimetres

CT: Computerized tomography

DCIS: Ductal carcinoma in-site

EORTC: European Organization for Research and Treatment of Cancer

FFPE: Formalin Fixed Paraffin Embedded

HRQoL: Health related quality of life

HTA : health technology assessment

LCIS: Lobular carcinoma in situ

MIBC: Muscle invasive bladder cancer

MMC: Mitomycin-C

NHS: National Health Service

NIHR: National Institute for Health Research

NMIBC: Non-muscle invasive bladder cancer

PDD: Photo dynamic diagnosis

QALY: Quality adjusted life years

TURBT: Transurethral resection of bladder tumour

USS: Ultrasonography

WL: White light

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Management of the study is divided between the Clinical Trials & Statistics Unit at the Institute of Cancer Research (ICR-CTSU) and Centre for Healthcare Randomised Trials (CHaRT) at the University of Aberdeen.

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Independent Data monitoring committee members – Dr Angela Casbard (Chair), Professor Diane Witham, Mr Robert Mills, Dr Ed Wilson, Mr Paul Silcocks.

**Contributorship statement:**

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Rebecca Lewis: conception and design of the work, data collection, drafting of the article, critical revision of the article and final approval of the version to be published

Anne Duncan: conception and design of the work, data collection, drafting of the article, critical revision of the article and final approval of the version to be published

Alison McDonald: conception and design of the work, data collection, drafting of the article, critical revision of the article and final approval of the version to be published

Luke Vale: conception and design of the work, critical revision of the article and final approval of the version to be published

Steven Penegar: data collection, critical revision of the article and final approval of the version to be published

Jing Shen: design of the work, critical revision of the article and final approval of the version to be published

PHOTO TMG members: Trial management, data collection and final approval of the version to be published

Graeme Maclellan: design of the work, critical revision of the article and final approval of the version to be published

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Emma Hall: conception and design of the work, critical revision of the article and final approval of the version to be published

Rakesh Heer: conception and design of the work, drafting of the article, critical revision of the article and final approval of the version to be published

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## 11 **6. Figure Legends:**

12  
13 Figure 1: Tumour, Node, Metastasis (TNM) system of bladder cancer [2]  
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15 Figure 2: PHOTO trial study design summary  
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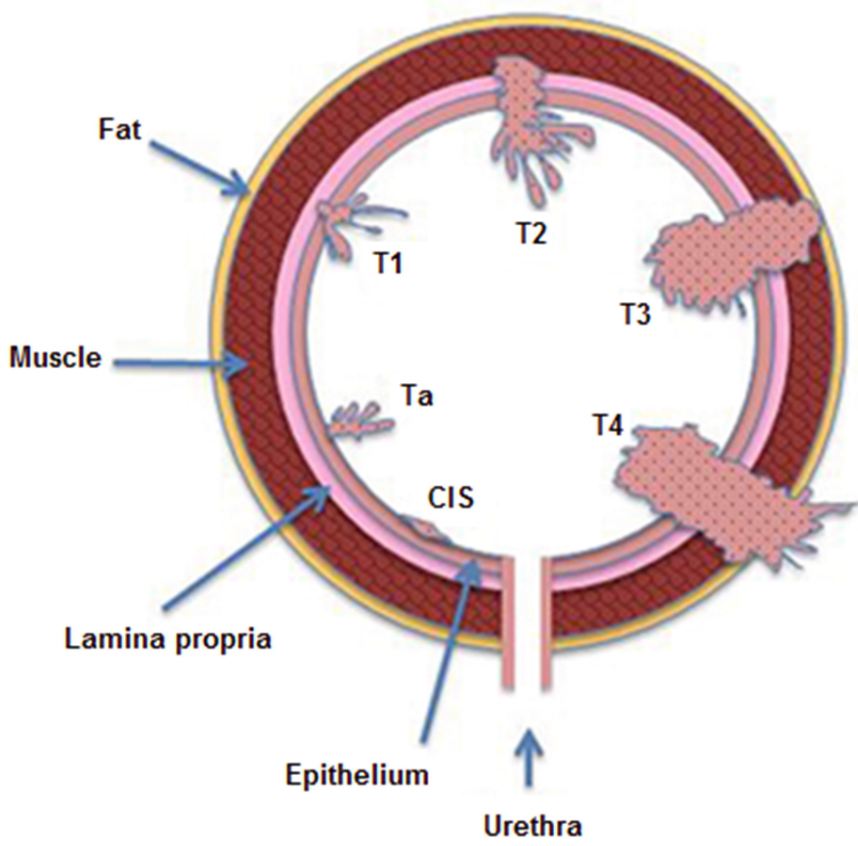


PHOTO Trial study design summary.

90x90mm (300 x 300 DPI)

## APPENDIX-I: NICR PHOTO-T study

### Sample Collection (per participant):

- (a) 2 x blood samples totalling 12.5ml (10ml Streck blood collection tube for circulating DNA analysis and 2.5ml PAXgene blood collection tube for circulating RNA analysis);
- (b) 2 x urine samples totalling 200ml (1 x 100ml for immediate translational processing and 1 x 100ml for biorepository storage), (c) 1 x FFPE core at baseline (plus core from recurrence, if occurs).

In total, 20 serially collected samples will be collected per PHOTO-T consented participant over the trial period (36 months), comprising 10 urine, 10 blood (5 DNA and 5 RNA) and 1 FFPE tumour tissue block. Collected at baseline (pre-treatment/TURBT) and treatment follow-up at 3, 12, 24 and 36 months or at recurrence (whichever comes first, predicted at 70% for the highest risk group over a trial period of 3 years).

Serial blood samples are requested for collection in clinic by research staff at participating investigator sites. Urine samples are provided at home by participants using specialist 'home collection' kits (home collection is preferable as sample quality in terms of genomic output is superior to clinically collected specimens) and FFPE blocks requested from Histopathology Departments of participating investigator sites retrospectively at the end of the trial.

# BMJ Open

## PHOTodynamic versus white light-guided treatment of non-muscle invasive bladder cancer: A randomised trial of clinical and cost effectiveness

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<b>Primary Subject Heading</b>:	Urology
Secondary Subject Heading:	Health economics, Oncology
Keywords:	bladder cancer, photodynamic diagnosis, quality of life, HEALTH ECONOMICS, Cost effectiveness, Sample biorepository

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6 PHOTodynamic versus white light-guided treatment of non-  
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Key words:

- Bladder cancer
- Photodynamic diagnosis
- Quality of life
- Health economics
- Cost effectiveness

- Sample biorepository

The authors declare that they have no competing interests.

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## **Abstract**

**Introduction:** Bladder cancer is the most frequently occurring tumour of the urinary system. Ta, T1 tumours and carcinoma in situ (CIS) are grouped as non-muscle invasive bladder cancer (NMIBC), which can be effectively treated by transurethral resection of bladder tumour (TURBT). There are limitations to the visualisation of tumours with conventional TURBT using white light illumination within the bladder. Incomplete resections occur from the failure to identify satellite lesions or the full extent of the tumour leading to recurrence and potential risk of disease progression. To improve complete resection, photodynamic diagnosis (PDD) has been proposed as a method that can enhance tumour detection and guide resection. The objective of the current research is to determine whether PDD-guided TURBT is better than conventional white light surgery and whether it is cost-effective.

**Methods and Analysis:** PHOTO is a pragmatic multi-centre randomised controlled trial (open parallel group, non-masked, superiority trial) comparing the intervention of PDD-guided TURBT with standard white light resection in newly diagnosed intermediate and high risk NMIBC within the UK NHS setting. Clinical effectiveness is measured with time to recurrence. Cost-effectiveness is assessed within trial via the calculation of incremental cost per recurrence avoided and incremental cost per quality adjusted life per year (QALY) gained over three years, and over long term through a modelling exercise over patients' life time.

**Ethics and dissemination:** Formal ethics review was undertaken with a favourable opinion, in line with UK regulatory procedures (REC reference number: 14/NE/1062; Trial registration: ISRCTN84013636). If reductions in time to recurrence is associated with long term patient benefits the cost-effectiveness evaluation will provide further evidence to inform adoption of the technology. Findings will be



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3 shared in lay media such as patient and charity forums and will be presented at key  
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5 meetings and published in academic literature.  
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### 10 **Article Summary:**

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14 Strengths and limitations of the PHOTO study include;

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19 • the effectiveness of the photodynamic diagnosis (PDD) for the initial resection  
20 of intermediate and high risk non-muscle invasive bladder cancer as part of  
21 routine care will be demonstrated with a pragmatic clinical trial design,  
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- 26 • full-health economic evaluation will provide high quality evidence of the  
27 burden of NMIBC for the NHS  
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- 30 • a well-characterised trial associated biorepository of longitudinal serially  
31 collected tissue samples  
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## 1. Background

Bladder cancer is the most frequently occurring tumour of the urinary system [1]. Staging of bladder cancer is described using the Tumour, Node, Metastasis (TNM) system [2]. Tumours confined to the epithelial lining (urothelium) are classified as stage Ta and those invading the lamina propria are classified as stage T1.

Ta and T1 tumours can be removed by transurethral resection (TURBT) that involves passing a cystoscope through the urethra into the bladder and resecting the tumour under direct visualisation. For therapeutic purposes Ta and T1 tumours are grouped together as non-muscle invasive bladder cancer (NMIBC). Grade (microscopic characteristics of the tumour cells) can be used to describe aggressiveness of cancers and are characterised as either low grade (relatively benign) or high grade (aggressive). NMIBC also include flat, high-grade tumours that are confined to the epithelium classified as carcinoma in situ (CIS).

Complete resection of the tumour with TURBT is essential to obtain good prognosis. It is thought that failure to identify satellite tumours or to appreciate the full extent of the tumours visualised during resection using conventional white light cystoscopy may be a factor in 20-40% of recurrent bladder tumours [3, 4]. Incomplete resection with TURBT is also associated with staging errors. In order to correct the staging errors associated with initial TURBT a second resection within 2-6 weeks is suggested for select group patients [5]. It has been postulated that development in cystoscopy imaging can improve resections and decrease the need for a second resection [6].

