A phase III randomised trial of **P**eri-**O**perative chemotherapy versus s**U**rveillance in upper **T**ract urothelial cancer

PROTOCOL

Version 5

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ICR The Institute of Cancer Research

CANCER RESEARCH UK

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This protocol describes the POUT trial and provides information about procedures for entering participants into this trial. The protocol should not be used as a guide for the treatment of other patients.

Every care was taken in the preparation of this protocol, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but centres entering participants for the first time are advised to contact ICR-CTSU to confirm they have the most recent version. Protocol amendments will be circulated to participating centres as they occur.

This clinical trial will be conducted in compliance with the protocol, all international guidelines, national laws and regulations of the countries in which the Clinical Trial is performed, as well as any applicable guidelines.

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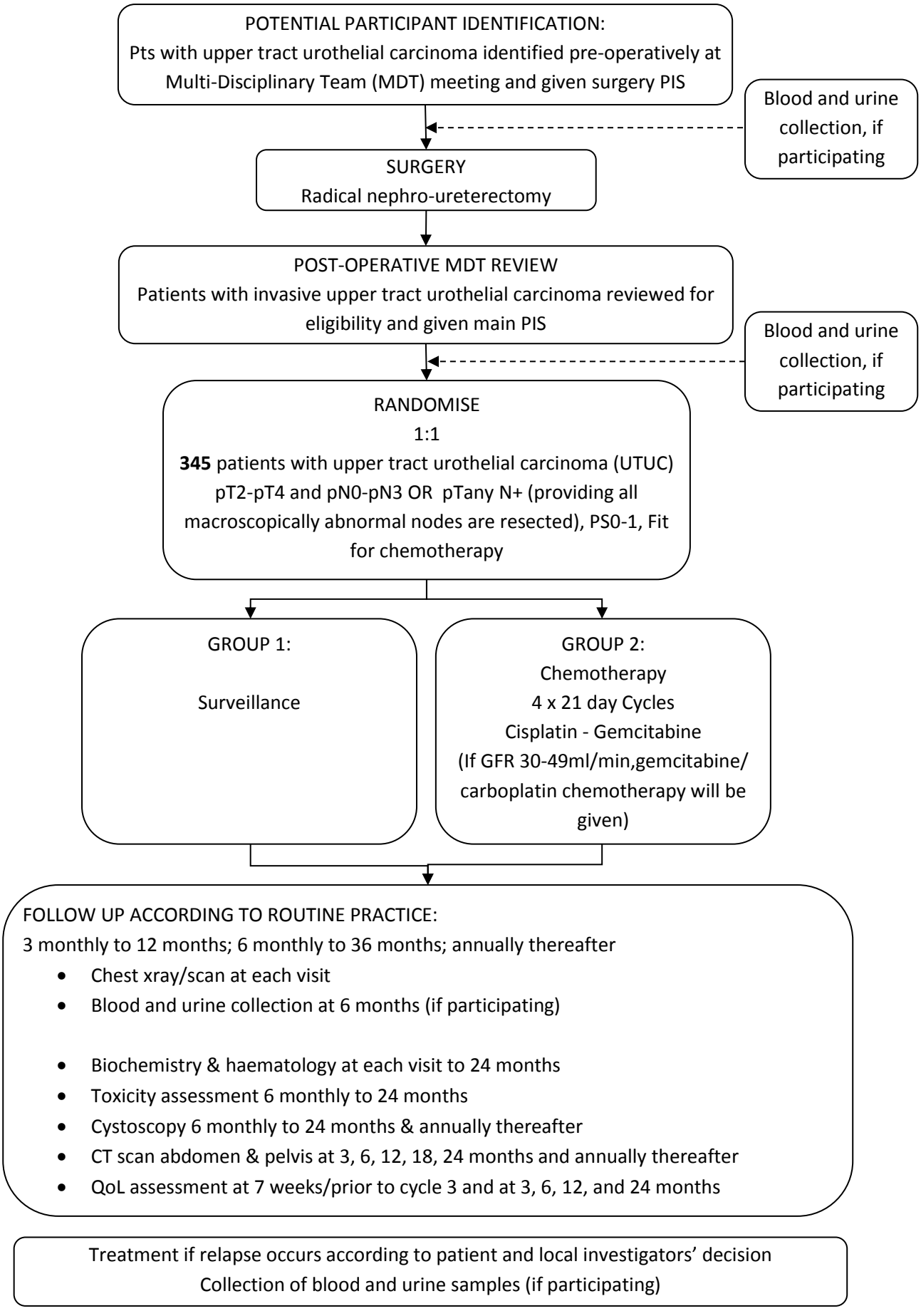
TRIAL SUMMARY

TITLE	POUT: A phase III randomised trial of **P**eri-**O**perative chemotherapy versus s**U**rveillance in upper **T**ract urothelial cancer
TARGET DISEASE	Upper Tract Urothelial Carcinoma (UTUC) (also known as upper urinary tract transitional cell carcinoma (TCC))
STUDY OBJECTIVES	To determine the efficacy, safety and effects on patients' quality of life of adjuvant chemotherapy in patients who have undergone radical nephro-ureterectomy for UTUC.
STUDY DESIGN	Phase III multicentre randomised controlled trial with initial recruitment optimisation stage
TRIAL POPULATION	Patients will be PS0-1, aged ≥ 18, post nephro-ureterectomy for upper tract urothelial carcinoma staged pT2-pT4 and pN0-pN3 OR pTany N+ (providing all macroscopically abnormal nodes are resected), They must be fit for chemotherapy, with a glomerular filtration rate (GFR) > 30 ml/min.
TREATMENT REGIMEN	Participants allocated to the chemotherapy group will receive four 21 day cycles of Gemcitabine-Cisplatin (If GFR 30-49 ml/min, gemcitabine-carboplatin chemotherapy will be given). Patients in the surveillance group will be closely monitored for signs of recurrence and will receive chemotherapy on recurrence if appropriate.
RECRUITMENT TARGET	345
PRIMARY ENDPOINT	• Disease-free survival (DFS)
SECONDARY ENDPOINTS	• Overall survival • Metastasis free survival • Incidence of bladder second primary tumours • Incidence of contralateral primary tumours • Acute and late toxicity • Treatment compliance • Quality of life (QoL)
FOLLOW UP	Follow up according to routine practice: • 3 monthly to 12 months; 6 monthly to 36 months; annually thereafter • At each visit: • Chest xray/scan, biochemistry & haematology • Cystoscopy 6 monthly to 24 months & annually thereafter • CT scan abdomen & pelvis at end of cycle 4/week 13, 6, 12, 18, 24 months and annually to year 5
TRANSLATIONAL STUDY SAMPLE COLLECTION (optional)	Pre-surgery: • Whole blood and first morning urine From nephro-ureterectomy: • Diagnostic tissue blocks Pre-randomisation, 6 months post randomisation and at recurrence: • Whole blood and first morning urine

TRIAL SCHEMA



1. INTRODUCTION

1.1. Upper tract urothelial carcinoma

Upper tract urothelial carcinoma (UTUC) is a rare tumour accounting for approximately 5% of all urothelial cell carcinomas with an estimated incidence of 2-4 cases per 100,000 individuals per year[1-3]. Incidence of UTUC is increasing[1, 3] and in 2008, a total of 751 cancers of the renal pelvis and ureter were registered in the UK[4]. Data from the BAUS Cancer Registry suggests that 48% of UTUC are muscle invasive[5] (a far higher proportion than for patients presenting with bladder cancer). The natural history from world-wide data shows that 60% of UTUC are found to be invasive at the time of diagnosis, compared with only 15% of bladder tumours. The majority of patients have stage T3 disease or above at the time of surgery[6] and where definitive nodal dissection is performed, 20-25% have pathological lymph node involvement on the surgical specimen[7]. The true incidence is difficult to ascertain, given inherent problems in diagnosis leading to late presentation. UTUC has a high rate (50%) of local recurrence[8] and of metastatic disease. Gold standard treatment involves radical nephro-ureterectomy, via an open or laparoscopic approach. Patients with muscle invasive UTUC have a high rate of loco-regional nodal metastases, associated with poorer outcome[9]. The impact of lymph node dissection (LND) on outcome has been examined in a limited number of non-randomised retrospective studies. Some case series suggest a survival benefit for those undergoing LND[7, 10, 11]. However, the impact of extended LND remains controversial and there are real difficulties in selecting which patients could benefit if LND were shown to be beneficial. Stage for stage, survival is poorer than for muscle invasive bladder cancer (MIBC). In 2005-07, one-year survival was 68% for females and 74% for males; for patients diagnosed in England in 2001-03, five year relative survival was 48% in females and 52% males[1]. The mortality to incidence ratio for UTUC is 0.34 compared with 0.20 for bladder cancer [12]. Finally, the anatomical site of the primary tumour is closely associated with prognosis: T3 ureteric tumours having a 24% 5 year survival compared with a 54% for renal pelvis tumours[13].

1.2. Evidence for chemotherapy in UTUC

There are limited studies in UTUC evaluating systemic chemotherapy in patients with locally advanced but completely resected tumours. The loco-regional recurrence rate in patients treated with radical nephro-ureterectomy alone is 45-60%[14] with 5 year survival rates of 0-34%. All studies are hampered by low patient numbers (less than 50 patients) and whilst some studies have shown improvements in overall survival, others have not. Studies in which no survival benefit has been demonstrated have been retrospective reviews using differing chemotherapy regimens, many of which would be considered inferior to current standard regimes for urothelial malignancies[15]. A recently published study compared the efficacy of 3 cycles of gemcitabine-cisplatin when given to patients with locally advanced TCC of the bladder and when given to patients with UTUC[16]. 64 patients were included and no differences in disease-free survival (DFS) or overall survival were seen. One small retrospective review[17] included 43 patients who were offered adjuvant chemotherapy after radical nephro-ureterectomy; 32 patients received chemotherapy, the remaining 11 refused. All had locally advanced (T3) or node positive disease. With 30 months median follow up, DFS was 63.6% (chemotherapy group) vs. 37.5% (surveillance) and 9/32 (32%) (chemotherapy) vs. 9/11 (81%) (surveillance) patients had died. Due to the paucity of data for systemic therapy in this patient group, existing European guidelines [18] state that the role of chemotherapy as adjuvant treatment in locally advanced or N+ tumours must be proved by prospective, randomised trials, and only recommend chemotherapy in the presence of systemic disease. These recommendations are based on Level 2 evidence (non-randomised studies), rather than on randomised controlled trial data.

1.3. Rationale for neoadjuvant chemotherapy in other urothelial tumours but not in UTUC

Urothelial malignancies are chemosensitive with the majority of the data based on experience in muscle invasive bladder cancer (MIBC). In bladder cancer, meta-analyses[19] have shown that cisplatin-based

combination neoadjuvant chemotherapy improves both DFS (hazard ratio (HR) = 0.78 95% CI: 0.71–0.86, p < 0.0001, equivalent to a 9% absolute improvement at 5 years) and overall survival (HR=0.86, 95% CI: 0.77-0.95, p=0.003, equivalent to a 5% absolute improvement at 5 years). For upper tract tumours, however, there is only a single published study of 15 patients evaluating pathological response to neoadjuvant chemotherapy prior to nephro-ureterectomy. This study was unable to address prognosis due to low patient numbers[20].

Furthermore, in UTUC it is difficult to obtain definitive histology and accurate staging pre-operatively. One study has shown that 12.8% of patients presumed on radiological and clinical grounds to have an UTUC had no tumour subsequently found in the surgical specimen[21]. Thus, although there is strong supporting evidence in favour of neoadjuvant chemotherapy in other urothelial cancers, routine use or evaluation of neoadjuvant chemotherapy in potentially resectable UTUC is not thought appropriate at this point in time as it could result in overtreatment of patients who either do not have UTUC, or who have non muscle invasive pathology.

