BladderPath

Image Directed Redesign of Bladder Cancer Treatment Pathways

Sponsor	University of Birmingham
Sponsor Protocol Number	RG-17_143
CRCTU Number	BL2102
ISRCTN Number	35296862
IRAS ID	210698

Version Number: 4.0a

Date: 10th September 2020

Funded by NIHR Health Technology Assessment Programme (project number: 14/08/60)

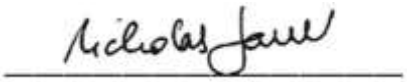
UNIVERSITY OF BIRMINGHAM

NHS National Institute for Health Research

SIGNATURE PAGE

BladderPath study Protocol, Version 4.0a, dated 10th September 2020

This protocol has been approved by:

Name:	Prof Nicholas D James	Study Role:	Chief Investigator
Signature:		Date:	10 Sep 2020

This protocol describes the BladderPath study and provides information about procedures for patients taking part in the BladderPath study. The protocol should not be used as a guide for treatment of patients not taking part in the BladderPath study.

AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
N/A	18-Aug-2018	2.0a	Notification	Change in Data Protection Regulations
SA01	19-Feb-2019	3.0	Substantial	Clarification of different methods of referral and communication between hospitals and patients, sources of referral, and order of consent/initial investigation process.
			Non-substantial	Update of study contact details. Schedule of events table - updated with clearer column headings, and reordered and updated footnotes. Study design, section 3, clarification that only randomised patients contribute to the sample size. Added definition of correct treatment Clarification of which patients contribute to the different stages. Eligibility criteria - addition of examples of types of foreign bodies that may preclude eligibility for the purpose of clarity. Clarification of who may obtain patients' consent. Introduction of Likert Scale - for clarification as the term "possible" and "probable" were found to be confusing to clinicians to make decisions for MRI on Pathway 2. A clear definition has been included following TMG discussions to avoid potential protocol deviation. Pathway 2: Clarification that participants may be randomised prior to urine cytology or biopsy pathology confirmation. Clarification that baseline blood sample will only be required for randomised participants, as will the baseline Questionnaire booklet.

				Clarification that follow-up Questionnaire booklets will be sent to patients by the BladderPath Study Office Addition of sentence clarifying the SAE reporting period. Addition of paragraph clarifying why and how *ad hoc* (treatment) data will be collected from non-English sites. Colour-coding of Table 4 plus the addition of all ad hoc forms for the purpose of clarity. Clarification of when English and non-English sites are to complete ad hoc forms. Statistical considerations: significant expansion of definitions previously listed in V2 protocol. Several minor typographical and grammatical corrections.
SA02	17-Sep-2019	4.0	Substantial	Addition of Qualitative sub-study details.
N/A	10-Sep-2020	4.0 (a)	Non-substantial Non-Notifiable	Inclusion of alternative arrangements for obtaining participants' informed consent to accommodate COVID-19 precautionary measures.

STUDY CONTACTS

Chief Investigator	Prof Nicholas James Cancer Centre Queen Elizabeth Hospital Edgbaston Birmingham B15 2TH		
Co-Investigator Urology	Prof James Catto Professor of Urological Surgery Department of Oncology The Medical School University of Sheffield Sheffield S10 2RX	**Co-Investigator Urology**	Mr Kieran Jefferson Consultant Urological Surgeon Urology University Hospitals Coventry and Warwickshire NHS Trust Coventry CV2 2DX
Co-Investigator Urology & Acting Chief Investigator	Mr Prashant Patel Consultant Urological Surgeon Institute of Cancer and Genomic Sciences University of Birmingham Birmingham B15 2TT	**Co-Investigator Medical Oncology**	Dr Mehran Afshar Consultant Medical Oncologist St George's University Hospitals NHS Foundation Trust London SW17 0QT
Co-Investigator Imaging	Prof Charles Hutchinson Professor of Clinical Imaging Population Evidence & Technologies University of Warwick University Hospitals Coventry and Warwickshire Coventry CV2 2DX	**Co-Investigator Imaging**	Dr Hassan Douis Consultant Radiologist Imaging X-ray University Hospitals Birmingham NHS Foundation Trust Queen Elizabeth Hospital Edgbaston Birmingham B15 2GW
Co-Investigator Imaging	Dr Steve Kennish Consultant Radiologist Royal Hallamshire Hospital Sheffield Teaching Hospitals NHS Trust Sheffield S10 2JF	**Co-Investigator Imaging**	Dr Rashid Amir Consultant Radiologist Imaging X-ray University Hospitals Birmingham NHS Foundation Trust Queen Elizabeth Hospital Edgbaston Birmingham B15 2GW
Co-Investigator Qualitative sub-study	Dr Veronica Nanton Senior Research Fellow Social Science & Systems in Health Division of Health Sciences Warwick Medical School University of Warwick Coventry CV4 7AL	**Researcher Qualitative sub-study**	Ms Julia Roscoe Research Associate Unit of Academic Primary Care Division of Health Sciences Warwick Medical School University of Warwick Coventry CV4 7AL

Co-Investigator Patient Involvement	Ms Jean Gallagher	**Co-Investigator Systems Biology**	Dr Richard Savage Associate Professor Systems Biology Centre University of Warwick Coventry CV4 7AL
Co-Investigator Biomarker Research	Dr Richard Bryan Senior Research Fellow Institute of Cancer and Genomic Sciences University of Birmingham Birmingham B15 2TT	**Co-Investigator Biomarker Research**	Dr Douglas Ward Senior Research Fellow Institute of Cancer and Genomic Sciences University of Birmingham Birmingham B15 2TT
Co-Investigator Statistics	Prof Nigel Stallard Professor of Medical Statistics and Head of Statistics and Epidemiology Group Statistics and Epidemiology Warwick Medical School University of Warwick Coventry CV4 7AL	**Co-Investigator Health Economics**	TBC
Co-Investigator Health Informatics	Ms Alicia Jakeman Health Informatics University Hospitals Birmingham NHS Foundation Trust Edgbaston Birmingham B15 2TH	**Lead Statistician**	Miss Sarah Pirrie Cancer Research UK Clinical Trials Unit (CRCTU) Institute of Cancer and Genomic Sciences University of Birmingham Birmingham B15 2TT
Statistician	Ms Wenyu Liu Cancer Research UK Clinical Trials Unit (CRCTU) Institute of Cancer and Genomic Sciences University of Birmingham Birmingham B15 2TT	**Trial Management Team Leader**	Dr Sarah Bowden Cancer Research UK Clinical Trials Unit (CRCTU) Institute of Cancer and Genomic Sciences University of Birmingham Birmingham B15 2TT
Senior Trial Coordinator	Mrs Ana Hughes Cancer Research UK Clinical Trials Unit (CRCTU) Institute of Cancer and Genomic Sciences University of Birmingham Birmingham B15 2TT	**Trial Coordinator**	Dr Ann M Pope Cancer Research UK Clinical Trials Unit (CRCTU) Institute of Cancer and Genomic Sciences University of Birmingham Birmingham B15 2TT

BladderPath Study Office

Cancer Research UK Clinical Trials Unit (CRCTU)

Institute of Cancer and Genomic Sciences

University of Birmingham Birmingham B15 2TT

Enquiries

☎ 0121 414 6372 🖷 0121 414 2230

✉ BladderPath@trials.bham.ac.uk

BladderPath Website URL address:

www.birmingham.ac.uk/research/activity/mds/trials/crctu/trials/Bladder-Path

Registration/Randomisation

www.cancertrials.bham.ac.uk

Emergency Registration/Randomisation

☎ 0121 414 6372 / 3793

Serious Adverse Event Reporting

Fax SAE Forms to:

🖷 0121 414 2230 / 7989

Or email to:

✉ reg@trials.bham.ac.uk

Qualitative sub-study contact details

Division of Health Sciences

Warwick Medical School

University of Warwick Coventry CV4 7AL

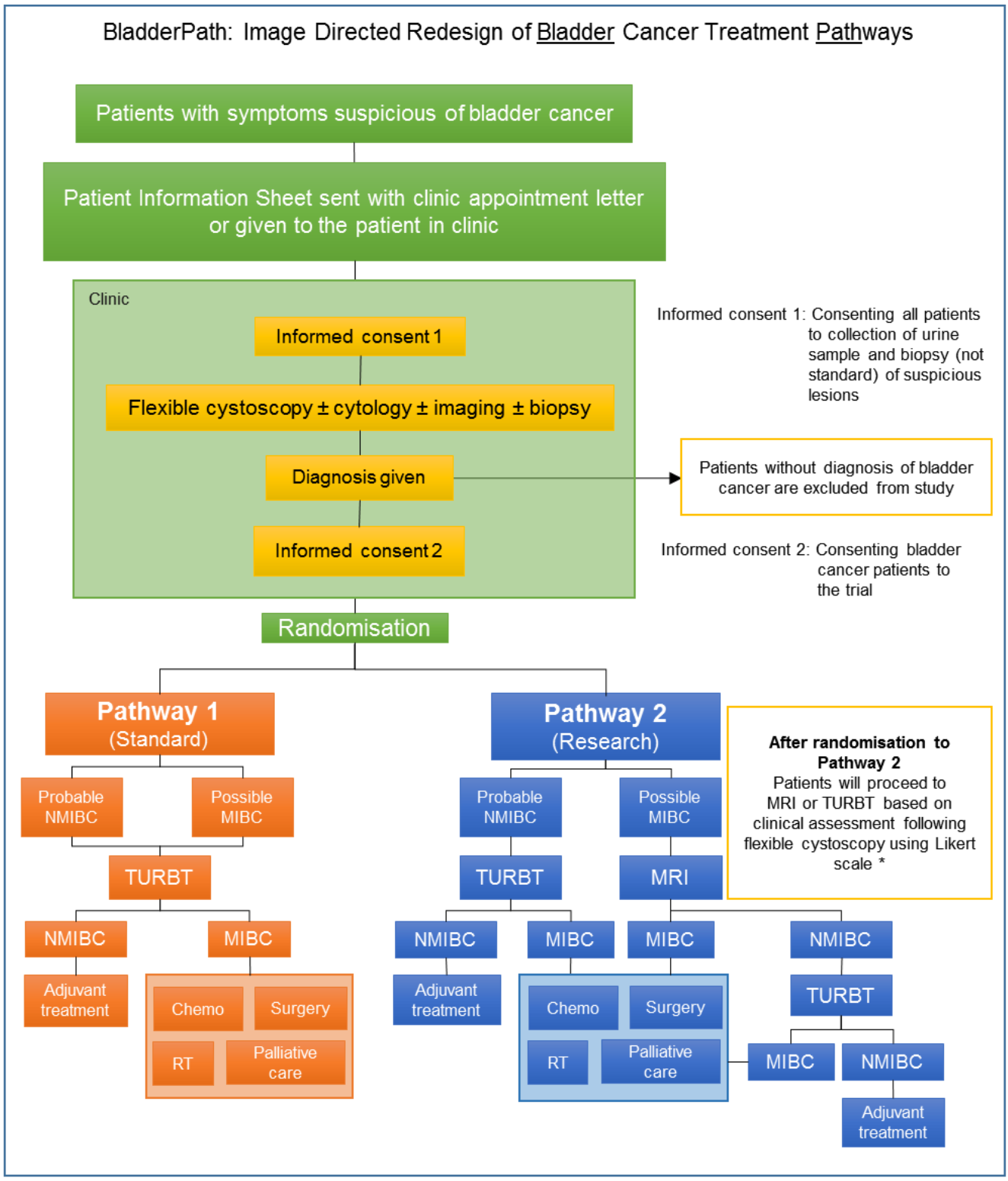
☎ 0247 6574025 / 0247 6151885

✉ V.Nanton@warwick.ac.uk ✉ J.Roscoe@warwick.ac.uk

STUDY SYNOPSIS

Title	BladderPath: Image Directed Redesign of Bladder Cancer Treatment Pathways
Design	Open label, multi-stage randomised controlled study with three overlapping stages: feasibility, intermediate and final efficacy stage
Patient population	Newly diagnosed bladder cancer patients
Sample size	Feasibility stage – 150 patients Intermediate stage – event driven, at least 20 possible MIBC patients with confirmed MIBC (approximately 80-100 patients will need to be recruited overall). Final clinical stage – event driven, at least 380 progression events, (approximately 950 patients)
Inclusion Criteria	• Patients attending clinic for the investigation of symptoms suspicious of bladder cancer (initial consent process) • Patients given a diagnosis of suspected bladder cancer and requiring a transurethral resection of a bladder tumour (TURBT) based on visual cystoscopic examination of the bladder (confirmatory consent process, post cystoscopy) • Provision of written informed consent
Exclusion Criteria	• Patients unable or unwilling to undergo MRI • Previous diagnosis of bladder cancer • Previous entry in the present study
Aim	The aim of the BladderPath study is to improve staging, accelerate treatment and reduce iatrogenic tumour spread in patients with muscle invasive bladder Cancer (MIBC) by avoiding TURBT, ultimately improving clinical outcomes. The hypothesis being tested is that substituting TURBT with multiparametric magnetic resonance imaging (mpMRI) (pathway 2) will avoid unnecessary surgery and reduce the time to radical treatment for MIBC
Primary Outcomes	Feasibility stage: proportion of possible MIBC patients randomised to pathway 2 who correctly follow the protocol Intermediate stage: time to correct treatment for MIBC patients Final clinical stage: clinical progression-free survival
Study duration	60 months
Study Office contact details	Cancer Research UK Clinical Trials Unit (CRCTU) Institute of Cancer and Genomic Sciences University of Birmingham Birmingham B15 2TT Tel: 0121 414 6372 Fax: 0121 414 2230 E-mail: BladderPath@trials.bham.ac.uk Website: www.birmingham.ac.uk/research/activity/mds/trials/crctu/trials/Bladder-Path

