BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	Draft
Article Type:	Protocol
Date Submitted by the Author:	n/a
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Keywords:	bladder cancer, photodynamic diagnosis, quality of life, HEALTH ECONOMICS, Cost effectiveness, Sample biorepository

Title page

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

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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.

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

shared in lay media such as patient and charity forums and will be presented at key meetings and published in academic literature.

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].

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

Surveillance of NMIBC is carried out with cystoscopy to detect recurrence early and allow treatment before progression. Clinical guidelines tailor follow up protocols according to the risk groups (low, intermediate and high) developed using clinical and histological parameters [7]. Advised follow-up of low risk is at three months and if negative the next cystoscopy is scheduled for nine months later and then yearly for five years. Patients with high-risk tumours have cystoscopy and urine cytology at three months. If negative, it is repeated every three months for two years, then every six months until five years, and annually thereafter [5]. The intensity of cystoscopic follow up for patients with intermediate risk is not clearly defined, for which a follow-up scheme in-between those described for low and high risk and is adapted according to personal and subjective factors [5].

1.1. Photodynamic diagnosis of NMIBC:

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

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

archives providing critical insights of the natural history of bladder cancer correlated with clinical detail for retrospective translational biomarker discovery, are lacking.

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.

iii. Additional objectives:

a. To model the safest and most cost-effective cystoscopic follow-up surveillance schedule;

b. To evaluate the learning curve for the procedure and account for its effects on outcomes of both PDD-guided and standard white light resections;

c. To establish a well-characterised cohort of serial samples from patients with intermediate and high-risk NMIBC including clinical data, urine, blood and tumour specimens for separately funded translational research.

2. Methods & Design

2.1. Study design

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

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 ≥ 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 (≥3cm OR two or more tumours OR flat velvety erythematous changes alerting a clinical suspicion of CIS).

  OR

  Suspicion of papillary bladder tumour ≥3cm 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 deterministic treatment allocation.

2.6. Outcome measures

2.6.1. Primary outcome measures

Clinical effectiveness: Time to recurrence is measured as time from randomisation to first recurrence.

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

2.6.2. Secondary outcome measures

Clinical effectiveness:

- Adverse events and complications up to 3 months from initial or second TURBT are captured and will be included in analysis.
- HRQOL is captured for each participant at baseline (prior to knowledge of treatment allocation), following surgery and at 3, 6, 12, 18, 24 and 36 months after randomisation.
- Disease progression is captured within the trial time. Patient life time projections will be made by using the trial data at baseline and supplementing as necessary from other published data.
- 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 National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0 framework (http://ctep.cancer.gov/) [15].

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								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	Annually thereafter
Visual diagnosis of IR/HR NMIBC	X												According to EAU guidelines
Medical history	X												
HRQoL questionnaire[1]		X		X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	
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	Treatment according to local practice
Histological confirmation of recurrence/ progression													X
Collection of FFPE tissue[3]			X										X
Urine sample collection[3]		X				X			X		X	X	X
Blood sample collection[3]		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

used to estimate incremental costs, recurrence avoided and QALYs and incremental cost per recurrence avoided and incremental costs per QALY.

An economic model will be developed to estimate relative rates of cost-effectiveness and cost-utility, at three years (to mirror the within trial analysis) and over a patient lifetime time horizon. An NHS perspective will be taken for the cost calculations. The model takes the form of a Markov state transition model that describes the consequences of different diagnosis and treatment strategies in terms of clinical and cost outcomes [6]. The rates of recurrence and progression recorded with the 3-year follow-up of the trial will be used to model short-term recurrence and progression rates. Further data required for the model relates to the transition and other probabilities of events beyond the 3 year follow-up, including the risk of recurrence and progression, probabilities of receiving different types of intervention should progression or recurrences occur, and risks of mortality (both from bladder cancer and other causes), will be sought through a structured systematic review of long-term outcomes of treatments of bladder cancer. The model will be used to produce estimates of costs, QALYs, recurrence rates and survival. Both costs and outcomes will be discounted at 3.5% in the base case analyses. Cost-effectiveness will be reported as incremental cost per QALY gained and incremental cost per recurrence avoided (at both 3 years and over the patient's lifetime). These data will be presented as point estimates and bootstrapping techniques will be used to estimate the statistical imprecision surrounding them. The results of this stochastic analysis will be presented as cost and QALY plots and as cost-effectiveness acceptability curves. Further deterministic sensitivity analyses will be conducted to explore other forms of uncertainty e.g. surrounding the choice of discount rate or around the unit costs of

equipment. The model will be probabilistic and distributions will be attached to all parameters, the shape and type of distribution will depend upon the data available and recommendations for good practice in modelling [17].

2.10. Patient and Public Involvement

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

3. PHOTO-Translational side study

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

Discussion

Bladder cancer is the most frequent urothelial cancer and the overall costs for treatment and follow-up remain higher than most other cancers [18]. Achieving complete resection of NMIBC with TURBT is associated with lower recurrence rates

in follow-up. However, it is unclear if this translates into lower progression rates in long-term follow-up. PDD guided initial TURBT is a technology that could improve resection and ultimately reduce recurrence and the need for further treatments. Studies on PDD have demonstrated the efficacy of the technology using strict study entry requirements, for which translation into daily clinical practice is limited. Therefore, in the PHOTO trial the effectiveness of the technology as part of routine care will be demonstrated with a pragmatic clinical trial design.

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

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

Evidence suggests that 20 cases are required for PDD naïve surgeons to gain competency the technology. This could act as a potential confounder on the clinical outcomes measured and therefore will be accounted for during analysis. Moreover,

the evidence is gained from small number studies and an evaluation of the learning curve of PDD will also be carried out.

The primary outcome of the study is time to recurrence measured from the day of randomisation to the day of subsequent biopsy with pathologically proven recurrence. If decrease in time to recurrence is associated with long term patient benefits the cost-effectiveness evaluation will provide further evidence for the NHS to decide on full adoption of the technology.

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

Funding acknowledgement

This project was funded by the NIHR HTA (project number 11/142/02)

Department of Health disclaimer

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

The PHOTO trial is sponsored by Newcastle upon Tyne Hospitals NHS Foundation Trust.

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:

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

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

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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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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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6. Figure Legends:

Figure 1: Tumour, Node, Metastasis (TNM) system of bladder cancer [2]

Figure 2: PHOTO trial study design summary

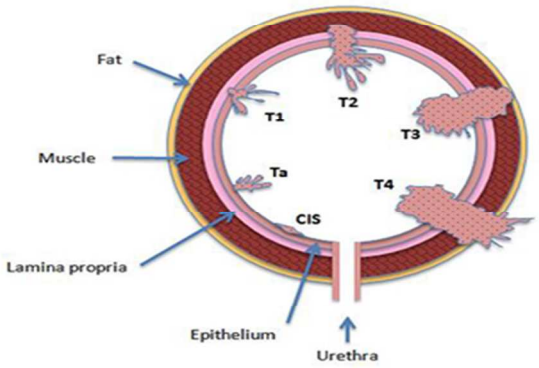

Figure 1: Tumour, Node, Metastasis (TNM) system of bladder cancer [2]

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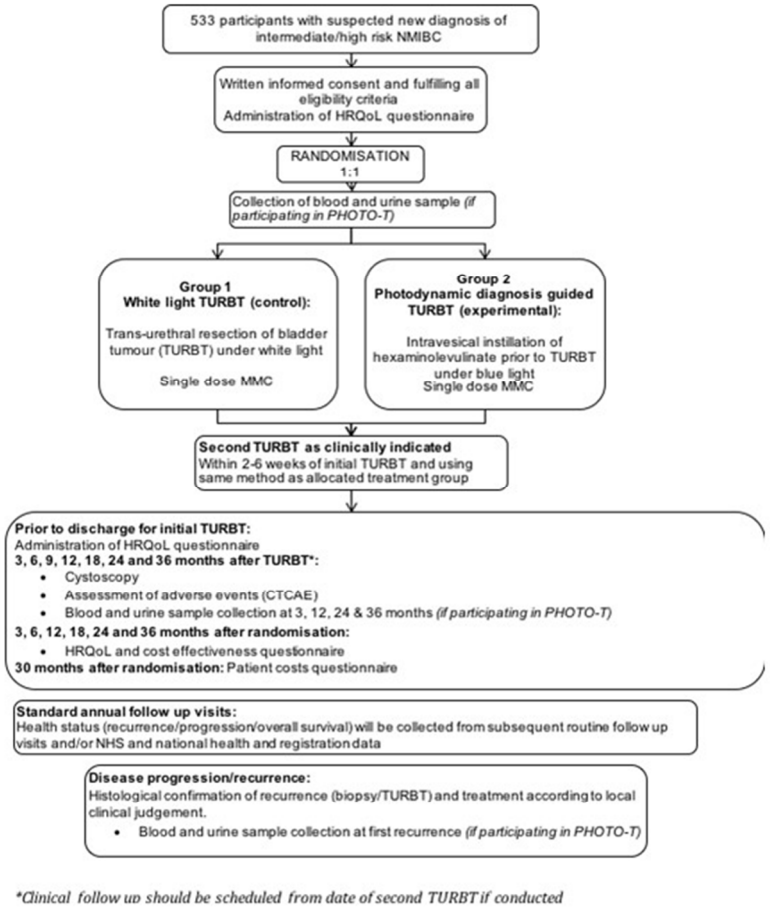

Figure 2: PHOTO trial study design summary

190x200mm (96 x 96 DPI)

Acknowledgement:

We would like to acknowledge the valuable support of the 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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PHOTO TMG members: Trial management, data collection and final approval of the version to be published

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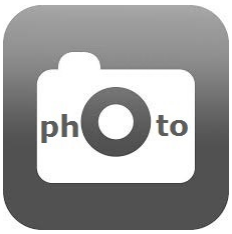
APPENDIX-I: NICR PHOTO-T study

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.