1.4. Evidence for adjuvant chemotherapy in other urothelial tumours

A meta-analysis of adjuvant chemotherapy in MIBC was underpowered and confounded by salvage chemotherapy being given on relapse[22]. Updated guidelines on the management of MIBC conclude that adjuvant chemotherapy should only be given in the context of clinical trials[23]. The EORTC 30994 trial of adjuvant chemotherapy in MIBC closed prematurely in 2008 due to lower than anticipated levels of recruitment, however with 284 randomised patients this remains the largest ever trial in this setting, and may make a major contribution to an updated meta-analysis. Several factors contributed to its poor accrual: a significant proportion of eligible patients not having recovered from cystectomy in time to commence chemotherapy; publication of the neoadjuvant meta-analysis during the recruitment period leading to a change in the standard of care; and exclusion (initially) of patients with a coincidental finding of prostate cancer. These issues are unlikely to hamper recruitment into a study of adjuvant chemotherapy in UTUC as patients have a more rapid recovery time after nephro-ureterectomy which allows chemotherapy delivery within a reasonable timeframe. In addition, for the reasons outlined in the above section, there are currently no ongoing phase III trials of neoadjuvant chemotherapy in this patient group.

1.5. Standard treatment

There is no international consensus on systemic treatment for non-metastatic UTUC. In the UK, there is no standard strategy for post-operative management of patients with muscle invasive or node positive UTUC. A recent survey completed by 21 UK centres has shown that whilst 12 offer surveillance as standard, 9 offer adjuvant chemotherapy on a “case by case” basis, in the absence of strong supporting data[24]. All respondents showed strong support for a study of adjuvant chemotherapy irrespective of whether they currently use adjuvant chemotherapy or recommend a policy of surveillance. Where adjuvant chemotherapy is considered, the regimes given are those mandated in this study.

2. TRIAL OBJECTIVES

2.1. Primary Objective

To determine whether adjuvant combination chemotherapy improves the disease-free survival for patients with resected histologically confirmed muscle invasive (pT2-T4, N0-3) or node positive upper tract urothelial carcinoma.

2.2. Secondary Objectives

The secondary objectives of the study are to evaluate:

- Whether adjuvant platinum-based chemotherapy improves overall survival in this patient group

- Whether adjuvant platinum-based chemotherapy improves metastasis free survival in this patient group.
- Whether adjuvant platinum-based chemotherapy reduces incidence of second primary urothelial cancers.
- The toxicity of chemotherapy in this patient group.
- The relative quality of life in patients undergoing adjuvant chemotherapy or surveillance in this patient group.
- How recommendations based on the findings of a qualitative study impact on recruitment and on study set up at subsequent sites.

3. TRIAL DESIGN

POUT is a multicentre phase III randomised controlled open label parallel group trial with an initial recruitment optimisation stage incorporating a qualitative recruitment processes study.
Patients who have undergone radical nephro-ureterectomy and resection of all macroscopically abnormal nodes, are surgically staged as pT2-pT4, N0-3 or pT1 and node positive and who are fit for adjuvant chemotherapy, will be randomised to four cycles of adjuvant platinum based chemotherapy (experimental group) or surveillance (control group). The primary endpoint is disease-free survival. Secondary endpoints include overall survival, toxicity and quality of life. Participants in both groups will be followed up according to recommended routine practice[25]. An embedded qualitative sub-study will run during the initial stages to investigate the understanding of POUT and the presentation of the trial to participants, with the aim of optimising recruitment rates. In addition, consent will be sought for collection of biological samples from participants for exploratory, hypothesis generating work and pre-operative CT urograms will also be collected to allow retrospective review and correlation with pathological staging.

4. PARTICIPANT SELECTION & ELIGIBILITY

4.1. Number of participants

The aim is to recruit 345 participants.

4.2. Source of participants

Participants will be recruited internationally from the appropriate clinics in participating centres.
Within the UK, potential participants will be identified in Urology clinics and discussed at Multi-Disciplinary Team (MDT) Meetings. It is preferable that potential participants with UTUC will be identified via the MDT pre-operatively and then be reviewed by the MDT with their pathology results to identify the final group of eligible patients according to the surgical specimen. Patients identified prior to receiving nephro-ureterectomy will receive the surgery Patient Information Sheet (PIS), and if interested in participation will be asked to bring their PIS to their first follow-up clinic post-operatively to act as a clinical reminder. Patients identified post-surgery, or those who were previously identified and are subsequently found to have muscle invasive disease will receive the main PIS.

4.3. Inclusion criteria

1. Written informed consent
2. ≥16 years of age
3. Post radical nephro-ureterectomy for upper tract tumour with predominant TCC component - squamoid differentiation or mixed TCC/SCC is permitted.
4. Histologically confirmed TCC staged pT2-pT4 pN0-3 M0 *or* pTany N1-3 M0 (providing all grossly abnormal nodes are resected). Patients with microscopically positive margins on pathology may be entered (providing all grossly abnormal disease was resected).

5. Satisfactory haematological profile (ANC> 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L) and liver function tests (bilirubin < 1.5 x ULN, AST and Alkaline phosphatase < 2.5 x ULN), Glomerular filtration rate ≥30 mls/min.
6. Fit and willing to receive adjuvant chemotherapy with first cycle to be commenced within 90 days of radical nephro-ureterectomy if allocated
7. WHO performance status 0-1.
8. Available for long-term follow-up

4.4. Exclusion Criteria

1. Evidence of distant metastases
2. Pure adenocarcinoma, squamous cell carcinoma or small cell or other variant histology
3. Un-resected macroscopic nodal disease
4. Concurrent muscle invasive bladder cancer (patients with concurrent non-muscle invasive bladder cancer (NMIBC) will be eligible)
5. GFR <30 ml/minute. NB Gemcitabine-carboplatin can only be given for patients with suboptimal renal function for cisplatin i.e. for GFR 30-49ml/min. Patients with poor performance status or co-morbidities that would make them unfit for chemotherapy are ineligible for the trial
6. Significant co-morbid conditions that would interfere with administration of protocol treatment
7. Pregnancy; lactating women or women of childbearing potential unwilling or unable to use adequate non-hormonal contraception (male patients should also use contraception if sexually active);
8. Previous malignancy in the last 5 years except for previous NMIBC, adequately controlled non melanoma skin tumours, CIS of cervix or LCIS of breast or localised prostate cancer in patients who have a life expectancy of over 5 years upon trial entry.

5. STUDY ENDPOINTS

5.1. Trial feasibility

During the first two years of accrual, recruitment rates will be a key outcome to determine continuation of the trial.

5.2. Primary

- Disease-free survival (DFS)

5.3. Secondary

- Overall survival
- Metastasis free survival
- Incidence of bladder second primary tumours
- Incidence of contralateral primary tumours
- Acute and late toxicity
- Treatment compliance
- Quality of life (QoL)

5.4. Exploratory

- Identification of diagnostic, prognostic and predictive biomarkers

6. SCREENING

6.1. Screening log

All participating centres will be required to keep a detailed log of all patients who undergo radical nephro-ureterectomy at their centre. This log will capture the following information:

- Number undergoing nephro-ureterectomy
- Number subsequently confirmed to have muscle invasive disease
- Number who are given surgery PIS
- Number given the main PIS
- Number of approached patients who accept or decline randomisation.
- Treatment allocation (randomised) or choice of treatment (not randomised)

These data will be used to inform the two year recruitment optimisation phase of the trial and no patient identifiable data will be collected at this stage.

6.2. Participation in other research

Patients who fulfil the eligibility criteria will be given the opportunity to participate in POUT if they have participated in other research prior to recruitment. POUT participants will not be permitted to participate in any other trials of investigational medicinal products whilst they are being treated within POUT or for four months afterwards. There are no other IMP trials currently running in this patient population in the UK so it is not anticipated that participants will be at risk of entering any other trials, however if new opportunities to participate in research arise these will be considered on a case by case basis by the Trial Management Group.

7. CONSENT & RANDOMISATION

7.1. Procedure for obtaining informed consent

7.1.1. Pre-surgery

At POUT centres which conduct surgery, patients scheduled for nephro-ureterectomy for suspected UTUC should be approached to discuss the possibility they may be eligible for the POUT trial. Patients should be provided with the brief surgery patient information sheet and asked to consider participation in the POUT translational sub-study (see Appendix A4). Consent for POUT-T should be obtained prior to acquisition of any pre-surgery research blood or urine samples.

7.1.1. Post surgery

Following nephro-ureterectomy, the Principal Investigator (or designated individual) should discuss the trial in more detail with potentially eligible patients, describing the purpose, alternatives, drug administration plan, research objectives and follow-up of the study. Patients should be provided with the main POUT patient information sheet and consent form for review and given sufficient time to consider participation in the study. Once a decision has been made to enter into the trial, a signature should be obtained from the patient to confirm consent. Consent for main trial participation should be obtained post-operatively and before any trial specific assessments prescribed by the protocol are performed. If the participant was not approached and consented for POUT-T participation prior to nephro-ureterectomy, they should be given the opportunity to participate following surgery.

Patients who consent to POUT may also be asked to consent to join the quality of life and qualitative studyies. If a patient declines participation in any or all of the substudies this will not result in ineligibility to participate in the main clinical trial and will not impact the medical care received.

Confirmation of the patient's consent and the informed consent process must be documented in the patient's medical notes. A copy of the signed consent form should be provided to the patient and the

original retained in the investigator site file, which must be available for verification by ICR-CTSU study staff or for regulatory inspection at any time.

7.2. Registration

Participants who consent to provide samples as part of POUT-T (see Appendix 4) prior to joining the main trial must be registered centrally with the trials unit (ICR-CTSU).

Patients should be registered by telephoning ICR-CTSU on:

+44 (0)20 8643 7150

09.00-17.00 (UK time) Monday to Friday

Registration should take place as close to the planned date of nephro-ureterectomy as possible.
A registration checklist must be completed prior to registration.
The following information will be required at registration:

- Name of hospital, consultant and person registering patient
- Confirmation that patient has given written informed consent for translational sub-study participation and access to their electronic healthcare records
- Patient's full name, hospital number, date of birth, postcode and NHS/CHI number (or equivalent for international participants)

7.3. Randomisation

All patients who consent to join the main POUT trial must be randomised centrally by the trials unit (ICR-CTSU) before trial treatment can commence.

Patients should be randomised by telephoning ICR-CTSU on:

+44 (0)20 8643 7150

09.00-17.00 (UK time) Monday to Friday

Randomisation should take place within 14 days prior to start date planned for chemotherapy if allocated. In exceptional circumstances, and after discussion with the Chief Investigator, this may be extended to 21 days. Chemotherapy should be planned to start no more than 90 days post nephro-ureterectomy.
Once written informed consent has been obtained, an eligibility and randomisation checklist must be completed prior to randomisation. The clinician / research nurse should contact ICR-CTSU to confirm eligibility and obtain a unique trial number and treatment allocation.
The following information will be required at randomisation:

- Name of Hospital, consultant and person randomising patient
- Confirmation that patient has given written informed consent for trial and for any sub-studies;
- Confirmation that patient is eligible for the trial by completion of the checklist;
- Patient's full name, hospital number, date of birth, postcode and NHS/CHI number (or equivalent for international participants)
- Date of diagnosis
- Date of nephro-ureterectomy
- Staging information
- Status of margins on pathological review of surgical specimen
- Proposed start date of chemotherapy, if allocated
- Intended type of chemotherapy, if allocated
- Registration number (if applicable)

The caller will be given the patient's unique randomisation number (Trial ID). The Trial ID together with the patient's initials and date of birth should be used on all Case Report Forms (CRFs) and correspondence relating to the patient.

7.4. Treatment Allocation

Treatment allocation will be 1:1 and will use a minimisation algorithm incorporating a random element. Written confirmation will be sent to the designated data contact and pharmacist (if allocated chemotherapy) at the randomising centre to confirm treatment allocation.

8. TRIAL EVALUATIONS

8.1. Baseline assessments

8.1.1. Pre-operative investigations

Information will be requested regarding the following standard pre-operative investigations conducted within 3 months prior to surgery:

- Chest X-ray or CT of chest
- Cystoscopy
- CT of abdomen and pelvis – recommended CT urogram

8.1.2. Pre-operative translational study samples (if participating)

For patients registered into the translational study prior to surgery (see Appendix 4), the following samples should be taken:

- Whole blood in EDTA tubes 2 x 6ml
- Whole blood in Streck tubes 2 x 10ml
- First morning urine Norgen Tube 1 x 50ml

8.1.3. Pre-randomisation investigations

The following assessments should be conducted prior to randomisation

- Measurement of Glomerular Filtration Rate (GFR) in ml/min by Cockroft Gault or Wright Calculation (Appendix 3), or isotope clearance GFR measurement (according to local practice). This should take place at least four weeks after radical nephro-ureterectomy to allow stabilisation post operatively.
- Haematology and biochemistry
- Physical examination
- Toxicity assessment (NCI CTCAE v4)
- Chest CT if not performed pre-operatively
- Cystoscopy if not performed within 3 months prior to surgery
- CT of abdomen and pelvis if pre-operative scan showed nodal disease (to be conducted at least 6 weeks post-surgery)
- Pregnancy test for females of child bearing potential

If participating in quality of life study:

- Quality of Life (EORTC QLQ C30 & EQ5D)

If participating in translational study:

- Whole blood in EDTA tubes 2 x 6ml
- Whole blood in Streck tubes 2 x 10ml
- First morning urine Norgen Tube 1 x 50ml

8.2. Pre-treatment (pre-cycle 1)

Pre-treatment investigations should be conducted prior to commencement of chemotherapy and do not need to be repeated for patients allocated to the surveillance group.