STUDY SCHEMA



*** Likert scale definition at flexible cystoscopy:**

1 = Strongly agree that the lesion is NMIBC
2 = Agree that the lesion is NMIBC

} Probable NMIBC (no MRI on either pathway)

3 = Equivocal (neither agree or disagree) that the lesion is NMIBC or MIBC
4 = Agree that the lesion is MIBC
5 = Strongly agree that the lesion is MIBC

} Possible MIBC – if randomised to Pathway 2 patient to proceed to MRI

SCHEDULE OF EVENTS

Visit No.	1	2		3	Follow-up[2]
Visit Reason	**Clinic visit for investigation of symptoms suspicious of bladder cancer (may be split over more than one visit depending on local practice)**	**MRI**	**TURBT**	**DTT [1]**	
Informed consent-1	✓				
Informed consent-2 [3]	✓				
Medical history	✓			✓	
Inclusion/exclusion criteria	✓				
Biopsy [4]	✓				
Translational Urine & Blood collection [5]	✓			✓	✓
Full blood count (FBC)	✓			✓	
Liver Function Test	✓			✓	
Urea + electrolytes	✓			✓	
Concomitant medication	✓				
MRI		✓			
TURBT			✓		
Treatment Decision				✓	
Quality of Life Questionnaire [6]	✓				✓
Health questionnaire [7]	✓				✓

1: Decision to treat (DTT) visits can occur multiple times if unsure of treatment. DTT visits will occur until decision regarding correct treatment has been achieved.

2: Follow-up data capture will be performed every 3 months until 12 months, every 6 months until 24 months and annually from 24 months to 5 years. Patients are not expected to attend clinic for study specific review after visit 3.

3: Due to post COVID-19 precautionary measures, alternative arrangements for obtaining a patient's informed consent may be made to reduce contact. Please refer to section 5.3.

4: Biopsy may be deferred until after randomisation to permit that only those patients having an MRI will need a biopsy.

5: Baseline urine sample to be collected for all consenting participants; blood sample at baseline only for randomised patients. Urine and blood collection will occur only once in the follow-up period and can be at any point after treatment during a routine visit.

6: EORTC-QLQ-BLM30 and EORTC-QCQ-30 will be used as the quality of life questionnaires, within a Patient Questionnaire Booklet, to be completed at initial clinic visit and at 3, 6, 9, 12, 18, 24 months and annually from 24 months up to 5 years post-randomisation, booklets to be sent directly to participants from the BladderPath Study Office.

7: EQ-5D-5L questionnaire (within the Patient Questionnaire Booklet) will be used as part of the health economics analysis, to be completed at initial clinic visit and at 3, 6, 9, 12, 18, 24 months and annually from 24 months up to 5 years post-randomisation, booklets to be sent directly to participants from the BladderPath Study Office.

ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
CIS	Carcinoma In Situ
CPFS	Clinical Progression Free Survival
BAUS	British Association of Urological Surgeons
BCG	Bacillus Calmette-Guerin
CRF	Case Report Form
CRCTU	Cancer Research Clinical Trials Unit
CSG	Clinical Studies Group
DMC	Data Monitoring Committee
DTT	Decision To Treat
EAU	European Association of Urology
eGFR	Estimated Glomerular Filtration Rate
FBC	Full Blood Count
FTP	File Transfer Protocol
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
ICUD	International Consultation on Urological Diseases
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
LFT	Liver Function Test
MDT	Multidisciplinary Team
MIBC	Muscle-Invasive Bladder Cancer
MRI	Magnetic Resonance Imaging
mpMRI	Multiparametric Magnetic Resonance Imaging
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMIBC	Non-Muscle-Invasive Bladder Cancer
NRES	National Research Ethics Service
PPI	Patient & Public Involvement

QoL	Quality of Life
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
TTCT	Time To Correct Treatment
TTDT	Time To Definitive Treatment
TURBT	Transurethral resection of bladder tumour
UCC	Urothelial Cell Carcinoma
UHB	University Hospitals Birmingham NHS Foundation Trust
WHO	World Health Organisation

TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE

1.1 Background

Bladder cancer is the fifth most common cancer in western society, with a rising global incidence and 430,000 new cases in 2012[1,2]. In the UK there are approximately 10,000 new cases and 5,000 deaths attributed to bladder cancer annually[3]. In western populations, over 90% of bladder cancers are urothelial cell carcinoma (UCC). Standard management follows a pattern established during the 1950s with the development of the rigid cystoscope. Prognosis has not improved in the last 30 years[3-5].

Standard management involves a pathway of diagnostic flexible cystoscopy followed by a transurethral resection of the bladder tumour (TURBT) with a rigid cystoscope. TURBT has the multiple purposes of diagnosis, staging and treatment of non-muscle invasive bladder cancer (NMIBC), i.e. removal of the tumour. Further treatment such as radical cystectomy or chemo-radiotherapy is then necessary for muscle invasive bladder cancer (MIBC).

For MIBC, this initial TURBT often understages invasion (up to 30% of MIBCs are initially staged as high grade NMIBC at first TURBT)[6], and may contribute to extra-vesical tumour dissemination through bladder perforation or venous emboli generated through the high-pressure resection process[7]. Cross-sectional pelvic imaging after TURBT impedes the accuracy of staging due to surgical artefacts (such as perivesical inflammation and reactive lymph nodes)[8-11].

Typically, the need for a TURBT, histopathological review and MDT decision-making adds at least 6-12 weeks to the pathway, prolonging the delay to commencing (the most appropriate) correct radical treatment for patients with MIBC[6, 12-14].

An ideal pathway would separate NMIBC patients from MIBC patients at the time of diagnosis. Faster and more accurate application of established technologies would streamline therapy, potentially improve outcomes and save clinical costs.

For the 75-80% of bladder cancer patients who present with NMIBC, tumour recurrence and progression following TURBT are significant issues, compelling current guidelines to recommend intense long-term surveillance by cystoscopy and urine cytology[15]. With the UK prevalence of bladder cancer estimated at 46,500, at any one time there will be 35-37,000 patients with NMIBC requiring such surveillance, performed as often as every 3 to 6 months at an estimated cost of at least £533 per flexible cystoscopy/cytology “episode” (as costed in 2010[16]). Around 30% of NMIBC cases will progress to MIBC and require additional therapy.

Around 20-25% of new bladder cancer patients present with *de novo* MIBC[17,18]. Survival with MIBC remains poor (27-50% five-year survival) and has not improved in 30 years[3]. The present pathway is largely geared to NMIBC and actively delays effective MIBC treatment, which is often carried out in a different hospital to initial diagnosis and TURBT, increasing handovers and therefore delays. In Birmingham, for example, many National Health Service (NHS) Trusts run haematuria clinics, a smaller number (but at least six) offer systemic chemotherapy, but only two carry out major pelvic surgery and only one radiotherapy. Early clarity on staging and diagnosis would facilitate more co-ordinated planning and treatment delivery. Similar considerations exist in all major healthcare systems worldwide.

This fragmented care with complicated staging and follow-up leads to the cumulative cost of treating bladder cancer exceeding all other forms of human cancer.

The standard shared patient pathway thus delays therapy for MIBC patients. There is a growing body of opinion that such pathways should separate earlier in order to more appropriately and expeditiously treat MIBC patients[4], and this is what we propose to evaluate here.

1.2 Staging and Treatment

The pros and cons of staging and treatment techniques for bladder cancer are summarised below, including the aim of TURBT in the settings of NMIBC and MIBC.

Table 1. Aim of TURBT in NMIBC and MIBC

Aim of TURBT	NMIBC	MIBC
Diagnosis	✓	✓
Staging	✓	Sometimes – understaging in up to 30%
Treatment	✓	No – may be harmful
Palliation of symptoms	Sometimes in cases of heavy bleeding	Sometimes in cases of heavy bleeding.

From the above, it is clear that the main functions of TURBT in MIBC are diagnosis of cancer and staging. Diagnosis does not require large quantities of tissue – very small amounts are sufficient to confirm the presence of high grade malignant cells to ascertain grade (as exemplified by the almost ubiquitous use of urine cytology). The main function of TURBT in MIBC therefore is to assess stage. Where muscle is adequately sampled and is found to contain tumour, a diagnosis of MIBC is correct by definition (although not a more comprehensive nodal or metastasis stage). The issue is the under staging of high-grade tumours due to inadequate sampling of muscle that subsequently turns out to be involved. As cystectomy is a recognised treatment for high risk NMIBC, either at diagnosis or after treatment failure such as Bacillus Calmette-Guerin (BCG), the false negative rate with respect to distinguishing NMIBC from MIBC in the highest risk cases can be estimated - this appears to be as high as 30%[3, 30], though will clearly vary depending on operator. Within this context we can assess the accuracy of MRI for the same purpose. The key factor here is the split between tumours of stage pT1 and below versus pT2 and above.

Thus, the diagnostic function of TURBT can be substituted by a smaller biopsy obtained during flexible cystoscopy. For staging, MRI has performance characteristics that exceed those reported for TURBT, are less subject to operator variability, and are amenable to external review. In most cases, the therapeutic benefit for TURBT in MIBC patients remains unproven, particularly if cystectomy is the preferred definitive treatment option. The literature on staging bladder cancer has been recently reviewed by Bouchelouche and co-workers[19]. A role for TURBT as palliation of severe symptoms from MIBC pending a definitive treatment decision will remain. Its precise magnitude will be quantified in this study but is likely to be limited as, in most cases, symptoms such as haematuria are intermittent (one of the factors leading to delayed presentation).

1.3 Hypothesis

The purpose of the BladderPath study is to evaluate a new pathway that would largely eliminate TURBT from the initial management of MIBC patients. This allows more expeditious treatments for both MIBC (by eliminating delays) and NMIBC (by reducing demand for TURBT). Our approach integrates flexible cystoscopy, urine cytology, biopsy and detailed imaging to confirm the diagnosis and stage of disease. Appropriate definitive radical therapy can then be rapidly commenced. This is paradigm-shifting in the context of bladder cancer but is standard practice in virtually every other solid tumour setting (e.g. prostate, breast, lung, etc.). Although TURBT is considered a standard part of care for NMIBC, for MIBC it is less obviously essential, particularly for patients undergoing subsequent radical surgery. This study will test the utility of TURBT and MRI as a component of care for MIBC in a randomised fashion.

1.4 Rationale

The prognosis for MIBC remains poor and has not changed for three decades[3-5]. Modern MRI approaches now have the ability to accurately stage bladder tumours[11,19-23] and experimental urinary biomarkers show great promise in identifying MIBC from a urine test with high sensitivity and specificity[24-26]. The platforms therefore exist to improve patient pathways, potentially leading to improved outcomes.