Recurrence and stage progression to muscle invasive (T2-T4) or metastatic cancer is more likely to occur in those with high-grade tumours with concomitant

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2  
3 CIS. CIS in particular can be easily missed using conventional white light guided  
4  
5 resection [6].  
6

7  
8 Surveillance of NMIBC is carried out with cystoscopy to detect recurrence early  
9  
10 and allow treatment before progression. Clinical guidelines tailor follow up protocols  
11  
12 according to the risk groups (low, intermediate and high) developed using clinical and  
13  
14 histological parameters [7]. Advised follow-up of low risk is at three months and if  
15  
16 negative the next cystoscopy is scheduled for nine months later and then yearly for  
17  
18 five years. Patients with high-risk tumours have cystoscopy and urine cytology at  
19  
20 three months. If negative, it is repeated every three months for two years, then every  
21  
22 six months until five years, and annually thereafter [5]. The intensity of cystoscopic  
23  
24 follow up for patients with intermediate risk is not clearly defined, for which a follow-  
25  
26 up scheme in-between those described for low and high risk and is adapted according  
27  
28 to personal and subjective factors [5].  
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### 35 1.1. Photodynamic diagnosis of NMIBC: 36

37  
38 As an attempt to improve resection rates, photodynamic diagnosis (PDD) has  
39  
40 been developed to enhance tumour detection and guide resection. A cystoscopy image  
41  
42 of WL vs PDD is presented in figure 1. Meta-analyses and systematic reviews of PDD  
43  
44 guided treatment of NMIBC have shown efficacy in tumour detection and reduction  
45  
46 in residual tumour compared with white light cystoscopy alone. These findings  
47  
48 translate into reduced recurrence rates [6, 8]. However, these trials were efficacy  
49  
50 studies and the systematic review called for a pragmatic study to allow better  
51  
52 interpretation of possible benefit into daily clinical practice.  
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### 58 1.2. Health economics of NMIBC: 59 60

1  
2  
3 NMIBC is one of the most costly cancers to manage on a per patient basis  
4  
5 because of its high prevalence, high recurrence rate, need for adjuvant treatments and  
6  
7 the requirement for long-term cystoscopic surveillance. The total cost of treatment  
8  
9 and 5-year follow-up of patients with NMIBC diagnosed in the United Kingdom has  
10  
11 increased from £73 million to £213 million from 2001 to 2012 (inflation corrected)  
12  
13 [9, 10]. From a patient perspective, there often are considerable anxieties about  
14  
15 recurrences, transurethral resection and progression, requiring additional therapies  
16  
17 with potential mortality and long-term morbidity (e.g. radical surgery). Transurethral  
18  
19 resection itself is associated with reduced quality of life, including both mental and  
20  
21 physical health domains; although these effects are usually transient [11]. Substantial  
22  
23 effects on health related quality of life (HRQoL) are most likely to come from  
24  
25 adjuvant intravesical treatments and radical or palliative treatments for progression  
26  
27 [12]. The cost-effectiveness of NMIBC treatment strategies has not been widely  
28  
29 studied.  
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### 38 1.3. NMIBC biomarkers and clinical impact:

39  
40 To date, existing non-invasive commercial biomarkers (primarily urinary) are not  
41  
42 embedded in routine clinical practice due to poor sensitivity, specificity and lack of  
43  
44 evidence. Several research bodies have recognized the lack of clinically useful  
45  
46 biomarkers for bladder cancer. “Fit for purpose” sample resources accessible to high-  
47  
48 throughput ‘omic’ technologies will afford the greatest opportunity to generate  
49  
50 translational hypotheses and ensure clinical validity and utility of putative candidate  
51  
52 markers/signatures [13, 14]. Robust, ‘future-proof’, longitudinal serial sample  
53  
54 archives providing critical insights of the natural history of bladder cancer correlated  
55  
56 with clinical detail for retrospective translational biomarker discovery, are lacking.  
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#### 1.4. Current research objectives:

More efficient management strategies to reduce NMIBC recurrence and hence decrease both the burden to patients and costs are urgently needed. PDD-guided initial TURBT has been identified as a technique that can help achieve these aims. The objective of the current research (PHOTO trial) is to determine whether photodynamic surgery guided by a fluorescent tumour marker is better than conventional white light surgery in the cystoscopic treatment of people with intermediate and high risk cancers confined to the bladder lining and whether its implementation is cost-effective. The trial includes a full assessment of the costs of patient management through the care pathway. Individual patient data from this trial will be used for subsequent mathematical modelling studies to investigate safe monitoring frequency. The Photodynamic versus white light-guided treatment of non-muscle invasive bladder cancer trial has the following research objectives:

##### i. Primary objectives:

Clinical effectiveness: To compare time to recurrence for each of the two treatment strategies, with a principal point of interest at 3 years.

Cost-effectiveness: To evaluate cost-effectiveness as measured by the incremental cost per recurrence avoided and the cost-utility as measured by the incremental cost per quality-adjusted life year (QALY) gained at three years and over patients' life time.

##### ii. Secondary objectives:

- a. To measure relative rates of disease progression at three years.
- b. To measure relative harms and safety.
- c. Patient lifetime HRQoL and cancer-specific survival.

- 1  
2  
3     iii. Additional objectives:  
4  
5     a. To model the safest and most cost-effective cystoscopic follow-up surveillance  
6  
7         schedule;  
8  
9  
10    b. To evaluate the learning curve for the procedure and account for its effects on  
11  
12         outcomes of both PDD-guided and standard white light resections;  
13  
14  
15    c. To establish a well-characterised cohort of serial samples from patients with  
16  
17         intermediate and high-risk NMIBC including clinical data, urine, blood and  
18  
19         tumour specimens for separately funded translational research.  
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22

## 23 24 **2. Methods & Design**

### 25 26 2.1. Study design

27  
28         PHOTO is a multi-centre randomised open parallel group non-masked superiority  
29  
30         trial comparing the intervention of PDD guided bladder tumour resection with  
31  
32         standard white light resection in patients with newly diagnosed intermediate and high  
33  
34         risk NMIBC. Apart from initial treatment, both groups will receive standard care,  
35  
36         including single dose intravesical mitomycin C within 24 hours of initial resection,  
37  
38         surveillance according to risk-adjusted schedules and adjuvant therapy as indicated by  
39  
40         current practice guidelines. The target number of patients to be recruited is 533 with a  
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42         trial specific follow-up of at least 36 months for each individual. The outline of the  
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44         study protocol is shown in Figure 2.  
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## 2.2. Intervention

The interventions being compared within PHOTO trial are:

- i. Photo dynamic diagnosis (PDD) guided trans-urethral resection (TURBT) (experimental group) vs;
- ii. Standard white light TURBT (control group)

All participants, unless there are clinical contra-indications, receive intravesical mitomycin C (40 mg in 40 ml saline), ideally within 6 hours following TURBT but otherwise within the inpatient setting before discharge.

### 2.2.1. Technique of photodynamic diagnosis

PDD requires preliminary instillation of the photosensitiser hexaminolevulinate (85 mg in 50 ml of phosphate buffered saline) into the participant's bladder through a urethral catheter. Participants are asked not to pass urine for at least one hour after insertion. Following operating theatre preparation according to local standard procedures and under appropriate anaesthesia, participants undergo TURBT of their bladder tumour under blue light (wavelength 380-450 nm) illumination of the bladder. The equipment required includes a specialised light source, cystoscope, light cables and cameras. When using PDD, normal bladder epithelium appears blue whilst red areas should be considered suspicious and should be resected.

### 2.2.2. Technique of standard white light cystoscopy

The control group does not have any preliminary photosensitiser instillation and undergo standard tumour localisation and resection under white light (wavelength 400-800 nm) illumination of the bladder.

### 2.3. Participants

In the PHOTO trial adult patients with a suspected new diagnosis of intermediate or high risk NMIBC are studied. Participants are identified prior to initial resection based on results of preliminary visual assessment via cystoscopy or imaging performed as part of standard evaluation for suspected urinary tract malignancy.

Patients with the following criteria are included in the PHOTO trial:

- Adult men and women aged  $\geq 16$  years.
- First suspected diagnosis of bladder cancer.
- Visual/ultrasound/Computerized tomography (CT) diagnosis of intermediate/high risk NMIBC.
- White light visual appearances of intermediate or high risk disease ( $\geq 3$ cm OR two or more tumours OR flat velvety erythematous changes alerting a clinical suspicion of CIS).

OR

Suspicion of papillary bladder tumour  $\geq 3$ cm based on ultrasound or CT scanning (without hydronephrosis).

- Written informed consent for participation prior to any study specific procedures.
- Willing to comply with the following life style guidelines:
  - Female participants must be surgically sterile or be post-menopausal, or must agree to use effective contraception after joining the study and for 7 days after treatment. Female participants must not breast feed for 7 days after treatment.



- Male participants must be surgically sterile or must agree to use effective contraception after joining the study and for 7 days after treatment.
- Effective contraception is defined as two forms of contraception, including one barrier method.

Exclusion criteria applied in the PHOTO trial are:

- Visual evidence of low risk NMIBC (solitary tumour < 3cm).
- Visual evidence of MIBC on preliminary cystoscopy, i.e. non-papillary or sessile mass (attached directly by its base without a stalk).
- Imaging evidence of MIBC – CT/USS (this includes the presence of hydronephrosis, which may be present despite clear imaging of MIBC in the bladder).
- Upper tract (kidney or ureteric) tumours on imaging.
- Any other malignancy in the past 2 years (except: non-melanomatous skin cancer cured by excision, adequately treated carcinoma in situ of the cervix, DCIS/LCIS of the breast or prostate cancer in patients who have a life expectancy of >5 years upon trial entry).
- Evidence of metastases.
- Porphyria or known hypersensitivity to porphyrins.
- Known pregnancy (based on history and without formal testing, in keeping with day-to-day NHS practice of PDD use).
- Any other conditions that in the Principal Investigator's opinion would contraindicate protocol treatment.
- Unable to provide informed consent.

- Unable or unwilling to complete follow-up schedule (including HRQoL questionnaires).

#### 2.4. Informed consent-ethics approval

Favourable ethical opinion for this research was provided by the Newcastle & North Tyneside 2 ethics committee (REC reference number: 14/NE/1062) in July 2014. The study complies with the Helsinki Declaration and the principles of Good Clinical Practice (GCP).

Potential participants are identified mainly through rapid access haematuria clinics at participating sites. An eligibility checklist is completed by the local Principal Investigator (or delegate) to assess fulfilment of the entry criteria for all patients considered for the study. Information from the diagnostic cystoscopy is used to assess eligibility.

All potentially eligible patients are provided with an information sheet to explain why they have been approached and the nature of the study. Eligible patients are asked to provide written informed consent for the study only after they have had sufficient time to consider the trial and had the opportunity to have any further questions addressed.

#### 2.5. Recruitment and randomisation

Eligible patients are centrally randomised using either the secure web-based or the 24-hour Interactive Voice Response randomisation system at the Centre for Healthcare Randomised Trials (CHaRT) in Aberdeen, using minimisation by centre and gender, to allocate participants 1:1 to the control and experimental groups. The minimisation algorithm incorporates a random element in order to prevent

1  
2  
3 deterministic treatment allocation. The trial was opened on the 23<sup>rd</sup> of October 2014  
4  
5 and recruitment was completed on 14<sup>th</sup> of February 2018. Over this period 22 centres  
6  
7 joined the study and contributed to recruitment.  
8  
9

## 10 11 12 13 14 15 2.6. Outcome measures 16

### 17 18 19 2.6.1. Primary outcome measures 20

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22 Clinical effectiveness: Time to recurrence is measured as time from randomisation to  
23  
24 first recurrence.  
25

26  
27 Cost effectiveness: A health economic model will be developed to calculate  
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29 incremental cost per recurrence avoided and incremental cost per QALY gained over  
30  
31 three years.  
32

### 33 34 35 2.6.2. Secondary outcome measures 36

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38 Clinical effectiveness:

- 39
- 40 • Adverse events and complications up to 3 months from initial or second TURBT  
41 are captured and will be included in analysis.  
42
  - 43 • HRQOL is captured for each participant at baseline (prior to knowledge of  
44 treatment allocation), following surgery and at 3, 6, 12, 18, 24 and 36 months  
45 after randomisation.  
46
  - 47 • Disease progression is captured within the trial time. Patient life time projections  
48 will be made by using the trial data at baseline and supplementing as necessary  
49 from other published data.  
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- Overall survival and bladder cancer specific survival will be compared between the two treatment arms. Minimum follow-up of the last included patient will be 3 years and maximum expected follow-up is 66 months.