- Estimation of GFR (Appendix 3). If the pre-randomisation GFR was calculated within three weeks of chemotherapy start date it does not need to be repeated. If measured by isotope clearance and normal this does not need to be repeated unless there has been a change in serum creatinine of greater than 20 %
- Haematology and biochemistry
- Physical examination
- Body surface area calculation
- Toxicity assessment (NCI CTCAE v.4)

8.3. Pre-cycles 2, 3 and 4, OR 4, 7 and 10 weeks post randomisation for surveillance participants

Pre-cycle investigations should be conducted within 48 hours prior to planned start date of cycle

- Haematology and biochemistry and ascertainment participants receiving chemotherapy are fit to receive next cycle
- Estimation of GFR for participants receiving chemotherapy
- Body surface area calculation for participants receiving chemotherapy
- Toxicity assessment (NCI CTCAE v.4)

8.4. Pre-cycle 3 OR 7 weeks post randomisation for surveillance participants

- Quality of Life (EORTC QLQ C30 & EQ5D)

8.5. End of cycle 4 OR 13 weeks post randomisation for surveillance participants

- Haematology and biochemistry
- Physical examination
- Toxicity assessment (NCI CTCAE v.4)
- CT of chest
- CT of abdomen and pelvis
- Quality of Life (EORTC QLQ C30 & EQ5D)

8.6. Post treatment

Clinical follow up will be in accordance with standard practice and will take place at 6, 9 and 12 months post randomisation, then 6 monthly to 36 months, and annually thereafter. For the purposes of POUT, the post 36 month annual follow up will be primarily to assess for signs of disease recurrence.
To be conducted at each follow up visit – 6, 9 and 12 months post randomisation, 6 monthly to 36 months, and annually thereafter:

- Chest x-ray or CT of chest

To be conducted 6 monthly to 24 months and annually thereafter:

- Cystoscopy – the first cystoscopy can be conducted at any timepoint within the first 6 months following randomisation in accordance with local practice. All subsequent cystoscopies should follow the POUT schedule.
- CT scan of abdomen and pelvis.

To be conducted at 6, 9, 12, 18 and 24 months only:

- Haematology and biochemistry
- To be conducted 6 monthly to 24 months only:
- Toxicity assessment (NCI CTCAE v.4)

To be conducted at 6, 12 and 24 months:

- Quality of Life (EORTC QLQ C30 & EQ5D) (administered by ICR-CTSU)

If participating in translational study:
To be conducted at 6 months:

- Whole blood in EDTA tubes 2 x 6ml
- Whole blood in Streck tubes 2 x 10ml
- First morning urine Norgen Tube 1 x 50ml

8.7. Procedure at recurrence

If participating in translational study:

- Whole blood in EDTA tubes 2 x 6ml
- Whole blood in Streck tubes 2 x 10ml
- First morning urine Norgen Tube 1 x 50ml

8.7.1. Recording recurrence

Any recurrence and treatment given should be recorded on the appropriate section of the CRF.

8.7.2. Local recurrence

Participants with local recurrence of the initial ureteric tumour should be treated according to clinical circumstances and should be managed at the local clinician's discretion. It is suggested that the investigations in the POUT follow up schedule are conducted when possible, however as a minimum participants should continue to be followed up for metastatic recurrence, survival, toxicity and quality of life.

8.7.3. Metastatic recurrence

All participants with regional nodal or metastatic disease should be treated at the discretion of the treating clinician. Participants should continue to be followed up for survival.

8.8. Management of bladder and contralateral primary tumours

New bladder and/or contralateral primary tumours should be managed according to local practice and details documented in the appropriate section of the CRF. Participants should continue to be followed up according to the trial follow up schedule for recurrence of initial UTUC tumour, survival, toxicity and quality of life.

8.9. Withdrawal from trial treatment and follow-up

Patients who do not receive their allocated treatment for any reason should be treated at the discretion of their clinician. Unless the patient requests otherwise all CRFs should be completed regardless of treatment actually received. A trial deviation form should be completed to record details of deviation from treatment allocation. Patients are asked prior to randomisation to consent to basic follow up information being provided from routine clinic visits should they withdraw from the study (see patient information sheet and consent form), and any patient unwilling to give that assurance prior to trial entry should not be randomised. Patients are however free to reverse their decision at any time without giving a reason. A trial deviation form should be completed for any patient who withdraws consent for information to be sent to the ICR-CTSU or for attending trial follow up visits. If this request is received after results have been published the course of action will be agreed between the Sponsor and independent Trial Steering Committee.

Should a patient become cognitively or physically incapacitated at any point during the trial they will be withdrawn for their own protection. If this were to happen during the course of the patient's chemotherapy their treatment should be reviewed as a clinical decision by the Principal Investigator at their centre. No further trial procedures will be carried out and no further data or biospecimens will be collected on behalf of the trial. Any data already collected about such patients will be fully anonymised. A trial deviation form should be completed for any patient withdrawn from the trial for this reason.

9. Schedule of assessments

Visit Time from randomisation (months)	Pre-operative standard investigations	Prior to randomisation	Pre cycle 1 +	Pre cycle 2*	Pre cycle 3*	Pre cycle 4*	End cycle 4*	6	9	12	18	24	30	36	48	60	Recurrence
Estimation of GFR[1]		X	X	X	X	X											
Haematology and biochemistry [2.]		X	X	X	X	X	X	X	X	X	X	X					
Physical examination		X	X				X										
Body surface area (BSA) calculation[3]			X	X	X	X											
Toxicity assessment[4]		X	X	X	X	X	X	X		X	X	X					
Chest X-ray or CT of chest	X							X	X	X	X	X	X	X	X	X	
CT of chest		X[#]					X										
Cystoscopy	X							X		X	X	X		X	X	X	
CT of abdomen and pelvis	X	X[Σ]					X	X		X	X	X		X	X	X	
QoL questionnaires[5]		X			X		X	X		X		X					
Blood and urine sample (POUT-T)[6]	X	X						X									X

+ for participants allocated to chemotherapy only [#] if not conducted pre-operatively [Σ] if pre-operative scan showed nodal disease

*for participants allocated to surveillance, 'pre cycle' assessments should be conducted at 4, 7, 10 and 13 weeks from randomisation. GFR estimation, BSA calculation and haematology and biochemistry assessment can be omitted at the 4, 7 and 10 week assessments.

1. Isotope clearance, Cockcroft Gault, Wright. (Appendix 3)
2. FBC (Hb, WBC, platelets, ANC), U & E (Na, K, urea, creatinine), LFTs (ALP, ALT, AST, bilirubin, albumin)
3. For participants allocated to chemotherapy only
4. NCI CTCAE v4
5. EORTC QLQ C30 & EQ5D. QoL questionnaires for UK participants will be administered by ICR-CTSU direct to participants' homes from month 6 onwards.
6. Whole blood (2 x 6ml EDTA tubes plus 2 x 10ml Streck tubes) and first morning void urine (1 x 50ml Norgen tube).

10. TREATMENT

10.1. Standard pre-trial treatment - surgery

A pre-operative CT urogram will be collected from each patient. However, alternative imaging including Intravenous Pyelogram (IVP) and contrast CT will be accepted, although CT-urogram is strongly recommended. All patients will require complete en bloc nephro-ureterectomy and resection of all macroscopic tumour, together with any macroscopic nodal disease. Laparoscopic or open surgery is permissible; however, where imaging suggests T3 or T4 disease or significant hydronephrosis, then open surgery is strongly recommended.

Several techniques to allow detachment of the distal ureter are permissible and will be selected based on tumour characteristics, in particular the tumour site. However whenever possible the ureter should be ligated or sealed distal to the tumour prior to mobilisation of the kidney. Acceptable surgical techniques include endoscopic resection, open excision with a bladder cuff, or extravesical excision (open or laparoscopic) providing the ureter has been completely removed.

Lymph node dissection is not mandated in patients with normal nodes on imaging. All abnormal lymph nodes seen on pre-operative imaging must be resected. Details will be collected about the extent of node dissection conducted for each participant.

For surgical quality assurance purposes, audit data which is routinely submitted to BAUS relating to the frequency and morbidity of laparoscopic and open nephrectomies, and nephro-ureterectomies will be collected. Further information about the dataset required can be obtained from the ICR-CTSU. Each set of data will be approved by the surgical sub-group of the Trial Management Group prior to surgical centres opening.

10.2. Surveillance

Patients allocated to surveillance will be seen at 4, 7, 10 and 13 weeks post randomisation - equivalent to the end of cycle in patients receiving chemotherapy - in order to collect details of early treatment failure in this group and comparative data relating to toxicity and quality of life. Patients on surveillance will then be followed up for signs of recurrence at the same intervals as those who received chemotherapy (see section 8.7, schedule of assessments).

10.3. Chemotherapy

Chemotherapy should commence within 90 days of nephro-ureterectomy. If non muscle-invasive bladder cancer (NMIBC) is also present, standard induction and maintenance intravesical treatment will be deferred until systemic chemotherapy is complete (for participants allocated to the chemotherapy group).

NB: If participants are unfit for gemcitabine-cisplatin for reasons other than renal function e.g. performance status or co-morbidities, they are ineligible for the trial, gemcitabine-carboplatin will be given for suboptimal renal function only.

Creatinine clearance can be calculated using any established method. It is recommended that the Cockcroft-Gault formula should be used, however the Wright formula is acceptable (Appendix 3). It is mandatory that centres use the same method of calculation for all POUT participants throughout treatment and for the duration of the trial and the centre must notify ICR-CTSU of its policy for creatinine clearance calculation prior to recruiting its first participant.

10.4. Drug administration

Treatment will be repeated every 21 days. Four cycles of treatment will be given.Estimation of GFR according to local practice prior to each cycle of chemotherapy is mandatory.

The participant's BSA will determine the dose of gemcitabine and cisplatin (if using). Weight should be monitored with each cycle of treatment and BSA should be recalculated for each cycle.
The participant's baseline GFR will determine the dose of carboplatin unless the serum creatinine changes >20% from the pre-treatment value. It is acceptable to recalculate the dose of carboplatin at each cycle if this is your hospital's local policy.
Stated doses of chemotherapy below are mandatory, and the following treatment schedule is recommended, however administration times and dilution according to local practice may also be used. Dose capping and banding may be performed according to local practice.

10.5. Gemcitabine dose

1000mg/m^2 day 1 and day 8 as 30 minute intravenous infusion.

10.5.1. Known gemcitabine toxicities

The maximum tolerated dose of gemcitabine is affected by the administration schedule. The dose limiting toxicity is myelosupression. Nausea and vomiting are common, but are usually mild to moderate. Diarrhoea, stomatitis, fever, dyspnoea, paresthesia, flu-like symptoms, skin rash with or without pruritus, oedema and alopecia also occur rarely. Transient elevations of serum transaminases, proteinuria and haematuria are common. Haemolytic uremic syndrome has been reported.

10.6. Cisplatin dose

70mg/m^2 day 1 as a 4 hour intravenous infusion.
If the patient's calculated or measured GFR is 50-70 mls/min then it is recommended that the cisplatin dose is split over 2 days (35mg/m2 /day) and given on day 1 and 2 if this is standard practice locally.

10.6.1. Known cisplatin toxicities

The main toxicity associated with cisplatin is renal tubular damage leading to renal insufficiency and possible renal failure. This can produce elevations in urea and creatinine and decreases in creatinine clearance. Hypomagnesaemia and hypokalaemia can occur. Other toxicities include nausea and vomiting, alopecia, myelosuppression, peripheral neuropathy and decreased auditory function. Hypersensitivity reactions have been observed in both untreated and pre-treated patients.