In order to change the current pathway, we need to show that alternatives to TURBT exist for staging, and that faster treatment will improve outcomes.

1. Do we need TURBT for histology?
    a. Flexible cystoscopy can give accurate tumour histological diagnosis and grading but does not assess muscle-invasion.
2. Can we replace TURBT for detailed assessment of the bladder tumour?
    a. TURBT is frequently inaccurate and operator dependent – up to 30% of tumours assessed as high grade NMIBC at TURBT are subsequently diagnosed as invasive (MIBC) on repeat TURBT or at cystectomy[6, 27].
    b. Guidelines recommend repeat TURBT for patients staged G3pT1 because of the high incidence of under staging – further delaying correct treatment in some patients with MIBC[6,27]
    c. Sensitivity and specificity of mpMRI for separating NMIBC from MIBC are 94% and 100%, respectively[11, 19-23]
    d. Substituting MRI for TURBT should not compromise staging and may improve it.
3. Is TURBT an essential component of treatment?
    a. There are no randomised data on this topic – this is one of the aims of this study.
    b. Evidence exists that TURBT may increase local tumour dissemination[28] and lead to increases in circulating tumour cells[7].
    c. In most other oncology settings, imaging and biopsy are sufficient for correct treatment; in some cases imaging alone is sufficient (e.g. kidney cancer and upper tract urothelial cancer). Few tumour sites use an intermediate piecemeal debulking ahead of definitive therapy[29].
4. Does delaying the correct definitive treatment affect prognosis?
    a. Typical duration from first clinic visit to correct definitive treatment within the NHS for MIBC is around 100 days[17, 30, 31]
    b. There is evidence that delay can affect prognosis for MIBC[12-14]
    c. Hence reducing delay should improve prognosis.

2. AIMS, OBJECTIVES AND OUTCOME MEASURES

2.1 Aims and Objectives

The aims of the BladderPath study are to evaluate whether it is possible to expedite radical treatment for patients with MIBC using MRI rather than TURBT to diagnose and more accurately and rapidly stage their cancer. We hypothesise this may improve outcomes from MIBC by reducing the time from diagnosis to radical treatment.

2.2 Outcome Measures

The primary and secondary outcomes change as we go through the study. These are summarised in Table 2.

Table 2. Primary and Secondary Outcomes

	Primary Outcomes	Secondary Outcomes
Feasibility stage	The proportion of possible MIBC patients randomised to pathway 2 who correctly follow pathway protocol	• Overall proportion of patients who correctly follow protocol on each pathway for all randomised patients • Recruitment and retention rates at each study site • Counts of each type of correct treatment
Intermediate stage	The time to correct treatment (TTCT) for patients who were initially classified as possible MIBC and then were confirmed to have MIBC	• TTCT for all randomised patients • TTCT for probable NMIBC patients confirmed as NMIBC • Time to definitive treatment (TTDT) for all randomised patients • All outcomes reported at stage 1 will be repeated if the first two stages are not conducted at the same time
Final clinical stage	Clinical progression-free survival (CPFS)	• Cost effectiveness of each pathway • Patient Quality of life • The proportion of patients who correctly follow pathway protocol • TTCT for all possible MIBC patients • TTCT for all probable NMIBC patients • TTCT for all MIBC patients • TTCT for all NMIBC patients • Time to definitive treatment (TTDT) for all randomised patients • Time to each treatment type • Time to recurrence, progression or metastatic disease progression • Number and percentage of recurrences; progressions and incidence of metastatic disease • Number of each type of treatment(s) received • Accuracy of MRI/TURBT by comparison with histological confirmed diagnoses • Overall and disease-free survival • Number of unnecessary radical cystectomies • Number of protocol related SAEs

3. STUDY DESIGN

This is an open label phase II/III randomised controlled study with three overlapping stages:

Feasibility stage: the estimated sample size for this stage is 150 randomised patients.

Intermediate stage: the estimated sample size for this stage is event driven and requires at least 20 possible MIBC patients with confirmed MIBC to have correct treatment across both treatment arms (approximately 80-100 patients recruited overall). 'Correct treatment' is defined as TURBT for patients with NMIBC and either systemic chemotherapy, radiotherapy, cystectomy or palliative care for patients with MIBC.

Final clinical stage: The estimated sample size for this stage is event driven and requires at least 380 progression events, (approximately 950 patients).

Patients randomised at the feasibility stage will also contribute to the intermediate stage and both will also be included in the final stage.

4. ELIGIBILITY

Patients are eligible to be included in the study if they meet the following criteria:

4.1 Inclusion criteria

1. Provision of written informed consent
2. Patients must be ≥18 years of age
3. Patients attending clinic for the investigation of symptoms suspicious of bladder cancer (initial consent process)
4. Patients given a diagnosis of suspected bladder cancer and requiring a TURBT based on visual cystoscopic examination of the bladder (confirmatory consent process, post cystoscopy)

Note: as the study does not involve additional drug therapy or ionising radiation, there are no restrictions on women of childbearing potential.

4.2 Exclusion criteria

1. Patients unable or unwilling to undergo MRI. Criteria include but is not exclusive of the presence of foreign bodies (e.g. hip replacement) or MRI incompatible pacemakers, claustrophobia, adverse reactions to MRI contrast media and eGFR < 40 ml/min/1.73m^2
2. Patients who are pregnant or breastfeeding
3. Previous diagnosis of bladder cancer
4. Previous entry into the present study
5. Patients not suitable/fit for TURBT

Note: The study does not include upper age related exclusion criteria.

5. SCREENING AND CONSENT

5.1 Screening

In principle, all patients referred for investigation of symptoms suspicious of bladder cancer, will be eligible for this study. In general, the Patient Information Sheet (PIS) and a cover letter will be sent to the patients along with the clinic appointment letter. Where Haematuria Clinic appointments are made in a different way, e.g. online by the GP or by telephone/text to the patient from the hospital, or the patient is identified at a different urology clinic, the PIS may be given to the patient while attending the clinic.

5.2 Informed Consent

It is the responsibility of the Investigator at each site to obtain written informed consent for each patient prior to performing any study related procedure. The Principal Investigator (PI) may delegate the task of obtaining of patients' consent to members of their research team. As long as the Principal Investigator has delegated this task to the individual on the Site signature & delegation log, the designee is appropriately trained in the consent process and the Trust allow consent to be taken by non-medically qualified members of the research team.

A Patient Information Sheets (PIS) is provided to facilitate this process. Investigators or designee must ensure that they adequately explain the aim, study procedures, anticipated benefits and potential hazards of taking part in the study to the patient. The Investigator should also stress that the patient is completely free to refuse to take part or withdraw from the study at any time. The patient should be given ample and appropriate time (e.g. 24 hours) to read the Patient Information Sheet and to discuss their participation with others outside of the site research team. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate in the study without giving a reason must be respected.

If the patient expresses an interest in participating in the study they should be asked to sign and date the latest version of the Informed Consent Forms (see section 5.3). The Investigator or designee must then sign and date the forms; where possible this should be done during the same visit, but due to post-COVID-19 precautionary measures may need to be counter-signed retrospectively (please refer to section 5.3). A copy of the Informed Consent Form should be given to the patient, a copy should be filed in the hospital notes, and the original placed in the Investigator Site File (ISF). Once the patient is entered into the study the patient's trial number should be entered on the Informed Consent Forms maintained in the ISF. In addition, if the patient has given explicit consent a copy of the signed Informed Consent Forms must be sent in the post to the Study Office for review.

Details of the informed consent discussions should be recorded in the patient's medical notes, this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the study and the version number of the PIS and GDPR addendum to the PIS and Informed Consent Forms.

Patients that consent to take part in the BladderPath study should also be given the opportunity to participate in the qualitative sub-study. A separate Patient Information Sheet is provided for this sub-study (see Section 9 for additional information). Sites will be notified when sub-study accrual has been met.

Throughout the study the patient should have the opportunity to ask questions about the study and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient in which case the process above should be followed and the patient's right to withdraw from the study respected.

Electronic copies of the PIS and the GDPR Addendum to the PIS and Informed Consent Forms are available from the study website or Study Office and should be printed or photocopied onto the headed paper of the local institution.

Details of all patients approached about the study should be recorded on the Patient Screening/Enrolment Log and with the patient's prior consent their General Practitioner (GP) should also be informed that they are taking part in the study. A GP Letter is provided electronically for this purpose.

5.3 Informed Consent Process

Informed consent for BladderPath is a two-stage process.

Stage 1: The PIS, GDPR addendum and a cover letter will typically be sent to patients along with their clinic appointment letter. The PIS and cover letter will include details of how to contact the research team, should the patient wish to gain more details about the study. At the clinic if the patient agrees to take part in the study, they will sign Informed Consent 1 (ICF-1) before any clinical assessments are carried out to allow the collection of an additional biopsy and urine samples for research purposes.

Where local procedures preclude this, or patients are identified at other clinics, the PIS and GDPR addendum may be given in clinic and if the patient would like to take part they may need to attend a second clinic visit to sign the Informed Consent Forms or consent remotely over the telephone. Where

a patient consents verbally, they will have to confirm this electronically either via text, email with or without a photograph or scan of the signed Informed Consent Forms, by audio-recorded message (e.g. answerphone) or by post. Unless the wet copies of the forms were posted to the research team, patients who provide consent remotely should bring the wet copies of the forms along to their next hospital appointment, i.e. TURBT or MRI appointment. The designated research team member would then countersign the original forms (see Stage 2 for further information on this).

Stage 2: Following a diagnosis of suspected bladder cancer, or a high degree of clinical suspicion for high grade, muscle invasive bladder cancer, the patient will be screened for eligibility and invited to sign Inform Consent Form 2 (ICF-2) for full study participation and collection of additional blood samples for research purposes.

However, subsequent to the COVID-19 pandemic and precautions brought in to prevent the potential spread of the disease, the method of obtaining patient consent was adjusted for precautionary reasons.

Patients found to have suspected bladder cancer during flexible cystoscopy that don't sign ICF2 whilst in clinic, will be given the PIS, ICF2 and Qualitative Sub-study PIS and consent form (plus a copy of the Quality of Life (QoL) questionnaires booklet) to take home to consider if they would like to take part in main study. Where the PIS is provided to a potential study patient after receiving their initial bladder cancer diagnosis, then ICF1, ICF2 and the Qualitative sub-study information and consent forms should be given to the patient to take home to read and consider.

Patients will be contacted a day or two later by a member of the site's research team able to obtain patient consent, to discuss the study further and answer any questions raised by the patient. If the patient chooses to participate they will be asked to confirm their verbal consent over the telephone via electronic means such as email, text or sending a photograph or scan of their signed consent form(s) if possible, to permit randomisation. This verbal and electronic consent will be annotated in the patient's medical notes.

Following randomisation into the study the patient should be instructed to bring their signed consent form(s) along when they next attend hospital for their allocated procedure, i.e. TURBT or MRI appointment. The wet copy of the consent form(s) will be signed retrospectively by a member of the research team taking consent.

In addition, if they choose to participate, patients are asked to provide separate consent for the qualitative sub-study (see Section 9. 1.1).

6. STUDY ENTRY

6.1 Registration/Randomisation

Prior to recruitment of patients into the study, the Principal Investigator for each site, or their designee, should have returned all required documentation to the Study Office, and the site personnel involved with BladderPath must have received appropriate training from the Trial Coordinator or designee.

6.1.1 Registration procedure

If the patient agrees to take part in the study by signing the first informed consent form (ICF-1) when attending the clinic, the patient will be registered into the study.

Registrations will be made via the online electronic remote data capture system (eRDC) by logging on to: https://www.cancertrials.bham.ac.uk, as soon as logistically feasible after obtaining consent so that the patient's trial number (TNO) may be used to label the urine sample tube.

Login details for the online website will be provided by the Study Office as part of site initiation.

The following information will be required at registration:

- Name of hospital, consultant and person registering the patient
- Confirmation that the patient is eligible for the study by completing the Eligibility Checklist
- Confirmation that the patient has given written informed consent

- Patient's full name, full postal address, hospital number, date of birth and NHS number

At the end of the registration procedure the patient will be allocated with a unique TNO, a Confirmation of Registration report should be printed and filed in the ISF along with the original signed ICF-1.