Cost effectiveness:

- Estimation of the incremental cost per recurrence avoided using the economic model over the patients' lifetime.
- Estimation of the incremental cost per QALY gained using the economic model over the patients' lifetime.

### 2.6.3. Additional outcomes measures

Schedules for follow-up: Using data from within the trial and, if appropriate, from other relevant sources, the risk of recurrence at each interval surveillance cystoscopy will be described to then model the most safe and efficient surveillance follow-up schedule.

The effect of PDD guided resection experience (learning curve) on clinical effectiveness: A subgroup analysis comparing outcomes from PDD-experienced and PDD-naïve surgeons (determined at baseline) will be conducted. Also for PDD-naïve surgeons an assessment of learning curve will be undertaken by comparing increasing experience and recurrence, in both PDD and WL resections.

### 2.7. Tracking and monitoring adverse events

Direct surgically related post-operative events occurring within 30 days following the first TURBT or second TURBT if required will be assessed using The Clavien Dindo classification for surgical complications. Events occurring up to 3 months after TURBT (second TURBT if required) will be assessed and recorded using the

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2  
3 National Cancer Institute Common Terminology Criteria for Adverse Events  
4  
5 (CTCAE) v4.0 framework (<http://ctep.cancer.gov/>) [15].  
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## 10 2.8. Trial assessment and measures

11 PHOTO trial schedule of assessment and investigations are summarised in Table

12  
13  
14 1. Routine attendances for diagnosis and staging of new bladder cancers are used to  
15 establish eligibility, which includes obtaining the medical history. Eligible patients  
16 who consent for the trial are administered HRQoL questionnaires prior to primary  
17 TURBT and prior to discharge.  
18  
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22

23  
24 Time to recurrence will be measured from the day of randomisation to the day of  
25 subsequent biopsy with pathologically proven recurrence. Data will be collected from  
26 the following routine visits; 3, 6, 9, 12, 18, 24 and 36 months post initial TURBT (or  
27 second TURBT if required). Associated costs and changes in HRQoL will be  
28 measured. These will be collected by postal questionnaires sent directly to  
29 participants at 3, 6, 12, 18, 24 & 36 months post randomisation.  
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37 Disease progression will be assessed using results of further resection or imaging  
38 during follow-up. Progression will be defined as increase of stage into MIBC or  
39 development of nodal or metastatic disease. In addition, patients showing failure to  
40 respond to intravesical treatment (e.g. BCG failure) will also be captured.  
41  
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47 The relative changes in HRQoL resulting from the physical and psychological  
48 benefit together with any harms associated with each strategy and with subsequent  
49 necessary cancer treatment will be measured using the generic EQ-5D-3L  
50 questionnaire, cancer specific EORTC-QLQ-C30 and disease-specific EORTC QLQ-  
51 NMIBC24 questionnaire completed by the participant.  
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Effect of PDD guided resection experience on clinical effectiveness: All recruiting surgeons will complete a learning curve questionnaire to elicit their white light and PDD resection experience prior to any recruitment. The subsequent accruing experience of each surgeon will be captured on case report forms. Early recurrence (12 weeks) will be used as a proxy of incomplete resection.

Table 1, Schedule of investigations/assessments in PHOTO trial

Visit/Assessment	Pre- randomisation screening	Pre-treatment	TURBT	Prior to discharge	Surveillance								Annually thereafter	At first disease recurrence/progression	
					Second TURBT (as clinically indicated)	3 months post treatment	6 months post treatment	9 months post treatment	12 months post treatment	18 months post treatment	24 months post treatment	36 months post treatment			
Visual diagnosis of IR/HR NMIBC	X														
Medical history	X														
HRQoL questionnaire <sup>1</sup>		X		X	X	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>		
TURBT according to treatment allocation with post treatment MMC instillation			X												
Second TURBT, if required, according to treatment allocation					X										
Assessment of adverse events (CTCAE & Clavien Dindo)						X									
Cystoscopy						X	X	X	X	X	X	X			
Histological confirmation of recurrence/ progression															X
Collection of FFPE tissue <sup>3</sup>			X												X
Urine sample collection <sup>3</sup>		X				X			X		X	X			X
Blood sample collection <sup>3</sup>		X				X			X		X	X			X

Footnotes

1. EORTC QLQ-C30 & NMIBC24, EQ-5D-3L
2. Questionnaire sent by-post directly to participant
3. If patient consented to participation in PHOTO-T (as this is archived pathology the tissue may be requested at an interval from the diagnostic resection/recurrence).

For peer review only

## 2.9. Sample size

We aim to detect an absolute reduction in recurrence at three years of 12%; from 40% (under the conservative assumption that all the patients recruited are intermediate risk patients with a probability of recurrence of 0.4 at 3 years) to 28% (similar effect sizes of photodynamic therapy are reported in both intermediate and high risk groups) this will be equivalent to a relative reduction of 30%.

Recruitment of 533 participants (214 recurrences) will detect a hazard ratio of 0.64 between experimental and control strategies and provide, using the log-rank test, 90% power at a 2-sided 5% significance level. This calculation assumes 2.5 years incremental recruitment, a minimum of three years follow-up and a 6.4% follow-up attrition at end of year three. To achieve this we plan to use 30 secondary care sites that would see new bladder cancers diagnoses, from which we will exclude patients with MIBC (20%) and, from the remaining NMIBCs, exclude low risk disease (50%). Furthermore, we predict only 30% of these patients will be recruited based on willingness to participate or missed opportunities for recruitment.

## 2.10 Health economics analysis

A within trial cost-effectiveness analysis will be conducted to calculate incremental cost per recurrence avoided and incremental cost per QALY gained over three years. Data on costs, recurrence and QALYs for each participant will be recorded in the trial and used to estimate mean cost, recurrence and QALYs for each intervention group. As the time horizon of the trial is three years these data will be discounted at 3.5% [16]. The cost, recurrence avoided and QALY data will then be used to estimate incremental costs, recurrence avoided and QALYs and incremental cost per recurrence avoided and incremental costs per QALY.



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6 An economic model will be developed to estimate relative rates of cost-  
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8 effectiveness and cost-utility, at three years (to mirror the within trial analysis) and  
9  
10 over a patient lifetime time horizon. An NHS perspective will be taken for the cost  
11  
12 calculations. The model takes the form of a Markov state transition model that  
13  
14 describes the consequences of different diagnosis and treatment strategies in terms of  
15  
16 clinical and cost outcomes [6]. The rates of recurrence and progression recorded with  
17  
18 the 3-year follow-up of the trial will be used to model short-term recurrence and  
19  
20 progression rates. Further data required for the model relates to the transition and  
21  
22 other probabilities of events beyond the 3 year follow-up, including the risk of  
23  
24 recurrence and progression, probabilities of receiving different types of intervention  
25  
26 should progression or recurrences occur, and risks of mortality (both from bladder  
27  
28 cancer and other causes), will be sought through a structured systematic review of  
29  
30 long-term outcomes of treatments of bladder cancer. The model will be used to  
31  
32 produce estimates of costs, QALYs, recurrence rates and survival. Both costs and  
33  
34 outcomes will be discounted at 3.5% in the base case analyses. Cost-effectiveness will  
35  
36 be reported as incremental cost per QALY gained and incremental cost per recurrence  
37  
38 avoided (at both 3 years and over the patient's lifetime). These data will be presented  
39  
40 as point estimates and bootstrapping techniques will be used to estimate the statistical  
41  
42 imprecision surrounding them. The results of this stochastic analysis will be presented  
43  
44 as cost and QALY plots and as cost-effectiveness acceptability curves. Further  
45  
46 deterministic sensitivity analyses will be conducted to explore other forms of  
47  
48 uncertainty e.g. surrounding the choice of discount rate or around the unit costs of  
49  
50 equipment. The model will be probabilistic and distributions will be attached to all  
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3 parameters, the shape and type of distribution will depend upon the data available and  
4  
5 recommendations for good practice in modelling [17].  
6

#### 7 8 2.10. Patient and Public Involvement 9

10 Patient involvement was ensured at the early stages of protocol development and  
11  
12 contributed to user-lead development of outcomes of value to patients in  
13  
14 the design of the trial. Additionally, the patient journey of patient representatives was  
15  
16 investigated through the diagnosis and treatment of bladder cancer, which includes an  
17  
18 anonymised account impact on his quality of life. This helped understand the burden  
19  
20 of the intervention on patients. A patient representative was involved as a co-  
21  
22 investigator and member of the trial steering committee helping manage and analyse  
23  
24 the implications of the research.  
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27

#### 28 2.11. PHOTO-Translational side study 29

30 PHOTO Translational (PHOTO-T) aims to establish a well-characterised trial  
31  
32 associated biorepository of longitudinal serially collected tissue samples (blood, urine  
33  
34 and FFPE). The collection of samples from PHOTO patients is optional with every  
35  
36 PHOTO-T consented participant collecting a urine and blood sample at baseline (pre-  
37  
38 treatment/TURBT) and 3, 12, 24 and 36 months treatment follow-up or at recurrence  
39  
40 (whichever comes first, predicted at 70% for the highest risk group over a trial period  
41  
42 of 3 years). A FFPE core at baseline (plus recurrence, if occurs) will also be collected  
43  
44 (supplement).  
45  
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### 51 3. Discussion 52

53 Bladder cancer is the most frequent urothelial cancer and the overall costs for  
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55 treatment and follow-up remain higher than most other cancers [18]. Achieving  
56  
57 complete resection of NMIBC with TURBT is associated with lower recurrence rates  
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3 in follow-up. However, it is unclear if this translates into lower progression rates in  
4  
5 long-term follow-up. PDD guided initial TURBT is a technology that could improve  
6  
7 resection and ultimately reduce recurrence and the need for further treatments.  
8  
9

10 Studies on PDD have demonstrated the efficacy of the technology using strict study  
11  
12 entry requirements, for which translation into daily clinical practice is limited.  
13

14 Therefore, in the PHOTO trial the effectiveness of the technology as part of routine  
15  
16 care will be demonstrated with a pragmatic clinical trial design.  
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18

19 PHOTO trial includes measurement of HRQoL using EQ-5D at the time of  
20  
21 initial treatment and surveillance. The measurement of HRQoL around the time of the  
22  
23 cystoscopy and TURBT can be particularly dynamic due to an acute deterioration in  
24  
25 health score associated with the invasive procedure followed by a typical rapid  
26  
27 recovery [11, 19]. Therefore, a side study was developed, where patients are recruited  
28  
29 from the PHOTO trial to evaluate the acute deterioration in quality of life by  
30  
31 suspected diagnosis or TURBT around the time of resection. This side study will use  
32  
33 a time trade off exercise and the outcomes will supplement the calculation of QALYs  
34  
35 in the health economic model.  
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39