10.7. Carboplatin dose

Carboplatin should be given instead of cisplatin only for participants with a creatinine clearance of 30-49ml/min.
AUC 4.5 or AUC 5 (according to local practice) calculated according to the Calvert formula.
Carboplatin should only be given for patients who are fit for chemotherapy and fulfil all trial entry criteria but have GFR 30-49 ml/min. Patients who would be unsuitable or unfit for cisplatin due to comorbidities or performance status should NOT be included in the POUT trial.
Carboplatin AUC 4.5 is recommended, however AUC 5.0 may be used at the discretion of the Principal Investigator, if AUC 5 is the standard local carboplatin dose used in combination with gemcitabine for urothelial tumours. Centres must specify before recruitment begins whether AUC 4.5 or AUC 5 will be their standard dose for POUT participants.
The Calvert formula will be used to determine dosage:

Dose (mg) = target AUC (mg/ml x min) x [GFR ml/min + 25]

Note: With the Calvert formula, the total dose of carboplatin is based upon renal function, not body surface area.

10.7.1. Known carboplatin toxicities

Common toxicities associated with carboplatin include allergy (rash often with pruritus), hypersensitivity reactions (usually after > 6 cycles), alopecia (very occasionally), nausea and vomiting, bone marrow suppression, flushing effects, nephrotoxicity, fatigue, neurotoxicity, nausea and vomiting.

10.8. Supportive care

Pre and post-chemotherapy hydration and infusion rates should be according to local practice. A suggested day case fluid protocol for day 1 of gemcitabine-cisplatin treatment is shown below:
Prior to cisplatin:

- Gemcitabine 1000mg/m^2 (in 0.25-0.5L 0.9% sodium chloride) over 30 minutes
- 1L 0.9% sodium chloride (including 20mmol potassium and 10 mmol magnesium ions) over 2 hours
- Mannitol (200mls 10% over 15 mins)

Cisplatin:

- Cisplatin 70mg/m2 (in 1L 0.9% sodium chloride) over 4 hours
- With 1L of 0.9% sodium chloride (including 40 mmol potassium ions) over 4 hours

Post cisplatin hydration:

- 1L 0.9% sodium chloride (including 20mmol potassium and 10 mol magnesium ions) over 1 hour.

Additional hydration/diuretics should be given as required in accordance with local practice to replace any fluid lost as a result of emesis and/or diuresis.
It is advised that participants receive pre-medication with appropriate anti-emetics which may include a 5HT-3 antagonist, aprepitant and dexamethasone according to local practice. G-CSF is not recommended but may be used at the discretion of the investigator.
If there is persistent nausea and vomiting additional anti-emetics should be given as per local practice. In addition to dose modifications stated below, toxicities should be managed symptomatically in accordance with local practice.

10.9. Concomitant medication

Medication considered necessary for the participants' welfare and which is not expected to interfere with the evaluation of the study drugs may be given at the discretion of the investigator. Relevant concomitant medications must be recorded on the appropriate pages of the CRF.

10.10. Dose modifications

Dose modifications should be made on the basis of blood tests performed no earlier than 24 hours prior to chemotherapy administration. Chemotherapy should only commence on planned day 1 cycle 1 if the patient still meets the eligibility criteria for the trial. If a delay of greater than two weeks is necessary then the patient should not receive chemotherapy.
In the event of emergent toxicity, dose modifications or discontinuation of treatment should be implemented according to the criteria below. Toxicity will be graded using NCI CTCAE version 4.
Haematological toxicities should be managed in accordance with tables 1 and 2 below. Non-haematological toxicities must have resolved to ≤ grade 2 before the next cycle of treatment is given.
If the patient has not recovered to grade ≤2 from a toxicity experienced during their previous cycle by planned day 1 of the next cycle, treatment may be postponed for up to 2 weeks. If a delay of greater than

two weeks is necessary for recovery from drug toxicity, then the patient should not receive further chemotherapy.
If dose reductions have been made during treatment, doses should not be re-escalated (on any treatment day) for any subsequent cycles. Any further dose modifications are at the Principal Investigator's discretion but should be discussed with the Chief Investigator, via the ICR-CTSU.
Any missed doses or dose reductions and associated toxicities should be documented on the appropriate CRF.

10.10.1. Gemcitabine dose levels

A maximum of two dose reductions will be permitted:

- Dose level 2 is 750 mg/m^2
- Dose level 3 is 500 mg/m^2

10.10.2. Cisplatin dose levels

A maximum of two dose reductions will be permitted:

- Dose level 2 is a reduction to 85% of initial cisplatin dose
- Dose level 3 is a reduction to 75% of initial cisplatin dose

10.10.3. Carboplatin dose levels

A maximum of one dose reduction will be permitted from AUC 4.5 to AUC 3.5. For centres specifying at the outset that AUC 5 is their standard treatment, a maximum of one dose reduction from AUC 5 to AUC 4 will be permitted.

10.11. Day 8 cycles 1-4

If a day 8 chemotherapy dose is missed or withheld due to toxicity it should not be given at a later time, i.e. the cycle should continue with one dose not given.

10.11.1. Haematological toxicities

Dose adjustments for myelosuppression should be made on the basis of absolute neutrophil count (ANC) and platelet count according to the following table.

Table 1. Day 8 dose reductions due to haematological toxicity

ANC (x 10^9/L)		**Platelets (x 10^9/L)**	**Dose gemcitabine**
≥1.0	and	≥75	1000 mg/m^2
0.5≤ANC<1.0	And/or	50≤platelets<75	750 mg/m^2
<0.5	And/or	<50	Omit day 8 dose Reduce one dose level with all subsequent cycles (Table 2)

Day 8 treatment for subsequent cycles should be given according to Table 2.

10.11.2. Liver Toxicity

Day 8 gemcitabine doses should be omitted, not delayed, in case of grade 3 or 4 transaminitis (ie ALT or AST > 5 x ULN).

10.12. Cycles 2-4

10.12.1. Haematological toxicities

If absolute neutrophil count <1.5 x 10^9/L or platelet count <100 x 10^9/L on planned day 1 of cycles 2-4, delay start of the cycle for up to 2 weeks until recovery above these levels.
If the patient had their dose reduced due to a haematological toxicity in a previous cycle see Table 2 for subsequent dosing.

Table 2. Dosing after haematological toxicity in previous cycle

Toxicity (at any point in previous cycle)	Cisplatin or carboplatin dose modification	Gemcitabine dose modification
ANC ≤0.5 x 10^9/L for ≥5 days	Decrease by one dose level	Decrease by one dose level
ANC ≤0.5 x 10^9/L for <5 days	No change	Decrease by one dose level
Febrile neutropenia ANC<1.0 x 10^9/L and temperature ≥ 38.5°C or requiring hospitalisation or neutropenic sepsis ANC <1.0 x 10^9/L and positive blood cultures	Decrease by one dose level	Decrease by one dose level
Platelets 25-75 x10^9/L	No change	Decrease by one dose level
Platelets <25x10^9/L (CTCAE toxicity grade 4) at any point during the previous cycle	Decrease by one dose level	Decrease by one dose level

10.12.2. Neurotoxicity

Dose reductions for cisplatin should not be made routinely on the basis of grade 1 or 2 neurotoxicity. In cases of grade 3 or 4 neurotoxicity, cisplatin should be permanently stopped and may be replaced with carboplatin, at the discretion of the investigator. Participants should continue to receive gemcitabine on day 1 and 8.

10.12.3. Renal toxicity

In the event of renal toxicity, dose reductions for cisplatin should be according to Table 3.

Table 3. Dose reductions due to renal toxicity

GFR (ml/min)	Percent of Full Dose Cisplatin
≥ 70 ml/min.	100%
50-69 ml/min.	100% may be given over 2 days according to local practice (day 1 and 2)
30-49 ml/min.	Substitute carboplatin AUC 4.5 (or AUC 5.0 according to local practice as specified prior to centre initiation)

If GFR <30ml/min all chemotherapy should be stopped and further cycles should not be given unless there is a reversible cause such as dehydration, urine retention, hydronephrosis. If this can be treated with

improvement of renal function to GFR > 30 ml/min within two weeks after the planned start date of the next cycle, treatment should be given with cisplatin dose in accordance with Table 3 above.

10.12.4. Liver toxicity

If gemcitabine was withheld in a previous cycle due to grade 3 or 4 transaminitis, further chemotherapy should not be given until toxicity has resolved to grade 2 or less. If prior toxicity has resolved to grade 2 or less, gemcitabine should be reduced by one dose level for all subsequent cycles of treatment. Careful monitoring of liver function should be performed if ALT or AST levels become elevated during treatment.

10.12.5. Other toxicities

Table 4 provides guidelines for subsequent dosing following worst CTCAE grade of toxicities not specified above.

Table 4. Dose reductions due to other toxicities

CTCAE grade	Cisplatin or carboplatin dose modification	Gemcitabine dose modification
0-2 (and grade 3 nausea/vomiting)	No change	No change
3 (except nausea and vomiting)	Reduce by one dose level or withhold*	Reduce by one dose level
4	Withhold*	Withhold or reduce by one dose level

* This decision will depend on the type of non-haematological toxicity and is at the discretion of the Prinicipal Investigator.

10.13. Treatment discontinuation

If the patient has not recovered from a toxicity (≤ grade 2) experienced during their previous cycle by planned day 1 of the next cycle, treatment may be postponed for up to 2 weeks. If a delay of greater than two weeks is necessary for recovery from drug toxicity, then the patient should be withdrawn from treatment.
If GFR falls to <30ml/min and does not resolve, chemotherapy should be stopped.

10.14. If a decision is made to permanently discontinue treatment this should be reported on the appropriate CRF and data should continue to be collected according to the trial follow up schedule.Drug supplies and labelling

All chemotherapy and supportive medication is to be sourced and funded locally. Gemcitabine and cisplatin or carboplatin chemotherapy are investigational medicinal products within POUT and will be prescribed by the investigator and dispensed from hospital pharmacy from hospital stock for the duration of the trial. In addition to the local pharmacy label, the infusion bag should be labelled as a minimum with the trial identifier and statement ‘for clinical trial use only’. Drug formulation, storage, accountability and destruction will be in accordance with local policy.
Additional information on the safety and administration of these drugs can be found in the relevant Summary of Product Characteristics (SmPC).

11. PHARMACOVIGILANCE

11.1. Adverse Event Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease associated with the use of a study drug, whether or not considered related to the study drug. Signs and symptoms of metastatic disease, as determined by the local clinical investigator, are not adverse events.*

Adverse Reaction (AR): all untoward and unintended responses to the study drug related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions i.e. an AR is possibly, probably or definitely related to the study drug. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR): Any untoward medical occurrence or effect which occurs within 30 days of the patient receiving study drug that at any dose:

- results in death: the patient's death is suspected as being a direct outcome of the AE.
- is life-threatening: refers to an event in which the subject was at risk of death at the time of the event. It also refers to an event that would result in death with the continued use of the product; it does not refer to an event which hypothetically might have caused death if it were more severe.
- requires hospitalisation, or prolongation of existing inpatient hospitalisation: admission to hospital overnight or prolongation of a stay in hospital was necessary as a result of the AE. Outpatient treatment in an emergency room is not itself an SAE, although the reasons for it may be. Hospital admissions/surgical procedures planned for a pre-existing condition before a patient is randomised to the study are not considered SAEs, unless the illness/disease deteriorates in an unexpected way during the study.
- results in persistent or significant disability or incapacity: the AE results in a significant or persistent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.
- is a congenital anomaly or birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

N.B. progressive disease and death due to disease are not considered SAEs but should be reported on the relevant forms (i.e. progression form for relapse and death form for death).

Suspected Unexpected Serious Adverse Reaction (SUSAR): Any serious adverse event with a suspected relationship to study drug that is not listed on the Investigator Brochure and, in the opinion of the Chief Investigator, is unexpected.

11.2. Causality (Relationship to Study Drug)

Many adverse events that occur in this trial, whether they are serious or not, will be known treatment related toxicities. The Principal Investigator is responsible for the assessment of causality of serious adverse events (see definitions of causality table).

If there is any doubt about the causality of an event, the investigator should inform ICR-CTSU who will notify the Chief Investigator. ICR-CTSU of the Chief Investigator may contact the drug manufacturer and/or other clinicians if specific advice or further information is required.