Emergency registration

If there are any problems with online registration, a paper Eligibility Checklist and registration form should be completed. These details should then be phoned through to the Study Office using the numbers below:

☎ 0121 414 6372 / 3793; 9am-5pm Monday to Friday

6.1.2 Randomisation procedure

If the patient is subsequently given a diagnosis of suspected bladder cancer and would still like to take part in the study, the patient will sign Informed Consent Form 2 (ICF-2) and will be randomised into the study.

Randomisation will be done online via the online electronic remote data capture system (eRDC) by logging on to: https://www.cancertrials.bham.ac.uk.

A completed Eligibility Checklist must be sent to the Study Office as soon as possible after randomisation.

At the end of the randomisation procedure a Confirmation of Randomisation report should be printed and filed in the ISF along with the original signed ICF-2.

Emergency randomisation

If there are any problems with online randomisation, a paper eligibility checklist and randomisation form should be completed. These details should then be phoned through to the Study Office using the numbers below:

☎ 0121 414 6372 / 3793; 9am-5pm Monday to Friday

Randomisation will be performed using minimisation on a 1:1 basis with the following stratification variables:

- Patient sex: male or female
- Age: <75 years old or ≥75 years old
- Clinician assessment: probable NMIBC or possible MIBC

The randomisation is not blinded, and therefore both participant and the health care team will know which pathway has been allocated to the participant.

7. STUDY PROCEDURE

The study is comparing TURBT with MRI for the initial assessment of possible MIBC. Patients will be randomised to either Pathway 1 or 2 following their cystoscopy result and confirmation of suspicion of NMIBC or MIBC. The definition of likelihood of MIBC is based on the Likert Scale where 1 and 2 are considered probable NMIBC and 3, 4 and 5 are considered possible MIBC.

Likert scale definition at flexible cystoscopy:

1 = Strongly agree that the lesion is NMIBC

2 = Agree that the lesion is NMIBC

3 = Equivocal (neither agree or disagree) that the lesion is NMIBC or MIBC

4 = Agree that the lesion is MIBC

5 = Strongly agree that the lesion is MIBC

7.1 Pathway 1 (Standard Pathway)

The current standard of care pathway comprises flexible cystoscopy in clinic combined with upper tract imaging and potentially cross sectional imaging of the bladder/pelvis. The establishment of such 'rapid access', 'urgent referral' or 'haematuria clinics' was first described in 1994 [35,36].

7.1.1 TURBT

Transurethral resection of the bladder tumour should be conducted as recommended by the European Association of Urology (EAU) and British Association of Urological Surgeons (BAUS). In particular, resection of the exophytic component should be performed using a rigid resectoscope. Sampling of the underlying detrusor muscle is necessary, as is recording of the clinical stage following resection (complete, incomplete, semi-fixed, fixed mass etc.). Bladder neck or urethral sampling should be performed in patients suitable for neobladder reconstruction. Sampling of areas suspicious of carcinoma in situ (red areas or fluorescent with blue light) should be undertaken. A separate biopsy of the bladder tumour base should be taken. All samples should be sent for histopathological reporting and reviewed at a suitable clinical meeting.

7.2 Pathway 2 (Research Pathway)

Instead of TURBT, patients identified as possible MIBC patients (as defined by Likert scale 3,4,5) will undergo mpMRI.

Criteria for diagnosing patients as possible MIBC are as follows:

1. Appearance on flexible cystoscopy
    - This includes the presence of a solid tumour in the bladder or a tumour seen infiltrating into the bladder wall or a solid tumour or mixed solid/papillary morphology.
    - This may also include the presence of a semi-fixed mass within the bladder found by examination before or after the flexible cystoscopy.
2. Cytological: The presence of high grade urothelial cells in either the urine cytology or in the flexible cystoscopy biopsy
3. If suitable, imaging obtained (e.g. CT Urography). This may also be used to identify possible MIBC.

Where possible, biopsy of suspicious lesions should be carried out during the flexible cystoscopic procedure to support the diagnosis. The endoscopist carrying out the flexible cystoscopy will be asked to assess the likelihood that a bladder tumour is muscle invasive or not. This information will be annotated in the source data and used to direct patients who are randomised to Pathway 2 to the relevant TURBT or MRI cohort.

Participants diagnosed with suspected bladder cancer based on visual cystoscopic examination of the bladder will be able to discuss continuing into the main, randomised part of the study with their Investigator; further confirmatory consent will be sought if the patient is willing to continue. Patients that did not have a biopsy taken at initial cystoscopy, or where the biopsy does not confirm bladder cancer for technical reasons (e.g. necrotic material only) may still enter the study and be randomised if the treating clinician has a high degree of clinical suspicion of bladder cancer. In these circumstances, the patient will need a confirmatory tissue sample either taken at TURBT or via a further diagnostic cystoscopy with or without TURBT if randomised to MRI.

Patients found to have low grade lesions or where pathology of biopsies does not confirm bladder cancer, will not be eligible for randomisation or to sign consent form 2 (ICF-2); these patients will proceed with standard NHS care.

7.2.1 mpMRI

Imaging will be carried out as per the Imaging Manual. The scans should be initially read at the local centre but secondary central reading by a certified radiologist will be performed for quality assurance and further research purposes.

7.3 Assessments

7.3.1 Initial clinical assessment (visit 1)

Note this may be split over more than 1 visit depending on local practice.

- Medical history
- Full blood count (FBC)
- Liver function test (LFT)
- Urea & electrolytes (U+Es)
- Collection of urine and blood* samples for translational research
- Concomitant medication
- Tumour biopsy, either via flexible cystoscopy at initial visit or after randomisation if patient is having an MRI. Patients having a TURBT after randomisation will not need a biopsy.
- Patient completion of Questionnaire Booklet

** Blood sample for randomised patients only*

7.3.2 Study procedure (visit 2)

- Review of adverse events

7.3.3 Decision to treat (visit 3)

- Medical history
- FBC
- Liver function test (LFT)
- Urea & electrolytes (U+E)
- Collection of urine and blood samples for translational research
- Review of adverse events

7.3.4 Follow-up (3, 6, 9, 12, 18, 24 months and annually to 5 years)

- Collection of urine and blood samples for translational research (only once at any point after treatment during a routine visit)
- Randomised patients complete Questionnaire Booklet

7.4 Sample Collection

Table 3 summarises the samples that are to be taken during the study.

Table 3. Samples to be taken

Sample	Routine	Biomarker sub-study
Blood *	10 ml	10 ml + 3.5 ml (additional)
Urine *	200 ml	50 ml (taken from the routine sample)
Tumour biopsy	Biopsy sufficient to confirm malignancy (This may include material from the TURBT, if this occurs)	Biopsy sufficient for DNA extraction. Minimum 0.2 mm

** Notes: 1) It is intended that blood samples will be collected at baseline and visits 3 & 4 for randomised patients only, when research funding has been secured*

2) Collection of urine samples at visits 3 & 4 is also subject to securing funding.

7.5 Treatment recommendations

Please refer to National Institute for Health and Care Excellence (NICE) guidelines for bladder cancer treatment and management[32]. Other relevant guidelines such as the European Association of Urology (EAU) guidelines[15] or other local guidelines may also be followed. It should be noted however, that as this is an ethically approved, peer reviewed trial assessing an alternative initial management pathway, it is acceptable to vary the initial management in line with the approved protocol.

7.6 Compliance

All analyses will be by intention to treat. The initial feasibility stage will assess compliance with the protocol and feasibility of implementation.

7.7 Concomitant illness and medication

The intervention is an imaging-directed pathway for diagnosis and staging. Patients will inevitably have concomitant illnesses that will affect compliance with both treatment pathways. Concomitant illness and medication will be recorded at study entry. Aside from contra-indications to mpMRI, there are no medication- or illness-related exclusions. This will ensure the broadest possible applicability of findings from the study.

7.8 Patient follow-up

Patients will be followed-up every 3 months until 12 months, every 6 months until 24 months and annually from 24 months to 5 years from the date of randomisation.

7.9 Patient Reported Outcomes

Patients will be asked to complete a questionnaire booklet at baseline and subsequent follow-up points (as detailed in section 7.3) that will document factors that may influence:

- Quality of life (EORTC-QLQ-BLM30 and EORTC-QCQ-30
- Health economics (EQ-5D-5L questionnaire)

Patients will complete the first questionnaire booklet at the initial clinic visit or at home after choosing to take part in the randomised study. A member of the research team will discuss how to complete the questionnaires with the patient and answer any questions they may have. If the initial questionnaire booklet is completed at home, the patient should return it to the research team at their next hospital visit.

Subsequent questionnaire booklets will be posted out to patients by the Study Office with a stamped-addressed envelope for the return of completed booklet. A copy of completed booklets will not be sent to site.

Patients will be sent a reminder to complete the questionnaire booklet 1 month after the booklet should have been received.

Completed questionnaire booklets will be regarded as source data for the purposes of this study.

7.10 Patient Withdrawal

Participants may discontinue taking part in the study at any time without prejudice. Unless a participant explicitly withdraws their consent, they should be followed-up wherever possible and data collected as per the protocol until the end of the study. Bio-specimens (urine, blood and tumour samples) obtained prior to study discontinuation will continue to be utilised (anonymously) for translational research unless such consent is explicitly withdrawn.

Participants may be withdrawn from the study at the discretion of the investigator and/or Trial Steering Committee due to safety concerns or due to any condition which in the opinion of a local investigator might interfere with the safety of the patient or the evaluation of the study objectives.

8. ADVERSE EVENT REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with the Research Governance Framework for Health and Social Care and the requirements of the National Research Ethics Service (NRES). Definitions of different types of AE are listed in Appendix 2. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the protocol.

8.1 Reporting Requirements

8.1.1 Adverse Events

MRI and TURBT are both well documented and widely used procedures. As the safety profiles of both procedures are well characterised, only Serious Adverse Events (SAEs) experienced due to the procedures are to be reported.

8.1.2 Serious Adverse Events

Investigators should report AEs that meet the definition of an SAE (see Appendix 2 for definition) and are not excluded from the reporting process as described below.

8.1.2.1 Expected Serious Adverse Events

It is not expected that any AEs occurring as a result of participation in the study will need to be reported as an SAE. For study purposes the following AEs are considered *expected* and should, therefore, not be reported on an SAE form:

- Anaemia
- Bladder discomfort/pain
- Bladder perforation
- Bleeding resulting in clot retention
- Constipation
- Contrast reaction
- Diarrhoea
- Deep Vein Thrombosis (DVT)
- Fever
- Gout
- Haematuria
- SAEs that are thought to have occurred as a result of the patient's cancer treatment
- SAEs that are related to symptoms or progression of the patient's cancer
- Insomnia
- Nausea
- Post-operative dysuria
- Prolonged catheterisation
- Skin rash
- Urethral stricture
- Urinary frequency
- Urinary retention
- Urinary tract infection
- Vomiting
- Increased white blood cell count
- SAEs that are related to pre-existing condition
- Death from cancer, as a result of the patient's cancer treatment or from a pre-existing medical condition

This is not an exclusive list and Investigators should only report SAEs which are not expected as part of the study procedure (TURBT/MRI).

8.2 Reporting Period

Where an event is determined to be an SAE, the reporting period will be 30 days from the date of the trial procedure, i.e. MRI or TURBT.

8.3 Reporting Procedure

As the only study intervention is MRI, 'Patient Safety Incidents' are predicted to be rare. 'Patient Safety Incidents' are defined as 'any unintended or unexpected incident, which could have or did lead to harm for one or more patients' (also may be referred to as adverse incidents, clinical errors or near-miss). The Principal Investigator at each centre should ensure their NHS Trust is notified of any patient safety incidents, according to local policy. NHS Trusts should report all incidents to the National Patient Safety Agency.

8.3.1 Site

8.3.1.1 Serious Adverse Events

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in the Investigator Site File (ISF).

AEs defined as serious and which require reporting as an SAE (excluding events listed in Section 8.1.2.1 above) should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.0.