The PHOTO Trial

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

Version 1.0

16/06/2014

Funding: National Institute for Health Research

Sponsor: The Newcastle upon Tyne Hospitals NHS Foundation Trust

Protocol code: ICR-CTSU/2014/10045

REC Reference:

ISRCTN:

The Newcastle upon Tyne Hospitals NHS Foundation Trust

Newcastle University

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University of Aberdeen

PHOTO protocol

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ICR-CTSU (a UKCRC registered and NCRI accredited clinical trials unit) and CHaRT (a UKCRC registered clinical trials unit) are responsible for the central coordination of the trial on behalf of the sponsor.

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Andrew Johnston (On behalf of sponsor)		Xx/xx/2014

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CONTENTS

1 Glossary

5-ALA	5-aminolaevulinic acid
AE	Adverse Event
AJCC	American Joint Committee on Cancer
BCG	Bacillus Calmette-Guérin
BOXIT	A randomised phase III placebo-controlled trial evaluating the addition of celecoxib to standard treatment of transitional cell carcinoma of the bladder
CEA	Cost Effectiveness Analysis
CEVR	Centre for the Evaluation of Value and Risk in Health
CHaRT	Centre for Healthcare Randomised Trials (CHaRT), University of Aberdeen
CIS	Carcinoma In Situ
CT	Computerized Tomography
DMC	Data Monitoring Committee
EAU	European Association of Urology
EORTC	European Organisation for Research and Treatment of Cancer
GP	General Practitioner
HAL	Hexaminolevulinate
HRQoL	Health related quality of life
HTA	Health Technology Assessment
ICR-CTSU	Clinical Trials and Statistics Unit at The Institute of Cancer Research, London
MIBC	Muscle invasive bladder cancer
MMC	Mitomycin C
NCIN	National Cancer Intelligence Network
NHS	National Health System
NIHR	National Institute of Health Research
NMIBC	Non-muscle invasive bladder cancer
PDD	Photodynamic diagnosis
PIS	Patient Information Sheet
QALY	Quality Adjusted Life Year
RCT	Randomised controlled trial
TURT	Transurethral resection
UICC	International Union Against Cancer
USS	Ultrasound Scan

PHOTO protocol

2 Trial Summary

Short title:	Photodynamic guided treatment for bladder cancer
Chief Investigator:	Mr Rakesh Heer
Sponsor:	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder:	NIHR
Study design:	Patient randomised controlled, non-masked parallel group study.
Target study population:	New diagnoses of IR and HR NMIBC based on visual characteristics

Study Intervention: Participants in the experimental arm will undergo instillation of photosensitiser (hexaminolevulinate) into the bladder through a urethral catheter for 1 hour followed by cystoscopic resection of bladder tumour using Photodynamic diagnosis (PDD) under blue light. The control group of patients will undergo standard white light tumour resection. In addition, some patients may undergo a second resection 2 to 6 weeks after the initial resection, which is a part of the initial treatment. Apart from initial treatment, both groups will receive usual care, including single dose intravesical mitomycin C (MMC), re-resection as indicated and surveillance and adjuvant therapy according to standard clinical practice [1].

Primary objectives:	(1) Clinical effectiveness: compare time to recurrence, for each of the two treatment strategies, with a principal point of interest at 3 years. (2) Cost-effectiveness: Evaluate cost-effectiveness by the incremental cost for recurrence avoided and cost-utility as the incremental cost per quality-adjusted life year (QALY) gained at three years.
Secondary objectives:	(1) Clinical effectiveness: (a) Measure relative rate of disease progression at 3 years, (b) measure relative harms and safety, (c) measure Health Related Quality of Life (HRQoL) and cancer specific survival. (2) Economic evaluation: Model costs and health state changes over a patient lifetime to estimate the incremental cost per recurrence avoided, costs to the NHS, and incremental cost per QALY. (3) (a) Model the safest and most cost-effective cystoscopic follow-up surveillance schedule; (b) Evaluate the learning curve for the procedure and account for its effects on outcomes of both PDD-guided and standard white light resections; (c) Establish a well-characterised cohort of patients with intermediate and high-risk non-muscle invasive bladder cancer (NMIBC) including clinical data, urine, blood and tumour specimens that would be available for separately funded research of basic science and translational studies.

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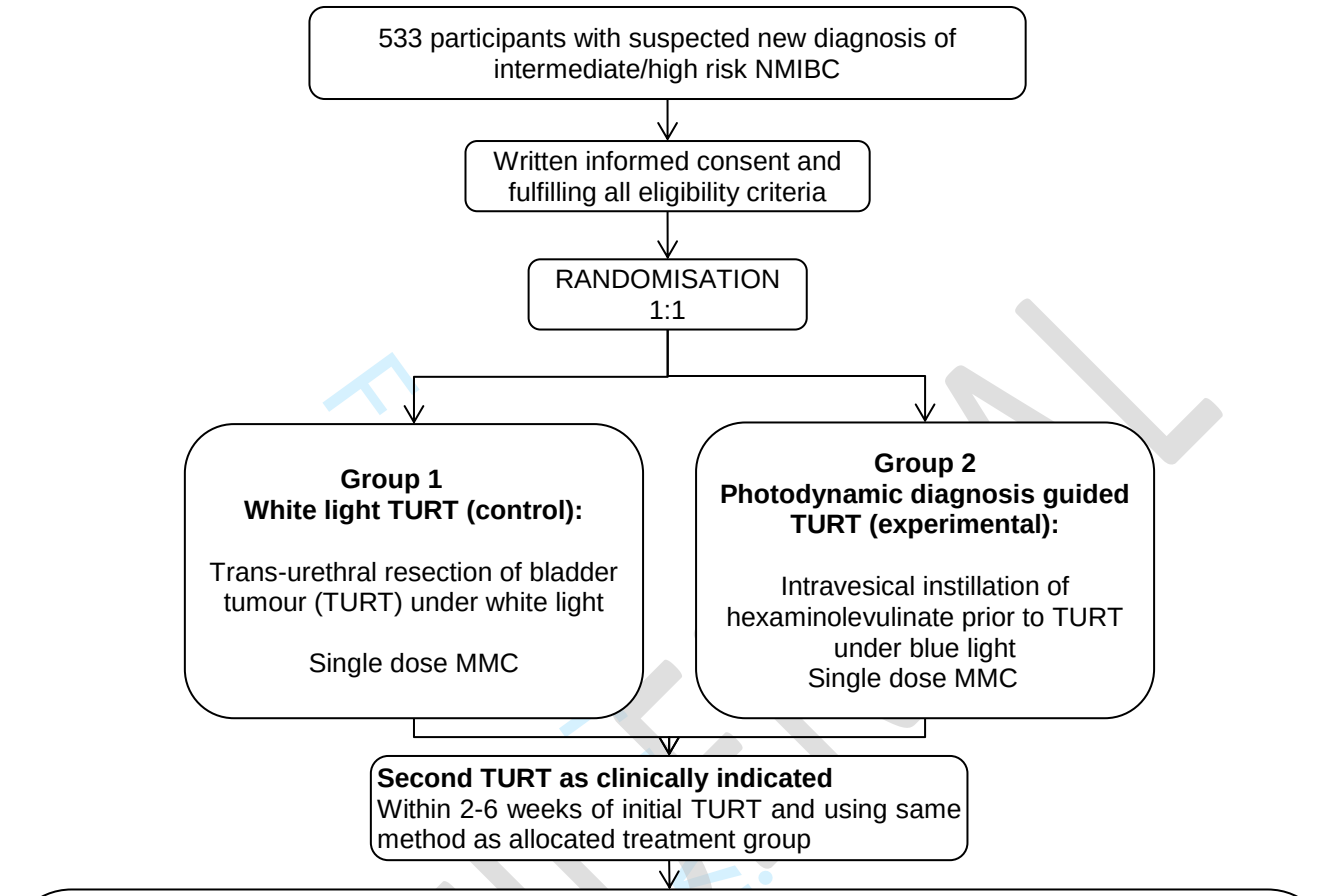
Trial Schema:



Prior to discharge for initial TURT:
Administration of HRQoL questionnaire
3, 6, 12, 18, 24 and 36 months after TURT*:

- Cystoscopy
- Assessment of adverse events (CTCAE)
- Urine sample collection (if participating in PHOTO), (not at 9 month visit)
- Blood sample collection (if participating in PHOTO-T) , (not at 9 month visit)

3, 6, 12, 18, 24 and 36 months after randomisation:

- HRQoL and cost effectiveness questionnaire – administered by CHaRT

30 months after randomisation: Patient costs questionnaire – administered by CHaRT

Standard annual follow up visits:
Health status (recurrence/progression/overall survival) will be collected from subsequent routine follow up visits and/or NHS and national health and registration data

Disease progression/recurrence:
Treatment according to local clinical judgement.
At first recurrence, if participating in PHOTO-T, collection of:

- Fresh tumour and bladder tissue
- Urine sample collection
- Blood sample collection

**Clinical follow up should be scheduled from date of second TURT if conducted*

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3 Introduction

3.1 Bladder Cancer

3.1.1 Incidence of bladder cancer

Bladder cancer is the most frequently occurring tumour of the urinary system, with over 10,300 new cases diagnosed each year in the UK [2, 3]. Histologically over 90% of diagnoses are of the transitional cell carcinoma type. Bladder cancer is the fourth most common cancer in men and the eleventh most common in women [2, 3]. The mean age at diagnosis is 71, with 8 in 10 cases occurring in people aged 65 and older. Cigarette smoking is causally related to over a third of people with bladder cancer diagnosed in the UK and is also a risk factor for progression to cancer-related death [4, 5].