Table 5. Definitions for Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial drug
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out

11.3. Expectedness

Adverse events which are expected to occur with gemcitabine, cisplatin/carboplatin treatment, are listed in the Summary of Product Characteristics. The expectedness of an SAE will be assessed by the Chief Investigator (or the CIs delegate) in accordance with this information.

11.4. Reporting Serious Adverse Events (SAEs) to ICR-CTSU

Any SAE that occurs from randomisation to study treatment and up to 30 days following the last dose of study drug must be reported. SAEs only need to be reported for participants randomised to receive chemotherapy.
All SAEs should be reported to ICR-CTSU, within 24 hours of the Principal Investigator (or designated clinical representative) becoming aware of the event, by completing the trial specific SAE forms and faxing to:

The ICR-CTSU safety desk
Fax no: +44 (0) 208 722 4368
For the attention of the POUT Trial team

All SAE forms must be completed, signed and dated by the Principal Investigator or designated clinical representative.

11.5. Review of Serious Adverse Events (SAEs)

Reported SAEs will be assessed by the Chief Investigator (or designated representative) for causality and expectedness. *NB. The Chief Investigator cannot down grade the Principal Investigator's assessment of causality.*

SAEs assessed as having a causal relationship to study drug and as being unexpected (SUSARs) will undergo expedited reporting to the relevant authorities by ICR-CTSU or local representative (see Section 10.5 for details of SAE reporting).
Centres should respond as soon as possible to requests from the Chief Investigator or his designate (via ICR-CTSU or local representative) for further information that may be required for final assessment of the SAE.

11.6. Expedited Reporting of SUSARs

If an SAE is identified as being a SUSAR by the Chief Investigator expedited reporting will be initiated by ICR-CTSU. If a SUSAR is fatal or life threatening, the timeframe for reporting to the regulatory authorities is within 7 days of being notified of the event. For non-fatal or non-life threatening events the time frame for reporting is within 15 days of being notified of the event. ICR-CTSU will report any additional relevant information as soon as possible, or within 8 days of the initial report of a fatal/life threatening SUSAR.
ICR-CTSU will report SUSARs to:

- The UK Competent Authority (MHRA)
- The UK Main Research Ethics Committee (SUSARs originating in the UK only)
- The Eudravigilance Database (SUSARs originating in EU Member States only. UK and third country SUSARs are reported to Eudravigilance by the MHRA)
- The Sponsor
- All Investigators at regular intervals

The centres in each participating country will report SUSARs, as per their local requirements, to:

- The national Competent Authority
- Independent Ethics Committees
- Local Investigators

In all instances ICR-CTSU will require confirmation of onward reporting within specified timelines from international participating centres.

11.7. Follow up of Serious Adverse Events

Centres should continue to follow up SAEs until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised. Information on SAE outcome should be completed on the relevant part of the original SAE form and faxed to ICR-CTSU as soon as the Principal Investigator becomes aware.

11.8. Annual Reporting of Serious Adverse Reactions (including SUSARs)

Annual reports will be submitted on the anniversary of the date when the Clinical Trial Authorisation was granted in each country. This will include a listing of all serious adverse reactions (including SUSARs), and any relevant information from the IDMC.
ICR-CTSU will prepare the annual report as per local requirements, and provide these to:

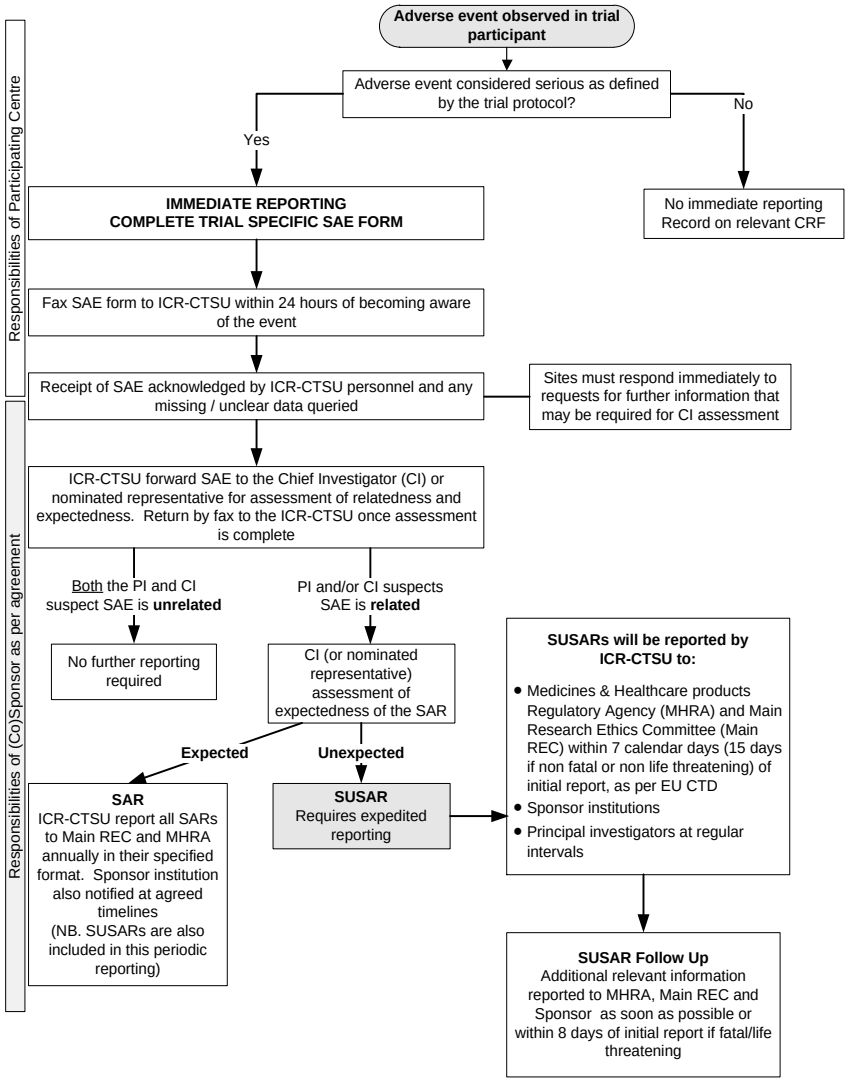
- The MHRA
- The UK Main REC
- The Sponsor

ICR-CTSU will prepare annual reports and send these to each participating international centre, so that these may be formatted according to local requirements and forwarded, as per their local requirements to:

- the Competent Authority
- Independent Ethics Committees

in each participating country.

Figure 1 Flow diagram for UK SAE reporting, and action following report



NB. All SAEs should continue to be followed up as specified in the protocol.

12. STATISTICAL CONSIDERATIONS

12.1. Trial Design

POUT is a multicentre phase III randomised controlled open label parallel group trial of chemotherapy versus surveillance in patients who have received nephro-ureterectomy for muscle invasive or node positive upper tract urothelial carcinoma. There is an integrated initial recruitment optimisation stage that incorporates a qualitative recruitment processes study.

12.2. Treatment Allocation

Participants will be randomised between chemotherapy and surveillance on a 1:1 basis. Treatment allocation is by minimisation with a random element; stratification variables will be listed in the statistical analysis plan.

12.3. Primary Endpoint Definition

The primary endpoint is disease-free survival (DFS). The main time point of interest is three years after randomisation. DFS is defined as the time from randomisation to the first of:

- Death (any cause)
- Metastases
- Any ureteric or renal bed recurrence (invasive or non-muscle invasive),

12.4. Secondary Endpoint Definitions

- Trial feasibility, defined by recruitment rate over first two years
- Treatment compliance (in the chemotherapy arm)
- Acute toxicity (on-treatment / up to 3 months post-randomisation)
- Late toxicity (6 months – 2 years)
- Quality of life (QoL) as measured by the EORTC QLQ-C30 and EQ5D modules. Domains of interest include Global health/QL, functioning domains and items relating to fatigue and side-effects associated with Gemcitabine-Cisplatin/Gemcitabine-Carboplatin
- Progression to muscle invasive disease in the bladder
- Second primary cancer in the bladder
- Contralateral second primary UTUC
- Metastasis free survival, defined as time from randomisation to any distant metastases or death.
- Overall survival, defined as the time from randomisation to death from any cause

12.5. Sample Size

It is assumed that 3 year DFS in the control group will be 40%. A meta-analysis of adjuvant chemotherapy for MIBC reported a DFS HR of 0.62 (95% CI 0.46–0.83, p=0.001) in favour of cisplatin-based combination chemotherapy vs. no chemotherapy. In the absence of any similar meta-analyses in UTUC, POUT has been powered to detect a relative effect size of a similar magnitude.
169 participants per group (338 participants and 172 events in total) would be sufficient to detect a 15% improvement in 3 year DFS (HR=0.65) with 2-sided 5% significance and 80% power. In 338 participants there is also 79% power (2-sided 5% alpha) to detect a 15% improvement in overall survival from 50% to 65% at 5-years. The target sample size is increased to 345 participants in total to allow for 2% loss to follow-up. As UTUC is a rare cancer, recruitment is expected to take approximately 5 years.

12.6. Analysis Plan

The primary analysis of DFS will be event driven. DFS and time to event endpoints will be analysed by the logrank test and summarised by a HR with 95% CI. The primary time-point of interest is 3 years. Estimates of event rates will be calculated using the Kaplan-Meier method. The Cox proportional hazard model will be used to adjust for type of chemotherapy and known prognostic factors including nodal status. Methods to account for non-proportionality will be used if appropriate.
Acute and late toxicity will be summarised by the proportions experiencing grade ≥3 side effects with comparisons made using chi-squared based tests or Fisher's exact test if expected cell frequencies are less than 5. In addition, methods for ordinal data will be used. Standard algorithms will be used to derive scores from and handle missing data in QoL questionnaires. Treatment groups will be compared at individual time-points and analyses to account for the longitudinal nature of the data (generalised estimating equations) may be used. To assess incidence of second primary urothelial cancers, the

proportion of patients with second primary urothelial cancers will be reported, along with its 95% CI, for each group.
Feasibility will be analysed at interim analyses using recruitment rates as described in the following section. Compliance will be summarised by proportion of participants adhering to allocated treatment, and by summarising dose intensity in the chemotherapy group.
The study is not powered to conduct formal sub-group analyses. Exploratory analyses will include description of treatment effects by anatomical site of disease (renal pelvis vs. ureter), chemotherapy regimen, type of surgery/ extent of lymph node dissection and nodal status. Interim analyses will be undertaken at least annually and reviewed and reported upon by an Independent Data Monitoring Committee.
Further details of analysis methods will be specified in a Statistical Analysis Plan in accordance with ICR-CTSU Standard Operating Procedures.

12.7. Interim analyses and stopping rules

12.7.1. Feasibility of recruitment

The trial has an initial recruitment optimisation phase which incorporates trial set-up, patient pathway mapping and the qualitative sub-study. Recruitment milestones have been set as follows: 9 centres open within 6 months, 18 within 12 months; 22 patients recruited within 12 months, 75 within 24 months. It is anticipated that approximately 45 centres will be opened over 3-3.5 years.
Progress against these milestones will be monitored and formally reviewed by the Independent Data Monitoring Committee (IDMC) and Trial Steering Committee (TSC). The methods described by Carter [26] will be used to review likely duration to reach the required sample size. If, two years after opening the study, it appears unlikely that the target sample size / target number of events will be reached with at most a 1 year extension, the IDMC and TSC will consider closing the study early on the basis of inadequate recruitment.
Simulations of the likely recruitment rates have been undertaken using a variety of assumptions regarding the number of eligible patients, consent rates and rates at which centres will open. These suggest that the recruitment target of 345 patients in 5 years is achievable with at least 80% probability; with an annual accrual rate of 120 patients once 45 centres are open.

12.7.2. Early stopping rule for efficacy

For interim analyses of DFS, it is proposed to use a Peto-Haybittle stopping rule ($p<0.001$) addressing both efficacy (rejecting H_o) and inefficacy (rejecting H_1). Based on the experience of Gem-Cis in other urothelial cancers severe toxicity is not anticipated and thus there is no a priori defined early stopping rule for toxicity. The IDMC will review safety and emerging efficacy data at least annually.