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed together with a SAE Fax Cover Sheet to the Study Office using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the SAE Form with an SAE Fax Cover Sheet to:

Fax number: 0121 414 2230 / 7989

Alternatively, SAEs may be emailed to reg@trials.bham.ac.uk

On receipt the Study Office will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed or emailed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the Study Office.

The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the Study Office should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the Study Office in the post and a copy kept in the ISF.

Investigators should also report SAEs to their own Trust in accordance with local practice.

8.3.1.2 Provision of follow-up information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

8.3.2 Study Office

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the study treatment will be regarded as a related SAE. The Clinical Coordinator will also assess all related SAEs for expectedness. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected and related SAE.

8.3.3 Reporting to the main Research Ethics Committee

8.3.3.1 Unexpected and Related Serious Adverse Events

The Study Office will report all events categorised as Unexpected and Related SAEs to the main Research Ethics Committee (REC) within 15 days.

8.3.3.2 Other safety issues identified during the course of the study

The main REC will be notified immediately if a significant safety issue is identified during the course of the study.

8.3.4 Investigators

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the study will be reported to principal investigators. A copy of any such correspondence should be filed in the ISF.

8.3.5 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

9. SUB-STUDIES

9.1 Qualitative Sub-study

The qualitative sub-study extends throughout all phases of the study. The overarching aim is to understand patients', their partners', relatives' or friends' views and experiences of the BladderPath trial, and those of the healthcare professionals of the study and the new pathway over time.

First, we aim to explore the recruitment process. We recognise the sensitivity of recruiting patients to a study immediately following the delivery of bad news and we would like to investigate whether this is undertaken in a way that is acceptable to patients and healthcare professionals and whether there are ways in which the recruitment process may be improved.

The qualitative investigation will provide insights into patients' experiences of the recruitment process and patient decision-making regarding participation. In addition, we recognise that clinic staff involved in recruitment may have differing views on the potential change in the pathway of care and may vary in the way the trial is described to patients, introducing a possible source of recruitment bias.

It will also identify differences in attitudes to the study between various members of staff, and variation in the way that the study is presented to patients at the point of recruitment to the study.

Subsequently, we plan to investigate the views of patients, their partners, relatives or friends regarding participation in the trial and whether their experiences match the expectations they had at the outset.

The research team conducting and transcribing the interviews will be based at the University of Warwick.

Participants approached about the sub-study will also be asked to sign an informed consent form. If the participant's interview is not conducted in person, informed consent will be obtained over the telephone and audio-recorded. Where a Consent Form is signed a copy must be sent in the post to the Study Office for review.

9.1.1 Patients participating in BladderPath

Patients who agree to take part in the qualitative sub-study, if selected, will be contacted by the researcher to arrange an appointment with them to interview them in person at a location of the patient's choice or, if that is not suitable, by telephone. Patients will be interviewed after randomisation; a second interview will be undertaken three to six months following the initial interview. The second interview will capture reflections on study participation and views of concordance between expectations of the study as understood at the time of consent and the experience of participation. We aim to recruit up to 25 patients for the initial interview and up to 15 patients for the second interview across all participating sites.

We will interview approximately equal numbers of patients in each arm of the study. We will aim to include patients of both genders and seek maximum variation in socio-demographic characteristics, in particular in terms of ethnicity, age and social class.

9.1.1.1 Data collection

Semi-structured face-to-face interviews of up to 30 minutes will be undertaken, preferably in participants' own homes or in another location of the patient's choice, or by telephone if this is not possible. Interviews will be carried out to explore patients' understanding, perceptions and experience of the study recruitment procedure and their decision-making process. Interviews will be audio-recorded and transcribed verbatim.

9.1.2 Partner, relative or friend

A sample of partners, relatives or friends of participating patients will be approached via the patient to take part in an interview three to six months after the patient entered the BladderPath study, either by themselves (preferable) or as a dyad.

We aim to recruit up to 15 partners, relatives or friends of patients consenting for interview across all participating sites.

9.1.2.1 Data collection

Semi-structured face to face interviews of up to 30 minutes will be undertaken preferably in participants' or partner, relative, friend' own homes or in another location of their choice but if this is not possible by telephone. Interviews will be carried out to explore partner, relative or friend understanding, perceptions and experience of the study from their perspective. Interviews will be audio-recorded and transcribed verbatim.

9.1.3 Healthcare Professional

A sample of healthcare professionals (HCPs) will be approached by a member of the research team to take part in an interview three to six months after the first patient was randomised at their site. The interview will explore their views of the study and of the recruitment and consent procedure.

We aim to recruit up to 20 HCPs involved in the consent process across all participating sites.

9.1.3.1 Data collection

This will involve a short semi-structured audio-recorded face-to-face or telephone interview of up to 30 minutes to explore the HCP's views of the study and of the recruitment and consent process. Interviews will be audio-recorded and transcribed verbatim.

9.2 Imaging Sub-study

Images will be collected into a central repository for future analysis. As and when protocols are developed, these will be submitted for separate ethical approval.

9.3 Biomarker Sub-study

A multitude of urinary biomarkers are described for bladder cancer based upon proteins, nucleic acids and other factors[33-35]. In addition, a number of platforms have been described, including ELISAs, PCR, sequencing and point-of-care tests. Furthermore, such urinary biomarkers may be diagnostic or prognostic. For example, our own expertise lies within the realms of protein ELISAs[36] and novel nucleic acid-based platforms[41,42]. However, a recent World Health Organisation (WHO)/International Consultation on Urological diseases (ICUD) consensus has concluded that *"Despite considerable advances in recent years, the authors feel that at this stage the added value of molecular markers for the diagnosis of urothelial tumours has not yet been identified. Current data suggest that some of these markers may have the potential to play a role in screening and surveillance of bladder cancer. Well-designed protocols and prospective, controlled trials will be needed to provide the basis to determine whether integration of molecular markers into clinical decision-making will be of value in the future"*[35]. A study such as BladderPath thus represents an excellent opportunity to validate novel urinary biomarkers versus the final diagnosis of the patient and versus established commercially-available and FDA-approved biomarkers (e.g. NMP22[16]), and in the real-world setting of haematuria clinic (where only 10-20% of patients will be diagnosed with bladder cancer[37]).

In the first instance, we will utilise BladderPath urine samples to validate a non-invasive diagnostic urinary DNA assay. The assay is currently being developed and optimised using urine samples already

collected as part of other ethically-approved projects[41,46]. The final version of this assay will then be validated in urine samples collected from patients recruited to BladderPath. The primary endpoints are the sensitivity and specificity for the diagnosis of bladder cancer; secondary endpoints include assay failure rate and prognostic utility. This biomarker project ("AmpseqUr") has been peer-reviewed and funded by Cancer Research UK.

Although beyond the scope and the funding of the current protocol, urine samples collected as part of BladderPath will also be utilised in subsequent applications to investigate the sensitivities, specificities, and prognostic capabilities of:

- Protein biomarkers
- Nucleic acid biomarkers
- Commercially-available biomarkers

In addition, there is increasing interest in the detection and use of circulating tumour DNA (ctDNA in blood plasma) for the diagnosis and prognostication of malignancy[38-40]. We will therefore also take blood samples for this purpose.

As and when we obtain funding for further studies beyond AmpseqUr, these will be detailed in the Biomarker Sub-study Manual and submitted for separate ethical approval.

10. DATA HANDLING AND RECORD KEEPING

10.1 Data Collection

Electronic Case Report Forms (eCRFs) will be developed to collect all required study data.

Ultimately the intent is to capture as much study data as possible from Hospital Episode Statistics (HES) and other electronic NHS databases. The plan being that the eCRFs will be prepopulated with data from HES. As participating Trusts need to collect this data for their HES feeds, we can use the same data to pre-populate the CRFs for items such as radiotherapy, chemotherapy and surgery (including surveillance cystoscopy and cystectomy) before sending the pre-populated forms to the research site team. The site research team will then need to verify and if necessary correct data found to be inaccurate in HES (e.g. presence of absence of recurrence) or not collected (e.g. quality of life). This will allow us to collect key data essentially in near to "real time" to allow rapid assessment of study outcomes. We believe this will reduce the burden of data collection, increase accuracy and reduce timelines.

The results of various audits conducted at University Birmingham Hospitals NHS Trust (UHB), have informed data collection techniques for the trial.

Consent to capture data from HES will be requested from all patients taking part in the study on the informed consent forms. The intent is to collect data regularly and clarification forms will be sent to sites after initial data capture from HES. Patient identifiers (NHS numbers) and additional items such as gender, date of birth, hospital and enrolment dates will be sent by the Study Office, as well as a study identifier created for this purpose to the University Hospitals Birmingham NHS Foundation Trust (UHB) Informatics Team through a secure FTP (File Transfer Protocol) site. This initial transfer of patient identifiable data will only occur once per patient.

The UHB Informatics Team has access to national HES data supplied with an eight week lag and therefore can provide this data for all study patients regardless of the site they were recruited and treated at. The Informatics Team will match the study numbers with the relevant data from HES and send this back to the study management team through the secure FTP site, the unique trial number and relevant HES items will be returned to the trial management team. The Study Office will generate queries based on the data captured from HES and send these to the site research team via an electronic system. The site research team will respond via the same electronic system. Tools for data management will be developed in collaboration with programmers at the CRCTU and the UHB Informatics team. Quality of life data will be captured both through questionnaires. Health Economic data will be captured using both paper forms to be filled out by patients as well as directly from HES. Data collection will be piloted in a few different centres and tested for reproducibility. Any issues will be addressed and changes implemented if necessary and the data capture plan updated as appropriate.

For non-English sites, including Wales, Scotland and Northern Ireland, due to differences between the national electronic systems used to store digital NHS data; such data will not be accessible to the investigators and therefore not used to pre-populate the eCRF. Treatment, Follow-up and other ad hoc Forms will therefore be entered onto the database in full by the sites' research teams, as soon as possible after relevant events. This also means that non-NHS sites can also participate either within or outside the UK.

The method described above of pre-populating the eCRF with data obtained via HES for English patients is still to be finalised. Prior to implementation site are required to complete the eCRF manually. Treatment, Follow-up and other ad hoc Forms will therefore be entered onto the database in full by the sites' research teams, as soon as possible after relevant events.

The Case Report Form (CRF) will comprise the following forms:

Table 4. CRFs collected

Form	Summary of data recorded	Schedule for submission
ALL PATIENTS		
Eligibility Checklist	Confirmation of eligibility and satisfactory staging investigations where necessary	Faxed as soon as possible after randomisation
Registration Form	Patients details, confirmation of eligibility criteria, optional consent issues	Online: after consent form 1
RANDOMISED PATIENTS ONLY (all forms completed online)		
Randomisation Form	Patients details; confirmation of eligibility criteria, result of randomisation pathway allocation, optional consent issues	Online: after consent form 2
Baseline Form	Details of baseline assessments	As soon as possible after study entry
Flexible Cystoscopy Form	Details of the procedure	As soon as possible after procedure If a biopsy was taken, send a copy of corresponding pathology report to Study Office for data to be entered centrally *NB. copy pathology reports must be pseudo-anonymised, giving only the patient's TNO.*
TURBT Form	Details of the TURBT procedure	As soon as possible after procedure Send copy of corresponding pathology report to Study Office for data to be entered centrally *NB. copy pathology reports must be pseudo-anonymised, giving only the patient's TNO.*
MRI Form	Details of the MRI procedure	As soon as possible after procedure
Pathology Form	A copy of pathology reports should be sent to the Study Office for data to be entered centrally. *NB. copy pathology reports must be pseudo-anonymised, giving only the patient's TNO.*	As soon as pathology report available

Staging Form	Details of planned treatment	As soon as possible after treatment has been decided *NB. Only one form expected*
Follow-up Form	Details of investigations/treatment during follow-up period	Every 3 months from randomisation up to 12 months, every 6 months from randomisation between 12 months and 24 months and annually thereafter
Recurrence Form	Reporting of any local recurrence or progression	As soon as becoming aware of the recurrence
Systemic Chemotherapy Form	Documentation of chemotherapy regime and cycles given	Either when prompted by the Study Office (English sites) or at the end of the course of treatment (non-English sites)
Intravesical Therapy Form	Documentation of intravesical chemotherapy regime and cycles to be given	Either when prompted by the Study Office (English sites) or as soon as possible after intravesical treatment has commenced. (non-English sites)
End of Intravesical Therapy Form	To report end date of intravesical chemotherapy	Immediately upon termination of treatment
Radiotherapy Form	Documentation of treatment given plus details of any synchronous chemotherapy treatment *NB. Relevant chemotherapy form to be completed*	Either when prompted by the Study Office (English sites) or at the end of the course of treatment (non-English sites)
Cystectomy Form	Documentation of surgical treatment Send a copy of the corresponding pathology report to Study Office for data to be entered centrally *NB. copy pathology reports must be pseudo-anonymised, giving only the patient's TNO.*	Either when prompted by the Study Office (English sites) or at the end of the course of treatment (non-English sites)
Death Form	Date and cause of death	Immediately upon notification of patient's death
Deviation Form	Completed in the event of a deviation from the protocol	Immediately upon discovering deviation
Withdrawal Form	Used to notify the Study Office of patient withdrawal from the study	Immediately upon patient withdrawal

This study will use an eCRF system for completion of the majority of the CRFs, the exceptions being the Eligibility Checklist, the SAE form and Quality of Life Questionnaires.