3.1.2 Histopathology of bladder cancer

The extent of bladder cancer spread is described using the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) Tumour, Node, Metastasis (TNM) staging system[6]. Tumours confined to the epithelial lining (urothelium) are classified as stage Ta and those invading the lamina propria are classified as stage T1 (figure 1). Ta and T1 tumours can be easily removed by transurethral resection, and therefore, are grouped together as non-muscle invasive bladder cancer (NMIBC) for therapeutic purposes. NMIBC also include flat, high-grade tumours that are confined to the epithelium classified as carcinoma in situ (CIS).

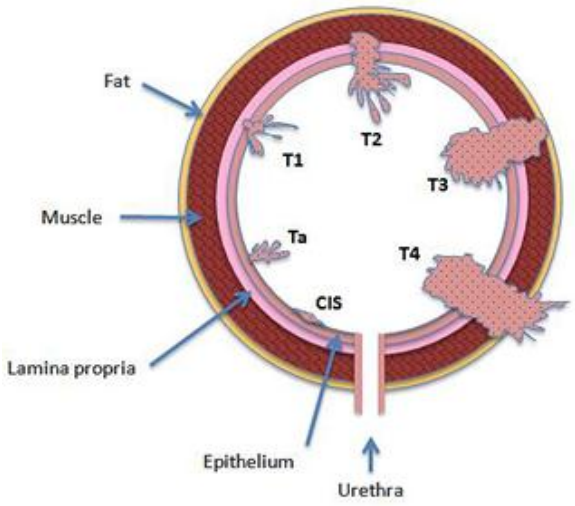

Figure 1, Classification of bladder tumours

3.1.3 Presentation and diagnosis of bladder cancer

The most common presentation of bladder cancer is haematuria, which may be associated with additional symptoms such as dysuria, increased frequency, urgency of urination, failed attempts to urinate or urinary tract infection. Haematuria is either visible or non-visible. Non-visible haematuria is detected by reagent stick (dipstix) or microscopic examinations, often included in standard primary care assessments for a well-person check or in the investigation of urinary symptoms. Bladder cancer is detected in approximately 10% of patients with visible haematuria and 3–5% of those with dipstix or microscopic haematuria aged over 40 years [7, 8]. Therefore, these patients are urgently referred for assessment in

rapid access haematuria clinics in secondary care, where bladder tumours are usually diagnosed visually by cystoscopy under local anaesthetic or, less frequently, on imaging by ultrasound scanning or computerised tomography (CT). Visual appearances of bladder cancer are then confirmed formally by histology from cystoscopic transurethral resection (TUR) under general anaesthetic.

3.1.4 Initial management of NMIBC

About 80% of people with a new diagnosis of bladder cancer will have NMIBC and will be initially treated by TURT. The subsequent goal in the management of NMIBC is the prevention of recurrence and progression to higher stage, life threatening, muscle invasive disease. 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 being overlooked or incompletely resected [9, 10]. Tumour seeding following resection and urothelium that may be genetically "primed" for new tumours developing (field change) are other factors that are considered relevant and will impact on recurrence rates independent of the completeness of resection. Recurrence and stage progression to muscle invasive or metastatic cancer is more likely to occur in those with high grade tumours with concomitant CIS. CIS in particular, which is a flat tumour, can be easily missed using conventional white light guided resection [11].

Incomplete resection during the initial TURT has been associated with staging errors. Understaging of T2 disease has been demonstrated in 5 to 27% of cases [1,12, 13]. In order to overcome the staging errors associated with the initial TURT a second resection within 2-6 weeks has been suggested in a select group of patients. It has also been noted that until new emerging techniques (e.g. PDD) are proved to be beneficial with further studies, re-staging TURT should be used to correct staging errors. The EAU guideline recommends a second TURT in the following cases [1]:

- if there was no muscle in the specimen after initial resection (with exception of Ta, LG/G1 tumours and primary CIS)
- in all T1 tumours
- in all high grade/G3 tumours, except primary CIS.

3.1.5 Risk of recurrence and stage progression

Both clinical and histological parameters can be used to estimate individual risk for recurrence and progression of NMIBC to muscle invasive bladder cancer (MIBC). Based on this, the European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary group has developed an algorithm that calculates probabilities for recurrence and progression, which are integral to the current European Association of Urology (EAU) practice guidelines [1, 14]. These probabilities are based on: number of tumours, tumour size, prior recurrence, histological T-stage, presence of CIS and tumour grade. At 3 years, the risks for recurrence and progression are summarised in Table 1 (http://www.eortc.be/tools/bladdercalculator). The EAU guideline cancer management plan is tailored to the risk categories in terms of intensity of follow up and use of adjuvant therapies.

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Table 1; EORTC bladder cancer recurrence and progression probability according to risk group stratification

Recurrence Risk Group (score)	Probability of recurrence at 3 years	Progression risk group (score)	Probability of progression at 3 years
Low risk (0)	25%	Low risk (0)	0.8%
Intermediate risk (1-9)	40-56%	Intermediate risk (2-6)	4%
High risk (10-17)	75%	High risk (7-23)	11-30%

3.1.6 Current strategies to reduce recurrence and progression of bladder cancer

High quality resection: A high-quality TURT aims to completely eradicate Ta-T1 tumours and to accurately stage disease at first presentation. The high variability recorded in 3-month recurrence rates between centres indicates that TURT can often be incomplete in up to 20% of cases [15, 16]. Training and technology to improve completeness of resection are thought to be one of the most important modifiable factors in reducing recurrence [17].

Adjuvant therapy: A meta-analysis of seven randomised trials showed that a single instillation of chemotherapy (mitomycin C (MMC), epirubicin, or doxorubicin) leads to a decrease of 39% in the odds of recurrence (OR 0.61; 95% CI:0.49-0.75, p <0.0001;) [18]. For patients with intermediate risk disease, additional courses of either intravesical chemotherapy or intravesical immunotherapy with Bacillus Calmette-Guérin (BCG) for a minimum of one year is advised [15, 18-20]. However use of BCG, with its greater toxicity profile than that associated with MMC, tends to be reserved for those at high risk of progression. A randomised controlled trial (RCT) published in 2013 showed that 3 year maintenance BCG instillations reduce the risk of recurrence compared with 1 year regimens in high risk patients, however not all patients are able to tolerate this treatment for this duration [21]. In some instances, immediate cystectomy is recommended depending on high risk factors and patient preference [1]. Intravesical adjuvant therapies are associated with treatment morbidity, affecting quality of life, and associated costs [22].

Surveillance: Frequent cystoscopic follow up is advised to detect recurrence early and allow treatment before progression. This is tailored according to the risk groups with patients with high risk tumours recommended to have cystoscopy and urine cytology at three months. If negative, it is repeated every three months for two years, every four months in the third year, then every six months in the fourth and fifth years, and annually thereafter [23].

3.2 Photodynamic Diagnosis

3.2.1 Mechanism

Photodynamic diagnosis (PDD) can enhance tumour detection during the initial cystoscopic diagnosis and TURT treatment of bladder cancer [11]. PDD utilises photosensitising agents with a high selectivity for accumulation within tumour cells. When the photosensitiser is excited at a specific wavelength, it re-emits light at a different wavelength for detection [24]. Photosensitising agents that can be administered intravesically include 5-aminolaevulinic acid (5-ALA), hexaminolevulinate (HAL) and hypericin. Esterification of 5-ALA to HAL results in a more rapid cellular uptake and subsequently a brighter fluorescence of the cancer is seen [25]. The HAL product Hexvix® (PhotoCure, Norway) is the only agent for NMIBC PDD licensed in the European Union (marketed through Ipsen, France) and United States (as Cysview™).

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3.2.2 Diagnostic accuracy

A recent systematic review suggested that PDD offered greater diagnostic accuracy in detecting NMIBC compared with conventional white light cystoscopy, based on a total of 27 studies enrolling 2949 participants [11]. The pooled estimates (95% CI) for patient-level analysis comparing PDD against white light showed increased diagnostic sensitivity from 71% (49 - 93%) to 92% (80-100%), but decreased specificity from 72% (47- 96%) to 57% (36% - 79%). In particular, there was better performance in detecting higher-risk disease (intermediate and high risk) using PDD over white light diagnosis, which included diagnosis of CIS which could otherwise be easily missed (sensitivity 83 % (41 - 100%) vs. 32% (0% - 83%)). This work also suggested that PDD-guided treatment was no better than white light for patients with low risk disease.

3.2.3 Clinical outcomes

Based on data from four studies, the systematic review concluded that improved diagnostic accuracy with PDD translated into a reduced recurrence rate [11]. Compared with white light-guided TURT, the use of PDD guided TURT was associated with fewer tumours at three months follow up with a relative risk (95% CI) of 0.37 (0.20–0.69).

The benefit of PDD-guided resection in reducing tumour recurrence in the longer term (12-24 months) was less clear, with effect estimates favouring PDD but without statistical significance. There is therefore still uncertainty around any potential longer term patient benefit for PDD, particularly when applied to routine care in a pragmatic NHS setting.

PDD treatment using HAL is regarded as a safe procedure. Following intravesical administration of HAL no systemic side effects have been reported [26-28]. In general, there is no difference in the rates of adverse events between PDD-guided treatment and white light cystoscopy alone [29-32].

3.2.4 Learning curve

Evidence suggests that as few as 20 cases are required for surgeons to become competent in use of PDD [33]. However, these preliminary data are based on small numbers and better characterisation of learning curve is required. In addition, anecdotal accounts from experts (UK PDD users group) describe that the adoption and use of PDD results in a “bystander” effect of improving standard white light resection. This is thought to occur because the surgeon inherently starts to appreciate more subtle white light visual characteristics in keeping with cancer through repeated rounds of feedback from the photodynamic mapping; however, this is a potential phenomenon that has not been evaluated. If the potential bystander effect of photodynamic resection improving white light resection is a real phenomenon, then there may be a significant role for this technology to play in better training the general urology surgeon in acquiring more effective competencies in white light resection.

3.2.5 Evaluations of potential health economic impact of PDD:

The recent systematic review and meta-analysis included economic modelling of cost-effectiveness of PDD, the performance of biomarkers (FISH, ImmunoCyt and NMP22) and cytology [11]. Although the differences in outcomes and costs between different detection methods appeared to be modest, the decision about which strategy to adopt depended upon society’s willingness to pay for additional gain. The NIHR Health Technology Assessment (HTA) was unable to undertake a cost-utility analysis due to the lack of relevant health utility

data and therefore, although strategies that replaced white light with PDD resulted in a gain in life years, it was unclear whether this justified the extra costs [11]. To address this, more details on the long term outcomes of clinical effectiveness; HRQoL data (as QALYs) and a full assessment of all treatment costs are required to better inform this analysis and will be undertaken in this study.

3.3 Efficacy of PDD guided bladder cancer treatment and need for an effectiveness study

Meta-analyses and systematic reviews of PDD guided treatment of NMIBC have shown efficacy in tumour detection and reduction in residual tumour compared with white light cystoscopy alone. These findings translate into reduced recurrence rates [11, 29]. However, all these studies are an evaluation made by strict study criteria which do not allow an interpretation into daily clinical practice. The missing information on effectiveness of use in routine care of PDD guided treatment will be sought in this study.

3.4 Study rationale

3.4.1 Health need

Although many NMIBCs are readily treatable with cystoscopic resection it remains 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 during 2001–02 in the United Kingdom was £64 million [11, 34]. 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 [35]. Substantial effects on HRQoL are most likely to come from adjuvant intravesical treatments and radical or palliative treatments for progression [36]. More efficient management strategies to reduce NMIBC recurrence and hence decrease both the burden to patients and costs to the NHS are urgently needed.

3.4.2 Expressed need

The recent NIHR HTA evidence synthesis, calling for a large RCT assessing outcome in the longer term across multiple sites in the NHS setting, outlined an opportunity to model surveillance and to consider a role for exploring additional biomarkers for detection of recurrence [11].

3.4.3 Sustained interest and intent

Bladder cancer is a high priority area for research into clinical and cost-effective management and the findings from the PHOTO trial are likely to remain highly relevant and important to the needs of the NHS over the next 20 years, the expected life span of the equipment for the PDD technology. A further compelling reason for the study is the current piecemeal adoption of PDD within the NHS, resulting in variation in provision of PDD service. This gives further urgent need for better quality evidence to guide providers of bladder cancer services and the relevant practice guidance authorities to make early decisions around wholesale adoption or disinvestment in PDD technology.

3.4.4 Capacity to generate new knowledge

The PDD HTA evidence synthesis found uncertainty regarding cost-effectiveness and the benefit of PDD-guided resection in the longer term that cannot be resolved by the existing body of research [11]. Specifically, the evidence synthesis was unable to undertake a cost-utility analysis due to the lack of relevant health utility data; and the modelling of longer term clinical trajectory and health economic consequences of wider use of PDD performed for this review was limited by this inadequate data. The PHOTO trial plans to acquire appropriate medium-term HRQoL data, as captured by QALYs, to allow overall health benefit to be measured in terms of both clinical and cost-effectiveness. The trial will also provide new information on the learning curve for the technology, optimum surveillance frequency, and establish a biobank to test assays for detection of recurrent disease.

4 Objectives

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 worthwhile for the NHS

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 modelling studies to investigate safe monitoring frequency.

4.1 Primary objectives

4.1.1 Clinical effectiveness

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

4.1.2 Cost-effectiveness

To evaluate cost-effectiveness by the incremental cost for recurrence avoided (incremental cost-effectiveness ratio) and cost-utility as the incremental cost per quality-adjusted life year (QALY) gained at three years.

4.2 Secondary objectives

4.2.1 Clinical effectiveness

(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.

4.2.2 Economic evaluation

To model costs and health state changes over a patient lifetime to estimate the incremental cost per recurrence avoided, costs to the NHS, and incremental cost per QALY

4.3 Additional objectives

(a) To model the safest and most cost-effective cystoscopic follow-up surveillance schedule;

(b) To evaluate the learning curve for the procedure and account for its effects on outcomes of both PDD-guided and standard white light resections;

(c) To establish a well-characterised cohort of patients with intermediate and high-risk NMIBC including clinical data, urine, blood and tumour specimens for separately funded genotypic and phenotypic studies.

5 Study Design

PHOTO is a multi-centre randomised open parallel group non-masked superiority trial comparing the intervention of PDD guided bladder tumour resection with standard white light resection in patients with newly diagnosed intermediate and high risk NMIBC. Apart from initial treatment (initial TURT with or without second TURT), both groups will receive standard care, including single dose intravesical mitomycin C within 24 hours of initial resection, surveillance according to risk-adjusted schedules and adjuvant therapy as indicated by current practice guidelines. The target number of patients to be recruited is 533 with a trial specific follow up of at least 36 months for each individual.

5.1 Primary outcome measures

5.1.1 Clinical effectiveness

Time to recurrence will be measured as time from randomisation to first recurrence.

5.1.2 Cost-effectiveness

Cost-effectiveness will be calculated from comparison of the healthcare, personal and societal costs incurred for each resection strategy with respect to reduction of recurrence and quality adjusted life years (QALYs) derived from health related quality of life (HRQoL) measures over the three years.

5.2 Secondary outcome measures

5.2.1 Clinical effectiveness

5.2.1.1 Safety and complications

Adverse events and complications during the duration of the study will be included in descriptive analyses.

5.2.1.2 HRQoL

Will be compared at three years. Subsequently, these outcomes will be modelled over a patient lifetime time horizon, using trial and other data.

5.2.1.3 Disease progression

Will be compared at three years. Given the expected rarity of disease progression in this cohort during the formal study period, modelling will be undertaken at three years using trial and other published data, and will include a projection over the patient lifetime (15-20 years).

5.2.1.4 Overall survival and bladder cancer specific survival

We will compare the two randomised groups for all causes mortality at the time of the analysis of the primary outcome (minimum follow up 3 years, maximum expected follow up 66 months).

5.2.2 Cost-effectiveness

We will model costs and health state changes over a patient lifetime to estimate the incremental cost per recurrence avoided, QALYs and costs to the NHS. This will be based

on the updated version of the existing NIHR HTA economic model using three year data from within the trial and other longer term published data.

5.3 Additional outcome measures

5.3.1 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.

5.3.2 The effect of PDD 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.

6 Participants

The population to be studied will be adult patients with a suspected new diagnosis of intermediate or high risk NMIBC. Participants will be identified prior to initial resection based on results of preliminary visual assessment via cystoscopy or imaging performed as part of a standard evaluation for suspected urinary tract malignancy in NHS rapid-access haematuria clinics or equivalent.

6.1 Inclusion criteria

1) Adult men and women aged ≥ 16 years
2) First suspected diagnosis of bladder cancer
3) Visual/ultrasound/CT diagnosis of intermediate/high risk NMIBC:
   a) White light visual appearances of intermediate or high risk disease (> 3cm, two or more tumours, or flat velvety erythematous changes alerting a clinical suspicion of CIS).
   b) Suspicion of papillary bladder tumour > 3cm based on ultrasound or computerized tomography (CT) scanning (without hydronephrosis)
4) Written informed consent for participation prior to any study specific procedures
5) Willing to comply with life style guidelines

6.2 Exclusion criteria

1) Visual evidence of low risk NMIBC (solitary tumour < 3cm)
2) Visual evidence of MIBC on preliminary cystoscopy, i.e. non-papillary or sessile mass (attached directly by its base without a stalk)
3) Imaging evidence of MIBC – CT/USS (this includes the presence of hydronephrosis, which may be present despite clear imaging of MIBC in the bladder)
4) Upper tract (kidney or ureteric) tumours on imaging
5) 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)
6) Evidence of metastases

7) Porphyria or known hypersensitivity to porphyrins
8) Known pregnancy (based on history and without formal testing, in keeping with day-to-day NHS practice of PDD use)
9) Any other conditions that in the Principal Investigator's opinion would contraindicate protocol treatment
10) Unable to provide informed consent
11) Unable or unwilling to complete follow up schedule (including questionnaires)

6.3 Eligibility criteria for study centres

Centres must have or be willing to obtain PDD equipment to be eligible for the study. To ensure expeditious trial completion sites with a good recruitment record in NMIBC according to the NIHR Cancer Research Network (NCRN) portfolio study database will be preferentially enrolled.

6.4 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.

7 Screening, Recruitment and Consent

7.1 Identification of participants

Potential participants will mainly be identified through rapid access haematuria clinics at participating sites. An eligibility checklist should be 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 should be used to assess eligibility.

Initial identification of potential participants must occur within the national cancer target framework of 62 days from general practitioner (GP) referral to treatment, prior to baseline randomisation.

7.2 Screening log

All participating sites will be required to keep a log, based on review at multidisciplinary team (MDT), of all patients with first visual diagnosis of intermediate or high risk (IR/HR) NMIBC on cystoscopy who are potentially eligible for this study. This log should be submitted to ICR-CTSU on request. The information collected will include:

- Date patient identified
- Screening outcome (patient approached/accepted participation/declined participation)
- Reasons for not approaching / declining participation (if available)

- Trial ID (if applicable)

This information will be used by the PHOTO Trial Management Group to monitor recruitment activity. No patient identifiable data should be sent to ICR-CTSU.

7.3 Procedure for obtaining informed consent

The Principal Investigator (or designated individual) must ensure that each trial patient is fully informed about the nature and objectives of the trial and the possible risks associated with participation. Participants should be given the current NHS Research Ethics Committee (REC) approved PHOTO patient information sheet (PIS) for their consideration. Patients should only be asked to consent to the study after they have had sufficient time to consider the trial and the opportunity to ask any further questions.

No protocol required assessments should be conducted until the PHOTO consent form has been signed and dated by both the patient and the Investigator, unless they are performed routinely as part of standard patient care.

Patients who consent to PHOTO will be asked to consent to participate in the PHOTO sub-studies. If participants express an interest to withdraw from the sub-studies then this will not result in ineligibility to participate in the main clinical trial and will not impact the medical care received.

Confirmation of the patient's consent and the informed consent process must be documented in the patient's medical notes. A copy of the signed consent form should be provided to the patient and the original retained in the investigator site file, which must be available for verification by ICR-CTSU/CHaRT study staff. The right to refuse to participate without giving reasons will be respected.

7.4 Participation in other clinical trials

Patients who fulfil the eligibility criteria will be given the opportunity to participate in PHOTO even if they have participated in other clinical trials prior to recruitment.

Participation in other clinical trials whilst participating in PHOTO will be considered on a trial by trial basis by the PHOTO Trial Management Group.

8 Randomisation

Randomisation will be undertaken centrally 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 will incorporate a random element in order to prevent deterministic treatment allocation.

The Principal Investigator (PI) or individual with delegated authority will perform the randomisation. After checking the patient eligibility, initials and gender will be entered into the web-based system, which will return the allocation status.

To protect against bias in the pre-treatment assessment of HRQoL, participants should not be informed of their allocated treatment group following randomisation but may be informed at the time of surgery if they ask. It may also become apparent because of the need for catheterisation prior to PDD resection.

Each centre will have a unique ID for the telephone service which will identify both the trial and the centre thus ensuring correct allocation of study number for the participant. The secure trial website will be accessed via password protected logins with appropriate role based permissions. Further details can be found in the Operating Manuals.

9 Trial Treatment

9.1 Health technologies being assessed

The interventions being compared within PHOTO are:

(1) Photo dynamic diagnosis (PDD) guided trans-urethral resection (TURT) (experimental group) vs;

(2) Standard white light TURT (control group)

9.1.1 PDD guided TURT of bladder tumour:

The experimental technology consists of the 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 should be instructed 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 should undergo TUR 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 should appear blue whilst red areas should be considered suspicious and should be resected.

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

9.1.2 Standard white light (Control)

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

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

9.2 Supportive care and concomitant therapy

Supportive care should be given in accordance with local clinical practice. Any medication considered necessary for the participants' welfare and which is not expected to interfere with the study interventions may be given at the discretion of the investigator.

All supportive care and concomitant medication must be recorded in the participant's notes, as well as the appropriate section of the Case Report Form (CRF). There are no investigational medicinal products within PHOTO and any supportive medication or contrast

agents should be prescribed by the investigator and dispensed from hospital stock for the duration of the trial.

9.3 Second resection

In accordance with the EAU guidelines, a second TURT is recommended in the following situations:

- After incomplete initial TURT;
- If there was no muscle in the specimen after initial resection (with exception of Ta G1 tumours and primary CIS);
- In all T1 tumours;
- In all G3 tumours, except primary CIS.

If required, the second resection should take place using the same method (PDD guidance or white light) as the participant's trial treatment allocation. Second TURT should ideally take place 2-6 weeks after initial TURT. The procedure should include resection of the primary tumour site.

9.4 Adjuvant therapy

Adjuvant therapy should be prescribed according to local clinical judgement in accordance with participant characteristics and EAU guidelines.

10 Trial Assessments

10.1 Screening assessments

Routine attendances for diagnosis and staging of new incidence of bladder cancer should be used to establish eligibility. These should include:

- Medical history

10.2 Pre-treatment assessments

The following assessments should be conducted prior to primary TURT

- Administration of HRQoL questionnaire
- Urine sample collection (if participating in PHOTO-T)
- Blood sample collection (if participating in PHOTO-T)

10.3 Prior to discharge

- Administration of HRQoL questionnaire

10.4 Post-treatment follow-up

Patients should be followed up following TURT according to standard practice. Data will be collected from the following routine visits.

10.4.1 3, 6, 12, 18, 24 and 36 months post treatment (initial or second TURT, if required)

- Cystoscopy

- Assessment of adverse events (CTCAE, (Clavien Dindo grading [37] at 3 months only))
- Urine sample collection if participant consented to PHOTO-T at 3, 12, 24 and 36 months
- Blood sample collection if participant consented to PHOTO-T at 3, 12, 24 and 36 months

Sample collection procedures are detailed in Appendix 1.

10.4.2 3, 6, 12, 18, 24 and 36 months post randomisation

- Administration of HRQoL and health service utilisation questionnaire (sent directly to the participant by CHaRT)

10.4.3 30 months post randomisation

- Patient Costs questionnaire (sent directly to participant by CHaRT)

10.5 Procedure at disease progression/recurrence

Participants should be treated according to local clinical judgement at disease progression/recurrence. If participating in PHOTO-T the following samples should be collected at first recurrence:

- Fresh tumour and bladder tissue
- Urine sample collection
- Blood sample collection

10.6 Discontinuation from follow-up or withdrawal from trial

Participants have the right to withdraw from the study at any time for any reason, and without giving a reason. If a participant withdraws from the trial a change of status form should be submitted stating whether the participant has withdrawn consent for information to be sent to CHaRT or whether they simply no longer wish to attend trial follow up visits.

Consent will be sought from participants at study entry for collection of data captured as part of routine clinical practice and to retain data already collected should they chose to withdraw at any stage from all or part of the follow up schedule.

PHOTO protocol

10.7 Schedule of investigations/assessments conducted at centres

Visit/Assessment	Pre- randomisation screening	Pre-treatment	TURT	Prior to discharge	Second TURT (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	thereafter	At disease recurrence/progression
Visual diagnosis of IR/HR NMIBC	X												According to EAU guidelines	Treatment according to local practice
Medical history	X													
HRQoL questionnaire[1]		X		X										
TURT according to treatment allocation with post treatment MMC instillation			X											
Second TURT according to treatment allocation					X									
Assessment of adverse events (CTCAE & Clavien Dindo[2])						X	X		X	X	X	X		
Cystoscopy						X	X	X	X	X	X	X		
Collection of fresh tumour and bladder tissue[3]			X											X
Urine and blood sample collection[3]		X				X			X		X	X		X

Footnotes

1. EORTC QLQ-C30 & NMIBC24, EQ-5D; subsequent questionnaires administered by CHaRT
2. Clavien Dindo assessment at 3 months only
3. If patient consented to participation in PHOTO-T

10.8 Data processing

Clinical data will be entered into the database via the secure trial website by the local investigator or delegate for each hospital site, together with data from questionnaires completed at clinic. Staff at CHaRT and ICR-CTSU will work closely with site staff to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

Follow-up questionnaires to participants will be sent from and returned to CHaRT. Questionnaires and up to two reminders will be sent to participants by post, email or phone, taking into account any preferences they may have for mode of communication, at 3, 6, 12,

18, 24, 30 and 36 months post randomisation. Participant identifiable data will be required to administer these questionnaires. These data will be encrypted and will only be available to trials unit staff who require access. Participants will be identified on case report forms and the database by a unique study identifier.