40 The high costs of bladder cancer to health care systems has usually been  
41  
42 obtained from weak data and the true costs are unclear. The pragmatic design of the  
43  
44 PHOTO trial alongside the robust data collection for a full-health economic  
45  
46 evaluation will provide high quality evidence of the burden of NMIBC for the NHS.  
47  
48 Moreover, it will also provide a cost effectiveness comparison of white light vs PDD-  
49  
50 guided initial TURBT resections.  
51  
52  
53

54 Evidence on the required cases for PDD naïve surgeons to gain competency  
55  
56 the technology is weak. This could act as a potential confounder on the clinical  
57  
58 outcomes measured and therefore will be accounted for during analysis. Moreover, an  
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3 evaluation of the learning curve of PDD will also be carried out using the forms filled  
4  
5 in by surgeons.  
6  
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8 The primary outcome of the study is time to recurrence measured from the day  
9  
10 of randomisation to the day of subsequent biopsy with pathologically proven  
11  
12 recurrence. If decrease in time to recurrence is associated with long term patient  
13  
14 benefits the cost-effectiveness evaluation will provide further evidence for the NHS to  
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16 decide on full adoption of the technology.  
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#### 4. List of abbreviations

CIS: Carcinoma in-situ

cm: centimetres

CT: Computerized tomography

DCIS: Ductal carcinoma in-site

EORTC: European Organization for Research and Treatment of Cancer

FFPE: Formalin Fixed Paraffin Embedded

HRQoL: Health related quality of life

HTA : health technology assessment

LCIS: Lobular carcinoma in situ

MIBC: Muscle invasive bladder cancer

MMC: Mitomycin-C

NHS: National Health Service

NIHR: National Institute for Health Research

NMIBC: Non-muscle invasive bladder cancer

PDD: Photo dynamic diagnosis

QALY: Quality adjusted life years

TURBT: Transurethral resection of bladder tumour

USS: Ultrasonography

WL: White light

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The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

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Management of the study is divided between the Clinical Trials & Statistics Unit at the Institute of Cancer Research (ICR-CTSU) and Centre for Healthcare Randomised Trials (CHaRT) at the University of Aberdeen.

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Independent Data monitoring committee members – Dr Angela Casbard (Chair), Professor Diane Witham, Mr Robert Mills, Dr Ed Wilson, Mr Paul Silcocks.

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Rebecca Lewis: conception and design of the work, data collection, drafting of the article, critical revision of the article and final approval of the version to be published

Anne Duncan: conception and design of the work, data collection, drafting of the article, critical revision of the article and final approval of the version to be published

Alison McDonald: conception and design of the work, data collection, drafting of the article, critical revision of the article and final approval of the version to be published

Luke Vale: conception and design of the work, critical revision of the article and final approval of the version to be published

Steven Penegar: data collection, critical revision of the article and final approval of the version to be published

Jing Shen: design of the work, critical revision of the article and final approval of the version to be published

PHOTO TMG members: Trial management, data collection and final approval of the version to be published

Graeme Maclennan: design of the work, critical revision of the article and final approval of the version to be published

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Rakesh Heer: conception and design of the work, drafting of the article, critical revision of the article and final approval of the version to be published

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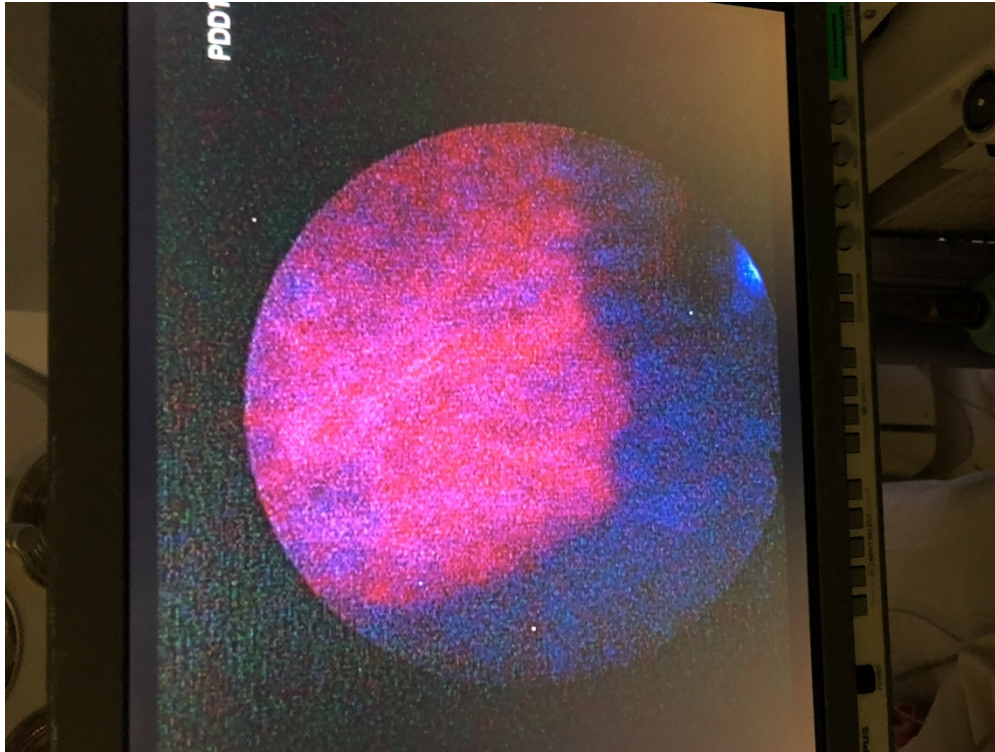
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## 12 **6. Figure Legends:**

13  
14 Figure 1: White light (a) and blue light (photodynamic) (b) cystoscopy image of the  
15 bladder from a patient diagnosed with CIS. On PDD the area with CIS appears red  
16 whilst with WL the area is unclear.  
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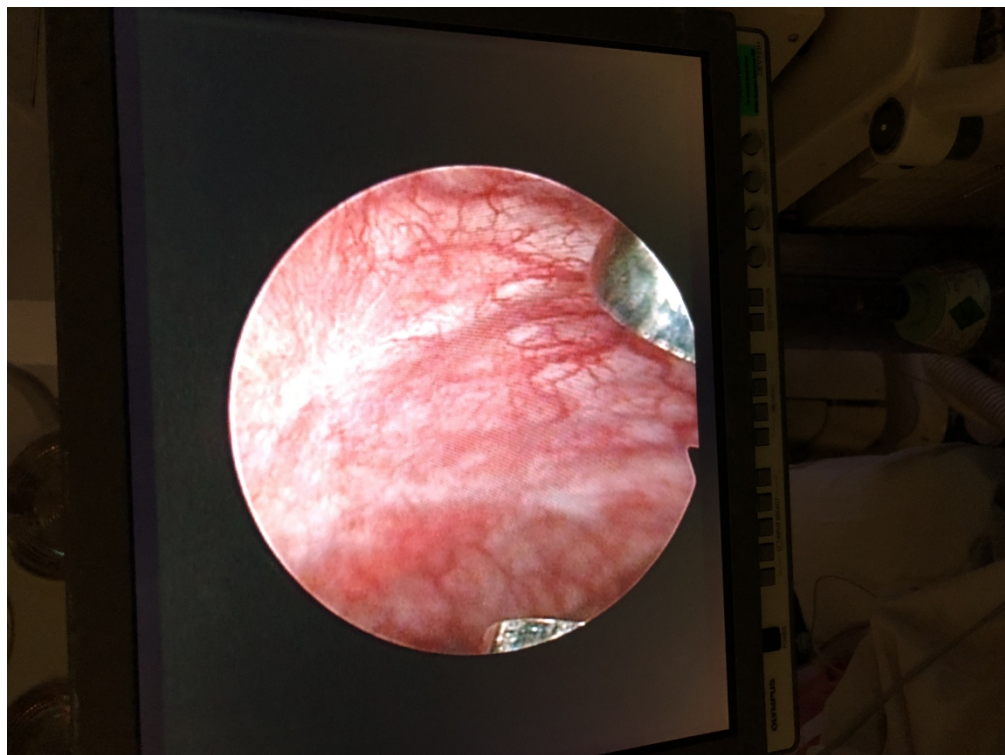
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21 Figure 2: PHOTO trial study design summary  
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White light (a) and blue light (photodynamic) (b) cystoscopy image of the bladder from a patient diagnosed with CIS. On PDD the area with CIS appears red whilst with WL the area is unclear.

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White light (a) and blue light (photodynamic) (b) cystoscopy image of the bladder from a patient diagnosed with CIS. On PDD the area with CIS appears red whilst with WL the area is unclear.

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## APPENDIX-I: NICR PHOTO-T study

### Sample Collection (per participant):

- (a) 2 x blood samples totalling 12.5ml (10ml Streck blood collection tube for circulating DNA analysis and 2.5ml PAXgene blood collection tube for circulating RNA analysis);
- (b) 2 x urine samples totalling 200ml (1 x 100ml for immediate translational processing and 1 x 100ml for biorepository storage), (c) 1 x FFPE core at baseline (plus core from recurrence, if occurs).

In total, 20 serially collected samples will be collected per PHOTO-T consented participant over the trial period (36 months), comprising 10 urine, 10 blood (5 DNA and 5 RNA) and 1 FFPE tumour tissue block. Collected at baseline (pre-treatment/TURBT) and treatment follow-up at 3, 12, 24 and 36 months or at recurrence (whichever comes first, predicted at 70% for the highest risk group over a trial period of 3 years).

Serial blood samples are requested for collection in clinic by research staff at participating investigator sites. Urine samples are provided at home by participants using specialist 'home collection' kits (home collection is preferable as sample quality in terms of genomic output is superior to clinically collected specimens) and FFPE blocks requested from Histopathology Departments of participating investigator sites retrospectively at the end of the trial.

# BMJ Open

## PHOTodynamic versus white light-guided treatment of non-muscle invasive bladder cancer: A study protocol for a randomised trial of clinical and cost effectiveness

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022268.R2
Article Type:	Protocol
Date Submitted by the Author:	22-May-2019
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<b>Primary Subject Heading</b>:	Urology
Secondary Subject Heading:	Health economics, Oncology
Keywords:	bladder cancer, photodynamic diagnosis, quality of life, HEALTH ECONOMICS, Cost effectiveness, Sample biorepository

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Manuscripts

1 Title page

2 PHOTodynamic versus white light-guided treatment of non-  
3 muscle invasive bladder cancer: A study protocol for a  
4 randomised trial of clinical and cost effectiveness

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9 Mariappan <sup>10</sup>( $\bar{\tau}$ ), Ghulam Nabi<sup>11</sup>( $\bar{\tau}$ ), Joanne Creswell<sup>12</sup>( $\bar{\tau}$ ), Henry Lazarowicz<sup>13</sup>( $\bar{\tau}$ ),  
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12 \*Authors have provided equal contribution and are joint first authors.

13 \*\*Joint senior authors.

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47 Key words:

- 48
- 49 • Bladder cancer
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- 51 • Photodynamic diagnosis
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- 53 • Quality of life
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- 55 • Health economics
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9 52 The authors declare that they have no competing interests.