The CRFs must be completed by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within the timeframe listed above.

Entries on paper CRFs should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and the data accurate.

Where paper forms are completed the originals should be sent to the Study Office and a copy filed in the Investigator Site File.

Study forms may be amended by the Study Office, as appropriate, throughout the duration of the study. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

10.2 Archiving

It is the responsibility of the Principal Investigator to ensure all essential study documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, patients' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 15 years after the end of the study. Do not destroy any documents without prior approval from the CRCTU Document Storage Manager.

11. QUALITY MANAGEMENT

11.1 Site Set-up and Initiation

All sites will be required to sign a Clinical Study Site Agreement prior to participation. In addition all participating Investigators will be asked to sign the necessary agreements including an Investigator Registration Form and supply a current Curriculum Vitae (CV) to the Study Office. All members of the site research team will also be required to sign the Site Signature and Delegation Log, which should be returned to the Study Office. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the study design, protocol procedures, adverse event reporting, the collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the study. The Study Office must be informed immediately of any change in the site research team.

11.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the BladderPath Quality Management Plan. Additional on-site monitoring visits may be triggered for example by poor CRF return, poor data quality, high SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required, the Study Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the BladderPath study staff access to source documents as requested.

11.3 Central Monitoring

Where a patient has given explicit consent sites are requested to send in copies of signed Informed Consent Forms for in-house review.

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming Case Report Forms for compliance with the protocol, data consistency, missing data and timing. Sites will be sent Data Clarification Forms requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or Good Clinical Practice (GCP), and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the study protocol to the main Research Ethics Committee (REC).

11.4 Audit and Inspection

The Investigator will permit study-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

11.5 Notification of Serious Breaches

The sponsor of the study is responsible for notifying the REC in writing of any serious breach of:

- The conditions and principles of GCP in connection with the study, or
- The protocol relating to the study, within seven days of becoming aware of a breach.

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the study, or
- The scientific value of the study.

Sites are therefore requested to notify the Study Office of a suspected study-related serious breach of GCP and/or the study protocol. Where the Study Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Study Office in providing sufficient information to report the breach to REC where required and in undertaking any corrective and/or preventive action.

12. END OF STUDY DEFINITION

The end of study will be three months after the last patient has a minimum of five years follow-up. The Study Office will notify the main REC that the study has ended and a summary of the clinical study report will be provided within 12 months of the end of study.

13. STATISTICAL CONSIDERATIONS

13.1 Definitions of outcome measures

The proportion of possible MIBC patients randomised to Pathway 2 who correctly follow pathway protocol

Defined as the number of possible MIBC patients randomised to Pathway 2 who have an MRI at the appropriate stage of the pathway as a proportion of all possible MIBC patients randomised to Pathway 2.

Overall proportion of patients who correctly follow protocol on each pathway for all randomised patients

For Pathway 1, defined as the number of probable NMIBC and possible MIBC patients randomised to Pathway 1 who receive a TURBT at appropriate pathway stage as a proportion of all patients randomised to Pathway 1.

For Pathway 2, defined as the number of probable NMIBC patients on Pathway 2 who have a TURBT plus the number of possible MIBC patients on Pathway 2 who have an MRI divided by all patients randomised to Pathway 2.

Recruitment and retention rates at each study site

Defined as the number of patients randomised and the number of patients registered but not yet randomised at each study site.

Counts of each type of treatment

Defined as the number (and proportion) of patients in each pathway who received TURBT, systemic chemotherapy, radiotherapy, cystectomy or decision for palliative care

Definitive treatment

Under NHS guidelines, the definitive treatment for bladder cancer is TURBT. In BladderPath study, TURBT is used for diagnosis and also treat as the definitive treatment for all patients who were initially classified as probable NMIBC and for those who were randomised to Pathway 1 and classified as possible MIBC. For patients who were randomised to Pathway 2 and initially classified as possible MIBC, the definitive treatment includes TURBT, systemic chemotherapy, radiotherapy, cystectomy and palliative care only.

Correct treatment

The correct treatment is TURBT for NMIBC patients. For MIBC patients, the correct treatment includes systemic chemotherapy, radiotherapy, cystectomy and palliative care only.

Time to correct treatment (TTCT)

For NMIBC patients is defined as the number of whole days between the date of randomisation and TURBT.

For MIBC patients is defined as the number of whole days between the date of randomisation and the first date of systemic chemotherapy, radiotherapy, cystectomy or date of decision for best supportive care only.

Time to definitive treatment

For Pathway 1 is defined as the interval in whole days between the date of randomisation and TURBT

For Pathway 2 is defined as the interval in whole days between the date of randomisation and TURBT for those deemed probable NMIBC and as between date of randomisation and the first date of TURBT, systemic chemotherapy, radiotherapy, cystectomy or date of decision for best supportive care only for those deemed possible MIBC.

Clinical progression-free survival (CPFS)

Defined as the number of whole days between date of randomisation and one of the following events, whatever occurs first:

- Diagnosis of distant metastases
- Diagnosis of loco-regional nodal recurrence
- Diagnosis of muscle invasive tumour recurrence in the bladder

- Diagnosis of non-muscle invasive tumour recurrence in the bladder
- Diagnosis of upper tract urothelial cancer or urethra
- Death from bladder cancer

Patients with no evidence of clinical progression will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.

Time to each treatment type

Defined as the number of days between date of randomisation to TURBT, systemic chemotherapy, radiotherapy, cystectomy or decision for palliative care only.

Time to metastatic disease progression

Defined as the number of whole days between the date of randomisation and the date of detection of first distant progression or death from bladder cancer. Patients with no evidence of metastatic disease progression will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.

Time to loco-regional progression

Defined as the number of whole days between the date of randomisation and the earliest date of detection of loco-regional progression or death from bladder cancer.

Loco-regional progression is defined as recurrence in the bladder +/- local extension and recurrence outside the bladder but within the true pelvis. Local recurrence will be classified as non-invasive (≤pT1 including Carcinoma In Situ (CIS)) or invasive (unequivocal clinical or pathological evidence of muscle wall invasion ≥ pT2). Regional recurrence includes pelvic lymph node recurrence within the true pelvis. Patients with no evidence of loco-regional progression will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.

Number and percentage of recurrences, progressions or incidence of metastatic disease
Defined as separate counts of the number of patients who experience recurrences, progressions, metastatic disease progression and the number of instances experienced by each patient.

Accuracy of MRI/TURBT by comparison with histologically confirmed diagnoses
Defined separately for MRI and TURBT using sensitivity, specificity and likelihood ratios. Sensitivity will provide information on the ability of each test to identify disease and the specificity the ability of each test to identify the absence of disease. The likelihood ratios both positive and negative will allow post-test calculations of the probability of disease.

Disease-free survival time
Defined as the number of whole days between the date of randomisation and the earliest date of detection of loco-regional or distant progression, or date of death from bladder cancer. Patients with no evidence of disease progression will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.

Overall survival time
Defined as the number of whole days between the date of randomisation and date of death from any cause; patients who do not die during the course of the study will be censored at the date last known to be alive.

Number of unnecessary radical cystectomies
Defined as the number of patients who are confirmed as NMIBC after cystectomy, unless the MDT decision was that cystectomy was the correct therapy in a patient known to have high grade NMIBC during staging.

Number of protocol related serious adverse events (SAEs)
The number of protocol related SAEs overall and split by pathway.

13.2 Power and sample size

The overall sample size required for the BladderPath trial is 950 patients.

13.2.1 Feasibility stage

This stage will evaluate 150 patients entered into the study, which allows for qualitative checks of feasibility to be made such as willingness of patients to be randomised into the study. Quantitatively, we will consider feasibility to have been demonstrated if we observe at least 80% of possible MIBC patients correctly follow Pathway 2. Of the 150 patients recruited for this stage, 75 patients will be randomised to Pathway 2. We expect that around 50% of the Pathway 2 patients will be diagnosed as possible MIBC; which results in a sample of around 38 patients scheduled to have a MRI. The power of observing feasibility is dependent on the true proportion of patients who correctly follow the pathway. The probability of observing that 80% of the sample correctly follows the protocol for a selection of suitable true proportions is given in the table below, which provides good power to detect feasibility.

Table 5. Probability of a successful feasibility stage given 80% of possible MIBC patients are observed to correctly follow the pathway

True proportion	Probability of observing feasibility
80%	66%
83%	81%
85%	90%
87%	95%
90%	99%

13.2.2 Intermediate stage

In this stage, we check that Pathway 2 will reduce the TTCT for MIBC patients compared to Pathway 1. The estimated sample size for this stage is event driven and requires at least 20 MIBC patients to have correct treatment across both pathways.

To account for patients with longer times on the waiting list being prioritised for treatment, we first assume that the hazard of treatment changes over time and follows a Weibull distribution in both pathways. We further assumed that the TTCT in Pathway 1 has a median of 100 days and 95th percentile 150 days and the effects of Pathway 2 is to reduce the median TTCT by 30 days to 70 days for MIBC patients. Assuming that the distribution of the TTCT follows a Weibull distribution with the same shape parameter as Pathway 1 and that the usual proportional hazards assumption holds; the hazard ratio for the two study arms is 3.6. Hence, using the log-rank test, to have 80% power to detect a hazard ratio of 3.6 would require a total of 20 patients with MIBC and to have 90% power would require a total of 26 patients. We will focus on patients initially diagnosed as possible MIBC for the intermediate stage since the two pathways do not differ for probable NMIBC patients. Around 20-25% of new BC patients present with de novo MIBC. Hence, to recruit a total of 20 MIBC patients in the population we focus on, *approximately 80-100* patients *will need* to be *recruited*. At 90%, this would increase to approximately 130 patients.

13.2.3 Definitive stage – Final Clinical Stage

This stage tests the effect of Pathway 2 on the longer term clinical endpoints. The anticipated duration is 30 months in 15 regional referral centres. The estimated total sample for this stage is 380 progression events; or approximately 950 patients with bladder cancer.

For this stage, the primary outcome is clinical progression-free survival and is designed to detect a reduction in progression events in Pathway 2 such that the hazard ratio is 0.75. Assuming that the proportional hazards assumption holds, to detect a hazard ratio of 0.75 with 80% power requires observation of 380 progression events and with 90% power requires observation of a total of 510 progression events. To detect this effect at 2 years follow up, assuming an overall recurrence rate of 40%, will require 950 (80% power) or 1275 (90% power) patients. Similar to the intermediate stage, the

power for this stage is event driven and hence will depend on the number of observed events and not the number of patients recruited.

13.3 Statistical analysis of efficacy and harms

13.3.1 Feasibility stage

Descriptive statistics on recruitment and consent rates will be calculated and assessed to ensure study feasibility. The numbers of patients assigned to each of the MIBC and NMIBC pathways in both arms will be calculated (i.e. numbers in each of boxes A-D in the study flow diagram). Of the patients who are initially given a diagnosis of possible MIBC (Box D), the proportion and 95% confidence interval (CI) of patients who correctly receive the MRI as planned will be calculated. The image-directed pathway will be considered feasible if this proportion exceeds 80%.