13. TRIAL MANAGEMENT

13.1. Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, Co-investigators and identified collaborators, the Trial Statistician and the Trial Manager. Selected Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of centres and professional groups. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG have operational responsibility for the conduct of the trial. Where possible, membership will include a lay/consumer representative. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

13.2. Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be set up and will include an independent Chairman (not involved directly in the trial other than as a member of the TSC) and not less than two other independent members. It is the role of the TSC to monitor progress of the trial and to ensure there is adherence to the protocol and the principles of Good Clinical Practice. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU

13.3. Independent Data Monitoring Committee (IDMC)

An IDMC will be convened to monitor the progress of the trial. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU. The IDMC will meet in confidence at regular intervals, and at least annually. A report of the findings and recommendations will be produced following each meeting. This report will be submitted to the TMG and TSC, and if required, the main REC and the MHRA.

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

14. RESEARCH GOVERNANCE

14.1. Sponsor responsibilities

The sponsor of this clinical trial is The Institute of Cancer Research (ICR).

This Clinical Trial will be conducted in accordance with the ethical principles laid down by the Declaration of Helsinki, 1964 and as amended in 1996 and the principles of Good Clinical Practice.

This Clinical Trial will also be conducted in compliance with the trial protocol, all applicable international guidelines, and the national laws and regulations of the countries in which the Clinical Trial is performed. ICR agree to allow inspection of their premises by the competent authorities when requested.

The Institute of Cancer Research has sponsorship responsibility for:

- Giving notice of amendments to CTA or protocol, make representations about amendments to licensing authority;
- Giving notice when the trial has ended;
- Ensure the research is conducted in accordance with Good Clinical Practice;
- Pharmacovigilance:
    - Keeping records of all adverse events reported by investigators;
    - Ensuring recording and prompt reporting of serious adverse reactions to the Chief Investigator;
    - Reporting to the MHRA and main REC any serious adverse events which the Chief Investigator considers to be SUSARs;
    - Ensuring investigators are informed of SUSARs;
    - Ensuring SUSARs including those in third countries are entered into European database;
    - Providing annual list of SUSARs and a safety report.

The following sponsor responsibilities have been delegated:

To the Chief Investigator:

- Selection of investigators;
- Obtaining a favourable ethics opinion and ensuring any amendments have been approved;

- Take appropriate urgent safety measures;
- Prompt decision as to which serious adverse events are SUSARs, and prompt reporting of that decision to Section of Clinical Trials, ICR-CTSU, The Institute of Cancer Research for onward reporting to the licensing authority and sponsoring institutions (in his absence this responsibility is delegated to a named deputy).

To the lead Pharmacist at the Chief Investigator's Institution (Lancashire Teaching Hospitals NHS Foundation Trust):

- Oversight of IMP to include review of initial regulatory submissions, any protocol amendments or new guidance related to IMP management.

Responsibilities of the Chief Investigator and Lead Pharmacist are defined in an agreement between Lancashire Teaching Hospitals NHS Foundation Trust and The Institute of Cancer Research.
The Institute of Cancer Research is responsible for administering funding and co-ordinating any required legal agreements and investigator statements.
The delegation of sponsorship responsibilities does not impact on or alter standard NHS indemnity cover. The agreement of delegated responsibilities is viewed as a partnership and as such it is necessary to share pertinent information between The Institute of Cancer Research and Lancashire Teaching Hospitals NHS Foundation Trust/Chief Investigator, including proposed inspections by the MHRA and/or other regulatory bodies.

14.2. Principal investigators' responsibilities

Responsibilities of each Principal Investigator and participating centre will be detailed in a contract with the sponsor.
Principal Investigator responsibilities include putting and keeping in place arrangements to run the trial at their site according to the trial protocol and applicable guidance notes, local regulations and the principles of GCP. The above responsibilities include, but are not limited to, ensuring that:

- the applicable ethical and institution specific approvals are in place before recruiting participants;
- sufficient data is recorded for all participants to enable accurate linkage between hospital records and CRFs;
- source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits;
- all staff involved with the trial are trained in and work to the applicable regulatory requirements;
- original consent forms are personally signed and dated by both the patient and investigator or delegated representative and are kept together in a central log together with a copy of the specific patient information sheet(s) given at the time of consent;
- all essential documents are retained in accordance with local regulations;
- staff comply with the protocol and Trial Guidance Notes for the trial.
- SAEs are reported to the ICR-CTSU within the timelines detailed above

14.3. Local pharmacy responsibilities

Each pharmacy department must designate a responsible person for ensuring that:

- investigational products are handled and stored safely and properly
- investigational products' receipt, accountability and destruction records are maintained according to local policy

- investigational products are dispensed in accordance with the protocol;
- any unused products are destroyed according to local practice

15. TRIAL ADMINISTRATION & LOGISTICS

15.1. Centre initiation

Prior to activation for recruitment, participating centres will be required to provide the ICR-CTSU with the following set of data/documents as a minimum:

- Confirmation of local R&D approval
- Completed centre agreement
- Signed and dated PI CV
- Nephrectomy dataset
- Confirmation of local carboplatin dose for administration to all trial participants receiving carboplatin (AUC 4.5 or AUC 5)
- Confirmation of method of calculation of Creatinine clearance for use for all trial participants
- Local contact details
- Log of delegated responsibilities

15.2. Data acquisition

ICR-CTSU is responsible for the central coordination of data management and statistical analysis of trial data. ICR-CTSU will supply CRFs to participating sites for the collection of trial specific data. The Trial Management Group reserves the right to amend or add to the CRF as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by centres in accordance with the guidelines provided by ICR-CTSU.

The clinical data should be reported on the POUT case report forms (CRFs) to the ICR-CTSU in a timely manner. Specific guidance on how data will be collected will be detailed in trial guidance notes. On receipt at ICR-CTSU, CRFs will be recorded as received and any missing data will be reported to the originating site.

15.3. Central data monitoring

ICR-CTSU will review incoming CRFs for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be sent to the relevant centre for resolution. Following initial review, the CRF data items will be entered into the clinical study database held at ICR-CTSU.

Data will be further reviewed for data anomalies / missing data, by central statistical monitoring. Any systematic inconsistencies identified may trigger monitoring visits to centres.

15.4. On-site monitoring

If a monitoring visit is required, ICR-CTSU will contact the centre to discuss dates of proposed visit. Once a date has been confirmed, the centre should ensure that the relevant patient source documents are available for monitoring.

If any problems are detected in the course of the monitoring visit, ICR-CTSU will work with the Principal Investigator to resolve issues and, if necessary, to determine the centre's future participation in the study.

ICR-CTSU staff conducting on-site monitoring will review essential documentation and carry out source data verification to confirm compliance with the site agreement and trial protocol, and to ensure the protection of patients' rights as detailed in the Declaration of Helsinki 1964 as amended October 1996.

15.5. Completion of the study and definition of study end date

The study end date is deemed to be the date of last data capture.

15.6. Archiving

Essential documents are those that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the data collected. Essential documents will be maintained at ICR-CTSU in a way that will facilitate the management of the trial, audit and inspection. They should be retained for a sufficient period (at least 15 years) for possible audit. Documents should be securely stored and access restricted to authorised personnel.

Essential Documents should also be archived at each participating centre in accordance with local regulations.

16. PATIENT PROTECTION

The trial will have received ethical, regulatory and institution specific approvals prior to recruitment of any participants into the study.

Participants will be asked to sign and date the trial consent forms after receiving both verbal and written information about the trial. All consent forms must be countersigned by the Principal Investigator or a designated individual. A record listing the designated individuals and the circumstances under which they may countersign consent forms must be clearly documented at the research site as part of the Delegation of Responsibilities Log. This log, together with original copies of all signed patient consent forms, must be available for inspection.

16.1. Participant confidentiality

Participants will be asked to consent to their full name being collected at randomisation in addition to their date of birth, postcode (or equivalent) and hospital/healthcare number (to allow for possible tracing through national health records to assist with long term follow up and linkage to routine collected health records). The personal data recorded on all documents will be regarded as confidential, and any information which would allow individual participants to be identified will not be released into the public domain.

Each investigator should keep a separate log of all participants' Trial IDs, names, addresses and hospital/healthcare numbers. The investigator must maintain trial documents, which are to be held at the participating centres (e.g. participants' written consent forms), in strict confidence. The investigator must ensure the participants' confidentiality is maintained.

ICR-CTSU will maintain the confidentiality of all patient data received and will not reproduce or disclose any information by which participants could be identified. Representatives of ICR-CTSU, the regulatory authorities and ethics committees may be required to have access to participants' notes and study records for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

16.2. Data protection

ICR-CTSU will comply with all applicable data protection laws. Any requests from participants for access to data about them held at ICR-CTSU should be directed to the Trial Manager in the first instance who will refer the request to the Data Protection Officer at The Institute of Cancer Research.

16.3. Liability and insurance

The Sponsors have taken out an insurance policy to cover their study responsibilities, and certification of this will be provided to the regulatory authorities as required. ICR-CTSU will need to be satisfied that all participating sites have appropriate indemnity arrangements in place.

17. FINANCIAL MATTERS

The trial is investigator designed and led and has been approved by the Clinical Trials Advisory & Awards Committee (CTAAC) of Cancer Research UK.
ICR has received funding from Cancer Research UK for the central coordination of the trial.
In the UK, the trial meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England. The trial is part of the National Institute for Health Research (NIHR) portfolio by virtue of its approval by CTAAC. Therefore, National Cancer Research Network (NCRN) resources should be made available for the POUT trial to cover UK specific research costs.
Country specific funding, if outside the UK, will be sourced and coordinated by the centres in each participating country.

18. PUBLICATION POLICY

The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, led by the Chief Investigator and ICR-CTSU Scientific Lead and appointed from amongst the Trial Management Group, and participating clinicians. All participating centres and clinicians will be acknowledged in this publication together with staff from the ICR-CTSU. All presentations and publications relating to the trial must be authorised by the Trial Management Group, on whose behalf publications should usually be made. Authorship of any secondary publications e.g. relating to the various biological studies will reflect the intellectual and time input into these studies, and will not be the same as on the primary publication. No investigator may present or attempt to publish data relating to the POUT trial without prior permission from the Trial Management Group.

19. ASSOCIATED STUDIES

19.1. Quality of Life

Health Related Quality of Life (HRQL) will be a secondary endpoint in the main trial and will be analysed as described in the statistical analysis plan.
Further details are given in Appendix 1.

19.2. Qualitative recruitment sub-study (QRS)

The aim of the QRS in POUT is to work with RCT staff to understand the recruitment process in the early stages, so that any design or conduct problems can be raised and changes put in place (see Appendix 2). It will also be used to determine any staff training that need to be developed or feedback given to staff. There are several distinct parts to Phase I that are intended to provide information about recruitment as it happens, and to provide the basis for the plan of action to improve it. The parts listed in the Appendix are not necessarily employed sequentially and some may not always be required. The ethnographic nature of the QRS means that the research moulds itself around the needs of the research and is completed when theoretical saturation is reached.
The audio-recording stage of this study completed in April 2015.

19.3. POUT Translational study

Patients planned to receive a nephro-ureterectomy for suspected UTUC will be asked to consent to provide pre-surgery blood and urine samples and for the collection of routine diagnostic formalin fixed paraffin embedded tumour samples.

If POUT participants are identified after surgery, they will be asked to consent to access to diagnostic samples at this time point. POUT participants will also be asked to provide blood and urine samples prior to randomisation, at 6 months following randomisation and at recurrence.

These samples will be collected to enable the analysis of the pathogenesis of UTUC and the identification of prognostic, predictive and diagnostic biomarkers. Samples will be stored at the Human Biomaterials Resource Centre at the University of Birmingham. Further details are provided in Appendix 4.

19.4. Imaging biomarkers study

Participants will be asked at study entry for consent for access to pre-operative CT urograms. Images will be collected for a study which will be the subject of a separate funding application to evaluate the prognostic value of pre-operative CT urograms. This retrospective review is intended to correlate imaging with pathological staging and may allow better prediction of subsequent muscle invasive pathology.

A1. APPENDIX 1– QUALITY OF LIFE STUDY

A1.1. Background

The primary outcome of POUT is disease-free survival with health-related quality of life (HRQL) as a secondary endpoint. If the trial demonstrates a clear DFS advantage in the chemotherapy group, provision of detailed HRQL information alongside survival data will fully inform patients of both benefits and possible negative consequences of treatment.

The objective of HRQL assessment within the main trial, therefore, is to describe and compare the impact of both chemotherapy and surveillance on physical, social and emotional well-being. The HRQL issues that will be considered will include generic functional and symptom aspects of HRQL and disease specific issues relevant to chemotherapy.

The main focus of quality of life assessment in patients with UTUC has been on the outcome of surgical technique, e.g. open versus laparoscopic nephro-uretectomy. As with all types of bladder cancer there is a significant lack of QL research. There is a particular shortage however of literature on QL in UTUC. UTUC is a rare cancer and to date there are no published UTUC QL reports based on mode of therapy [27]. It is for these reasons that there lies a difficulty in interpreting the data available. Published research demonstrates results from patients who have been followed up over varying lengths of time. Any research thus far only reports data on small samples of patients.

Research assessing the differences between surgical techniques suggests that laparoscopic nephro-ureterectomy has some advantages over open nephro-ureterectomy such as improved patient convalescence, decreased pain, shorter hospitalisation and improved aesthetics [28, 29]. Dybowski, et al. carried out a study comparing the ailments of patients who had undergone a nephro-ureterectomy performed through either one incision or two incisions [30]. Only 26 out of the 44 patients completed a 10 items questionnaire to assess associated ailments and the impact on their QL. There were no statistical differences between the two groups, however younger patients reported more ailments and poorer quality of life.

Mills et al. noted that QL may be affected by concern over risk of recurrence, the necessity of regular ureteroscopies during surveillance following treatment [27]. There are some possible risks associated with ureteroscopies, such as perforation of the ureter.

Bamias et al. assessed the efficacy and safety of biweekly carboplatin/gemcitabine in 34 patients with advanced urothelial cancer who were unfit for cisplatin-based chemotherapy as well as its effect on quality of life [31]. Their findings indicated that baseline QL assessment was a predictor of progression free survival (when the QL score was dichotomised around the median score of 58). Only 25 patients in total completed the QL questionnaire before and after chemotherapy. No significant differences were found between the functional and symptom domains, however global status and QL was improved after chemotherapy (p=0.010). Their overall findings intimate that QL instruments may be of use in the choice of treatment in elderly individuals.

A1.2. Hypothesis

In this study it is hypothesised that more side effects will be reported during the initial phase of the trial by patients on the experimental arm due to the adjuvant chemotherapy toxicities. It is also hypothesised that in the experimental arm there will be fewer patients with recurrent disease; therefore this improved clinical outcome may reflect in a better QL outcome long-term. In participants randomised to the surveillance arm, it is hypothesised that they may report poorer QL due to raised concerns over the possibility of relapsing.

A1.3. Quality of life measures

Quality of life will be assessed with the EORTC Quality of Life Questionnaire (QLQ-C30) version 3 [32] and the EQ5D.

The QLQ-C30 is a generic cancer instrument composed of multi-item and single scales. These include five functional scales (physical, role, emotional, social and cognitive function), three symptom (fatigue, nausea and vomiting and pain) and a global health status/QL scale and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). All scales and single items meet the required standards for reliability and validity.

The EQ-5D is a standardised instrument for use as a measure of general health. It includes a simple descriptive profile comprising mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and a single index value for health status.

A1.4. Study design

Patients are eligible for the HRQL assessment in this study if they fulfil the eligibility criteria and complete the baseline HRQL questionnaires before randomisation. Participants will be informed in the patient information sheet that they will have their HRQL assessment regularly while involved in this trial. HRQL will be a secondary endpoint in the main trial and evaluated in a longitudinal design for in all patients entered in this study.

A1.5. Timing of data collection

Patients will be asked to complete HRQL questionnaires within *14 days prior to* randomisation. Patients will be asked to fill out the questionnaires as completely and accurately as possible. The average time to complete the entire questionnaire is 10-15 minutes. Initial QL booklets will be administered by the centre: patients on the surveillance arm will complete questionnaires at 7 weeks and 3 months after randomisation and patients on the adjuvant chemotherapy arm will complete questionnaires at the end of cycle 2 and at 3 months post randomisation. Further assessments will be sent to patients' homes by the ICR-CTSU at 6, 12 and 24 months. This will total six HRQL assessments per participant. The target timeframe for completion of follow up questionnaires will be +/- two weeks of the scheduled follow-up assessment.

A1.6. Compliance

Missing data may hamper assessment of HRQL in clinical trials. This may be because centres do not collect the questionnaires at the appropriate time (unit non-response), or because patients may miss questions within the questionnaires (item non-response). The latter problem occurs less than 2% on average with the QLQ-C30 instrument and should not be a problem. The former problem is particularly important if patients have advanced cancer and low performance scores. It may be minimised by ensuring that participating centres are properly informed and motivated about HRQL assessment. From 6 months from randomisation the follow up QL assessments will be co-ordinated by the ICR-CTSU who will directly send out postal questionnaires. One reminder will be made with a second questionnaire (including a stamped addressed envelope). During the study, compliance with completing QL questionnaires will be monitored.

A1.7. Statistical considerations

The primary endpoint for assessing quality of life is the global health/quality of life subscale. According to the EORTC reference manual [33], for this subscale a difference of 8 points is considered clinically relevant & standard deviation for GU cancers is 22.2 points. Using a two-sided 5% significance level there is 87% power to detect an 8-point difference in this subscale in 151 patients per group (assuming 88% participation in QL study).

Analysis of quality of life will include between group comparisons at individual time points. Methods to model changes over time, such as generalised estimating equations, will be explored. Scales of interest will be analysed using total scale score (e.g. ANCOVA of change from baseline); dichotomisation of scales or individual items of relevance will also be considered where clinically relevant, analysed by chi-square-based or Fisher's exact test as appropriate. To account for multiple testing, only p-values below $p<0.01$ will be considered statistically significant on endpoints other than the primary QL endpoint.

A2. APPENDIX 2: QUALITATIVE RECRUITMENT SUB-STUDY (QRS)

The following relates to the QRS which has now closed.

A2.1. The QRS - Phase I

The aim of the QRS is to work with RCT staff to understand the recruitment process in the early stages, so that any design or conduct problems can be raised and changes put in place. It will also be used to determine any staff training that needs to be developed or feedback given to staff. There are several distinct parts to Phase I that are intended to provide information about recruitment as it happens, and to provide the basis for the plan of action to improve it. The parts listed below are not necessarily employed sequentially and some may not always be required. The ethnographic nature of the QRS means that the research moulds itself around the needs of the research and is completed when theoretical saturation is reached (that is, new data collection does not materially add to the findings).

A2.1.1. Patient pathway through eligibility and recruitment

A comprehensive process of logging of potential RCT participants through screening and eligibility phases will be put in place in order to ensure compliance with the CONSORT checklist and to monitor recruitment. The main trial team will request all the centres provide a flow chart of the anticipated recruitment pathway that maps the patient's journey beginning from the point of diagnosis to making a decision about participation in the RCT.

The logs and flow charts will be assessed for complexity and compliance with the protocol and variation between centres. In particular, the logs will give an indication of the numbers of eligible patients and particular points where they are 'lost' from the RCT. They will also indicate levels of equipoise – as evidenced by the numbers rejecting participation in the RCT and the selection of particular treatments. Flow charts will indicate the degree of complexity of participation and variability between centres.

A2.1.2. In-depth interviews and investigator meetings

In-depth, semi-structured interviews will be conducted with three groups:

(a) Members of the TMG, including the CI and those most closely involved in the design, management, leadership and coordination of the trial
(b) Clinical and recruitment staff across the range of clinical centres involved in the RCT.
(c) A sample of patients agreeing to or refusing randomisation

Interview topic guides will be used to ensure similar areas are covered in each interview, based on those used in previous studies, but also encouraging the informants to express their own views about the RCT and its recruitment difficulties.

Informants in group (a) will be asked about the background, development and purpose of the RCT, including their knowledge of the evidence and equipoise; their role in the trial and recruitment, including their expectation of the pathway through eligibility and recruitment. They will also be asked to provide a short summary of the RCT for the interviewer, as if s/he were a patient.

Informants in group (b) who directly recruit to the trial will also be asked the questions about their knowledge of the evidence and personal views about equipoise; the recruitment pathway, how they feel the protocol fits their clinical setting and any adjustments they think are needed. They will also be asked how they explain the RCT and the interventions and controls to patients and the randomisation process, and will be asked to audio-record their appointments with patients.

Informants in group (c) will include patients who agree to randomisation and accept or refuse the allocation, or refuse randomisation and choose their treatment. They will be asked about their

understanding of the POUT trial, their experience of recruitment and their reflections on the patient information sheet.
Informants will be purposively sampled. It is expected that the CI and most of the TMG will be interviewed. However, in this large RCT, it will be necessary to sample clinicians and recruiters. Initially, those having attempted recruitment will be selected, followed by further theoretical sampling based on emerging findings – for example the need to recruit clinicians from a particular specialty or centre.
It is likely in the early stages of the RCT, particularly in the feasibility phase of an RCT likely to experience recruitment difficulties that the CI, TMG and clinical investigators will meet several times during the first 6 months. The QRS team will ask to observe these meetings and to audio-record them with permission. The QRS researchers will discuss the agenda with the CI, with the aim of fostering discussion particularly about issues of eligibility and equipoise. The meetings will also be a forum to discuss the findings of the QRS, and to deliver training or advice about recruitment.
Interviews and meetings will be audio-recorded and transcribed with consent. Recordings may be transcribed verbatim whole or in selected parts, as necessary for comprehensive analysis. Some recordings are best listened to and notes made, with transcription of particularly salient sections – rather than the whole interview, for increased efficiency. Transcripts and notes will be analysed thematically by the QRS researcher, using techniques of constant comparison and case-study approaches. This will involve detailed coding, and then comparing emerging themes and codes within transcripts and across the dataset looking for shared or disparate views among TMG members, specialist clinicians and recruiters, and within or between centres or specialties. The coding will be carried out using qualitative data analysis software such as ATLAS-ti or NVivo. The initial coding will be cross-checked by another researcher and discussed with the QRS PI, with inconsistencies resolved by discussion. Detailed descriptive accounts of the themes and cases will then be produced by the QRS researcher.
Interviews and meetings will provide data about the evidence underlying the RCT, including the importance of the question and the commitment of staff to it, as well as individual clinical equipoise; the application of the protocol in clinical centres and any logistical issues; and suggestions about reasons for recruitment difficulties and potential solutions from those working closely with the RCT.

A2.1.3. Audio-recording of recruitment appointments

The importance of audio recording discussions about RCT recruitment will be emphasised to the CI and TMG, and RCT-specific methods of communicating this with recruiters will be explored. It has been shown previously that recruiters tend to be unfamiliar with audio-recording and, even if they agree to it, often resist making successful recordings. It will be emphasised that the feedback to them will be confidential and positive (not critical). The CI and TMG will be asked to discuss this with recruiters and attempt to identify a 'recruitment appointment' suitable for recording. In this RCT it may not be straight-forward as the recruitment pathway may be complicated and include several meetings. However, previous research has shown that the most important occasion is the meeting where randomisation is discussed and offered.
The QRS team will work with the CI/TMG to identify centres where audio-recording of recruitment appointments would be most appropriate and feasible. These will be based on the existing screening log information, initially focusing on centres that attempt recruitment; and later driven by theoretical sampling following data analysis.
One main point of contact (usually the lead research nurse) will be identified per centre and digital audio-recorders will be provided; the number of recorders required for the RCT will depend on the number of actively recruiting staff in the centre and the logistics and geographic location of recruiters. Recruitment staff will be requested to audio-record all appointments where they provide information to patients and

attempt to recruit them to the RCT. Documents explaining the ethical requirements of audio-recording of patient appointments (Patient and Researcher Information Sheets and consent forms for audio-recording) and Standard Operating Procedures (SOPs) to help with the operation of the recorder, dictation of patient/recruiter/recording identifiers, naming and transferring of the recording to the computer and then to the QRS team will be provided to centres in 'Recruiter Packs'.

Audio-recordings of appointments will be analysed as described above for interviews, with the addition of some of the techniques of focussed CA – conversation analysis – pioneered in previous studies. CA techniques will be used to identify and document aspects of informed consent and information provision that is unclear, disrupted or hinders recruitment. Recordings will be listened to by the recruiter and notes made about the content of the appointment, including the basic content covered, the order of presentation of RCT arms and other treatment options, time spent on interventions and controls, and time spent describing both the RCT design and the randomisation process. An assessment will be made as to whether the appointment is recruiter- or participant-led, and also the degree to which there is evidence that the participant has understood the key issues of equipoise, randomisation, participation in the RCT, the option to choose their treatment, and the option to withdraw from research at any time.

The QRS researcher will document these details and provide an account for the QRS PI. When at least three recordings have been analysed, the QRS researcher and PI will decide what confidential feedback will be given to the recruiter. Issues to be fed back to the RCT CI/TMG, or to be used anonymously in training programmes will be discussed and defined.

These data will form the basis for feedback to individuals and to determine the content of its information, and training programmes to be initiated in Phase II.

a) Study documentation

The CI/TMG will be working on the RCT protocol, ethical approval and governance documents during the early stages of the QRS. Patient information sheets (PIS) and consent forms will be scrutinised by the QRS team to identify aspects that are unclear or potentially open to misinterpretation, the clarity of the lay presentation of the evidence, and the balance of information on the different arms in the RCT and its adverse events. The information from the study documents will be compared with the findings from the interviews and recorded appointments, to identify any disparities or improvements that could be made.

b) Evidence base

The CI/TMG will be asked for the main systematic reviews or published research evidence justifying the need for the RCT (this is also likely to be contained within the protocol and original research proposal). They will be asked about any recent evidence that supports or threatens the RCT. If, during the interviews and recorded appointments, it becomes clear that equipoise is an issue in the RCT or clinicians report other evidence as influential, it may be necessary to ask the CI/TMG to undertake a rapid literature review.

A2.2. QRS Phase II

A2.2.1. Feedback to CI/TMG

The QRS researcher and PI will present a summary of anonymised findings emerging from parts 1-5 to the RCT CI and TMG, identifying any aspects of RCT design and conduct that could be hindering recruitment with the supporting evidence. There are likely to be several meetings regularly during the feasibility phase of the study to present these findings and discuss a plan of action to try to improve recruitment, if this proves necessary. The plan will be agreed by the RCT CI/TMG and QRS PI and team. No activities will be undertaken by the QRS team without the prior approval of, and collaboration with, the RCT CI and TMG. The degree of involvement by the CI/TMG will be at their discretion. However, it is likely that the activities

in the plan will need leadership from the CI/TMG as well as the QRS team if they are to be acceptable to the RCT team and thus effective.

A2.2.2. Contents of the plan of action

The plan for the RCT will be focussed on the issues emerging from the ethnographic investigation (QRS) of the RCT and thus based on the details of the RCT and how it has been applied in clinical centres. It is likely that some aspects will be generic, such as difficulties explaining randomisation. The plan is likely to include some or all of: reconsideration of study information, advice about presenting the study, discussions about equipoise or evidence, issues with patient pathways and logistical issues. These may be addressed by a new patient information sheet, additional documents or training for recruiters.

A3. APPENDIX 3: CREATININE CLEARANCE CALCULATION

Creatinine clearance may be calculated by any established method. The recommended method is Cockcroft & Gault, but other methods are acceptable. Centres must notify the ICR-CTSU of their intended policy for calculation prior to recruitment of their first participant and the specified method must be used for the duration of the trial.

A3.1. Cockcroft & Gault calculation

Men:

$$\text{Creatinine Clearance } (\text{ml/min}) = \frac{(140\text{-age}) \times \text{mass(kg)} \times 1.23}{\text{Serum Creatinine } (\mu\,\text{mol/L})}$$

Women:

$$\text{Creatinine Clearance } (\text{ml/min}) = \frac{(140\text{-age}) \times \text{mass(kg)} \times 1.04}{\text{Serum Creatinine } (\mu\,\text{mol/L})}$$

A3.2. Wright formula

Jaffe Serum Creatinine without CK:

$$\text{GFR} = \frac{(6580 - (38.8 \times \text{age})) \times \text{BSA} \times (1 - (0.168 \times \text{sex}))}{\text{Serum Creatinine } (\mu\text{mol/L})}$$

sex: female = 1, male = 0

Enzymatic Serum Creatinine without CK:

$$\text{GFR} = \frac{(6230 - (32.8 \times \text{age})) \times \text{BSA} \times (1 - (0.23 \times \text{sex}))}{\text{Serum Creatinine } (\mu\text{mol/L})}$$

sex: female = 1, male = 0

A4. APPENDIX 4: POUT TRANSLATIONAL SUBSTUDY (POUT-T)

A4.1. Introduction

There are similarities between UTUC and urothelial carcinoma of the bladder, in particular the urgent and unmet need for the identification of new drug targets, and the discovery and validation/qualification of accurate diagnostic, prognostic and predictive biomarkers [34-36].
Collection of suitable longitudinal samples within today's clinical trials is essential to provide the raw material on which such developments will rest. The POUT clinical trial represents an excellent vehicle to collect such biospecimens from patients diagnosed with UTUC, and to subsequently utilise them as outlined below (subject to separate funding applications). The utilisation of samples collected at several different timepoints in a patient's treatment and follow-up means that the POUT-T hypotheses can be investigated in the most robust fashion, and the objectives are more likely to be achieved.

A4.2. OBJECTIVES

A4.2.1. To investigate the molecular pathogenesis of UTUC

By sequencing tumour DNA obtained from formalin-fixed paraffin-embedded (FFPE) tissue samples (tissue blocks) and comparing the sequences with germline DNA obtained from peripheral blood samples (EDTA tubes), it will be possible to develop a picture of the somatic mutations and other genomic and epigenomic alterations that accompany the development and progression of UTUC. Such alterations may be general to all UTUC s or be specific to an individual's UTUC, or be a combination of both [37-47]. UTUCs occur within the Lynch syndrome spectrum of cancers. As such, these cancers arise through microsatellite instability (MSI) following loss of DNA mismatch repair (MMR). Whilst Lynch Syndrome tumours represent 1-5% of all UTUC, a further 10-15% of sporadic UTUCs also exhibit MSI through epigenetic loss of MMR [48, 49].

The analysis of RNA (by qRT-PCR, etc.) and protein expression (by immunohistochemistry, etc.) will identify the downstream importance of these genomic/epigenomic alterations, and hence also identify the key molecular pathways that are driving UTUC pathogenesis. The approaches described above may also lead to the identification of novel therapeutic targets [37, 43, 44, 46].

A4.2.2. To identify prognostic and predictive biomarkers

The use of DNA sequencing platforms to define genomic and epigenomic alterations could reveal important prognostic and predictive biomarkers. Tumours with MSI are biologically distinct from cancers arising through other malignant pathways. It is hypothesised that UTUC with MSI would be resistant to cisplatin-based chemotherapy (as seen in colonic tumours) and have a better clinical outcome than suggested by their stage and grade.

A number of potentially prognostic tissue biomarkers have already been identified for urothelial bladder carcinoma [50-52], and are currently being validated in the Bladder Cancer Prognosis Programme (BCPP) cohort [53]. In the first instance these molecular markers will be assessed for their prognostic value in UTUC in FFPE tissues by immunohistochemistry, followed by other markers.

Such prognostic or predictive biomarkers may also be identified in cellular or cell-free DNA obtained from urine samples (*Norgen* tubes) or peripheral blood samples (*Streck* tubes).

A4.2.3. To identify diagnostic biomarkers

Urine samples (*Norgen* tubes) will be used to investigate biomarkers with potential diagnostic utility. These may include DNA mutations, epigenetic alterations, cell-free DNA and microRNAs (which may be general to all UTUCs or be specific to an individual's UTUC). For example, in UTUC with MSI, tumour recurrence in the bladder could potentially be detected using microsatellite analyses of exfoliated urinary cells (rather than through endoscopy) since these tumours are mostly monoclonal in origin [40, 54, 55].

As described for the BCPP biospecimens, urine is a rich source of transitional cell carcinoma related proteins [56-58], some of which may have utility for the non-invasive diagnosis or risk stratification of UTUC. Within POUT-T it is intended to undertake urinary biomarker discovery using proteomic and metabolomic approaches.
All of the above diagnostic biomarker candidates may also have predictive and prognostic utility [39, 44, 52, 56, 59, 60].

A4.3. POUT laboratory manual

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

A4.4. METHODS

A4.4.1. Sample collection

All POUT-T participants will be asked to provide consent for access to their diagnostic paraffin-embedded tumour tissue from nephro-ureterectomy. These will be collected via periodic formal requests to the Histopathology Departments. An appropriate post-operative period will be allowed to pass before such requests are made, so that pathology review will be completed before any tissue blocks are transferred. The participant's centre will be able to recall the tissue blocks at any time. Such tissue will be utilised for immunohistochemistry and DNA/RNA analyses. Patients will be asked to consent to allow access to their electronic healthcare records for follow-up relating to patient and disease status.

In addition, POUT-T participants will be requested to provide the following specimens pre-operatively, post operatively, 6 months following surgery and at disease recurrence**:**

- **2 x 6ml whole blood** in EDTA tubes [61, 62] (for germline DNA analyses, etc).
- **2 x 10ml whole blood** in *Streck* Cell-Free DNA™ BCT tubes [63-65] (for cell-free DNA analyses, etc).
- **1 x 50ml first morning urine** [66] in *Norgen* collection tubes(for DNA, proteome and metabolome analyses).

Patients with UTUC who are not identified prior to surgery should be approached about participation in POUT-T at the same time as they are approached about participation in the main trial.

A4.4.2. Human Biomaterials Resource Centre

Biospecimen collection will be co-ordinated by a dedicated team at the Human Biomaterials Resource Centre (HBRC) at the University of Birmingham working in close collaboration with the POUT Trial team at ICR-CTSU. The HBRC is an HTA-licensed facility dedicated to the collection, processing and storage of appropriately consented, high quality human biomaterials for research. The facility offers high quality storage with 24 hour monitoring and call-out, and back up biospecimen storage space. HBRC is ethically-approved (09/H1010/75) and has been supported through the Birmingham Science City *Experimental Medicine Network of Excellence* project. All specimens will be anonymised with a unique specimen number, and linkage to patient details and clinical data will only be possible by ICR-CTSU.

A4.4.3. Preparation & Sample Processing

Central processing is recognised to be an important element of biospecimen collection [62], and so sample collection will be co-ordinated by HBRC, including:

- Liaison with the POUT Trial Manager/ICR-CTSU and the POUT Chief Investigator.
- Preparation, labelling and distribution of specimen receptacles/tubes to POUT centres.
- Biospecimen transfer from site to HBRC
- Biospecimen processing.
- Quality control, quality assurance, pathology review, governance and reporting.

Quality control will be undertaken at the University of Birmingham after one year of sample collection to assess and validate the samples. This will be repeated annually for a randomly-selected 10% of samples collected in that year.

The planned experimental analyses described above will be undertaken at the University of Birmingham (supervised by Dr RT Bryan) and at the University of Sheffield (supervised by Mr. JW Catto). However, some of these analyses may also be carried out by third parties (either by other academic institutions collaboratively, or by commercial organisations performing these analyses as a service).

A4.4.4. Tissue Access Arrangements

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

A5. APPENDIX 5: GLOSSARY

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under Curve
BAUS	The British Association of Urological Surgeons
CIS	Carcinoma In Situ
CRF	Case Report Form
DFS	Disease free survival
EORTC	European Organisation for Research and Treatment of Cancer
FBC	Full Blood Count
G-CSF	Growth Colony-Stimulating Factors
GFR	Glomerular Filtration Rate
HR	Hazard Ratio
HRQL	Health Related Quality of Life
IDMC	Independent Data Monitoring Committee
LCIS	Lobular Carcinoma In Situ
LFT	Liver Function Test
MDT	Multi-disciplinary team
MIBC	Muscle invasive bladder cancer
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMIBC	Non-muscle invasive bladder cancer
PI	Principal Investigator
PIS	Patient Information Sheet
QoL	Quality of Life
QRS	Qualitative Recruitment Study
R&D	Research and Development
RCT	Randomised controlled trial
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCC	Transitional Cell Carcinoma
TMG	Trial Management Group
TSC	Trial Steering Committee
U+E	Urea & Electrolytes
ULN	Upper Limit of Normal
UTUC	Upper Tract Urothelial Carcinoma
WBC	White Blood Cell
WHO	World Health Organisation

A6. APPENDIX 6: REFERENCES

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