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1  
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3 55 **Abstract**  
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5 56 **Introduction:** Bladder cancer is the most frequently occurring tumour of the urinary  
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7 57 system. Ta, T1 tumours and carcinoma in situ (CIS) are grouped as non-muscle  
8  
9 58 invasive bladder cancer (NMIBC), which can be effectively treated by transurethral  
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11 59 resection of bladder tumour (TURBT). There are limitations to the visualisation of  
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13 60 tumours with conventional TURBT using white light illumination within the bladder.  
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15 61 Incomplete resections occur from the failure to identify satellite lesions or the full  
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17 62 extent of the tumour leading to recurrence and potential risk of disease progression.  
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19 63 To improve complete resection, photodynamic diagnosis (PDD) has been proposed as  
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21 64 a method that can enhance tumour detection and guide resection. The objective of the  
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23 65 current research is to determine whether PDD-guided TURBT is better than  
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25 66 conventional white light surgery and whether it is cost-effective.  
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30 67 **Methods and Analysis:** PHOTO is a pragmatic multi-centre randomised controlled  
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32 68 trial (open parallel group, non-masked, superiority trial) comparing the intervention of  
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34 69 PDD-guided TURBT with standard white light resection in newly diagnosed  
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36 70 intermediate and high risk NMIBC within the UK NHS setting. Clinical effectiveness  
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38 71 is measured with time to recurrence. Cost-effectiveness is assessed within trial via the  
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40 72 calculation of incremental cost per recurrence avoided and incremental cost per  
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42 73 quality adjusted life per year (QALY) gained over three years, and over long term  
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44 74 through a modelling exercise over patients' life time.  
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49 75 **Ethics and dissemination:** Formal ethics review was undertaken with a favourable  
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51 76 opinion, in line with UK regulatory procedures (REC reference number: 14/NE/1062;  
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53 77 Trial registration: ISRCTN84013636). If reductions in time to recurrence is  
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55 78 associated with long term patient benefits the cost-effectiveness evaluation will  
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57 79 provide further evidence to inform adoption of the technology. Findings will be  
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3 80 shared in lay media such as patient and charity forums and will be presented at key  
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5 81 meetings and published in academic literature.  
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10 83 **Article Summary:**  
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15 85 Strengths and limitations of the PHOTO study include;  
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19 87 • the effectiveness of the photodynamic diagnosis (PDD) for the initial resection  
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21 88 of intermediate and high risk non-muscle invasive bladder cancer as part of  
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23 89 routine care will be demonstrated with a pragmatic clinical trial design,  
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25 90 • full-health economic evaluation will provide high quality evidence of the  
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27 91 burden of NMIBC for the NHS  
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29 92 • a well-characterised trial associated biorepository of longitudinal serially  
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## 95 1. Background

96 Bladder cancer is the most frequently occurring tumour of the urinary system [1].  
97 Staging of bladder cancer is described using the Tumour, Node, Metastasis (TNM)  
98 system [2]. Tumours confined to the epithelial lining (urothelium) are classified as  
99 stage Ta and those invading the lamina propria are classified as stage T1.

100 Ta and T1 tumours can be removed by transurethral resection (TURBT) that  
101 involves passing a cystoscope through the urethra into the bladder and resecting the  
102 tumour under direct visualisation. For therapeutic purposes Ta and T1 tumours are  
103 grouped together as non-muscle invasive bladder cancer (NMIBC). Grade  
104 (microscopic characteristics of the tumour cells) can be used to describe  
105 aggressiveness of cancers and are characterised as either low grade (relatively benign)  
106 or high grade (aggressive). NMIBC also include flat, high-grade tumours that are  
107 confined to the epithelium classified as carcinoma in situ (CIS).

109 Complete resection of the tumour with TURBT is essential to obtain good  
110 prognosis. It is thought that failure to identify satellite tumours or to appreciate the  
111 full extent of the tumours visualised during resection using conventional white light  
112 cystoscopy may be a factor in 20-40% of recurrent bladder tumours [3, 4]. Incomplete  
113 resection with TURBT is also associated with staging errors. In order to correct the  
114 staging errors associated with initial TURBT a second resection within 2-6 weeks is  
115 suggested for select group patients [5]. It has been postulated that development in  
116 cystoscopy imaging can improve resections and decrease the need for a second  
117 resection [6].

118 Recurrence and stage progression to muscle invasive (T2-T4) or metastatic  
119 cancer is more likely to occur in those with high-grade tumours with concomitant

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3 120 CIS. CIS in particular can be easily missed using conventional white light guided  
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5 121 resection [6].  
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8 122 Surveillance of NMIBC is carried out with cystoscopy to detect recurrence early  
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10 123 and allow treatment before progression. Clinical guidelines tailor follow up protocols  
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12 124 according to the risk groups (low, intermediate and high) developed using clinical and  
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14 125 histological parameters [7]. Advised follow-up of low risk is at three months and if  
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16 126 negative the next cystoscopy is scheduled for nine months later and then yearly for  
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18 127 five years. Patients with high-risk tumours have cystoscopy and urine cytology at  
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20 128 three months. If negative, it is repeated every three months for two years, then every  
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22 129 six months until five years, and annually thereafter [5]. The intensity of cystoscopic  
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24 130 follow up for patients with intermediate risk is not clearly defined, for which a follow-  
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26 131 up scheme in-between those described for low and high risk and is adapted according  
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28 132 to personal and subjective factors [5].  
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### 33 34 35 134 1.1. Photodynamic diagnosis of NMIBC: 36

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38 135 As an attempt to improve resection rates, photodynamic diagnosis (PDD) has  
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40 136 been developed to enhance tumour detection and guide resection. A cystoscopy image  
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42 137 of WL vs PDD is presented in figure 1. Meta-analyses and systematic reviews of PDD  
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44 138 guided treatment of NMIBC have shown efficacy in tumour detection and reduction  
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46 139 in residual tumour compared with white light cystoscopy alone. These findings  
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48 140 translate into reduced recurrence rates [6, 8]. However, these trials were efficacy  
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50 141 studies and the systematic review called for a pragmatic study to allow better  
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52 142 interpretation of possible benefit into daily clinical practice.  
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### 56 143 57 58 144 1.2. Health economics of NMIBC: 59 60

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3 145 NMIBC is one of the most costly cancers to manage on a per patient basis  
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5 146 because of its high prevalence, high recurrence rate, need for adjuvant treatments and  
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7 147 the requirement for long-term cystoscopic surveillance. The total cost of treatment  
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10 148 and 5-year follow-up of patients with NMIBC diagnosed in the United Kingdom has  
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12 149 increased from £73 million to £213 million from 2001 to 2012 (inflation corrected) [9,  
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14 150 10]. From a patient perspective, there often are considerable anxieties about  
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16 151 recurrences, transurethral resection and progression, requiring additional therapies  
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18 152 with potential mortality and long-term morbidity (e.g. radical surgery). Transurethral  
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20 153 resection itself is associated with reduced quality of life, including both mental and  
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22 154 physical health domains; although these effects are usually transient [11]. Substantial  
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24 155 effects on health related quality of life (HRQoL) are most likely to come from  
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26 156 adjuvant intravesical treatments and radical or palliative treatments for progression  
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28 157 [12]. The cost-effectiveness of NMIBC treatment strategies has not been widely  
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33 158 studied.

### 34 35 36 37 38 160 1.3. NMIBC biomarkers and clinical impact:

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40 161 To date, existing non-invasive commercial biomarkers (primarily urinary) are not  
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42 162 embedded in routine clinical practice due to poor sensitivity, specificity and lack of  
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44 163 evidence. Several research bodies have recognized the lack of clinically useful  
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46 164 biomarkers for bladder cancer. “Fit for purpose” sample resources accessible to high-  
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48 165 throughput ‘omic’ technologies will afford the greatest opportunity to generate  
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50 166 translational hypotheses and ensure clinical validity and utility of putative candidate  
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52 167 markers/signatures [13, 14]. Robust, ‘future-proof’, longitudinal serial sample  
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54 168 archives providing critical insights of the natural history of bladder cancer correlated  
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56 169 with clinical detail for retrospective translational biomarker discovery, are lacking.  
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5 171 1.4. Current research objectives:  
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7 172 More efficient management strategies to reduce NMIBC recurrence and hence  
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10 173 decrease both the burden to patients and costs are urgently needed. PDD-guided initial  
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12 174 TURBT has been identified as a technique that can help achieve these aims. The  
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14 175 objective of the current research (PHOTO trial) is to determine whether  
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16 176 photodynamic surgery guided by a fluorescent tumour marker is better than  
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18 177 conventional white light surgery in the cystoscopic treatment of people with  
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20 178 intermediate and high risk cancers confined to the bladder lining and whether its  
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22 179 implementation is cost-effective. The trial includes a full assessment of the costs of  
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24 180 patient management through the care pathway. Individual patient data from this trial  
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26 181 will be used for subsequent mathematical modelling studies to investigate safe  
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28 182 monitoring frequency. The Photodynamic versus white light-guided treatment of non-  
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30 183 muscle invasive bladder cancer trial has the following research objectives:  
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33 184 i. Primary objectives:  
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36 185 Clinical effectiveness: To compare time to recurrence for each of the two treatment  
37  
38 186 strategies, with a principal point of interest at 3 years.  
39

40 187 Cost-effectiveness: To evaluate cost-effectiveness as measured by the incremental  
41  
42 188 cost per recurrence avoided and the cost-utility as measured by the incremental cost  
43  
44 189 per quality-adjusted life year (QALY) gained at three years and over patients' life  
45  
46 190 time.  
47  
48

49 191 ii. Secondary objectives:  
50  
51

52 192 a. To measure relative rates of disease progression at three years.  
53

54 193 b. To measure relative harms and safety.  
55

56 194 c. Patient lifetime HRQoL and cancer-specific survival.  
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3 195    iii.    Additional objectives:  
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5 196    a.    To model the safest and most cost-effective cystoscopic follow-up surveillance  
6  
7 197        schedule;  
8  
9  
10 198    b.    To evaluate the learning curve for the procedure and account for its effects on  
11  
12 199        outcomes of both PDD-guided and standard white light resections;  
13  
14 200    c.    To establish a well-characterised cohort of serial samples from patients with  
15  
16 201        intermediate and high-risk NMIBC including clinical data, urine, blood and  
17  
18 202        tumour specimens for separately funded translational research.  
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## 204    **2. Methods & Design**

### 205    2.1. Study design

206        PHOTO is a multi-centre randomised open parallel group non-masked superiority  
207        trial comparing the intervention of PDD guided bladder tumour resection with  
208        standard white light resection in patients with newly diagnosed intermediate and high  
209        risk NMIBC. Apart from initial treatment, both groups will receive standard care,  
210        including single dose intravesical mitomycin C within 24 hours of initial resection,  
211        surveillance according to risk-adjusted schedules and adjuvant therapy as indicated by  
212        current practice guidelines. The target number of patients to be recruited is 533 with a  
213        trial specific follow-up of at least 36 months for each individual. The outline of the  
214        study protocol (Version 4, 02/02/2018) is shown in Figure 2.

215

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3 216 2.2. Intervention  
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5 217 The interventions being compared within PHOTO trial are:  
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7  
8 218 i. Photo dynamic diagnosis (PDD) guided trans-urethral resection (TURBT)

9  
10 219 (experimental group) vs;  
11

12 220 ii. Standard white light TURBT (control group)  
13

14 221 All participants, unless there are clinical contra-indications, receive intravesical  
15

16 222 mitomycin C (40 mg in 40 ml saline), ideally within 6 hours following TURBT but  
17

18 223 otherwise within the inpatient setting before discharge.  
19  
20  
21  
22  
23

24 225 2.2.1. Technique of photodynamic diagnosis  
25

26 226 PDD requires preliminary instillation of the photosensitiser hexaminolevulinate  
27

28 227 (85 mg in 50 ml of phosphate buffered saline) into the participant's bladder through a  
29

30 228 urethral catheter. Participants are asked not to pass urine for at least one hour after  
31

32 229 insertion. Following operating theatre preparation according to local standard  
33

34 230 procedures and under appropriate anaesthesia, participants undergo TURBT of their  
35

36 231 bladder tumour under blue light (wavelength 380-450 nm) illumination of the bladder.  
37  
38  
39

40 232 The equipment required includes a specialised light source, cystoscope, light cables  
41

42 233 and cameras. When using PDD, normal bladder epithelium appears blue whilst red  
43

44 234 areas should be considered suspicious and should be resected.  
45  
46  
47  
48

49 236 2.2.2. Technique of standard white light cystoscopy  
50

51 237 The control group does not have any preliminary photosensitiser instillation and  
52

53 238 undergo standard tumour localisation and resection under white light (wavelength  
54

55 239 400-800 nm) illumination of the bladder.  
56  
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3 241 2.3. Participants  
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5 242 In the PHOTO trial adult patients with a suspected new diagnosis of intermediate  
6  
7 243 or high risk NMIBC are studied. Participants are identified prior to initial resection  
8  
9 244 based on results of preliminary visual assessment via cystoscopy or imaging  
10  
11 245 performed as part of standard evaluation for suspected urinary tract malignancy.  
12  
13

14 246 Patients with the following criteria are included in the PHOTO trial:

- 15  
16  
17 247 • Adult men and women aged  $\geq 16$  years.  
18  
19 248 • First suspected diagnosis of bladder cancer.  
20  
21 249 • Visual/ultrasound/Computerized tomography (CT) diagnosis of  
22  
23 250 intermediate/high risk NMIBC.  
24  
25 251 • White light visual appearances of intermediate or high risk disease ( $\geq 3$ cm OR  
26  
27 252 two or more tumours OR flat velvety erythematous changes alerting a clinical  
28  
29 253 suspicion of CIS).  
30  
31  
32  
33 254 OR  
34  
35 255 Suspicion of papillary bladder tumour  $\geq 3$ cm based on ultrasound or CT  
36  
37 256 scanning (without hydronephrosis).  
38  
39 257 • Written informed consent for participation prior to any study specific  
40  
41 258 procedures.  
42  
43 259 • Willing to comply with the following life style guidelines:  
44  
45 260 ○ Female participants must be surgically sterile or be post-menopausal,  
46  
47 261 or must agree to use effective contraception after joining the study and  
48  
49 262 for 7 days after treatment. Female participants must not breast feed for  
50  
51 263 7 days after treatment.  
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3 264           ○ Male participants must be surgically sterile or must agree to use  
4  
5 265           effective contraception after joining the study and for 7 days after  
6  
7 266           treatment.  
8  
9  
10 267           ○ Effective contraception is defined as two forms of contraception,  
11  
12 268           including one barrier method.

13  
14  
15 269 Exclusion criteria applied in the PHOTO trial are:

- 16  
17 270           • Visual evidence of low risk NMIBC (solitary tumour < 3cm).  
18  
19 271           • Visual evidence of MIBC on preliminary cystoscopy, i.e. non-papillary or  
20  
21 272           sessile mass (attached directly by its base without a stalk).  
22  
23 273           • Imaging evidence of MIBC – CT/USS (this includes the presence of  
24  
25 274           hydronephrosis, which may be present despite clear imaging of MIBC in the  
26  
27 275           bladder).  
28  
29 276           • Upper tract (kidney or ureteric) tumours on imaging.  
30  
31 277           • Any other malignancy in the past 2 years (except: non-melanomatous skin  
32  
33 278           cancer cured by excision, adequately treated carcinoma in situ of the cervix,  
34  
35 279           DCIS/LCIS of the breast or prostate cancer in patients who have a life  
36  
37 280           expectancy of >5 years upon trial entry).  
38  
39 281           • Evidence of metastases.  
40  
41 282           • Porphyria or known hypersensitivity to porphyrins.  
42  
43 283           • Known pregnancy (based on history and without formal testing, in keeping  
44  
45 284           with day-to-day NHS practice of PDD use).  
46  
47 285           • Any other conditions that in the Principal Investigator's opinion would  
48  
49 286           contraindicate protocol treatment.  
50  
51 287           • Unable to provide informed consent.  
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3 288 • Unable or unwilling to complete follow-up schedule (including HRQoL  
4  
5 289 questionnaires).  
6  
7  
8 290

9  
10 291 2.4. Informed consent-ethics approval

11  
12 292 Favourable ethical opinion for this research was provided by the Newcastle &  
13  
14 293 North Tyneside 2 ethics committee (REC reference number: 14/NE/1062) in July  
15  
16  
17 294 2014. The study complies with the Helsinki Declaration and the principles of Good  
18  
19 295 Clinical Practice (GCP).  
20

21 296 Potential participants are identified mainly through rapid access haematuria  
22  
23  
24 297 clinics at participating sites from the UK. An eligibility checklist is completed by the  
25  
26 298 local Principal Investigator (or delegate) to assess fulfilment of the entry criteria for  
27  
28 299 all patients considered for the study. Information from the diagnostic cystoscopy is  
29  
30 300 used to assess eligibility.  
31  
32

33 301 All potentially eligible patients are provided with an information sheet to explain  
34  
35 302 why they have been approached and the nature of the study. Eligible patients are  
36  
37 303 asked to provide written informed consent for the study only after they have had  
38  
39 304 sufficient time to consider the trial and had the opportunity to have any further  
40  
41 305 questions addressed.  
42  
43  
44 306

45  
46  
47 307 2.5. Recruitment and randomisation

48  
49 308 Eligible patients are centrally randomised using either the secure web-based or  
50  
51 309 the 24-hour Interactive Voice Response randomisation system at the Centre for  
52  
53 310 Healthcare Randomised Trials (CHaRT) in Aberdeen, using minimisation by centre  
54  
55 311 and gender, to allocate participants 1:1 to the control and experimental groups. The  
56  
57 312 minimisation algorithm incorporates a random element in order to prevent  
58  
59  
60

1  
2  
3 313 deterministic treatment allocation. The trial was opened on the 23<sup>rd</sup> of October 2014  
4  
5 314 and recruitment was completed on 14<sup>th</sup> of February 2018. Over this period 22 centres  
6  
7 315 joined the study and contributed to recruitment. List of sites participating are available  
8  
9 316 on <http://www.isrctn.com/ISRCTN84013636>.

11  
12 317

## 14 318 2.6. Outcome measures

16  
17 319

### 19 320 2.6.1. Primary outcome measures

21 321 Clinical effectiveness: Time to recurrence is measured as time from randomisation to  
22  
23 322 first recurrence.

25 323 Cost effectiveness: A health economic model will be developed to calculate  
26  
27 324 incremental cost per recurrence avoided and incremental cost per QALY gained over  
28  
29 325 three years.

31  
32 326

### 35 327 2.6.2. Secondary outcome measures

37 328 Clinical effectiveness:

- 39  
40 329 • Adverse events and complications up to 3 months from initial or second TURBT  
41  
42 330 are captured and will be included in analysis.
- 44 331 • HRQOL is captured for each participant at baseline (prior to knowledge of  
45  
46 332 treatment allocation), following surgery and at 3, 6, 12, 18, 24 and 36 months  
47  
48 333 after randomisation.
- 50 334 • Disease progression is captured within the trial time. Patient life time projections  
51  
52 335 will be made by using the trial data at baseline and supplementing as necessary  
53  
54 336 from other published data.

- 1  
2  
3 337 • Overall survival and bladder cancer specific survival will be compared between  
4  
5 338 the two treatment arms. Minimum follow-up of the last included patient will be 3  
6  
7 339 years and maximum expected follow-up is 66 months.  
8  
9

10 340 Cost effectiveness:

- 11  
12 341 • Estimation of the incremental cost per recurrence avoided using the economic  
13  
14 342 model over the patients' lifetime.  
15  
16  
17 343 • Estimation of the incremental cost per QALY gained using the economic  
18  
19 344 model over the patients' lifetime.  
20  
21

22 345

### 23 346 2.6.3. Additional outcomes measures

24  
25 347 Schedules for follow-up: Using data from within the trial and, if appropriate,  
26  
27 348 from other relevant sources, the risk of recurrence at each interval surveillance  
28  
29 349 cystoscopy will be described to then model the most safe and efficient surveillance  
30  
31 350 follow-up schedule.  
32  
33

34  
35 351 The effect of PDD guided resection experience (learning curve) on clinical  
36  
37 352 effectiveness: A subgroup analysis comparing outcomes from PDD-experienced and  
38  
39 353 PDD-naïve surgeons (determined at baseline) will be conducted. Also for PDD-naïve  
40  
41 354 surgeons an assessment of learning curve will be undertaken by comparing increasing  
42  
43 355 experience and recurrence, in both PDD and WL resections.  
44  
45  
46

47 356

### 48 49 357 2.7. Tracking and monitoring adverse events

50  
51 358 Direct surgically related post-operative events occurring within 30 days following  
52  
53 359 the first TURBT or second TURBT if required will be assessed using The Clavien  
54  
55 360 Dindo classification for surgical complications. Events occurring up to 3 months after  
56  
57 361 TURBT (second TURBT if required) will be assessed and recorded using the National  
58  
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2  
3 362 Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0  
4  
5 363 framework (<http://ctep.cancer.gov/>) [15].  
6  
7  
8 364

9  
10 365 2.8. Trial assessment and measures

11  
12 366 PHOTO trial schedule of assessment and investigations are summarised in Table

13  
14 367 1. Routine attendances for diagnosis and staging of new bladder cancers are used to  
15  
16 368 establish eligibility, which includes obtaining the medical history. Eligible patients  
17  
18 369 who consent for the trial are administered HRQoL questionnaires prior to primary  
19  
20 370 TURBT and prior to discharge.  
21  
22

23  
24 371 Time to recurrence will be measured from the day of randomisation to the day of  
25  
26 372 subsequent biopsy with pathologically proven recurrence. Data will be collected from  
27  
28 373 the following routine visits; 3, 6, 9, 12, 18, 24 and 36 months post initial TURBT (or  
29  
30 374 second TURBT if required). Associated costs and changes in HRQoL will be  
31  
32 375 measured. These will be collected by postal questionnaires sent directly to participants  
33  
34 376 at 3, 6, 12, 18, 24 & 36 months post randomisation.  
35  
36

37  
38 377 Disease progression will be assessed using results of further resection or imaging  
39  
40 378 during follow-up. Progression will be defined as increase of stage into MIBC or  
41  
42 379 development of nodal or metastatic disease. In addition, patients showing failure to  
43  
44 380 respond to intravesical treatment (e.g. BCG failure) will also be captured.  
45  
46

47 381 The relative changes in HRQoL resulting from the physical and psychological  
48  
49 382 benefit together with any harms associated with each strategy and with subsequent  
50  
51 383 necessary cancer treatment will be measured using the generic EQ-5D-3L  
52  
53 384 questionnaire, cancer specific EORTC-QLQ-C30 and disease-specific EORTC QLQ-  
54  
55 385 NMIBC24 questionnaire completed by the participant.  
56  
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386 Effect of PDD guided resection experience on clinical effectiveness: All  
 387 recruiting surgeons will complete a learning curve questionnaire to elicit their white  
 388 light and PDD resection experience prior to any recruitment. The subsequent accruing  
 389 experience of each surgeon will be captured on case report forms. Early recurrence  
 390 (12 weeks) will be used as a proxy of incomplete resection.

391 Table 1, Schedule of investigations/assessments in PHOTO trial

Visit/Assessment	Pre- randomisation screening	Pre-treatment	TURBT	Prior to discharge	Surveillance								Annually thereafter	At first disease recurrence/progression	
					Second TURBT (as clinically indicated)	3 months post treatment	6 months post treatment	9 months post treatment	12 months post treatment	18 months post treatment	24 months post treatment	36 months post treatment			
Visual diagnosis of IR/HR NMIBC	X														
Medical history	X														
HRQoL questionnaire <sup>1</sup>		X		X	X	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>		
TURBT according to treatment allocation with post treatment MMC instillation			X												
Second TURBT, if required, according to treatment allocation					X										
Assessment of adverse events (CTCAE & Clavien Dindo)						X									
Cystoscopy						X	X	X	X	X	X	X			
Histological confirmation of recurrence/ progression															X
Collection of FFPE tissue <sup>3</sup>			X												X
Urine sample collection <sup>3</sup>		X				X			X		X	X			X
Blood sample collection <sup>3</sup>		X				X			X		X	X			X

392 Footnotes

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2  
3 393 1. EORTC QLQ-C30 & NMIBC24, EQ-5D-3L  
4 394 2. Questionnaire sent by-post directly to participant  
5 395 3. If patient consented to participation in PHOTO-T (as this is archived pathology the tissue may be requested  
6 396 at an interval from the diagnostic resection/recurrence).  
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## 397 2.9. Sample size

398 We aim to detect an absolute reduction in recurrence at three years of 12%; from  
399 40% (under the conservative assumption that all the patients recruited are  
400 intermediate risk patients with a probability of recurrence of 0.4 at 3 years) to 28%  
401 (similar effect sizes of photodynamic therapy are reported in both intermediate and  
402 high risk groups) this will be equivalent to a relative reduction of 30%.

403 Recruitment of 533 participants (214 recurrences) will detect a hazard ratio of  
404 0.64 between experimental and control strategies and provide, using the log-rank test,  
405 90% power at a 2-sided 5% significance level. This calculation assumes 2.5 years  
406 incremental recruitment, a minimum of three years follow-up and a 6.4% follow-up  
407 attrition at end of year three. To achieve this we plan to use 30 secondary care sites  
408 that would see new bladder cancers diagnoses, from which we will exclude patients  
409 with MIBC (20%) and, from the remaining NMIBCs, exclude low risk disease (50%).  
410 Furthermore, we predict only 30% of these patients will be recruited based on  
411 willingness to participate or missed opportunities for recruitment.

## 413 2.10 Health economics analysis

414 A within trial cost-effectiveness analysis will be conducted to calculate  
415 incremental cost per recurrence avoided and incremental cost per QALY gained over  
416 three years. Data on costs, recurrence and QALYs for each participant will be  
417 recorded in the trial and used to estimate mean cost, recurrence and QALYs for each  
418 intervention group. As the time horizon of the trial is three years these data will be  
419 discounted at 3.5% [16]. The cost, recurrence avoided and QALY data will then be  
420 used to estimate incremental costs, recurrence avoided and QALYs and incremental  
421 cost per recurrence avoided and incremental costs per QALY.

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5 423 An economic model will be developed to estimate relative rates of cost-  
6  
7 424 effectiveness and cost-utility, at three years (to mirror the within trial analysis) and  
8  
9 425 over a patient lifetime time horizon. An NHS perspective will be taken for the cost  
10  
11 426 calculations. The model takes the form of a Markov state transition model that  
12  
13 427 describes the consequences of different diagnosis and treatment strategies in terms of  
14  
15 428 clinical and cost outcomes [6]. The rates of recurrence and progression recorded with  
16  
17 429 the 3-year follow-up of the trial will be used to model short-term recurrence and  
18  
19 430 progression rates. Further data required for the model relates to the transition and  
20  
21 431 other probabilities of events beyond the 3 year follow-up, including the risk of  
22  
23 432 recurrence and progression, probabilities of receiving different types of intervention  
24  
25 433 should progression or recurrences occur, and risks of mortality (both from bladder  
26  
27 434 cancer and other causes), will be sought through a structured systematic review of  
28  
29 435 long-term outcomes of treatments of bladder cancer. The model will be used to  
30  
31 436 produce estimates of costs, QALYs, recurrence rates and survival. Both costs and  
32  
33 437 outcomes will be discounted at 3.5% in the base case analyses. Cost-effectiveness will  
34  
35 438 be reported as incremental cost per QALY gained and incremental cost per recurrence  
36  
37 439 avoided (at both 3 years and over the patient's lifetime). These data will be presented  
38  
39 440 as point estimates and bootstrapping techniques will be used to estimate the statistical  
40  
41 441 imprecision surrounding them. The results of this stochastic analysis will be presented  
42  
43 442 as cost and QALY plots and as cost-effectiveness acceptability curves. Further  
44  
45 443 deterministic sensitivity analyses will be conducted to explore other forms of  
46  
47 444 uncertainty e.g. surrounding the choice of discount rate or around the unit costs of  
48  
49 445 equipment. The model will be probabilistic and distributions will be attached to all  
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3 446 parameters, the shape and type of distribution will depend upon the data available and  
4  
5 447 recommendations for good practice in modelling [17].  
6  
7

#### 8 448 2.10. Patient and Public Involvement

9  
10 449 Patient involvement was ensured at the early stages of protocol development and  
11  
12 450 contributed to user-lead development of outcomes of value to patients in  
13  
14 451 the design of the trial. Additionally, the patient journey of patient representatives was  
15  
16 452 investigated through the diagnosis and treatment of bladder cancer, which includes an  
17  
18 453 anonymised account impact on his quality of life. This helped understand the burden  
19  
20 454 of the intervention on patients. A patient representative was involved as a co-  
21  
22 455 investigator and member of the trial steering committee helping manage and analyse  
23  
24 456 the implications of the research.  
25  
26  
27

#### 28 457 2.11. PHOTO-Translational side study

29  
30 458 PHOTO Translational (PHOTO-T) aims to establish a well-characterised trial  
31  
32 459 associated biorepository of longitudinal serially collected tissue samples (blood, urine  
33  
34 460 and FFPE). The collection of samples from PHOTO patients is optional with every  
35  
36 461 PHOTO-T consented participant collecting a urine and blood sample at baseline (pre-  
37  
38 462 treatment/TURBT) and 3, 12, 24 and 36 months treatment follow-up or at recurrence  
39  
40 463 (whichever comes first, predicted at 70% for the highest risk group over a trial period  
41  
42 464 of 3 years). A FFPE core at baseline (plus recurrence, if occurs) will also be collected  
43  
44 465 (supplement).  
45  
46  
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48

49 466

### 50 467 **3. Discussion**

51  
52 468 Bladder cancer is the most frequent urothelial cancer and the overall costs for  
53  
54 469 treatment and follow-up remain higher than most other cancers [18]. Achieving  
55  
56 470 complete resection of NMIBC with TURBT is associated with lower recurrence rates  
57  
58  
59  
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3 471 in follow-up. However, it is unclear if this translates into lower progression rates in  
4  
5 472 long-term follow-up. PDD guided initial TURBT is a technology that could improve  
6  
7 473 resection and ultimately reduce recurrence and the need for further treatments.  
8  
9 474 Studies on PDD have demonstrated the efficacy of the technology using strict study  
10  
11 475 entry requirements, for which translation into daily clinical practice is limited.  
12  
13 476 Therefore, in the PHOTO trial the effectiveness of the technology as part of routine  
14  
15 477 care will be demonstrated with a pragmatic clinical trial design.  
16  
17  
18

19 478 PHOTO trial includes measurement of HRQoL using EQ-5D at the time of  
20  
21 479 initial treatment and surveillance. The measurement of HRQoL around the time of the  
22  
23 480 cystoscopy and TURBT can be particularly dynamic due to an acute deterioration in  
24  
25 481 health score associated with the invasive procedure followed by a typical rapid  
26  
27 482 recovery [11, 19]. Therefore, a side study was developed, where patients are recruited  
28  
29 483 from the PHOTO trial to evaluate the acute deterioration in quality of life by  
30  
31 484 suspected diagnosis or TURBT around the time of resection. This side study will use  
32  
33 485 a time trade off exercise and the outcomes will supplement the calculation of QALYs  
34  
35 486 in the health economic model.  
36  
37  
38  
39

40 487 The high costs of bladder cancer to health care systems has usually been  
41  
42 488 obtained from weak data and the true costs are unclear. The pragmatic design of the  
43  
44 489 PHOTO trial alongside the robust data collection for a full-health economic  
45  
46 490 evaluation will provide high quality evidence of the burden of NMIBC for the NHS.  
47  
48 491 Moreover, it will also provide a cost effectiveness comparison of white light vs PDD-  
49  
50 492 guided initial TURBT resections.  
51  
52  
53

54 493 Evidence on the required cases for PDD naïve surgeons to gain competency  
55  
56 494 the technology is weak. This could act as a potential confounder on the clinical  
57  
58 495 outcomes measured and therefore will be accounted for during analysis. Moreover, an  
59  
60

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2  
3 496 evaluation of the learning curve of PDD will also be carried out using the forms filled  
4  
5 497 in by surgeons.

6  
7  
8 498 The primary outcome of the study is time to recurrence measured from the day  
9  
10 499 of randomisation to the day of subsequent biopsy with pathologically proven  
11  
12 500 recurrence. If decrease in time to recurrence is associated with long term patient  
13  
14 501 benefits the cost-effectiveness evaluation will provide further evidence for the NHS to  
15  
16 502 decide on full adoption of the technology.

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3 505 **4. List of abbreviations**  
4

5 506 CIS: Carcinoma in-situ  
6

7 507 cm: centimetres  
8

9  
10 508 CT: Computerized tomography  
11

12 509 DCIS: Ductal carcinoma in-site  
13

14 510 EORTC: European Organization for Research and Treatment of Cancer  
15

16 511 FFPE: Formalin Fixed Paraffin Embedded  
17

18 512 HRQoL: Health related quality of life  
19

20 513 HTA : health technology assessment  
21

22 514 LCIS: Lobular carcinoma in situ  
23

24 515 MIBC: Muscle invasive bladder cancer  
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26 516 MMC: Mitomycin-C  
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28 517 NHS: National Health Service  
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30 518 NIHR: National Institute for Health Research  
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32 519 NMIBC: Non-muscle invasive bladder cancer  
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34 520 PDD: Photo dynamic diagnosis  
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36 521 QALY: Quality adjusted life years  
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38 522 TURBT: Transurethral resection of bladder tumour  
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40 523 USS: Ultrasonography  
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42 524 WL: White light  
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10 533 **Department of Health disclaimer**  
11

12 534 The views expressed are those of the author(s) and not necessarily those of the NHS,  
13  
14 535 the NIHR or the Department of Health.  
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21 538 Trust.  
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27  
28 541 the Institute of Cancer Research (ICR-CTSU) and Centre for Healthcare Randomised  
29  
30 542 Trials (CHaRT) at the University of Aberdeen.  
31

32 543 Independent Trial steering committee members – Mr Peter Whelan (Chair), Dr  
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40 546 Professor Diane Witham, Mr Robert Mills, Dr Ed Wilson, Mr Paul Silcocks.  
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3 548 **Contributorship statement:**  
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5  
6 549 Zafer Tandogdu: conception and design of the work, drafting of the article, critical  
7  
8 550 revision of the article and final approval of the version to be published  
9

10  
11 551 Rebecca Lewis: conception and design of the work, data collection, drafting of the  
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13 552 article, critical revision of the article and final approval of the version to be published  
14

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16 553 Anne Duncan: conception and design of the work, data collection, drafting of the  
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18 554 article, critical revision of the article and final approval of the version to be published  
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21 555 Alison McDonald: conception and design of the work, data collection, drafting of the  
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23 556 article, critical revision of the article and final approval of the version to be published  
24

25  
26 557 Luke Vale: conception and design of the work, critical revision of the article and final  
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28 558 approval of the version to be published  
29

30  
31 559 Steven Penegar: data collection, critical revision of the article and final approval of  
32  
33 560 the version to be published  
34

35  
36 561 Jing Shen: design of the work, critical revision of the article and final approval of the  
37  
38 562 version to be published  
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41 563 PHOTO TMG members: Trial management, data collection and final approval of the  
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43 564 version to be published  
44

45  
46 565 Graeme Maclennan: design of the work, critical revision of the article and final  
47  
48 566 approval of the version to be published  
49

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51 567 John Norrie: conception and design of the work, critical revision of the article and  
52  
53 568 final approval of the version to be published  
54

55  
56 569 Emma Hall: conception and design of the work, critical revision of the article and  
57  
58 570 final approval of the version to be published  
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571 Rakesh Heer: conception and design of the work, drafting of the article, critical  
572 revision of the article and final approval of the version to be published

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For peer review only

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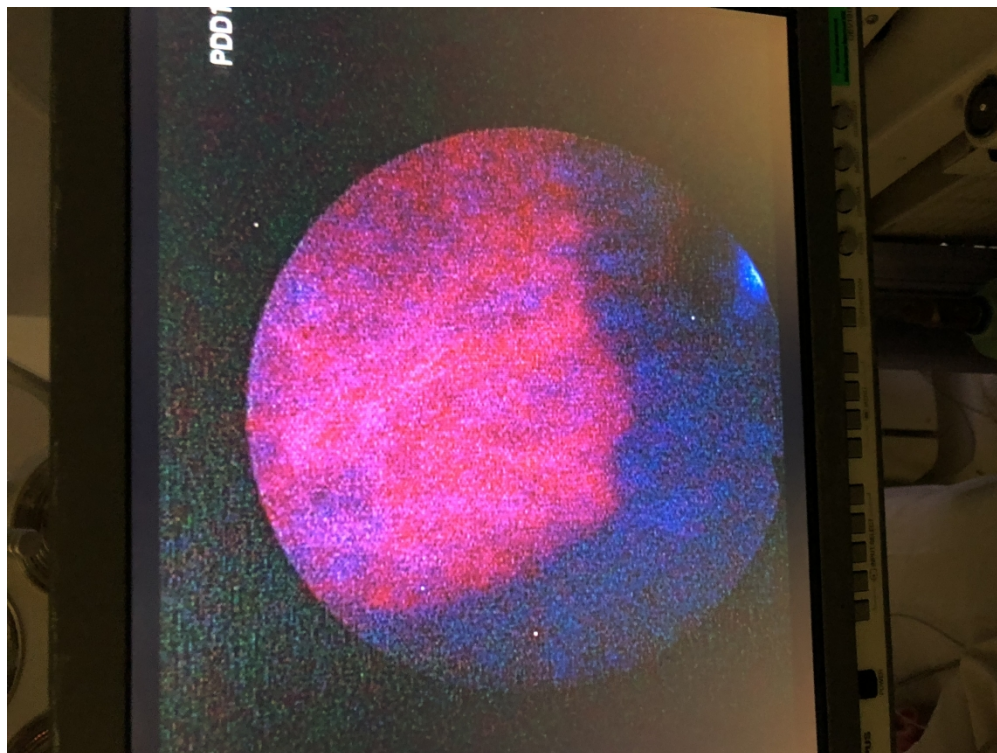
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## 12 **6. Figure Legends:**

13  
14 Figure 1: White light (a) and blue light (photodynamic) (b) cystoscopy image of the  
15 bladder from a patient diagnosed with CIS. On PDD the area with CIS appears red  
16 whilst with WL the area is unclear.  
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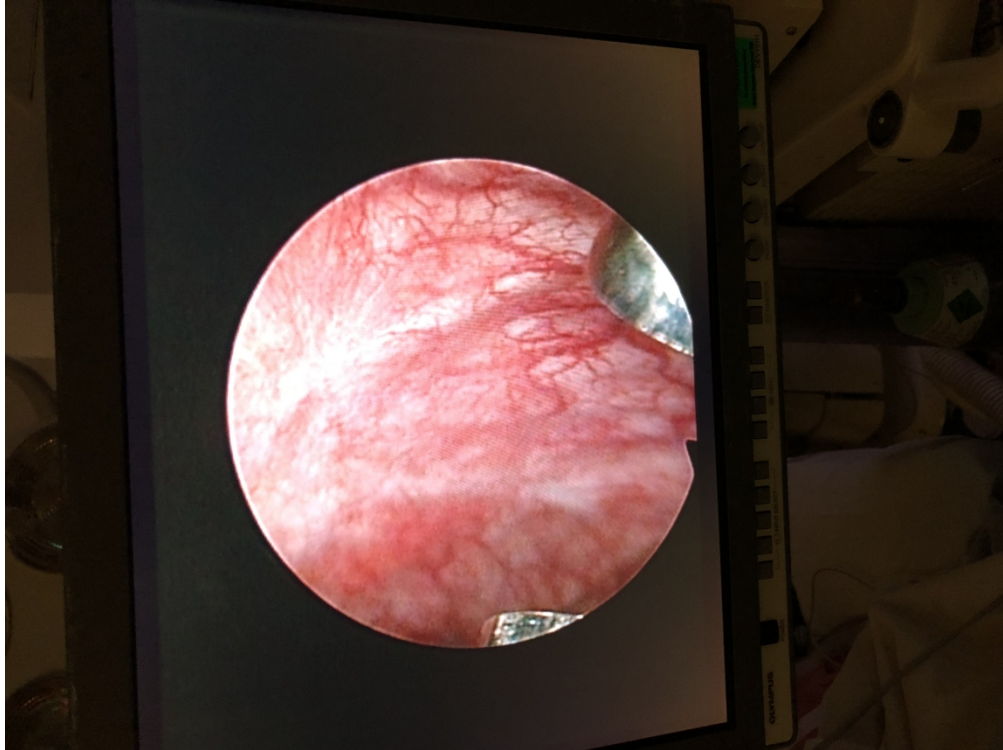
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21 Figure 2: PHOTO trial study design summary  
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White light (a) and blue light (photodynamic) (b) cystoscopy image of the bladder from a patient diagnosed with CIS. On PDD the area with CIS appears red whilst with WL the area is unclear.

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White light (a) and blue light (photodynamic) (b) cystoscopy image of the bladder from a patient diagnosed with CIS. On PDD the area with CIS appears red whilst with WL the area is unclear.

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## APPENDIX-I: NICR PHOTO-T study

### Sample Collection (per participant):

- (a) 2 x blood samples totalling 12.5ml (10ml Streck blood collection tube for circulating DNA analysis and 2.5ml PAXgene blood collection tube for circulating RNA analysis);
- (b) 2 x urine samples totalling 200ml (1 x 100ml for immediate translational processing and 1 x 100ml for biorepository storage), (c) 1 x FFPE core at baseline (plus core from recurrence, if occurs).

In total, 20 serially collected samples will be collected per PHOTO-T consented participant over the trial period (36 months), comprising 10 urine, 10 blood (5 DNA and 5 RNA) and 1 FFPE tumour tissue block. Collected at baseline (pre-treatment/TURBT) and treatment follow-up at 3, 12, 24 and 36 months or at recurrence (whichever comes first, predicted at 70% for the highest risk group over a trial period of 3 years).

Serial blood samples are requested for collection in clinic by research staff at participating investigator sites. Urine samples are provided at home by participants using specialist 'home collection' kits (home collection is preferable as sample quality in terms of genomic output is superior to clinically collected specimens) and FFPE blocks requested from Histopathology Departments of participating investigator sites retrospectively at the end of the trial.





SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description
<b>Administrative information</b>		
Title	1	2-4
Trial registration	2a	78
	2b	supplement
Protocol version	3	215
Funding	4	532
Roles and responsibilities	5a	549-573
	5b	538
	5c	541-547
	5d	541-547
<b>Introduction</b>		
Background and rationale	6a	97-170
	6b	207-224
Objectives	7	185-203
Trial design	8	206-215, 309-316
<b>Methods: Participants, interventions, and outcomes</b>		
Study setting	9	297-301. <a href="http://www.isrctn.com/ISRCTN84013636">http://www.isrctn.com/ISRCTN84013636</a> <a href="https://doi.org/10.1186/ISRCTN84013636">https://doi.org/10.1186/ISRCTN84013636</a>
Eligibility criteria	10	243-290
Interventions	11a	227-235
	11b	Not applicable

	11c	Not applicable
	11d	Not applicable
Outcomes	12	321-356
Participant timeline	13	367-397
Sample size	14	398-412
Recruitment	15	450-457

### **Methods: Assignment of interventions (for controlled trials)**

#### Allocation:

Sequence generation	16a	311-314
Allocation concealment mechanism	16b	311-314
Implementation	16c	309-311
Blinding (masking)	17a	Not applicable – surgical intervention
	17b	Not applicable – surgical intervention

### **Methods: Data collection, management, and analysis**

Data collection methods	18a	367-397
	18b	Protocol
Data management	19	Protocol
Statistical methods	20a	415-448 + Protocol
	20b	Protocol
	20c	Protocol

### **Methods: Monitoring**

Data monitoring	21a	546-547 & Protocol
	21b	Protocol
Harms	22	359-364
Auditing	23	Protocol

## Ethics and dissemination

Research ethics approval	24	76-78 & 293-294
Protocol amendments	25	78-82
Consent or assent	26a	297-300
	26b	461-462
Confidentiality	27	protocol
Declaration of interests	28	No conflict of interests
Access to data	29	Protocol
Ancillary and post-trial care	30	Protocol
Dissemination policy	31a	Protocol
	31b	Protocol
	31c	Protocol

## Appendices

Informed consent materials	32	Protocol
Biological specimens	33	459-465 & supplement

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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.