Secondary analyses

Other analyses at the feasibility stage will include descriptive statistics of the patients enrolled in the study and the proportions of each patient pathway (Boxes A-D) who correctly receive the allocated treatment pathway.

13.3.2 Intermediate stage

Kaplan-Meier estimates of TTCT for MIBC patients in each pathway will be evaluated. To compare the TTCT for MIBC between pathways, a Cox regression model will be constructed. Covariates added to the model will include: patient age, gender and study centre.

Secondary analyses

Intermediate stage secondary analyses will include a Cox regression model comparing the TTCT of all possible MIBC patients (i.e. not just those confirmed as MIBC patients but all patients that pass through box B and box D in the study flow diagram).

Descriptive statistics of pathway use will be updated from the feasibility stage, if the two stages do not occur simultaneously.

13.3.3 Definitive stage

The primary analysis of the study is the comparison of clinical progression-free survival for all randomised patients between the two pathways.

Assuming that proportional hazards holds, a Cox proportional hazards model will be generated to model the progression-free survival times on the two pathways. Variables that will be entered into the model will include: patient descriptive variables (age, gender, etc.); centre of recruitment, the initial diagnosis of tumour grade at randomisation (stratification group) and the initial cystoscopic assessment of possible MIBC.

The proportional hazards assumption will be checked. If the proportional hazards assumption does not hold then possible transformations and time varying effects will be considered to account for this.

Secondary analyses

Descriptive statistics will be produced.

Secondary analyses will include a Cox regression model comparing the TTCT of all patients (i.e. comparing TTCT for patients who pass through boxes A-D in the study flow diagram) and for the probable NMIBC patients (boxes A and C). Recurrence rates; overall and disease-free survival; time to definitive treatment; number of each type of treatment(s) received; accuracy of MRI/TURBT by comparison with histological confirmed diagnoses; number of unnecessary radical cystectomies; number of protocol related SAEs will also be calculated for each pathway. In addition, the outcome measures in the first two stages will be re-analysed.

13.4 Planned subgroup analyses

Subgroup analyses will be conducted at the final clinical stage according to:

- Initial diagnoses: possible MIBC vs. probable NMIBC
- Final diagnosis type: MIBC vs. NMIBC

- Multifocal vs. single invasive cancer
- Men vs. women
- Age stratified: <75 vs. ≥75

13.5 Qualitative sub-study analysis

The framework approach will be employed to analyse the patient interview data [43, 44]. This method produces structured outputs of summarised data and, as described by Gale *et al*, is recommended when a multidisciplinary research team with varying experience is involved in a project [44]. Analysis will involve a number of stages; first initial familiarisation with the transcripts by the qualitative research team, followed by close reading of the first five transcripts and the iterative generation of codes and categories leading to the development of the full analytic framework. This framework will be applied to the remainder of the data by the field researcher and a summary for each transcript charted into a coding matrix. The qualitative sub-study researchers will double code four transcripts to ensure rigour of the analysis.

Finally, themes or concepts will be identified and developed through an interpretative and reflective process involving members of the research team.

Healthcare professional (HCP) interview transcripts will be analysed with the method of template analysis [45]. In this process an initial template will be developed using *a priori* codes that reflect the aims of the investigation. This template can be extended when unanticipated data or sub categories become apparent in the coding process. Thematic development occurs through the identification of patterns and links in the coded data.

This method will also be applied to the analysis of the audio-recorded recruitment consultations.

Findings from initial interviews will be fed back to the wider project team at four to five months and considered together with recruitment rates. Where indicated, findings will be used to inform revisions to study information and to the recruitment strategy.

14. HEALTH ECONOMIC EVALUATION

An economic evaluation will be performed to estimate the incremental cost-effectiveness of the imaging-directed pathway compared with surgery-directed (standard) pathway for bladder cancer patients from a UK NHS and Personal Social Services (PSS) perspective. Hospital and community health and social care service use, such as inpatient stays, outpatient visits and medication use, will be collected from two principal sources (i) Hospital Episode Statistics (HES) data and (ii) self-reported participant questionnaires. The data collected in the participant questionnaires at each time point will also record direct non-medical costs borne by participants and carers as a result of participant attendance at hospital visits (including travel expenses), as well as indirect costs associated with work losses and impaired health status. Unit costs for each resource input will be obtained from a variety of primary and secondary sources, including national cost compendia such as the Department of Health's National Reference Costs, the British National Formulary and the Personal and Social Services Research Unit (PSSRU) compendium of Unit Costs of Health and Social Care. Participant health-related quality of life will be estimated using the EuroQol measure. Study participants will be asked to complete the EuroQol EQ-5D-5L at baseline and at 3, 6, 9, 12, 18, 24 months and annually from 24 months up to 5 years post-randomisation. Responses to the EQ-5D-5L will be converted into multi-attribute utility scores using newly established algorithms for this measure.

A within study economic evaluation will compare the outcomes and costs for the study comparators over the study follow-up period. First, a cost-consequence analysis will describe all outcomes related to the resource use profiles, costs and health consequences (side-effects, disease progression, recurrences) of the imaging-directed pathway compared with the TURBT directed (standard) pathway for bladder cancer patients. Subsequently, a cost-utility analysis will determine the incremental cost per quality-adjusted life year (QALY) associated with the imaging-directed pathway. Outputs of the economic evaluation will be presented as incremental cost-effectiveness ratios (ICERs); scatterplots of simulated ICER values on cost-effectiveness planes, cost-effectiveness acceptability curves (CEACs) and expected net benefit values assuming that the cost-effectiveness threshold varies across a range of values. Discounting of costs and health consequences will not be required for the within-study economic evaluation. Sensitivity analyses will be conducted adopting a broader societal perspective in the

economic evaluation, Regression analysis will be used to estimate the between-group differences in mean costs and QALYs. Interaction terms will be used to investigate possible treatment moderators that can identify participant subgroups for whom cost-effectiveness is predictably different, e.g. age, sex, or other relevant participant characteristics.

15. STUDY ORGANISATIONAL STRUCTURE

15.1 Sponsor

The study is sponsored by the University of Birmingham.

15.2 Coordinating Centre

The study is being conducted under the auspices of the CRCTU, University of Birmingham according to their local procedures.

15.3 Trial Management Group

The Chief Investigator, Co-investigators including the Trial Statistician, Trial Manager and Trial Coordinator and patient advocate will form the Trial Management Group (TMG). The TMG will be responsible for the day-to-day conduct of the study, meeting at regular intervals, usually be teleconference. They will be responsible for the set-up, promotion, on-going management of the study, the interpretation of the results and preparation and presentation of relevant publications.

15.4 Trial Steering Committee

The Trial Steering Committee (TSC) will be set up with an independent chairperson to oversee the study. Membership will be composed of selected TMG members, independent clinicians and at least one patient advocate. The TSC will meet shortly before commencement of the study and at least once a year (usually by teleconference), the meetings will usually be arranged to coincide with study milestones. The TSC will supervise the conduct of the study, monitoring progress including recruitment, data completeness, losses to follow-up, and deviations from the protocol. They will make recommendations about conduct and continuation of the study.

15.5 Data Monitoring Committee

Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the study, together with the results from other relevant research, justifies the continuing recruitment of further patients. The DMC will operate in accordance with a study specific charter based upon the template created by the Damocles Group. The DMC will is scheduled to meet at least one year after the study opens to recruitment and then annually thereafter until the study closes to recruitment, the meetings will usually be arranged to coincide with study milestones. Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the Trial Management Group who will convey the findings of the DMC to the Trial Steering Committee. The DMC may consider recommending the discontinuation of the study if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise patient safety.

15.6 Finance

This is a clinician-initiated and clinician-led research study funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) programme.

No individual per patient payment will be made to NHS Trusts, Investigators or patients.

16. ETHICAL CONSIDERATIONS

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, 1964, amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996 (website: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/).

The study will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Data Protection Act 1998 and Human Tissue Act 2004) and Good Clinical Practice (GCP). The protocol will be submitted to and approved by the main Research Ethics Committee (REC) prior to circulation.

Before any patients are enrolled into the study, the Principal Investigator at each site is required to obtain local Research & Development (R&D) approval. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the Study Office.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

17. CONFIDENTIALITY AND DATA PROTECTION

Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018. We will seek consent to access electronic records relating to the patient held within the NHS. These may include (but are not limited to), Hospital Episode Statistics (HES), radiotherapy records, electronic chemotherapy records, electronic GP records, other data held by Cancer Intelligence Units or the Registrar of Births Marriages and Deaths. The intent is to link the clinical study data to relevant data within these other databases in order to pre-populate the case record forms. The initial feasibility stage will identify which data items provide maximum utility for the study purposes. This will allow data collection to, as far as possible, utilise routinely collected data, removing the need for costly research nurse and data manager time. It will also ensure timeliness and accuracy of study data. For example, all UK Radiotherapy Departments use electronic treat and verify systems. Directly using these systems to produce a record of radiotherapy received for bladder cancer will thus be both timely and accurate as it will be the definitive record of treatment received. Similar considerations apply to chemotherapy systems and HES in relation to surgery, including cystoscopy. We believe the "real-time" use of these data can revolutionise study data collection, improving accuracy, increasing speed of collection and reducing costs. The study budget includes support for a statistician embedded within the informatics department at University Hospitals Birmingham NHS Foundation Trust (UHB) which has particular expertise in this area. This is a different approach to data collection to those usually employed, pilot studies carried out within UHB strongly support the potential utility of these methods. The principal barrier to these methods in the past has been consent to data sharing; hence this will be explicitly sought at study entry. Data linkage of this sort will be carried out within the NHS in the Informatics Department at UHB using pre-existing Information Governance procedures. As the HES data in particular is one of the main drivers of NHS funding, we will be using this to provide additional outcomes data for the health economics outcomes analysis. Data transferred to the CRCTU will be identified solely by a study number to ensure confidentiality.

The study will make extensive use of pre-existing NHS data to populate the case record forms. Care will be taken to restrict access to items strictly relevant to the study conduct.

With the patient's consent, their full name, gender, date of birth, NHS number, or in Scotland the Community Health Index (CHI), hospital number will be collected at study entry to allow tracing through Hospital Episode Statistics (HES), Cancer Registries, Cancer Intelligence Unit, NHS digital and other similar data sources kept by the NHS or related organisations if necessary.

Patients will be identified using only their unique trial number, initials and date of birth on the Case Report Form and correspondence between the Study Office and the participating site. However patients are asked to give permission for the Study Office to be sent a copy of their signed Informed

Consent Form which will not be anonymised. This will be used to perform in-house monitoring of the consent process. The Investigator must maintain documents not for submission to the Study Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete study records, provided that patient confidentiality is protected.

The Study Office will maintain the confidentiality of all patients' data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer (Cancer Registries, laboratory staff). Representatives of the BladderPath study team may be required to have access to patient's notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

Patient and Public Involvement (PPI)

The concept of the study is supported by the NCRI Bladder Clinical Studies Group (CSG). The CSG has two patient advocates who have participated in the study discussions at the Bladder CSG meetings; the BladderPath study has three patient advocates as members of either the Trial Management Group or Trial Steering Committee. The patient advocates have been involved in the review of the study design from a patient perspective and have helped with the design of the recruitment process and patient information sheet. A study website will be established and information about the study presented in lay and professional formats.

18. INSURANCE AND INDEMNITY

University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment.

In terms of liability at a site, NHS Trust and non-Trust hospitals have a duty to care for patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven.

The University of Birmingham cannot offer indemnity for non-negligent harm. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.

19. PUBLICATION POLICY

Results of this study will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Trial Management Group (TMG) and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the study was performed with the support of the University of Birmingham. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

20. REFERENCE LIST

1. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11. International Agency for Research on Cancer Web site. http://globocan.iarc.fr.

2. Ploeg M, Aben KH, Kiemeney L. The present and future burden of urinary bladder cancer in the world. World J Urol. 2009;27(3):289-93.

3. CRUK Cancerstats - Bladder Cancer 2014 [cited 2014 22/4/14]. Bladder cancer mortality and incidence rates]. Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/bladder/.