11 Adverse Event Reporting

11.1 Definitions

Adverse Event (AE): Any untoward medical event affecting a clinical trial participant.

Related AE: Any untoward medical event that has a reasonable causal relationship to PDD-guided TURT, standard white light TURT or the intravesical MMC.

Unexpected AE: An AE that is not listed in the study protocol as an expected occurrence in the circumstances of this trial.

Serious Adverse Event (SAE): an untoward occurrence that:

- Results in death
- Is life-threatening (refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the investigator

Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE. Complications occurring during such hospitalisation will be AEs or SAEs as appropriate.

11.2 Expected AEs

In this trial the following events, including common and rare, are potentially expected:

- Bladder discomfort/pain
- Haematuria
- Postoperative dysuria
- Bleeding resulting in clot retention
- Urinary retention
- Bladder perforation
- Urinary tract infection
- Skin rash
- Nausea
- Diarrhoea
- Vomiting
- Constipation

- Urinary frequency
- Fever
- Increase in white blood cell count
- Increased level of bilirubin
- Insomnia
- Headache
- Anaemia
- Gout
- DVT
- Prolonged catheterisation

11.3 Protocol specifications

For purposes of this protocol:

- SAEs that are classified as related and unexpected (i.e. not listed in 11.2 above) will be recorded and will require expedited reporting.
- Other related AEs will be captured through the CRF and participant questionnaires through the course of the study
- SAEs exclude routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- SAEs exclude elective or scheduled treatment for pre-existing conditions that did not worsen during the study.
- All confirmed and related AEs and SAEs must be recorded in the participant's medical notes.

11.4 Recording & Reporting Serious Adverse Events or Reactions:

Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the CHaRT trial manager in the first instance.

Adverse Event (AEs): Related, non-serious adverse events during study participation will be recorded on the study CRF or participant questionnaire. The individual investigator at each site will be responsible for managing all adverse events according to local practice.

Serious Adverse Event (SAEs): All related SAEs during study participation shall be recorded on the SAE form.

i). If the event is serious, related but potentially expected (listed in 11.2 above), a serious adverse event report form should be completed within seven days of the local investigator becoming aware. When the web-based form is completed, the trial office will be notified automatically.

ii). If the adverse event is serious, related and unexpected a serious adverse event report form should be completed within 24 hours of the local investigator being aware of the event. When the web-based form is completed, the Chief Investigator and the trial office will be notified automatically.

If the event is confirmed as being *serious* and *related* and *unexpected*, the CI or CHaRT trial manager will notify the sponsor within 24 hours of receiving the signed SAE notification.

The local PI will provide an assessment of the SAE. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up as soon as this becomes available. Relationship of the SAE to study procedures should be assessed by the investigator at site, as should the expected or unexpected nature of the AE.

CHaRT will report any related and unexpected SAEs to the main REC and the DMC within 15 days of the CI becoming aware of it. All related SAEs will be summarised and reported to the Ethics Committee, the Funder and the Trial Steering Committee in their regular progress reports.

Local investigators should report any SAEs as required by their local Research & Development Office.

12 Outcome Measures

12.1 Clinical effectiveness

12.1.1 Primary outcome:

Time to recurrence will be measured from the day of randomisation to the day of subsequent biopsy with pathologically proven recurrence. Some participants will present with symptoms prior to scheduled follow up and will then require earlier cystoscopy; these events will also be identified and used to measure time to recurrence, costs and changes to HRQoL. Patients will be censored at death from any cause or date of last follow-up visit at end of study.

12.1.2 Secondary outcome measures

12.1.2.1 Disease progression

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

Associated comorbidity and mortality from adjuvant treatments (e.g. radical surgery, radical radiotherapy or palliative chemotherapy) will be captured by HRQoL and assessment of harms (see below).

12.1.2.2 Safety and complications

Direct surgically related harms after TUR will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0 framework (http://ctep.cancer.gov/) and Clavien-Dindo classification for surgical complications[37]. Harms will also impact HRQoL, and will be captured as described below.

12.1.2.3 HRQoL

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 questionnaire and the disease-specific EORTC QLQ-NMIBC24 questionnaire completed by the participant at baseline (prior to knowledge of treatment allocation), following surgery and at 3, 6, 12, 18, 24 and 36 months after randomisation.

The measurement of HRQoL scores around the time of the cystoscopic resection can be particularly dynamic due to an acute deterioration in health score associated with the invasive procedure followed by a typical rapid recovery [35, 38] and will be accounted for by completion of the HRQoL measurements before and after surgical episodes, which will also be able to capture increasing anxiety associated with worsening diagnosis of recurrence or progression.

12.1.2.4 Bladder cancer specific survival

The time to bladder cancer specific death will be analysed using a competing risks approach (based on the Fine & Gray model [39]). Death from other causes will be considered a competing risk in the Cox proportional hazards model instead of assuming non-informative censoring, which would seem inappropriate in this context.

12.1.3 Additional outcome measures

12.1.3.1 Effect of PDD 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.

12.2 Cost effectiveness

12.2.1 Primary outcome

A full assessment of directly incurred costs and resource use associated with each treatment strategy will be recorded for each participant.

These costs will include the use of equipment, photosensitiser, cost associated with instillation of photosensitiser theatre time, overheads, length of hospitalisation, outpatient consultations, laboratory costs (cytology and biopsy analyses), adjuvant intravesical treatments, symptom management associated with treatments, and cost of more intensive treatment for progression (e.g. neo-adjuvant chemotherapy and radical surgery or radical radiotherapy; palliative management; increased follow up and investigations).

Further information on participant costs and use of primary care will be captured using a participant completed questionnaire administered at 3, 6, 12, 18, 24 and 36 months. Costs for healthcare services will be obtained from standard sources such as NHS reference Healthcare Resource Group (HRG) tariffs and the British National Formulary, from relevant manufacturers and suppliers and directly from secondary care centres. For each participant, measures of resource-use will be combined with unit costs to provide cost for that participant. For each participant, responses to the EQ-5D will be converted into health state utilities using UK population tariffs and used to estimate QALYs using the area under the curve approach.

12.2.2 Secondary outcomes

The use of services both for surveillance and for subsequent treatment will be modelled. The costs of these events will be based upon the estimates derived from within the trial and, where necessary, by revising the existing estimates for longer term events that are unlikely to be observed over the 3 year follow-up of the trial.

The existing economic model presents results in terms of incremental cost per life-year gained as there were too few data on health utilities to convert the analysis into a cost-utility analysis [40]. PHOTO directly addresses this information gap as health state utilities will be elicited as part of the trial. The trial data will be the main source for the economic model but it will be supplemented by additional focused searches of the literature and health economic data bases (e.g. the Centre for the Evaluation of Value and Risk in Health (CEVR) Cost Effectiveness Analysis (CEA) Registry; https://research.tufts-nemc.org/cear4/) to identify utility estimates for events (principally those that may occur in the longer term such as radical cystectomy for bladder cancer).

12.2.3 Additional outcome measures

12.2.3.1 Schedules for follow up

The most safe and efficient surveillance regimen will be modelled using PHOTO trial data and, with the appropriate approvals, contemporary patient-level data from the BOXIT trial (n=472) [41] and other relevant datasets.

12.2.3.2 Effects of learning curve

The effect of photodynamic resection experience on differential clinical effectiveness and on standard resection effectiveness (bystander effect) will be assessed using subgroup analysis comparing recurrence rates over time using our published expertise in statistical evaluation of learning curves in surgical trials.

13 Statistical Considerations

All statistical methods and assumptions will be pre-specified in a comprehensive Statistical Analysis Plan which will be authored by the study statistician and agreed by the grant holders, and have the approval of the Trial Steering Committee and the independent Data Monitoring Committee, and be finalised before the database is closed down for the final analysis.

A single main analysis is planned when follow-up data to a minimum of three years are complete or when the required numbers of events have been observed (whichever is sooner). Unmasked interim analyses will be conducted for the DMC meeting as determined by their agreed terms of reference. The statistical analysis will be based on all randomised participants as randomised, irrespective of subsequent compliance with the treatment allocated (i.e. following the intention to treat principle).

Statistical significance will be at the 5% level ($2p<0.05$). Secondary outcomes will be analysed using the appropriate generalised linear models (such as a linear model (analysis of covariance) or a logistic model for binary data). Any pre-specified sub-group analyses will use stricter levels of statistical significance ($2p<0.01$). All participants will remain in their allocated group for analysis (intention to treat). Missing data statistical modelling techniques will be used to make use of outcome assessments prior to 3 years, and sensitivity analyses conducted to assess the robustness of the treatment estimates to these approaches.

There are currently no planned interim analyses for efficacy to be considered by the DMC. They will however at an agreed time early enough in the study to be useful, look at the emerging event rates to make sure that the pre-specified power of the study is likely to be

maintained. Full details of the DMC's remit and frequency of meetings will be agreed at their first meeting, before any unblinded data is seen.

13.1 Primary Measures

13.1.1 Clinical effectiveness

The primary endpoint of time to recurrence and other time to event endpoints will be analysed by the log-rank test and summarised by a hazard ratio (HR) with 95% confidence interval (CI). The principal time point of interest is 3 years; estimates of event rates will be calculated using the Kaplan-Meier method with the HR from a Cox model to estimate the CI for the difference. The Cox proportional hazard model will be used to adjust for the minimization covariate factors gender and centre (the latter via a random effects frailty model). A further model including known prognostic factors (smoking status, risk group, presence or absence of CIS and grade of surgeon (consultant vs. other)). The use of cumulative incidence curves for time to recurrence/progression will also be explored.

Preplanned secondary analyses will include sub-group analysis defined by centre and previous PDD experience (see 13.3 below). If data is missing to a sufficient extent, the reasons for missing data will be examined and imputation techniques will be considered.

13.1.2 Cost effectiveness

Data on costs and QALYs for each participant will be used to estimate mean cost and QALYs for each intervention group. As the time horizon of the trial is three years these data will be discounted at 3.5%[3]. The cost and QALY data will then be used to estimate incremental costs and QALYs and incremental costs per QALY.

13.2 Secondary measures

13.2.1 Clinical effectiveness

Relative rates of progression at three years: Relative risk of recurrence in the two groups will be estimated using statistical methods appropriate for censored time to event data as outlined above. As previously discussed predictive models of progression are required and described below.

Harms and safety: Crude rates of complication frequency within 30 days of surgery will be presented according to the Clavien-Dindo reporting system. Other reported harms (CTCAE) will be summarised by the proportions experiencing grade ≥3 AEs with comparisons made using chi-squared based tests or Fisher's exact test if expected cell frequencies are less than 5. In addition, methods for ordinal data will be used/considered.

HRQoL: Changes to HRQoL will be measured by EQ-5D and EORTC QLQ-NMIBC24. Standard measure specific algorithms will be used to derive scores from and handle missing data in HRQoL questionnaires. Treatment groups will be compared at individual time points and analyses to account for the longitudinal nature of the data, such as area under the curve (AUC) approach, will also be used.

13.2.2 Cost effectiveness

Predictive model based analysis: The model developed for a previous photodynamic HTA Technology Assessment Report (HTA 07/02/01) [40] will be used and developed to estimate

relative rates of cost-effectiveness and cost-utility, at three years (to mirror the within trial analysis) and over a patient lifetime time horizon.

The model takes the form of a Markov state transition model that describes the consequences of different diagnosis and treatment strategies in terms of clinical and cost outcomes[40]. Both costs and outcomes will be discounted at 3.5% in the base case analyses. Further data required for the model relates to the transition and other probabilities of events occurring over the lifetime of patients. These probabilities include the risk of recurrence and progression as well as probabilities of receiving different types of intervention should progression or recurrences occur. Also included are risks of mortality (both from bladder cancer and other causes). The rates of recurrence and progression recorded with the 3-year follow-up of the trial will be used to model short term recurrence and progression rates. For data beyond this timeframe, a structured systematic review of long-term outcomes of treatments of bladder cancer will help inform the model of rates of recurrences, progression, and use of additional therapies (including the EORTC dataset of 837 NMIBCs with a median follow-up of 9.2 years and a combined analysis of recurrence and progression in 2596 NMIBC from seven EORTC trials)[14, 42].

Estimates of mortality will come from an updated review of the literature that was conducted for the previous HTA report [40]. The model will be used to produce estimates of costs, QALYs, recurrence rates and survival. Cost-effectiveness will be reported as incremental cost per QALY gained and incremental cost per recurrence avoided (at both 3 years and over the patient's lifetime). These data will be presented as point estimates and bootstrapping techniques will be used to estimate the statistical imprecision surrounding them. The results of this stochastic analysis will be presented as cost and QALY plots and as cost-effectiveness acceptability curves. Further deterministic sensitivity analyses will be conducted to explore other forms of uncertainty e.g. surrounding the choice of discount rate or around the unit costs of equipment. The model will be probabilistic and distributions will be attached to all parameters, the shape and type of distribution will depend upon the data available and recommendations for good practice in modeling (http://www.nicedsu.org.uk/TSD%2013%20model%20parameters.pdf). Additional analyses of the model will be conducted to estimate the incremental cost per recurrence avoided at both a 3-year and a lifetime time horizon.

13.3 Additional measures

Schedules for follow up: Test strategies for surveillance for bladder cancer will be established using previously characterized relevant cohorts (BOXIT) and then validated using data produced from the PHOTO Trial. The new data itself from this study will further inform this model. The Spanish cancer organisation (CUETO) is evaluating the use of ultrasound in place of cystoscopy for surveillance and with the appropriate approvals these data could also be included in our models of safety and efficiency.

The effect of photodynamic resection experience (learning curve) on clinical effectiveness: We will assess the likely impact of a potential learning curve on the trial result. Based on results of the surgeon's questionnaire, each will be classified as PDD experienced or naïve (using a threshold of over 30 cases performed).

A subgroup analysis comparing outcomes from experienced and naïve surgeons, including specific PDD and white light resection related outcomes, will assess the likely maximum

effect of experience on outcome in an NHS setting. Early recurrence (12 weeks) will be used as a proxy of incomplete resection. The subsequent accruing experience of each surgeon will be captured using the Case Report Form. This allows each randomised participant to be positioned on an individual surgeon learning curve. We will employ multilevel modelling to assess possible trends in outcomes to characterize any changes over time across the trial centres and model any differences between PDD experienced and naïve surgeons. Such analyses will provide evidence on the bystander effect where surgeons inherently start to appreciate more subtle white light visual characteristics in keeping with cancer through repeated rounds of feedback from the photodynamic mapping

13.4 Sample size calculation

We aim to detect an absolute reduction in recurrence at three years of 12%; from 40% (weighted average for intermediate and high risk disease, based on recurrence data from EORTC tables) 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%. This represents a plausible estimate of the minimal clinically important difference in NMIBC that will be sufficient to change practice guidelines: for example, a meta-analysis showing one immediate instillation of chemotherapy after TURT significantly reduced recurrence rate compared to TURT alone by an absolute reduction of 11.7% (from 48.4% to 36.7%; a relative risk reduction of 24.2%) informed the European Association of Urology guidelines to describe this as standard of care [18, 23]. It also aligns a conservative approximation of the 37% relative reduction found on recent meta-analysis of RCTs of PDD outcomes in NMIBC.

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.

14 Trial Management and Oversight Arrangements

14.1 Trial offices

The Trial Offices are the Clinical Trials and Statistics Unit at the Institute of Cancer Research (ICR-CTSU) and the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit, University of Aberdeen.

The trial offices will provide day to day support for the clinical centres, with ICR-CTSU leading on trial management and CHaRT coordinating data management and statistics. The Trial Manager at ICR-CTSU, in collaboration with the Trial Manager at CHaRT, will take responsibility for the day to day transaction of trial activities. The Data co-ordinator at CHaRT will provide clerical support to the trial, including organising all aspects of the postal questionnaires (mailing, tracking, and entering returned data using the trial web data entry portal).

14.2 Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, Scientific leads (ICR-CTSU & CHaRT), Health Economist, Co-investigators and identified collaborators, the Database Manager, Trial Statistician and Trial Managers. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups. Where possible, membership will include a lay/consumer representative.

The TMG will meet at regular intervals and at least annually. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG have operational responsibility for the conduct of the trial. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

14.3 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be set up and will comprise an independent Chairman and at least two further independent members with clinical or statistical expertise (at least one member must be a statistician). The TSC will meet at regular intervals, and at least annually.

The TSC will provide expert independent oversight of the trial on behalf of the Sponsor and funder. The Committee's terms of reference, roles and responsibilities will be defined in charter issued by ICR-CTSU.

14.4 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be set up to monitor the progress of the trial and will comprise a Chairman and at least two further members with clinical or statistical expertise (at least one member must be a statistician). Membership of the IDMC will be proposed by the TMG and approved by the TSC.

The IDMC will meet in confidence at regular intervals, and at least annually. A summary of findings and any recommendations will be produced following each meeting. This summary will be submitted to the TMG and TSC, and if required, the main REC.

The IDMC will reserve the right to release any data on outcomes or side-effects through the TSC to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.

The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by CHaRT.

15 Trial Administration, Logistics & Quality Assurance

15.1 Site activation

Before activating the trial, participating sites are required to sign an agreement accepting responsibility for all trial activity which takes place within their site.

Sites may commence recruitment once the site agreement has been signed by all required signatories, the required trial documentation is in place (as specified by ICR-CTSU) and a site initiation (visit or teleconference) has taken place. Site initiation visits will be conducted

at sites where the Principal Investigator has requested one or where ICR-CTSU deems it is appropriate.

15.2 Data acquisition

Electronic (e) Case Report Forms (CRF) will be used for the collection of trial data. CHaRT will provide guidance to sites to aid the completion of the eCRFs. The Trial Management Group reserves the right to amend or add to the eCRF template as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by sites in accordance with the guidelines provided by CHaRT.

15.3 Central Data Monitoring

Once data has been entered on the eCRF by the site personnel, CHaRT will review it for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be raised for resolution by the site.

Any systematic inconsistencies identified through central data monitoring may trigger an on-site monitoring visit.

15.4 On-Site Monitoring

If a monitoring visit is required, ICR-CTSU or CHaRT will contact the site to arrange the visit. Once a date has been confirmed, the site should ensure that full patient notes of participants selected for source data verification are available for monitoring.

Sponsor, ICR-CTSU or CHaRT staff conducting on-site monitoring will review essential documentation and carry out source data verification to confirm compliance with the protocol. If any problems are detected during the course of the monitoring visit, ICR-CTSU and CHaRT will work with the Principal Investigator or delegated individual to resolve issues and determine appropriate action.

The approach to, and extent of, on site monitoring will be specified in a trial monitoring plan and informed by a risk assessment undertaken prior to start of trial.

15.5 Definition of end of study

The end of study is deemed to be the date of the last data capture. The end of current trial funding is 31 August 2020.

15.6 Archiving

Essential trial documents should be retained according to local policy at sites and for a sufficient period for possible inspection by the regulatory authorities (at least 5 years after the end of study). Documents should be securely stored and access restricted to authorised personnel.

16 Research Governance

16.1 Sponsor responsibilities

The Sponsor of this clinical trial is The Newcastle upon Tyne Hospitals NHS Foundation Trust.

The responsibilities delegated to the Chief Investigator, ICR-CTSU and CHaRT are defined in an agreement between the institutions.

16.2 Participating site responsibilities

Responsibilities delegated to participating sites are defined in an agreement between the Sponsor and the individual site.

17 Participant Protection and Ethical Considerations

17.1 Trial Approvals

This trial has been formally assessed for risk by ICR-CTSU.

ICR-CTSU, on behalf of the Sponsor, will ensure that the trial has received ethics approval from an NHS REC for multi-centre trials and study wide governance approval via the NIHR Coordinated System for gaining NHS Permission. Before approaching potential participants, the Principal Investigator at each site is responsible for submitting Site Specific Information documentation to their local Research and Development department and obtaining NHS Management Permission.

17.2 Trial Conduct

This trial will be conducted according to the approved protocol and its amendments, supplementary guidance and manuals supplied by the Sponsor and in accordance with the Research Governance Framework for Health and Social Care and the Principles of Good Clinical Practice (GCP).

17.3 Participant confidentiality

Participants will be asked to consent to their full name being collected at trial entry in addition to their date of birth, hospital number, postcode and NHS number or equivalent to allow linkage with routinely collected NHS data.

Each investigator should keep a separate log of all participants' Trial IDs, names, addresses and hospital numbers. The investigator must retain trial documents (e.g. participants' written consent forms) in strict confidence. The investigator must ensure the participants' confidentiality is maintained at all times.

Representatives of the sponsor, ICR-CTSU or CHART may require access to participants' hospital notes for quality assurance purposes. The sponsor, ICR-CTSU and CHART will maintain the confidentiality of participants at all times and will not reproduce or disclose any information by which participants could be identified.

17.4 Data Protection Act (DPA)

PHOTO will comply with all applicable data protection laws.

Data collected during the course of the research will be kept strictly confidential and accessed only by members of the trial team. Participant's details will be stored on a secure database under the guidelines of the 1998 Data Protection Act and regular checks and monitoring are in place to ensure compliance. Data are stored securely in accordance with the Act and archived to a secure data storage facility. The senior IT manager at CHaRT (in collaboration with the Chief Investigator) will manage access rights to the data set.

Participants will be allocated an individual specific trial number and their details will be anonymised on the secure database. We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta-analyses. To comply with the 5th Principle of the Data Protection Act 1998, personal data will not be kept for longer than is required for the purpose for which it has been acquired.

17.5 Liability

Indemnity to meet the potential legal liability of investigators participating in this trial is provided by the usual NHS indemnity arrangements. There are no provisions for indemnity due to non-negligent harm.

18 Financial Matters

This trial is investigator designed and led and has been approved by the Health Technology Assessment stream of the National Institute for Health Research (NIHR).

Newcastle University has received funding from the NIHR for the central coordination of the trial. The trial meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England. The trial is part of the National Institute for Health Research Clinical Research Network (NCRN) portfolio. NCRN resources should therefore be made available for the trial to cover UK specific service support costs.

This is a non-commercial trial and as such is mandated to have indemnity in respect of negligent harm only; there is no provision for indemnity in respect of liabilities arising from non-negligent harm. Indemnity in respect of the management of the study will be provided through The Newcastle upon Tyne Hospitals NHS Foundation Trust, acting as sponsor of this study. The participating NHS Trusts have liability for clinical negligence that harms individuals toward whom they have a duty of care, and this will provide indemnity in respect of negligent harm arising in the conduct of the study. NHS Indemnity covers NHS staff and academic staff with honorary contracts conducting the trial. Indemnity in respect of liabilities arising from negligence in study design and protocol authorship will be provided by University insurance policies in respect of protocol authors whose substantive contract of employment is with a University and via NHS schemes for protocol authors whose substantive contract of employment is with the NHS.

19 Publication Policy

The main trial results will be published in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, consisting of members of the TMG. If all grant-holders and researcher staff fulfil authorship rules, group authorship will be used under the collective title of ‘the PHOTO Trial Management Group’. If one or more individuals have made a significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to the named individual(s) and the PHOTO Trial Group. Participating clinicians may be selected to join the writing group on the basis of intellectual and time input. All participating clinicians will be acknowledged in the publication.

Any presentations and publications relating to the trial must be authorised by the TMG. Authorship of any secondary publications e.g. those relating to sub-studies, will reflect intellectual and time input into these studies.

No investigator may present or attempt to publish data relating to the PHOTO trial without prior permission from the TMG.

20 Associated Studies

20.1 PHOTO-T: Translational sample collection

PHOTO-T includes the collection of serial blood and urine samples and fresh bladder epithelium and tumour tissue from initial TUR and any subsequent first recurrence. Consent will also be sought for access to routine diagnostic formalin fixed paraffin blocks from surgery. Participation in PHOTO-T is optional and may be activated in some or all sites subsequent to the main trial.

Further details of this sample collection are provided in Appendix 1.

PHOTO protocol

21 References

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A1. APPENDIX 1: PHOTO SAMPLE COLLECTION (PHOTO-T)

A1.1. Introduction

We will use the opportunity afforded by the trial to compile a clinically well-characterised patient cohort consisting of clinical data, urine, blood and tumour specimens for future research. The NIHR HTA evidence synthesis called for diagnostic cross-sectional studies comparing FISH, ImmunoCyt, NMP22 and voided urine cytology [40]. These tests do not have the performance characteristics to reliably detect recurrence when applied alone and it is as yet unknown if a combination test may overcome this issue. Novel assays, which detect genome or genome expression-wide alterations in urinary sediment cells, are currently in early phase development and have obvious advantages over single marker tests and small panels of markers.

This trial will construct a prospective urinary and tissue bio-repository that can be used to validate suitable biomarkers for the detection of recurrent disease. Baseline material including blood for germline DNA and paraffin-embedded and fresh tissue will be made available for future research into predictive and prognostic markers and new targets for treatment. Once established, separate funding will be sought for translational studies and the resource will be made available to research groups nationally and internationally.

A1.2. PHOTO laboratory manual

Detailed instructions for sample collection, processing, labelling and transportation are provided in the PHOTO laboratory manual. This is available on request from ICR-CTSU and should be referred to in conjunction with this protocol.

A1.2.1. PHOTO sample collection kits

Participating sites will be provided with sample collection and postage kits as required by ICR-CTSU.

A1.3. Samples

All PHOTO participants will be asked to provide consent for access to their diagnostic paraffin-embedded tumour tissue from initial and any subsequent TUR.

In addition, PHOTO-T participants will be ask to consent to collection of fresh tumour and bladder tissue at initial TUR and any subsequent recurrence. This sample should be stored in RNA Later solution to enable genetic assessment.

Participants will also be asked to provide the following specimens pre-operatively, and at 3, 12, 24 and 36 months post treatment until first recurrence**:**

- **1 x 7.5ml whole blood** in EDTA tubes
- **1 x 50ml urine**

Participants who withhold consent from the translational part of the trial will have the opportunity to be part of the clinical part of the PHOTO trial.

A1.3.1. Data collection

In addition to collection of data for the purposes of the trial, as described above, patients will be asked to consent to allow access to their electronic healthcare records to enable long term follow-up relating to disease status and survival. This will include long term NHS database linkage within an appropriate data protection and ethical framework.

A1.4. Sample shipping and storage

Fresh tumour, blood and urine samples should be shipped using the validated Royal Mail postal kit provided by ICR-CTSU to the central receiving laboratory at the Newcastle Biomedicine Biobank, a Human Tissue Authority licensed facility. All specimens will be anonymised with a unique specimen number, and linkage to participant details and clinical data will only be possible by the trials offices.

Paraffin blocks representative of the resected tumour will be requested retrospectively from Histopathology Departments at participating sites. Sections will be used for reference pathology validation, construction of a tissue microarray and to establish a DNA bio-repository for personalised detection assays.

A1.5. Tissue access arrangements

Samples will be held under the custodianship of the PHOTO Trial Management Group. Trial biospecimens will be registered on the appropriate databases.

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