4. Bryan RT, Kirby R, O'Brien T, Mostafid H. So much cost, such little progress. European urology. 2014;66(2):263-4.

5. Kaplan AL, Litwin MS, Chamie K. The future of bladder cancer care in the USA. Nature reviews Urology. 2014;11(1):59-62.

6. Kulkarni GS, Hakenberg OW, Gschwend JE, Thalmann G, Kassouf W, Kamat A, et al. An updated critical analysis of the treatment strategy for newly diagnosed high-grade T1 (previously T1G3) bladder cancer. European urology. 2010;57(1):60-70.

7. Engilbertsson H, Aaltonen KE, Bjornsson S, Kristmundsson T, Patschan O, Ryden L, et al. Transurethral Bladder Tumor Resection Can Cause Seeding of Cancer Cells into the Bloodstream. The Journal of urology. 2014. 2015 Jan;193(1):53-7.

8. Swinnen G, Maes A, Pottel H, Vanneste A, Billiet I, Lesage K, et al. FDG-PET/CT for the preoperative lymph node staging of invasive bladder cancer. European urology. 2010;57(4):641-7.

9. Maurer T, Souvatzoglou M, Kubler H, Opercan K, Schmidt S, Herrmann K, et al. Diagnostic efficacy of [11C]choline positron emission tomography/computed tomography compared with conventional computed tomography in lymph node staging of patients with bladder cancer prior to radical cystectomy. European urology. 2012;61(5):1031-8.

10. Vargas HA, Akin O, Schoder H, Olgac S, Dalbagni G, Hricak H, et al. Prospective evaluation of MRI, (1)(1)C-acetate PET/CT and contrast-enhanced CT for staging of bladder cancer. European journal of radiology. 2012;81(12):4131-7.

11. Rajesh A, Sokhi HK, Fung R, Mulcahy KA, Bankart MJ. Bladder cancer: evaluation of staging accuracy using dynamic MRI. Clinical radiology. 2011;66(12):1140-5.

12. Mahmud SM, Fong B, Fahmy N, Tanguay S, Aprikian AG. Effect of preoperative delay on survival in patients with bladder cancer undergoing cystectomy in Quebec: a population based study. The Journal of urology. 2006;175(1):78-83; discussion

13. Fahmy NM, Mahmud S, Aprikian AG. Delay in the surgical treatment of bladder cancer and survival: systematic review of the literature. European urology. 2006;50(6):1176-82.

14. Kulkarni GS, Urbach DR, Austin PC, Fleshner NE, Laupacis A. Longer wait times increase overall mortality in patients with bladder cancer. The journal of urology. 2009;182(4):1318-24.

15. Babjuk M, Burger M, Zigeuner R, Shariat SF, van Rhijn BW, Comperat E, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. European urology. 2013;64(4):639-53.

16. Mowatt G, Zhu S, Kilonzo M, Boachie C, Fraser C, Griffiths TR, et al. Systematic review of the clinical effectiveness and cost-effectiveness of photodynamic diagnosis and urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology for the detection and follow-up of bladder cancer. Health technology assessment. 2010;14(4):1-331, iii-iv.

17. Bryan RT, Zeegers MP, van Roekel EH, Bird D, Grant MR, Dunn JA, et al. A comparison of patient and tumour characteristics in two UK bladder cancer cohorts separated by 20 years. BJU international. 2013;112(2):169-75.

18. Boustead GB, Fowler S, Swamy R, Kocklebergh R, Hounsome L, Section of Oncology B. Stage, grade and pathological characteristics of bladder cancer in the UK: British Association of Urological Surgeons (BAUS) Urological Tumour Registry. BJU international. 2014;113(6):924-30.

19. Takeuchi M, Sasaki S, Naiki T, Kawai N, Kohri K, Hara M, et al. MR imaging of urinary bladder cancer for T-staging: a review and a pictorial essay of diffusion-weighted imaging. Journal of magnetic resonance imaging : JMRI. 2013;38(6):1299-309.

20. Takeuchi M, Sasaki S, Ito M, Okada S, Takahashi S, Kawai T, et al. Urinary bladder cancer: diffusion-weighted MR imaging--accuracy for diagnosing T stage and estimating histologic grade. Radiology. 2009;251(1):112-21.

21. Rosenkrantz AB, Mussi TC, Melamed J, Taneja SS, Huang WC. Bladder cancer: utility of MRI in detection of occult muscle-invasive disease. Acta radiologica. 2012;53(6):695-9.

22. Rosenkrantz AB, Haghighi M, Horn J, Naik M, Hardie AD, Somberg MB, et al. Utility of quantitative MRI metrics for assessment of stage and grade of urothelial carcinoma of the bladder: preliminary results. AJR American journal of roentgenology. 2013;201(6):1254-9.

23. Donaldson SB, Bonington SC, Kershaw LE, Cowan R, Lyons J, Elliott T, et al. Dynamic contrast-enhanced MRI in patients with muscle-invasive transitional cell carcinoma of the bladder can distinguish between residual tumour and post-chemotherapy effect. European journal of radiology. 2013;82(12):2161-8.

24. Shimwell NJ, Bryan RT, Wei W, James ND, Cheng KK, Zeegers MP, et al. Combined proteome and transcriptome analyses for the discovery of urinary biomarkers for urothelial carcinoma. British journal of cancer. 2013;108(9):1854-61.

25. Bryan RT, Shimwell NJ, Wei W, Devall AJ, Pirrie SJ, James ND, et al. Urinary EpCAM in urothelial bladder cancer patients: characterisation and evaluation of biomarker potential. British journal of cancer. 2014;110(3):679-85.

26. Bryan RT, Wei W, Shimwell NJ, Collins SI, Hussain SA, Billingham LJ, et al. Assessment of high-throughput high-resolution MALDI-TOF-MS of urinary peptides for the detection of muscle-invasive bladder cancer. Proteomics Clin Appl. 2011;5(9-10):493-503.

27. Stenzl A, Cowan NC, De Santis M, Jakse G, Kuczyk MA, Merseburger AS, et al. The updated EAU guidelines on muscle-invasive and metastatic bladder cancer. European urology. 2009;55(4):815-25.

28. Bryan RT, Collins SI, Daykin MC, Zeegers MP, Cheng KK, Wallace DM, et al. Mechanisms of recurrence of Ta/T1 bladder cancer. Annals of the Royal College of Surgeons of England. 2010;92(6):519-24.

29. Wilby D, Thomas K, Ray E, Chappell B, O'Brien T. Bladder cancer: new TUR techniques. World J Urol. 2009;27(3):309-12.

30. Wallace DM, Bryan RT, Dunn JA, Begum G, Bathers S, West Midlands Urological Research G. Delay and survival in bladder cancer. BJU international. 2002;89(9):868-78.

31. Begum G, Dunn JA, Bryan RT, Bathers S, Wallace DM, West Midlands Urological Research G. Socio-economic deprivation and survival in bladder cancer. BJU international. 2004;94(4):539-43.

32. NICE. Bladder cancer: diagnosis and management 2015 [updated 25 February 2015]. Available from:http://www.nice.org.uk/guidance/ng2/resources/bladder-cancer-diagnosis-and-management-of-bladder-cancer-51036766405.

33. Ye F, Wang L, Castillo-Martin M, McBride R, Galsky MD, Zhu J, et al. Biomarkers for bladder cancer management: present and future. American Journal of Clinical and Experimental Urology. 2014;2(1):1-14.

34. Kamat AM, Hegarty PK, Gee JR, Clark PE, Svatek RS, Hegarty N, et al. ICUD-EAU International Consultation on Bladder Cancer 2012: Screening, Diagnosis, and Molecular Markers. European urology. 2013;63(1):4-15.

35. Schmitz-Dräger BJ, Droller M, Lokeshwar VB, Lotan Y, Hudson MA, van Rhijn BW, et al. Molecular Markers for Bladder Cancer Screening, Early Diagnosis, and Surveillance: The WHO/ICUD Consensus. Urologia Internationalis. 2015;94(1):1-24.

36. Bryan RT, Regan HL, Pirrie SJ, Devall AJ, Cheng KK, Zeegers MP, et al. Protein shedding in urothelial bladder cancer: prognostic implications of soluble urinary EGFR and EpCAM. British journal of cancer. 2015;112(6):1052-8.

37. Edwards TJ, Dickinson AJ, Natale S, Gosling J, McGrath JS. A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven haematuria clinic. BJU international. 2006;97(2):301-5.

38. Ignatiadis M, Lee M, Jeffrey SS. Circulating Tumor Cells and Circulating Tumor DNA: Challenges and Opportunities on the Path to Clinical Utility. Clinical Cancer Research. 2015;21(21):4786-800.

39. Heitzer E, Ulz P, Geigl JB. Circulating Tumor DNA as a Liquid Biopsy for Cancer. Clinical Chemistry. 2015;61(1):112-23.

40. Chaudhuri AA, Binkley MS, Osmundson EC, Alizadeh AA, Diehn M. Predicting Radiotherapy Responses and Treatment Outcomes Through Analysis of Circulating Tumor DNA. Seminars in Radiation Oncology. 2015;25(4):305-12.

41. Ward DG, Baxter L, Gordon NS, Ott S, Savage RS, Beggs AD, James JD, et al. Multiplex PCR and Next Generation Sequencing for the Non-Invasive Detection of Bladder Cancer. PLoS One. 2016; 11(2)

42. Togneri FS, Ward DG, Foster JM, Devall AJ, Wojtowicz P, Alyas S, et al. Genomic complexity of urothelial bladder cancer revealed in urinary cfDNA. European Journal of Human Genetics.(2016); 24(8):1167-74

43. Ritchie, J. & Spencer, L. 1994. Qualitative data analysis for applied policy research by Jane Ritchie and Liz Spencer in A. Bryman and R. G. Burgess [eds.] 'Analysing qualitative data', (pp.173-194)

44. Gale NK et al.. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. (2013) *BMC Medical Research Methodology* 13**:**117 doi.org/10.1186/1471-2288-13-117

45. King, Nigel (2004) Using templates in the thematic analysis of text. In: Essential Guide to Qualitative Methods in Organizational Research. Sage, pp. 256-270. ISBN 9780761948872

46. Ward, Doug et al. Targeted deep sequencing of urothelial bladder cancers and associated urinary DNA: a 23-gene panel with utility for non-invasive diagnosis and risk stratification. 2019 May 11. doi: 10.1111/bju.14808

APPENDICES

APPENDIX 1 - WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human patients

Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964

and amended by the

29th World Medical Assembly, Tokyo, Japan, October 1975

35th World Medical Assembly, Venice, Italy, October 1983

41st World Medical Assembly, Hong Kong, September 1989

48th General Assembly, Somerset West, Republic of South Africa, October 1996

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human patients must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human patients.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person submitted to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human patients. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic principles

1. Biomedical research involving human patients must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human patients should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and

the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human patients should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human patient must always rest with a medically qualified person and never rest on the patient of the research, even though the patient has given his or her consent.

4. Biomedical research involving human patients cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the patient.

5. Every biomedical research project involving human patients should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the patient or to others. Concern for the interests of the patient must always prevail over the interests of science and society.

6. The right of the research patient to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the patient and to minimize the impact of the study on the patient's physical and mental integrity and on the personality of the patient.

7. Physicians should abstain from engaging in research projects involving human patients unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential patient must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the patient's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the patient is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the patient is a minor, permission from the responsible relative replaces that of the patient in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with professional care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical research involving human Patients (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The patient should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the patient.

APPENDIX 2 - DEFINITION OF ADVERSE EVENTS

Adverse Event

Any untoward medical occurrence in a patient or clinical study subject participating in the study which does not necessarily have a causal relationship with the treatment received.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Related Event

An event which resulted from the administration of any of the research procedures.

Serious Adverse Event

An untoward occurrence that:

- Results in death
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly/ birth defect
- Or is otherwise considered medically significant by the Investigator***

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Unexpected and Related Event

An event which meets the definition of both an Unexpected Event and a Related Event.

Unexpected Event

The type of event that is not listed in the protocol as an expected occurrence.

APPENDIX 3 - COMMON TOXICITY CRITERIA GRADINGS

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm