Randomised trial of Selective bladder Preservation Against Radical Excision (cystectomy) in muscle invasive T2/T3 transitional cell carcinoma of the bladder – feasibility study

PROTOCOL

Version 1.7

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This clinical trial protocol is intended to provide guidance and information only for the conduct of the SPARE Trial in participating centres. It is not for use as a guide for the management of other patients outside of the trial.

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The SPARE trial has been scientifically approved by the Clinical Trials Awards and Advisory Committee (CTAAC) of Cancer Research UK and the Medical Research Council (04/05/2006) and is thus part of the NCRN/NCRI portfolio of bladder cancer trials.

SPARE Trial (feasibility) - FINAL PROTOCOL VERSION 1.7: 29 March 2010

Approved by: 

Dr Robert Huddart — Date: 29 March 2010

Chief Investigator

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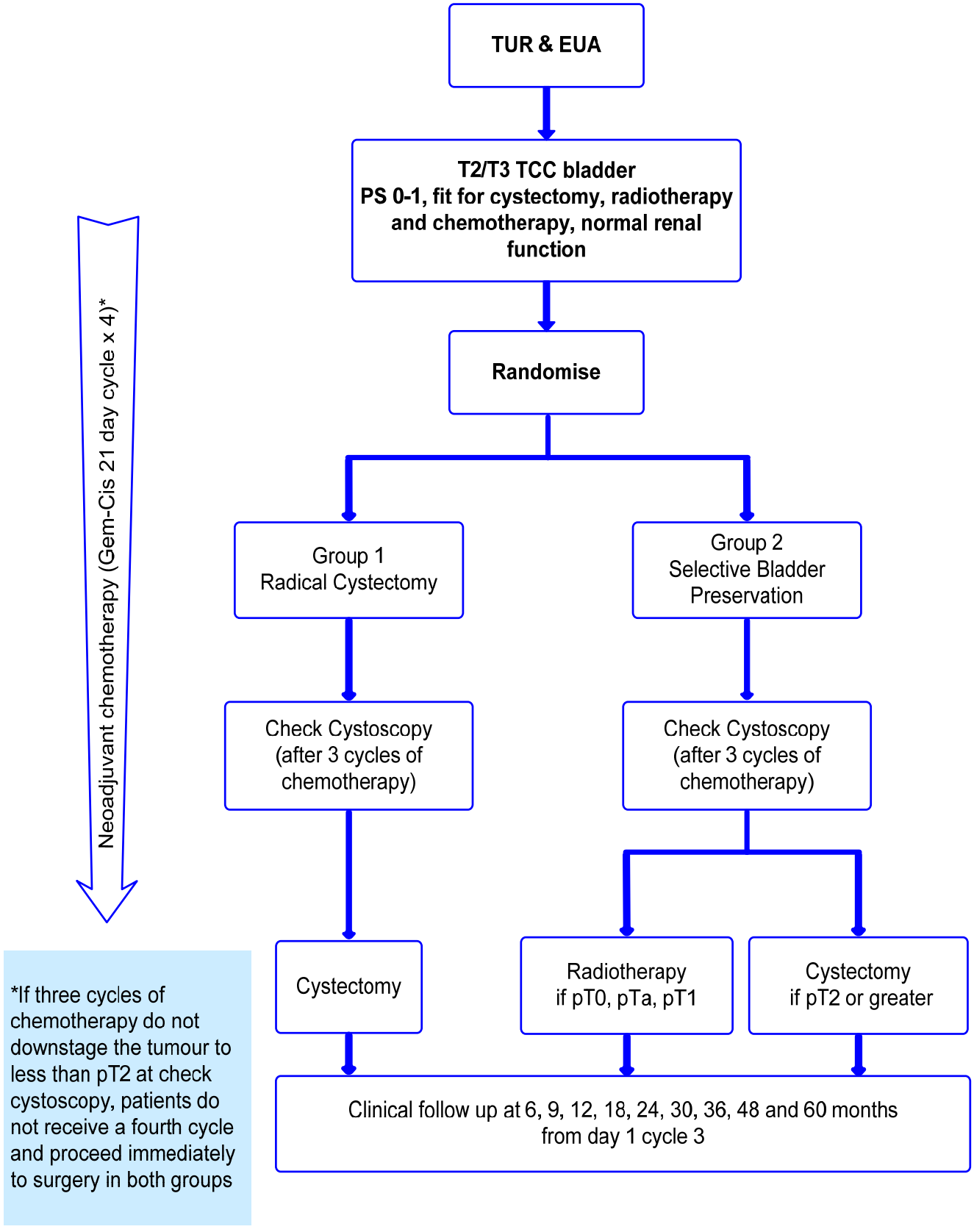
LIST OF ACRONYMS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under Curve
CGH	Comparative Genomic Hybridisation
CIS	Carcinoma In Situ
CMV	Cisplatin, Methotrexate and Vinblastine
CR	Complete Response
CTC	Common Toxicity Criteria
CTV	Clinical Target Volume
EDTA	Ethylenediaminetetraacetic Acid
EUA	Examination Under Anaesthetic
FBC	Full Blood Count
G-CSF	Growth Colony-Stimulating Factors
GFR	Glomerular Filtration Rate
GTV	Gross Target Volume
HR	Hazard Ratio
HRQL	Health Related Quality of Life
LCIS	Lobular Carcinoma In Situ
LFT	Liver Function Test
MVAC	Methotrexate, Vinblastine, Adriamycin and Cisplatin
PTV	Planning Target Volume
SAE	Serious Adverse Event
SBP	Selective Bladder Preservation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCC	Transitional Cell Carcinoma
TMG	Trial Management Group
TUR	Transurethral Resection
U+E	Urea & Electrolytes
ULN	Upper Limit of Normal
WBC	White Blood Cell

TRIAL SCHEMA



TRIAL SUMMARY

TITLE:

Randomised trial of selective bladder preservation against radical excision (cystectomy) in muscle invasive T2/T3 transitional cell carcinoma of the bladder (SPARE) – feasibility study.

OBJECTIVES:

Primary:

Feasibility study:

- To determine the feasibility and patient acceptability of a multi-centre phase III randomised trial of radical cystectomy versus selective bladder preservation (SBP); and
- To determine compliance rates with assigned treatment.

Main Trial:

- To determine if bladder preservation is non-inferior to radical cystectomy in responders to neo-adjuvant chemotherapy in terms of overall survival.

Secondary:

- To determine if patients randomised to a policy of SBP have non-inferior overall survival to patients randomised to radical cystectomy;
- To determine the rate of salvage cystectomy after bladder preservation;
- To determine and compare toxicity of treatment in both treatment arms;
- To determine and compare quality of life in both treatment arms; and
- To determine loco regional progression free, metastasis free and overall survival.

TRIAL DESIGN:

Randomised, multicentre phase III non-inferiority study with an initial feasibility stage.

TYPE AND NUMBER OF PATIENTS:

Patients will be male or female, ≥18 years of age with muscle invasive transitional cell carcinoma of the bladder, fit to undergo the protocol treatments.

Up to 110 patients will be randomised in the feasibility study.

If the feasibility study is successful approximately 1015 patients will be randomised in the main trial, (i.e. an additional 905 patients).

TRIAL TREATMENT:

During neo-adjuvant chemotherapy patients are randomised to selective bladder preservation (SBP) or radical cystectomy. Patients in the SBP arm will be cystoscopically assessed and those who have been downstaged to pTo, pTa or pT1 will receive radical radiotherapy after a 4th cycle of chemotherapy; if downstaging is not seen, patients will be recommended to undergo radical cystectomy.

ENDPOINTS

Feasibility Study

- Accrual rate
- Proportion of patients undergoing bladder preservation in SBP arm; and
- Proportion of patients undergoing cystectomy in surgery arm.

Main Trial:

Primary:

- Overall survival.

Secondary:

- Compliance with randomised treatment;
- Rate of salvage cystectomy after bladder preservation;
- Toxicity;
- Quality of life; and
- Loco regional progression free, metastasis free and overall survival.

1. Background

In the UK, 10,200 new cases of bladder cancer are diagnosed per year.[1] Approximately 18% are muscle invasive with 5 year survival rates of 60% and 40% for T2 N0 and T3 N0 disease respectively. Organ-sparing therapy in patients who could otherwise undergo radical surgery is now standard care in many malignancies including cancer of the breast, anus, head and neck and prostate where radical surgery can be avoided in most patients without compromising survival. In bladder cancer, the optimum strategy for control of local disease remains to be determined. Bladder-sparing techniques, using radiotherapy alone or multi-modality treatment to eradicate the primary tumour yet preserve bladder function, have been used but there is little randomised data comparing such approaches to radical surgery.[2,3,4]

1.1. Surgery

Radical cystectomy is regarded by many as the "gold standard" therapy for muscle-invasive bladder cancer.[5] Surgical removal of the bladder may attain local control but 20-30% of patients may develop a local relapse[6-9] and all patients will need reconstructive bladder surgery or an ileal diversion. As surgical techniques have advanced (reviewed in Cookson[5]), complications of radical cystectomy have decreased. However, the potential for early and late morbidity and mortality remains and cystectomy has considerable impact on quality of life (QL) particularly with regard to urinary diversion and sexual function. Whilst these side effects can be minimised with reconstructive surgery, this is not available to many UK patients, and may be unsuitable for a significant number of others due to co-existing medical problems or the pathological and/or anatomical nature of the tumour.[10]

1.2. Radiotherapy

Radical radiotherapy has been commonly used as an alternative to cystectomy especially in the UK. This approach suffers from a relatively high rate of incomplete response or local recurrence (up to 50% or more) with salvage cystectomy being used for failures.[11,12] A review by McBain and Logue[13] suggest that recent advances in the imaging, planning and delivery of radiotherapy offer the potential for extending its use and clinical effectiveness in muscle invasive bladder cancer. However, determining whether radiotherapy is an equivalent approach to radical cystectomy, in terms of survival, toxicity and QL, is difficult due to the lack of randomised studies.

1.3. Comparisons of Radiotherapy versus Surgery

Two non-randomised series have recently reported 5 year survival rates of 60% in 1054 patients managed by cystectomy[14] and 51% in 415 patients treated by radiotherapy.[15] Such results suggest superiority of surgery but a more detailed review revealed that the surgical series excluded 112 patients with inoperable disease and included 213 patients with superficial disease. Restricting the comparison to T2/T3 disease gives survival rates of 47% for radical cystectomy and 45% for conservative treatment.[16] A similar 5 year survival rate of 45% (60% for T2 tumours and 25% for T3 tumours) was also reported in a large cystectomy series.[17]

No published randomised trials have directly compared radiotherapy alone to surgery alone. The only comparative data comes from a meta-analysis of three trials comparing radiotherapy alone with pre-operative radiotherapy and cystectomy.[4] These trials, conducted in the 1970s-80s, randomised a total of 439 patients and showed a survival benefit for the combined modality arm (see 1.5). There have been considerable changes in both radiotherapeutic and surgical techniques since these trials were undertaken and their relevance to the modern era, especially as combined modality treatment is rarely utilised, is questionable.[4,18] The meta-analysis authors recommend trials of bladder preservation are undertaken to explore these issues.

1.4. Neo-adjuvant Chemotherapy

The use of neo-adjuvant and adjuvant chemotherapy has been explored in a number of clinical trials to improve prognosis of muscle invasive bladder cancer. This therapy is aimed at

treating micrometastatic disease present at the time of initial diagnosis and was recently reviewed by Sternberg.[19] In addition, neo-adjuvant chemotherapy provides predictive information with response to chemotherapy predicting better long term disease control.

The largest trial of neo-adjuvant combination chemotherapy is the EORTC/MRC study of 3 cycles of cisplatin, methotrexate and vinblastine (CMV) versus no chemotherapy followed by either radical radiotherapy or cystectomy.[20] Nine hundred and seventy six patients were randomised. The CMV arm was associated with significant improvements in metastasis free survival (53% versus 45% at 3 years, HR=0.79, 95% CI: 0.66 to 0.93, p=0.007) and overall survival (55.5% versus 50.0% at 3 years, HR=0.85, 95% CI: 0.71 to 1.02; p=0.075). Cystectomy was planned in 485 patients, radiotherapy in 415, and in 76 patients combined treatment was planned. Of 417 patients who underwent cystectomy, 32.5% in the CMV arm had no tumour in the cystectomy specimen, compared with 12.3% who did not receive chemotherapy, indicating an overall 22% pathological complete response rate of the primary tumour. After 7.4 years follow-up, combined modality treatment with CMV was associated with a 5.5% improvement in survival (p=0.048).[21]

A phase III Intergroup trial in the United States evaluated 3 cycles of neo-adjuvant methotrexate, vinblastine, adriamycin and cisplatin (M-VAC) chemotherapy. This trial, coordinated by SWOG with participation of the ECOG and CALGB, enrolled 307 patients, randomising 154 to cystectomy alone and 153 to cystectomy after neo-adjuvant M-VAC.[22] As in the EORTC/MRC trial, more patients in the chemotherapy arm had no residual disease in their cystectomy specimen (38% versus 15%). The median overall survival for patients receiving chemotherapy was longer at 77 months compared to 46 months (HR=1.33, 95% CI 1.00 to 1.76, p=0.06 after stratifying for age and tumour stage). This equated to a disease specific hazard ratio of 1.66 (95% CI: 1.22 to 2.45; p=0.002).

The international data on neo-adjuvant chemotherapy (excluding the Intergroup study which was published too late for inclusion) were included in an individual patient data meta analysis.[23] This confirmed that multi-agent neo-adjuvant chemotherapy reduces the risk of death by approximately 13% (HR=0.87 95% CI: 0.78 to 0.97, p=0.016), equating to a 5% absolute improvement in survival at 5 years. This is despite several trials using what would now be considered sub-optimal chemotherapy regimens.

Most randomised controlled trials of chemotherapy for bladder cancer utilised either M-VAC, CMV or other less intensive schedules. Recent randomised trials have demonstrated equivalent efficacy but lower toxicity for two new schedules, accelerated M-VAC[24] and gemcitabine/cisplatin[25], than for the gold standard M-VAC schedule. Though not formally tested in the neo-adjuvant setting these newer schedules are likely to obtain similar or improved results but be more easily tolerated than standard schedules.

1.5. Selective Bladder Preservation

A number of pilot studies have investigated whether response to chemotherapy can be used to select patients for conservative treatment. This process, termed selective bladder preservation (SBP) utilises the idea that response to initial treatment may identify a group of patients who may be particularly suitable for conservative treatment and bladder preservation.

Tumour cystoscopic response has been validated as a reliable outcome measure, with improved outcome associated with the absence of residual cancer.[22, 26, 27] Using this policy, patients obtaining a complete or good partial response after neo-adjuvant chemotherapy are selected for conservative treatment with radiotherapy and poor responders are managed by immediate surgery. This means that patients with a low chance of success with radiation are not denied cystectomy, whilst patients with a good chance of cure with conservative treatment can undergo this organ-sparing approach.

Much of this work has been piloted in Boston by Shipley and colleagues. They utilised complete transurethral resection (TUR), neo-adjuvant chemotherapy, and limited radiotherapy

with concomitant cisplatin prior to reassessment.[28] Data from RTOG trial 8802 which tested this approach showed 75% of patients achieved an initial pathological complete response (CR) after neo-adjuvant CMV and underwent organ conservative management with radiotherapy. Of these, 15% required salvage cystectomy giving bladder preservation rates of 60% with no negative impact on survival.[29]

In a similar approach, Sternberg and colleagues[27,30] used complete TUR and 3 cycles of M-VAC chemotherapy (with no radiotherapy). One hundred and four patients with T2-T4 N0 M0 TCC bladder cancer were recruited and at reassessment 49 patients (49%) were pT0 and 28 had superficial disease (pTa/pT1). Fifty-two patients underwent conservative treatment with TUR: 31(60%) remained alive after a median follow-up of 56 months and 23 (44%) maintained an intact bladder. Five-year survival was 67%. Thirteen responding patients underwent partial cystectomy of whom one required salvage cystectomy. Five-year survival in this group was 69%. Thirty nine patients underwent radical cystectomy; 39% remained alive after a median follow-up of 45 months and the 5-year survival rate was 46%.

Similar results have been obtained in a preliminary analysis of patients undergoing SBP at the Royal Marsden Hospital.[31] Twenty-five patients received neo-adjuvant chemotherapy (with accelerated M-VAC) and subsequent radiotherapy, based upon adequate cystoscopic response. Pathological CR was seen in 12/25 patients (48%), and pTa/pT1 in a further 7 patients (28%). Post chemotherapy cystectomy was advised for persistent pT2 disease in 3 patients (refused in 1). Two patients were not cystoscopically evaluated (1 due to concurrent medical problems) and 1 patient progressed on chemotherapy. To date there have been 3 recurrences (2 superficial CIS +/- T1 disease; 1 pT2). Seventeen (68%) patients have no sign of recurrence at a median of 12 months (range: 2-28 months) from treatment, with one instance of grade 4 toxicity reported.

Whilst having some late effects, high dose bladder irradiation seems to be well tolerated with preservation of sexual functioning in >60 % of patients.[32] The majority of patients undergoing bladder preservation have a normal bladder function, with approximately 20% of patients complaining of mild to moderate bowel symptoms and 20% suffering occasional urinary incontinence.[31] In Shipley's study of 190 patients treated with SBP no patients required cystectomy to treat radiation-induced bladder toxicity.[33]

The recent meta analysis[23] demonstrating a survival benefit of neo-adjuvant chemotherapy should mean an increasing number of patients will be recommended this treatment schedule. Together with centralisation of major urological surgery (recommended by NICE[34]), this provides an opportunity to explore issues of bladder preservation in a clinical trial. A randomised trial would confirm whether SBP is a safe and acceptable approach to muscle invasive disease and define the role of this treatment modality in this patient group. Recent experience from the ProtecT trial in early prostate cancer demonstrates that a randomised trial between a surgical and conservative treatment is possible in current UK uro-oncological practice.[35]

2. Aims of the study

2.1. Feasibility study

Primary

- To determine the feasibility and patient acceptability of a multi-centre phase III randomised trial of radical cystectomy versus selective bladder preservation (SBP); and
- To determine compliance rates with assigned treatment.

2.2. Main Trial

Primary

- To determine if bladder preservation is equivalent to radical cystectomy in responders to neo-adjuvant chemotherapy in terms of overall survival.

Secondary

- To determine if patients randomised to a policy of SBP have equivalent overall survival to patients randomised to radical cystectomy;
- To determine rate of salvage cystectomy after bladder preservation;
- To determine and compare the toxicity of treatment in both arms;
- To determine and compare quality of life in each treatment group; and
- To compare loco regional progression free and metastasis free survival between randomised treatments.

3. Trial Design

A multi-centre randomised phase III trial with an initial feasibility study comparing radical cystectomy with a strategy of SBP after neo-adjuvant chemotherapy in muscle invasive bladder cancer.

- **In the SBP arm**, patients will have a rigid cystoscopy after 3 cycles of neo-adjuvant chemotherapy to assess their response. If this shows significant histological down-staging with a pT1 or less tumour or a macroscopically normal bladder they will proceed to a 4th cycle of chemotherapy followed by radical radiotherapy. If they remain pT2 or greater, they will have radical cystectomy.

- **In the radical cystectomy arm**, patients will have a rigid cystoscopy after 3 cycles of neo-adjuvant chemotherapy to assess their response. If this shows significant histological down-staging with a pT1 or less tumour or a macroscopically normal bladder they will proceed to a 4th cycle of chemotherapy followed by radical cystectomy. If they remain pT2 or greater, they will have immediate radical cystectomy.

4. Patient selection and eligibility

4.1. Source of patients

Patients will be identified following transurethral resection (TUR) of the bladder. The investigator or a member of his/her team will be responsible for identifying suitable cases. Patients who are eligible will be approached by a research nurse or designated member of the investigator's team before the end of cycle 2 of neo-adjuvant chemotherapy.

4.2. Number of patients

The aim is to recruit up to 110 patients to the feasibility study. If this is achieved, it is estimated that a total of approximately 1015 patients will be required for the main trial, i.e. an additional 905 patients.

4.3. Inclusion criteria

Patients must satisfy all of the following to be eligible for the trial:

1. Histologically confirmed transitional carcinoma (TCC) of the bladder;
2. Age $\geq$18;
3. Clinical stage T2 or T3 N0 M0 (TNM Staging outlined in Appendix 1);
4. WHO performance status 0-1;
5. Fit for radical cystectomy;
6. Fit for radical radiotherapy;
7. Willing to receive or receiving* 3 cycles of gemcitabine-cisplatin or other protocol approved neo-adjuvant chemotherapy regimen (as detailed in Section 8) and willing and fit to receive a 4th cycle according to study protocol;
8. Satisfactory haematological profile (at time of chemotherapy administration) (Hb>10gms/dl, WBC >3.0 x 10^9/L, platelet count >150 x 10^9/L) and liver function tests (Bilirubin, AST, Alkaline phosphatase <1.5 x ULN)$^+$; and
9. Written informed consent and available for long-term follow-up.

* randomisation must take place prior to check cystoscopy following cycle 3

$^+$ patients receiving chemotherapy are expected to have a glomerular filtration rate > 50 mls/min though this is not part of formal inclusion criteria.

4.4. Exclusion criteria

Patients with any of the following are not eligible for the trial:

1. Adenocarcinoma, squamous cell carcinoma (SCC), small cell carcinoma or other variant histology (N.B. squamoid differentiation or mixed TCC/SCC is permitted);
2. Widespread carcinoma in situ (CIS) or CIS remote from muscle invasive tumour;
3. Previous invasive malignancy in the last 5 years. Patients with previous superficial TCC or CIS are eligible for entry into SPARE.
4. Patients with simultaneous upper tract , urethral or prostatic urethral TCC
5. Patients with direct prostatic urethral extension from bladder primary may be included if not involving prostatic stroma.
6. Untreated hydronephrosis*;
7. Previous pelvic radiotherapy;
8. Any contra indication to radical radiotherapy e.g. inflammatory bowel disease, radiosensitivity syndrome, severe diverticular disease;
9. Bilateral total hip replacements;
10. Pregnancy; or
11. Significant co-morbid medical conditions which would interfere with administration of any protocol treatment.

* Patients with hydronephrosis can be included if the kidney/ureter has been stented or nephrostomy has been inserted and renal function has been maintained to allow neoadjuvant chemotherapy to be administered satisfactorily.

5. Endpoints

5.1. Primary

- Accrual rate;
- Proportion of patients undergoing bladder preservation in SBP arm; and
- Proportion of patients undergoing cystectomy in surgery arm.

The primary endpoint for the main trial is overall survival.

5.2. Secondary

- Compliance with randomised treatment;
- Rate of salvage cystectomy after bladder preservation;
- Toxicity of treatment in both arms;
- Quality of life; and
- Loco regional progression free, metastasis free and overall survival.

5.3. Definition and recording of recurrence and disease progression

Disease progression is defined according to RECIST criteria i.e. an increase of 20% in the longest diameter (Appendix 1).

Recurrence is defined as clinical or radiological progression of disease from complete clinical remission. Recurrence may be:

> **Local**: recurrence in bladder +/- local extension. Local recurrence will be classified as non invasive ($\leq$ pT1 including CIS) or invasive (unequivocal clinical or pathological evidence of muscle wall invasion $\geq$ pT2).
>
> **Regional:** any recurrence outside the bladder (but not including contiguous local extension) including pelvic lymph node recurrence within the true pelvis.
>
> **Distant**: any recurrence beyond the true pelvis including common iliac and para aortic lymph nodes.

Details of <u>all</u> recurrences must be included on the case report forms along with their subsequent clinical response.

6. Randomisation

Randomisation is undertaken prior to check cystoscopy after cycle 3 of neo-adjuvant chemotherapy. It is recommended that randomisation takes place as soon as possible after consent is given. Central randomisation will be performed by the ICR Clinical Trials and Statistics Unit (ICR-CTSU), Institute of Cancer Research, Sutton. Treatment allocation will be 1:1 and will use computer generated random permuted blocks stratified by cancer centre.

Prior to randomisation an eligibility checklist must be completed by the clinician/research nurse.

The following information will be required at randomisation:

- Name of cancer centre, treating hospital, consultant and person randomising patient;
- Confirmation that patient is eligible for the trial by completion of the checklist;
- Confirmation that patient has given written informed consent for randomisation;
- Ascertainment of whether the patient has consented to ONS tracing
- Patient's full name, hospital number, date of birth and NHS number

- Ascertainment of whether the patient has given written informed consent for the quality of life sub-study and if so, confirmation that the baseline questionnaire has been completed.
- Ascertainment of whether the patient has given written informed consent for the biological material sub-study.

The caller will be given the patient's unique trial identification number (Trial ID) and treatment allocation.

Patients are randomised by telephone through the ICR-CTSU Tel**: 020 8643 7150 (09.00 – 17.00 Monday to Friday)**

7. Trial evaluations

7.1. Pre-randomisation

Patients will undergo assessment of their disease within 8 weeks prior to commencement of neo-adjuvant chemotherapy to include:

- Maximal TUR and EUA;
- Physical examination (including height, weight and body surface area) to assess fitness and WHO performance status;
- Chest X-ray or CT of chest;
- Full blood count, U+E, liver function tests (ALP and ALT or AST);
- MRI or CT scan of pelvis;
- Additionally
    a. For patients with a raised ALP - a bone scan and liver ultrasound or CT; or
    b. For patients with a raised ALT or AST - a liver ultrasound or CT scan.

Estimation of renal function (by EDTA clearance, 24 hour urine collection or Cockcroft Gault calculation) prior to chemotherapy is strongly recommended as part of optimal clinical care but is not a mandatory requirement of this study.

The baseline quality of life questionnaire should be administered within 14 days prior to randomisation. Patients who do not consent to this sub-study will not be excluded from the clinical trial.

The baseline toxicity score (CTC v3 and RTOG) should be recorded before day 1 cycle 3 of neo-adjuvant chemotherapy.

7.2. During and post-treatment follow-up

Follow-up of patients following radiotherapy/cystectomy is designed to reflect routine care.

Patients randomised to SBP

- Cystoscopy should be within 2-4 weeks after day 1 cycle 3 for assessment of response. The optimum time for cystoscopy is 3 weeks after day 1 cycle 3;
- If patients have responded to neo-adjuvant chemotherapy they will receive a 4th cycle of neoadjuvant chemotherapy prior to radiotherapy. During radiotherapy, patients should be seen according to standard care i.e. every 1-2 weeks for clinical assessment, FBC and U+Es. Study visits should be performed at the end of treatment and 4-6 weeks post treatment for clinical assessment and toxicity;
- If patients have NOT responded to neo-adjuvant chemotherapy they will receive radical cystectomy. Patients should be seen 4-6 weeks post treatment for clinical assessment and toxicity.

Patients randomised to radical cystectomy

- Cystoscopy should be within 2-4 weeks after day 1 cycle 3 for assessment of response. The optimum time for cystoscopy is 3 weeks after day 1 cycle 3;
- If patients have responded to neo-adjuvant chemotherapy they will receive a 4th cycle of neoadjuvant chemotherapy prior to cystectomy. If patients have not responded to neo-adjuvant chemotherapy they will proceed straight to cystectomy.
- All patients who have received radical cystectomy should be seen 4-6 weeks post treatment for clinical assessment and toxicity.

7.3. Long-term follow-up

Trial follow up will be conducted 6 months after day 1 cycle 3 of chemotherapy then 3 monthly during year 1, 6 monthly during years 2 to 3 and annually to 5 years. At each trial follow-up visit the following assessments will be required:

- Toxicity assessed by CTC version 3;
- Physical examination;
- CT imaging (at end of year 1 and 2);
- Cystoscopy – radiotherapy patients only.

Patients randomised to SBP and receiving radiotherapy should undergo cystoscopic assessment. The first check cystoscopy (rigid) should be performed 3 months after end of radiotherapy or 6 months after day 1 of cycle 3 neo-adjuvant chemotherapy, whichever is sooner.

Assessments due at the 4-6 weeks post treatment and 6 month follow-up visits do not need to be repeated should these visits fall within one month of each other. In this instance, toxicity information should be recorded on the appropriate section of the 6 month follow up form.

Following the five year follow up visit all reasonable attempts should be made by the hospital to supply basic annual follow up information to the Trials Office.

Should a patient become “lost to follow up”, if their GP is no longer able to provide information to the randomising centre, the Trials Office should be informed. The Trials Office will then apply to the Office of National Statistics’ General Register Office to either trace the patients’ new GP or give notification in the event of their death.

7.4. Schema of trial evaluations

Visit **Months from D1 Cycle 3**	Prior to random-isation **0**	**End cycle 3**	**During RT**	**4-6 weeks post treatment**	**6**	**9**	**12**	**18**	**24**	**30**	**36**	**48**	**60**
Exclusion/ Inclusion Criteria	X												
Cystoscopy (1)	X^{+}	X			X^{Σ}	X*	X*	X*	X*		X*	X*	X*
Physical examination	X		X	X	X	X	X	X	X	X	X	X	X
Haematology and biochemistry (2)	X		X			X							
Chest X-ray or CT of chest	X				X		X	X	X	X	X	X	X
MRI or CT of pelvis	X						X		X				
Bone scan and liver US or CT(3)	X												
Upper urinary tract imaging	ACCORDING TO BEST CLINICAL PRACTICE												
Study Blood sampling (4)	X												
Study tissue blocks (5)	X					X*	X*	X*	X*		X*	X*	X*
Adverse events and toxicity			X	X	X	X	X	X	X	X	X	X	X
HRQL questionnaires (6)	X			X		X	X		X		X	X	X

(1) + Date of cystoscopy, TUR, size of tumour, number of tumours, estimated stage and grade.
* All patients having received radiotherapy. First check cystoscopy should be a rigid cystoscopy, subsequent cystoscopies can be rigid or flexible according to local policy. Date of cystoscopy, presence or absence of tumour.
Σ All patients having received radiotherapy. Rigid cystoscopy 3 months after end of radiotherapy or 6 months after day 1 of cycle 3 neo-adjuvant chemotherapy, whichever is sooner.

(2) FBC, U+E, LFTs.

(3) For raised ALP, ALT or AST.

(4) Recommended taken at baseline.

(5) Tumour paraffin block from TUR at study entry.
+ All patients in SBP arm.
* All patients having received radiotherapy who show evidence of recurrence

(6) EORTC Quality of Life Questionnaire (QLQ-C30 version 3 plus BLM30). Pre-randomisation and 6 week post treatment questionnaire will be administered by centre, follow up questionnaires will be administered by ICR-CTSU

8. Neo-adjuvant chemotherapy

Patients will receive an initial 3 cycles of chemotherapy. Responding patients will receive a 4th cycle of neo-adjuvant chemotherapy. Non-responders will proceed to cystectomy following check cystoscopy after cycle 3 (see trial schema).

Gemcitabine/cisplatin is the recommended schedule for all patients. It is recognised that patients may have commenced on alternative chemotherapy schedules prior to entry on this study. Therefore a limited number of other recognised platinum-containing regimens have been approved for use within the SPARE trial by the Trial Management Group (TMG). If a patient has commenced an alternative schedule or if a centre is unable to use the gemcitabine/cisplatin regimen contact the trials office to discuss the patient's eligibility.

Any patient unable to receive cycles 1-3 of their chemotherapy after a delay of more than 2 weeks from the planned beginning of a new cycle should not be randomised in this trial and should proceed immediately to standard local treatment according to patient preference. If the fourth cycle of chemotherapy is delayed for > 2 weeks the patient should proceed to receive randomised treatment as soon as possible.

8.1. Drug Administration: Route and Dose Schedule

The following information in Sections 8.1, 8.2, 8.3 and 8.4 is for guidance only, for centres using the recommended gemcitabine/cisplatin schedule.

Body surface area calculation of the patient according to actual height and weight at the beginning of each cycle is mandatory.

The following gemcitabine/cisplatin schedule is recommended:

- **Gemcitabine** 1000mg/m^2 day 1 and day 8 as 30 minute intravenous infusion in 500ml sodium chloride; and
- **Cisplatin** 70mg/m^2 day 1 as a 4 hour intravenous infusion.
  Cisplatin will be administered after adequate hydration with at least 1 litre 0.9% normal saline with mannitol (100mls 10%) over 4 hours immediately prior to cisplatin infusion. Following this a continuous infusion of 0.9% sodium chloride x 2 litres over the next 6 hours to maintain a urine output of greater than 100 ml per hour is recommended. Patients should receive additional hydration (in accordance with guidelines at each investigator site) to replace any fluids lost as a result of emesis and/or diuresis.

  Urine output should be monitored and serum electrolytes and renal parameters followed appropriately. If the EDTA is $\leq$ 70 mls/min then cisplatin should be given over 2 days (35mg/m2 /day).

  It is advised that patients receive pre-medication with appropriate anti-emetics including a 5HT-3 antagonist and dexamethasone.

G-CSF is allowed but should be used in accordance with ASCO guidelines.[36]

Treatment will be repeated every 21 days. Three cycles of treatment are given neo-adjuvantly prior to cystoscopic evaluation. The 4th cycle is given if a response is observed on cystoscopy.

8.2. Formulation, Presentation and Storage

8.2.1. Cisplatin

Cisplatin (CDDP) is a planar inorganic metal salt that functions as an alkylating agent. In aqueous solution, the drug is aquated to a diaquo species as the two chloride groups leave the molecule. The reactive diaquo species binds to N7 residues of guanine bases on DNA resulting in stand scission, and intra and interstrand cross-linking.

Cisplatin is available in 50 and 100 mg vial containing a 1 mg/ml solution. Further dilutions should be done in Sodium Chloride 0.9% (500 ml in a 1-hour infusion). Neither cisplatin nor the drug reconstituted should be refrigerated.

8.2.2. Gemcitabine

Gemcitabine is supplied as a lyophilized powder in sterile vials containing 200 mg or 1 g of gemcitabine as the hydrochloride salt (expressed as the free base), mannitol, and sodium acetate (Gemzar).

The recommended diluent for reconstitution of Gemzar is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for

Gemzar upon reconstitution is 40 mg/mL. To reconstitute, add 5mL of 0.9% Sodium Chloride Injection to the 200 mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1 g vial.

The appropriate amount of drug may be administered as a continuous infusion for 30 minutes as prepared or further diluted with 0.9% Sodium Chloride Injection to a concentrations as low as 0.1 mg/mL.

When prepared as directed, Gemzar solutions are stable for 24 hours at controlled room temperature 20˚ to 25˚C (68˚ to 77˚F). Solutions of reconstituted Gemzar should not be refrigerated, as crystallization may occur. Unopened vials of Gemzar are stable until the expiration date indicated on the package when stored at controlled room temperature 20˚ to 25˚C (68˚to 77˚F).[37].

8.3. Drug toxicities

8.3.1. Cisplatin

The primary toxicity is renal insufficiency and possible renal failure from renal tubular damage. This can produce elevations in urea and creatinine and decreases in creatinine clearance. Hypomagnesemia and hypokalaemia can occur. Other toxicities include nausea and vomiting which can be minimized by pre-medication with anti-emetics, alopecia, myelosuppression, peripheral neuropathy and decreased auditory function. Hypersensitivity reactions have been observed in both untreated and pre-treated patients.

8.3.2. Gemcitabine

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

8.4. Recommended dose modifications

8.4.1. Dose reductions

Dose adjustments within a cycle will be made according to the guidelines shown in the following tables, based on weekly white blood cell (WBC) and platelet counts taken on the day of therapy, and on clinical assessment of non-haematological toxicity.

8.4.1.1. Haematological toxicity

Dose modifications day 1:

No new cycle should start unless:

- WBC ≥ 3.0 x 10^9/L;
- Absolute neutrophil count (ANC) >1.0 x10^9/L; and
- Platelets ≥ 100 x 10^9/L.

If a patient requires 2 weeks for haematological recovery, treatment should be continued with 75% of both drugs, provided that WBC is > 2.0 x 10^9/L and platelets are > 75 x 10^9/L.

A 25% dose reduction in both drugs is recommended for subsequent cycles if during the nadir one or more of the following occurs:

- Grade IV neutropenia (ANC <0.5 x10^9/L, platelets <10 x10^9/L) with fever ≥ 38.5C;
- Grade IV thrombocytopenia for more than 3 days; or
- Thrombocytopenia with active bleeding.

If afebrile grade IV neutropenia is seen on day 15, prophylactic ciprofloxacin 500 mg/12h x 7days should be used in subsequent cycles.

Dose modifications day 8:

The following dose adjustments for myelosuppression will be used:

Table 1: Day 8 dose reductions due to haematological toxicity

WBC		**Platelets**	Percent of Full Dose Gemcitabine
> 3.0	and	≥ 150	100
> 3.0	and	100-150	75
2.0-3.0	or	50-<100	50
< 2.0	or	< 50	Withhold

8.4.1.2. Neurotoxicity
In grade 3 or 4 neurotoxicity, cisplatin should be permanently stopped and replaced with carboplatin AUC 5 (Carboplatin dose = 5 x (GFR+25)). Patients will continue to receive gemcitabine on day 1 and 8 as per the above schedule.

8.4.1.3. Renal toxicity
In the event of renal toxicity, dose reductions for gemcitabine and cisplatin should be according to the table below.

Table 2: Dose reductions due to renal toxicity

GFR (ml/min.)	Percent of Full Dose Gemcitabine	Percent of Full Dose Cisplatin
≥ 70 ml/min.	100	100
50-69 ml/min.	100	100 to be given over 2 days†
< 50 ml/min.	----- *	Substitute carboplatin AUC 5**

Carboplatin will be given instead of cisplatin in case of renal function impairment.

† Cisplatin on either day 1 and 2 or day 1 and 8

* Patients will receive full dose gemcitabine unless the CTC grade for creatinine is > 3 (> 6x ULN), in which case the gemcitabine dose will be omitted.

** Carboplatin dose = AUC x (GFR+25)

8.4.1.4. Other toxicities
If any other grade 3/4 toxicity occurs (except fatigue, anaemia, alopecia, nausea or vomiting) treatment should be interrupted until resolved to grade 1 or less. If not resolved in 2 weeks post chemotherapy, assessment should be performed. Subsequent dose modifications are at investigator's discretion but should be discussed with the Principal Investigator.

If there is persistent nausea and vomiting, 5HT-3 inhibitors + dexamethasone should be given if not already given prophylactically.

8.4.2. Dosage adjustments in a cycle (delay, start of next cycle)

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

9. Randomised Treatment Post Neo-adjuvant Chemotherapy

9.1. Arm A: Radical cystectomy (control) arm

Patients randomised to radical cystectomy will undergo rigid cystoscopy 3 weeks after cycle 3 of neoadjuvant chemotherapy. Radical cystectomy will be performed between 4 and 6 weeks after day 1 of cycle 4 unless there is evidence of poor response (residual pT2 / macroscopic invasive tumour) when cystectomy will be performed as soon as possible and within 6 weeks of completing chemotherapy.

Radical cystectomy will be performed according to best standard and will include pelvic lymphadenectomy to remove at least 10 pelvic lymph nodes. Reconstructive surgery will be allowed and is recommended for all suitable patients. Patients not suitable or refusing reconstructive surgery will receive an ileal conduit. Surgical details are provided in section 10.

9.2. Arm B: Selective bladder preservation arm (SBP)

All patients randomised to selective bladder preservation (SBP) will undergo a rigid cystoscopy and resection of residual tumour or biopsy of tumour bed. This will be performed between 2-4 weeks following day 1 of cycle 3 neo-adjuvant chemotherapy.

- Patients with residual macroscopic invasive tumour will undergo immediate cystectomy as above. Patients with widespread/extensive CIS away from primary tumour bed may be considered for cystectomy at clinician's discretion. Cystectomy should be performed as soon as possible and within 6 weeks of completing chemotherapy.

- Patients with no visible residual tumour (cT0 or pT0) or residual but superficial tumour (pTa, pT1, localised CIS) will undergo attempted bladder preservation using radiotherapy.

  Patients proceeding to bladder preservation will receive a 4th cycle of neo-adjuvant chemotherapy (as detailed in Section 8) before commencing a radical course of radiotherapy. Radiotherapy should commence within 4-6 weeks of day 1 of cycle 4.

Guidance for patients who have not received their histology results prior to cycle 4 chemotherapy

For patients who have not received their histology results prior to starting cycle 4 of chemotherapy the following guidance should apply:

- Clear bladder – patient to have cycle 4
- Invasive disease present – patient proceeds to surgery, no CT
- Unsure – patient to have cycle 4 of chemotherapy

10. Surgical Protocol

Centres recruiting to SPARE will be expected to deliver surgical management that conforms to the standards set out in the NICE Improving Outcomes Guidance[34] and will be expected to be able to offer evidence of surgical quality assurance. Trial centres will be asked to specify:

- The centre at which cystectomy will be performed;
- The name of the responsible surgeon(s);
- Details of surgical activity (including annual number of patients undergoing cystectomy availability of reconstructive surgery, complication rates and 30 day mortality);
- Confirmation that surgical practice conforms to IOG guidance; and
- Confirmation that the treating centre can undertake the surgical protocol.

Data from each centre will be assessed by the surgical subgroup of the SPARE TMG.

Surgical techniques should follow the protocol as detailed below.

10.1. Cystoscopy, TUR and Bladder Mapping (prior to study entry)

A cystoscopy and trans-urethral resection (TURBT) of bladder tumour is performed to diagnose muscle invasive disease prior to neo-adjuvant chemotherapy. Staging of bladder cancer should include a minimum of a tumour biopsy including muscularis propria and bimanual examination under anaesthesia. All patients should have as complete resection of muscle invasive bladder cancer as possible to optimise further therapy. Additional resection biopsies of the prostatic urethra and bladder mapping by cold biopsy of four quadrants of the bladder is advised. Use of photodynamic assessment is allowed.

Ideally complete resection should be as a primary procedure at the time of the initial TURBT. But where initial procedure was biopsy only then a second TURBT should be performed with the aim of resecting as much tumour as possible though patients with incomplete resection may still be entered into the study.

10.2. Radical Cystectomy

Radical cystectomy may be performed by an open or minimal access approach. It is accepted that minimal access surgery (robotic or laparoscopic) has been introduced by a number of UK Centres over the past 5 years. Expertise in minimal access surgery may be variable and surgical teams participating in SPARE must submit on going and up to date audit activity demonstrating comparable outcomes data to open radical cystectomy for review by the SPARE surgical subcommittee.

Patients who are enrolled in SPARE and who have been randomised to cystectomy or who are not eligible for radiotherapy may be enrolled into BOLERO (Bladder: Open versus laparoscopic or robotic cystectomy), a feasibility study to determine whether patients agree to randomisation between open versus minimal access surgery.

In male patients the bladder peri-vesical fat, prostate and seminal vesicles should be excised. Urethrectomy is optional and is not a requirement in patients who want orthotopic reconstruction.

In female patients the uterus and cervix, ovaries, a strip of anterior vagina and the urethra will be excised. In patients undergoing orthotopic bladder reconstruction the urethra and vagina may be preserved if necessary.

10.3. Urinary diversion

An orthotopic reconstruction using small or large bowel is encouraged in suitable patients. Alternatively a standard ileal conduit should be performed. Non–standard techniques should be approved by the SPARE surgical subcommittee.

10.4. Lymph node dissection

Lymph node sampling will include dissection of obturator nodes and external iliac nodes to the level of the iliac bifurcation and internal iliac nodes from the right and left side of pelvis. The lateral limit of the dissection is the genito-femoral nerve on the psoas muscle and medial and posterior limits represented by the obturator nodes. The lymph node dissection should result in the removal of at least ten nodes.

Centres may elect to undertake a more extensive lymph node dissection to the level of the aortic bifurcation. If this is elected then aortic bifurcation dissection should be done on all patients entering the trial from that centre unless it is not justified for technical reasons.

11. Radiotherapy protocol

11.1. CT scanning for radiotherapy

CT scanning for radiotherapy should be according to local practice; however the following should be performed as a minimum:
Tumour, clinical and planning target volumes should be defined on CT slices taken at a maximum of 10mm intervals (8mm slice thickness) (5mm slices or less recommended). Patients should be scanned from the bottom of ischial tuberosities to 3 cm above the dome of the bladder or to the bottom of L5 (using the highest of these two points). Patients should be CT planned with an empty bladder. The rectum should be empty of flatus and faeces. Patients should be asked to empty their bladder 15 - 30 minutes prior to scan. Target outlining should be performed according to local practice.

11.2. Radiotherapy technique

Patients should be treated with an empty bladder. The clinical target volume (CTV) is the bladder tumour (GTV) plus outer bladder wall. Planning target volume (PTV) is CTV with a 1.5cm margin. Smaller and/or anisotropic margins and/or treatment using a full bladder can be used if image guided techniques (eg cone beam) are utilised. Such protocols should be discussed with and approved by the Chief Investigator or his delegated deputy in advance. It is recommended that the PTV is covered using an anterior and two lateral fields to encompass the PTV in the 95% isodose. Other field arrangements such as four field brick are permitted with prior agreement of the TMG. Exclusion of non-target tissue by conformal shielding is recommended but not mandatory and is undertaken at the discretion of treating physician. The maximum rectal dose to the posterior wall should be 80% of reference dose.

If preferred, patients may be treated with whole bladder and tumour boost provided:

- GTV + 1.5 cm margin receives 100% +/- 5% of prescribed dose; and
- Minimum dose to rest of PTV is 80% +/- 5% of target dose.

Detailed instruction in planning bladder radiotherapy is available on request from ICR-CTSU.

Image guided techniques using cone beam or similar techniques are allowable.

11.3. Radiotherapy dose

Patients should be treated by CT planned radical radiotherapy to deliver a minimum tumour dose of 64Gy in 32 fractions over 6.5 weeks. Where for logistic reasons this schedule cannot be delivered locally a dose of 55Gy in 20 fractions over 4 weeks may be used with prior agreement of the TMG.

The chosen radiotherapy dose should be stated by each centre prior to randomisation of their first patient. At any centre, all patients should receive the same total dose of radiotherapy.

Radiotherapy should commence within 4-6 weeks of day 1 cycle 4 of chemotherapy.

Randomised data on the efficacy of combined chemo-radiotherapy is limited. Entry into randomised controlled trials addressing the use of chemo-radiotherapy is permitted following agreement (on a trial by trial basis) by the TMG. Centres may also elect to use concomitant chemo-radiotherapy following discussion with the TMG.

11.4. Radiotherapy Quality Assurance

The trial centres will be asked to specify:

- The centre at which radiotherapy will be performed;
- The name of the responsible oncologists(s);
- Details of radiotherapy activity (including annual number of patients treated for bladder cancer);
- Confirmation that the treating centre can undertake the radiotherapy protocol; and

- Evidence of a relevant successful radiotherapy quality assurance in other NCRN trials of pelvic radiotherapy in the last 3 years (e.g. CHHIP, RADICALS, RT01, ProTect, CR07, ACTII, ASTEC, EORTC 229911)

For centres without previous NCRN quality assurance the Baseline Questionnaire for Centres Participating in National Clinical Trials must be submitted to the National Radiotherapy Trials QA team. Also, confirmation of an IPEM or regional audit should be provided to ICR-CTSU. If the centre did not participate in BC2001 then data should be provided on outlining for the first two radiotherapy patients treated within SPARE.

Centres will be asked to provide copies of the radiotherapy plan and dose volume histograms. A random audit of radiotherapy treatments will be performed as part of source document verification.

11.5. Patient care during radiotherapy

All patients should be asked about the use of over the counter medication and supplements. Although the use of antioxidants during radiation therapy remains controversial, two placebo-controlled randomised studies have shown an increased risk of local recurrence in patients receiving antioxidant supplementation during head and neck irradiation. In the absence of data for pelvic radiation, it is recommended that all over the counter supplements (except multivitamins) should be stopped two weeks prior to and during radiotherapy.[38,39]

12. Management of recurrence

12.1. Local recurrence

12.1.1. Patients treated with bladder preservation

Patients with local recurrence (SBP arm) will be treated according to clinical circumstances. It is recommended that:

- Patients with invasive recurrence (pT2 or greater) undergo a salvage cystectomy in a centre experienced in this procedure;
- Patients with superficial recurrence (G1/G2) should be treated by local resection +/- intravesical therapy; and
- The management of patients with CIS or pT1 G3 recurrence is controversial. Salvage cystectomy should be considered the safest gold standard option. A number of radiotherapy and SBP series have reported treating with local resection and BCG intravesical treatment. In these studies CR rates to resection and BCG or intravesical chemotherapy of over 70% are reported and long term control rates of 35-76%.[2, 15, 40-43] Therefore after patient counselling, resection and BCG may be considered as an alternative approach.

12.1.2. Patients treated with radical cystectomy

Patients with any recurrence following cystectomy should be treated at the discretion of treating physician. Patients should continue to be followed up for metastatic recurrence, survival and quality of life.

12.2. Metastatic recurrence

All patients with regional nodal or metastatic disease should be treated at the discretion of treating physician. Patients should continue to be followed up for survival and quality of life.

13. Adverse Events (AE)/Serious Adverse Events (SAE)

13.1. Definition of an Adverse Event

For the purpose of this trial, any detrimental change in the patient's condition subsequent to the start of the trial (i.e. randomisation) and during the follow-up period, which is not

unequivocally due to progression of disease (bladder cancer), should be considered as an AE. This will include AEs occurring after discontinuation of chemotherapy.

Whenever one or more signs and/or symptoms correspond to a disease or well-defined syndrome only the main disease/syndrome should be reported. For each sign/symptom the highest grade observed since the last visit should be reported.

13.2. Definition of Serious Adverse Events

A Serious Adverse Event (SAE) is defined as an untoward occurrence that:

- results in death;
- is life-threatening;
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect; or
- is otherwise considered medically significant by the investigator.

13.3. Reporting of Adverse Events

Adverse events will be collected from the time of randomisation to the end of the follow-up period. Adverse events should be recorded in the appropriate section of the CRF. Only the occurrence of the event and its severity require reporting.

All serious adverse events occurring **after the check cystoscopy following cycle 3 of chemotherapy and up to 60 days** after the last administration of definitive randomised treatment **must be reported within 24 hours of the event** using specific SAE forms. The forms must be sent by FAX to The Institute of Cancer Research – Clinical Trials and Statistics Unit (ICR-CTSU) on **020 8722 4368**. Initial notification must not be delayed for signature, but should be followed by a report signed and dated by the Principal Investigator or nominated representative as soon as possible. **Only those events not listed below as expected occurrences require expedited reporting.**

ICR-CTSU will send the SAE to the Chief Investigator (or nominated representative) for review of expectedness and relatedness.

A related adverse event is one for which the investigator assesses it resulted from administration of any of the research procedures.

An unexpected adverse event is any type of event not listed below as an expected occurrence.

During Chemotherapy:

- Please refer to appendix 2 on page 33 of the protocol.

During Radiotherapy:

- Fatigue;
- Nausea, vomiting;
- Dehydration, diarrhoea, constipation;
- Anaemia;
- Skin rashes and radiation skin toxicity;
- Peptic ulceration;
- Radiation proctitis;
- Urinary frequency, dysuria, urethritis, urinary incontinence; and
- Impotence.

Surgery:

- Post surgical complications (haemorrhage, wound infection, ileus, wound dehiscence, any complication related to neobladder formation or ileal diversion);
- Anaemia; and
- Renal failure, electrolyte disturbance.
- DVT, Pulmonary embolus
- Anastomotic leak
- Pneumonia
- Ureteric obstruction

13.4. Reporting related and unexpected SAEs

If an SAE is defined as related and unexpected ICR-CTSU will report this to the main REC within 15 days from the date the Chief Investigator or designated Co-Investigator became aware of the event.

13.5. Serious Adverse Event follow up

The subject must be followed up until clinical recovery is complete and laboratory tests have returned to normal, or until disease has stabilised. Information on final diagnosis and outcome of SAEs which may not be available at the time the SAE is initially reported should be forwarded to the ICR-CTSU in the timeframe requested.

14. Statistical considerations

14.1. Stratification

Patients will be stratified by cancer centre.

14.2. Choice of principal endpoints

The primary endpoints for the feasibility study are the total number of patients randomised and the proportion of patients undergoing bladder preservation in SBP arm and compliance with randomised treatment. If the feasibility study is successful the phase III trial will investigate several endpoints (including overall survival, recurrence, and quality of life).

14.3. Sample size calculations

For a phase III trial of bladder preservation to be considered feasible, it is recommended that the following criteria are met:

1) Accrual rate
   - 110 patients randomised during the three years of the feasibility study or;.
   - A sustainable accrual rate of at least 6 patients per month achieved prior to completing the three year feasibility phase.

2) Compliance

   SBP arm: The lower end of the one sided 95% CI of the proportion of patients randomised to SBP receiving radiotherapy to be greater than 60%.

   For a phase III trial to be considered feasible a bladder preservation rate of 60% will need to be excluded. If 39/55 patients in the SBP arm underwent radiotherapy this would allow the exclusion of a bladder preservation rate of less than 60% (if the true rate was 80%) with 95% power (one-sided alpha 0.1).

   Cystectomy arm: It is expected that 90% of patients in the radical cystectomy arm will undergo a radical cystectomy; with 55 patients in this arm it will be possible to estimate the proportion of patients accepting to undergo this operation with a 95% confidence interval of plus or minus 10% (80% to 97%).

The primary endpoint of the phase III trial will be overall survival. **The phase III trial will recruit 1015 patients**. This is based on demonstrating non-inferiority of SBP in terms of overall survival compared with cystectomy in responders to neo-adjuvant chemotherapy. The null hypothesis is that in terms of five-year overall survival, SBP is not inferior to a policy of treating all patients with cystectomy in the group of responders (i.e. overall survival in the SBP group is at most 8% worse). It is estimated that 80% of patients will respond to neoadjuvant chemotherapy and the five year overall survival rate of these patients will be 70%.[30] Assuming that SBP has no negative effect, a total of 812 patients are required in order to have an 80% chance of demonstrating that the two arms are equivalent (80% power, one-sided 5% significance level). To allow for 20% non-response to neo-adjuvant chemotherapy the total sample size for the trial will need to be 1015 patients. This number would also allow the comparison of the policy of SBP to be analysed in an ITT analysis with sufficient power. Assumptions and recruitment targets will be reviewed following analysis of the feasibility phase.

14.4. Analysis methods

14.4.1. Primary endpoint

Descriptive methods will be used to summarise the accrual rate in the feasibility study and the proportion of patients receiving radiotherapy in the SBP arm (with its attendant 95% confidence interval). The proportion of patients undergoing bladder preservation in the SBP arm is a composite endpoint based on response to neoadjuvant chemotherapy and acceptance of the treatment indicated on the basis of that response.

14.4.2. Secondary endpoints

In the feasibility stage, descriptive methods will be used to summarise secondary endpoints. Assessment of compliance will include the proportion of patients accepting randomised treatment strategy.

14.4.3. Main study

Survival analysis methods will be used to compare overall survival between allocated treatments for all randomised patients (i.e. intention to treat). Hazard ratios and Kaplan-Meier curves will be presented. Cox proportional hazard model will be used to adjust for known prognostic factors. Methods to account for non-proportionality will be used if appropriate. Similar methods will be used for secondary analyses comparing time loco-regional progression free and metastasis-free survival.

Toxicity will be compared using appropriate methodology for ordinal data. Dichotomisation of toxicity scales will be used to summarise proportions experiencing >= grade 2 side effects with comparisons made using chi-squared based tests. Standard algorithms will be used to derive scores from and handle missing data in Quality of Life questionnaires. Treatment groups will be compared at individual timepoints and analyses to account for the longitudinal nature of the data will consider changes from baseline. Generalised estimating equations will be used to adjust for important clinical and demographic factors. Appropriate adjustments will be made to allow for multiple comparisons.

Statistical methods will be further specified in a separate Statistical Analysis Plan.

14.4.4. Adjusting for non-compliance

If non-compliance is high in either or both of the arms of this trial we will endeavour to provide an estimate of the treatment effect which allows for the fact patients have switched treatment.[44,45] Robins et al related a patient's observed event time to an event time that would have been observed if the randomised treatment had been administered throughout follow up, assuming treatment has a multiplicative effect (e^{η}) on a patient's lifetime. A test-based process is used to find the value of η and its standard error such that the logrank statistic is equal to zero, i.e. the observed survival times in the two arms, incorporating switching, are completely explained by assuming a multiplicative treatment effect size of e^{η}. However, the

method used to correct for switching will depend on whether switching is informative; this will be determined by fitting the switch time as a time-dependent covariate in a Cox model independently in the two treatment arms. This will reveal whether there is evidence that patients are at greater risk of an event if they switch (compared to patients who did not switch).

14.5. Frequency of analyses

The Trial Management Group will monitor recruitment rates and the rate of bladder preservation in the SBP arm regularly. All data will be regularly reviewed (at least annually) by an independent Data Monitoring and Ethics Committee.

Data from the feasibility study will be analysed after recruitment of 110 patients or three years after the first patient is randomised (whichever is sooner). The independent Data Monitoring and Ethics Committee will review unblinded data from the feasibility stage and be asked to make a recommendation, on the basis of the available safety data and any early efficacy data, on the continuation of recruitment. The independent Trial Steering Committee will advise on continuation to the full phase III trial.

The principal analysis of the main trial will be event driven.

15. Research Governance

15.1. Trial Administration and Logistics

The Institute of Cancer Research (ICR) is the proposed sponsor of this study in line with the Research Governance Framework for Health and Social Care and the principles of GCP.

The Chief Investigator is Dr Robert Huddart. ICR-CTSU has overall responsibility for facilitating and coordinating the conduct of the trial and is also responsible for collating data obtained, and undertaking and reporting interim and final analyses.

15.1.1. Participating centres' responsibilities

Centres wishing to recruit to this study will be asked to provide evidence that they can deliver protocol treatment. This will include:

- Evidence that local practice conforms to the standards set in the NICE Improving Outcomes Guidance; and
- Evidence that surgical and radiotherapy quality assurance is available.

Responsibilities are defined in an agreement between an individual participating centre and The Institute of Cancer Research.

15.2. Investigator training

Prior to commencing trial recruitment, training will be provided to identified key individuals in each participating network by the Chief Investigator or delegate. Training will include discussion on the background to the study, evidence for selective bladder preservation and discussion on the issues of clinical equipoise. Experience developed from successfully recruiting centres and information from associated qualitative studies will be provided to participants at their initial training and subsequently on a regular basis. Participating centres will be asked to maintain a screening log. Randomisation acceptance rates will be monitored and additional support/training offered when lower than anticipated rates are encountered.

15.3. Case Report Forms

Case Report Forms (CRFs) should be completed for all patients and should not be made available to third parties.

CRFs should be completed as indicated in the Trial Guidance Notes held within the Site Investigator File. The completed CRF must be sent by the hospital to ICR-CTSU as soon as it

is due. A copy must be retained by the centre. If information is not known this must be clearly stated.

The Trial Management Group reserves the right to amend or add to the CRFs as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by centres with immediate effect.

15.4. Protocol compliance/on site monitoring

SPARE is being conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under Research Governance Framework for Health and Social Care.

Participating centres may be monitored by ICR-CTSU and possibly by Health Authorities to carry out source data verification, and confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki adopted by the 18th World Medical assembly, Helsinki, Finland, 1964 and later revisions (last revised Edinburgh 2000).[46] Copies of the Declaration may be obtained from ICR-CTSU on request. By participating in the SPARE trial the Principal Investigators at each centre are confirming agreement with his/her local NHS Trust to ensure that:

- Sufficient data are recorded for all participating patients 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 at their centre who are involved with the trial are trained appropriately;
- All original Consent Forms are dated and signed by both the patient and investigator, and are kept together in a central log together with a copy of the specific patient information sheet(s) the patient was given at the time of consent;
- Copies of CRFs are retained for 15 years to comply with international regulatory requirements; and
- Staff will comply with the Trial Guidance Notes for SPARE.

ICR-CTSU will monitor receipt of CRFs. They will also check incoming CRFs for compliance with the protocol, inconsistent and missing data.

ICR-CTSU will contact centres to discuss dates of any proposed monitoring visits. Once a date has been confirmed a list of names of patients whose notes will be monitored during the visit will be sent to the centre. This list will be sent out in advance to give sufficient time for the notes to be made available. Site monitoring will be conducted at least once at participating centres which have randomised a patient. It is likely that a random sample of notes will be selected for limited source document verification.

15.5. Trial Management

15.5.1. Trial Management Group

The Trial Management Group (TMG) includes the Chief Investigator (Dr RA Huddart), co-investigators and identified collaborators, the trial statistician and the trial co-ordinators. 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.

The design of the SPARE trial has been informed by a panel of consumers. Selected members of this panel will be invited to each TMG meeting to ensure, if possible, that consumers are represented at each meeting.

Not withstanding the legal obligations of the Sponsor and Chief Investigator, the TMG has operational responsibility for the conduct of the trial.

15.5.2. Trial Steering Committee

A Trial Steering Committee (TSC) monitors and supervises the progress of the trial. The role of the TSC is to provide overall supervision of the trial on behalf of the funding body. In particular, the TSC will concentrate on the progress of the trial, adherence to the protocol, patient safety and the consideration of new information. Day-to day management of the trial is the responsibility of the Chief Investigator and TMG.

Membership of the TSC is limited and includes an independent Chairman (not involved directly in the trial other than as a member of the TSC), not less than two other independent members, the Chief Investigator and the trial statistician.

Where possible, membership will include a lay/consumer representative. Trial co-ordinators and other key members of the TMG will attend meetings (as observers) as appropriate. Observers from the funding body and, if applicable, host institutions or sponsors will be invited to all meetings. The TSC will meet at least annually.

15.5.3. Data Monitoring Committee

An independent Data Monitoring and Ethics Committee (DMEC) has been established to oversee the safety and interim efficacy of the trial. This committee is constituted according to MRC Good Clinical Practice (MRC GCP). The DMEC will meet on a regular basis as they see fit, but no less than annually. Following each meeting, the DMEC will report their findings and recommendations to the TSC and to the TMG.

15.6. End of Study

For the purposes of ethics approval, the study end date is deemed to be the date of the last data capture.

15.7. Archiving

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced, for example CRFs, patient consent forms. These will be maintained at ICR-CTSU and at the Investigator Sites in a way that will facilitate the management of the trial, audit and inspection. They will be retained for a sufficient period (at least 15 years). The sponsor or trial organisers will notify the investigator sites of their responsibility for archiving essential documents. Documents will be securely stored and access will be restricted to authorised personnel. An archive log will be maintained to track archived documents.

15.8. Publishing policy

All publications and presentations relating to the trial will be authorised by the TMG. A Writing Committee may be appointed. Authorship will be determined by the TMG and will include the Chief Investigator, co-investigators, and trial statisticians. Further authorship will be determined by centre accrual. All participating centres will be acknowledged in the final manuscript according to patient accrual.

16. Confidentiality and Liability

16.1. Risk assessment

Prior to approval by the Committee for Clinical Research, this study was formally assessed for clinical risk using a generic risk assessment matrix.

16.2. Liability/Indemnity/Insurance

This study is an investigator-led trial endorsed by the Clinical Trials Awards and Advisory Committee (CTAAC) of Cancer Research UK and the UK Medical Research Council. Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements.

16.3. Patient Confidentiality

The patient's full name, date of birth, hospital number and NHS number will be collected at randomisation to allow tracing through national records. The personal data recorded on all documents will be regarded as confidential, and to preserve each subject's anonymity, only their initials and date of birth will be recorded on subsequent Case Report Forms. Patient addresses will be requested for distribution of quality of life questionnaires.

The investigator must keep a separate log of patients' trial numbers, names, and hospital numbers. The investigator must maintain, in strict confidence trial documents, which are to be held in the local hospital (e.g. patients' written consent forms). The investigator must ensure the patients' confidentiality is maintained.

ICR-CTSU will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, other than reporting of serious adverse events. Representatives of the trial team will be required to have access to patient notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times. In the case of special problems it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

17. Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical assembly, Helsinki, Finland, 1964 and later revisions (last revised Edinburgh 2000).[46]

It is the responsibility of the Chief Investigator to obtain a favourable ethical opinion (main REC approval).

It is the responsibility of the Principal Investigator at each participating Trust to obtain site-specific approval of the trial protocol and any subsequent amendments. All correspondence with the local REC should be filed by the Investigator.

From the time the trial is closed to recruitment, changes of Principal Investigator at participating sites will not necessitate the submission of a Site Specific Information form. Should a change occur during the follow up phase of the trial, the Trials Office should be notified of this and provided with a copy of the local R&D approval for the change. Contact details and an updated log of delegated responsibilities should also be provided to the trials office for the new Principal Investigator.

It is the responsibility of the Investigator to give each patient, prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. Patients must be informed about their right to withdraw from the trial and the possible risk involved. Written patient information must be given to each patient before enrolment. The written patient information is an approved Patient Information Sheet according to national guidelines. This outlines the Quality of Life study, and the collection of biological specimens. Patients will be encouraged to participate in these associated studies but, if they decline, this will not exclude them from the comparison of SBP and cystectomy.

It is the responsibility of the Principal Investigator to obtain signed informed consent from all patients prior to their inclusion in the trial.

18. Withdrawal of patients from study treatment

Patients who do not receive their allocated treatment for any reason should be treated at the discretion of their clinician. However, analyses of primary outcome data will be on the basis of intention to treat. Unless the patient requests otherwise, all CRFs, including long term follow

up, should be completed, regardless of treatment actually received. A trial deviation form should be completed to record details of deviation from treatment allocation, and also for any patient who withdraws consent for further follow up. Patients are asked prior to randomisation to consent to follow up should they withdraw from the treatment allocation (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 that decision at any time without giving a reason.

19. Financial Matters

The trial is investigator designed and led, and has been approved by the Clinical Trials Awards and Advisory Committee (CTAAC). It is endorsed by Cancer Research UK and meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England.

Research costs (to ICR-CTSU) are being funded by Cancer Research UK. If additional financial support is received from any other source, this will be made apparent to the approving Main REC and CTAAC, but will not require a protocol amendment.

No individual per patient payment will be made to trusts or investigators, but NCRN (or regional equivalent) network resources should be made available as the trial is part of the NCRI portfolio by virtue of its approval by CTAAC.

20. Associated studies

20.1. Quality of Life

Health Related Quality of Life (HRQL) will be a secondary endpoint in the main trial. Patients entered in the feasibility study will be included in the analysis of the main trial therefore HRQL will be assessed in these patients. The objective of HRQL assessment within the main trial is to describe and compare the impact of both radical cystectomy and selective bladder preservation 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 cystectomy and bladder preservation.

Further details are given in Appendix 3.

20.2. Qualitative study – Patients' Experience of Recruitment

A qualitative study will be initiated to support this protocol to prospectively examine the patients' experiences of the treatment approaches evaluated in this study. This will include examination of the issues regarding randomisation, clinical equipoise and developed patient information.

The patient interview sub-study will be an integral part of the feasibility study and will be performed on a random and selective basis. The aim is to include patients agreeing to randomisation, randomised patients declining allocated treatment and patients not agreeing to participation. The study will seek to understand the effects of information provided, and how information is delivered, on recruitment and randomisation rates. A representative sample will initially be studied but targeted sampling may also be initiated in centres with lower than expected recruitment rates or lower than expected acceptance of randomisation.

This sub-study has now closed to recruitment, having reached its target sample size.

Further details are given in Appendix 4.

20.3. Qualitative study – Recruitment Processes

A qualitative study will be initiated to support this protocol to prospectively examine the methods used by health professionals to approach and discuss SPARE with potential participants. The study aims to identify any potential barriers to recruitment and develop training to overcome these barriers.

Further details are given in Appendix 5.

20.4. Pathological tissue collection

Patients entered in the feasibility study will be included in the analysis of the main trial therefore pathological tissue will be requested from these patients.

Consent for access to paraffin blocks will be sought to allow collection of tissue sections for analysis at a later date. Patients will be asked to donate a 5-8ml blood sample collected in EDTA. Stored tissue and blood samples may be used to research biological predictors or markers of therapeutic response. Biological samples will be sent to University College London Hospitals NHS Foundation Trust for storage and cataloguing. The material will be used to form molecular expression and CGH arrays for subsequent analysis of indicators of response and outcome.

Further details are given in Appendix 6.

21. References

1 Cancer Research UK. CancerStats Incidence - UK. April 2006. http://www.cruk.org.uk/aboutcancer/specificcancers/bladdercancer?version=1

2 Shipley WU, Zietman AL, Kaufmen DS et al. Selective bladder preservation by trimodality therapy for patients with muscularis propria-invasive bladder cancer and who are cystectomy candidates – the Massachusetts General Hospital and Radiation Therapy Oncology Group experiences. Sem Rad Oncol 2005; 15(1): 36-41.

3 Rodel C, Weiss C, Sauer R. Organ Preservation by combined modality treatment in bladder cancer: the European perspective. Sem Rad Oncol 2005; 15(1): 28-35.

4 Shelley MD, Wilt TJ, Barber J, Mason MD. A meta-analysis of randomised trials suggests a survival benefit for combined radiotherapy and radical cystectomy compared with radical radiotherapy for invasive bladder cancer: are these data relevant to modern practice? Clin Onc 2004; 16(3): 166-171.

5 Cookson MS. The surgical management of muscle invasive bladder cancer: a contemporary review. Sem Rad Oncol 2005; 15(1): 10-18.

6 Hall CM, Dinney CP. Radical cystectomy for stage T3b bladder cancer. Semin Urol Oncol 1996; 14(2): 73-80.

7 Smith JA, Jr., Crawford ED, Paradelo JC, et al. Treatment of advanced bladder cancer with combined preoperative irradiation and radical cystectomy versus radical cystectomy alone: a phase III Intergroup study. J Urol 1997; 157(3): 805-7; discussion 807-808.

8 Whitmore WF Jr., Batata MA, Ghoneim MA et al. Radical cystectomy with or without prior irradiation in the treatment of bladder cancer. J Urol 1977; 118(1 Pt 2): 184-187.

9 Malmstram PU, Rintala E, Wahlqvist R et al. Five-year follow-up of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic Cystectomy Trial I. The Nordic Cooperative Bladder Cancer Study group [see comment]. J Urol 1996; 155: 1903-1906.

10 Hautmann RE, De Petriconi R, Gottfried H-W, et al. The ileal neobladder-complications and functional results in 363 patients after 11 years of follow-up. J Urol 1999; 161(2): 422.

11 Fossa SD, Waehre H, Aass N, et al. Bladder cancer definitive radiation therapy of muscle invasive bladder cancer. A retrospective analysis of 317 patients. Cancer 1993; 15: 3036-3042.

12 Parker CC, Huddart RA. Management of invasive bladder cancer. Br J Hosp Med 1996; 56(5): 213-218.

13 McBain CA, Logue JP. Radiation therapy for muscle invasive bladder cancer: treatment planning and delivery in the 21st century. Sem Rad Oncol 2005; 15(1): 42-48.

14 Stein JP, Lieskovsky G, Cote R et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1054 Patients J Clin Onvol 2001; 19(3): 666–675.

15 Rodel C, Grabenbaer GG, Kuhn R, et al. Combined modality treatment and selective organ preservation in invasive bladder cancer: long-term results J Clin Oncol 2002; 20(14): 3061–3071.

16 Hussain S, James N. Organ preservation strategies in bladder cancer. Expert Rev Anticancer Ther 2002 2(6) p641-651.

17 Dalbagni G, Genega E, Hashibe M et al. Cystectomy for bladder cancer: a contemporary series. J Urol 2001; 165: 1111-1116.

18 Horwich A, Huddart RA. Conservative treatment of bladder cancer. Clin Onc 2004; 16(3): 163-165.

19 Sternberg CN. Chemotherapy for local treatment of bladder cancer. Sem Rad Oncol 2005; 15(1): 60-65.

20 International Collaboration of Trialists. Neoadjuvant cisplatin, methotrexate and vinblastine chemotherapy for muscle invasive bladder cancer: a randomised controlled trial. Lancet 1999; 354: 533-540.

21 Hall RR. Updated results of a randomised controlled trial of neoadjuvant cisplatin (C), methotrexate (M), and vinblastine (V) chemotherapy for muscle invasive bladder cancer. Proc Ann Meet Am Soc Clin Oncol 2002; 21(1): 178a.

22 Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003; 349 (9): 859-866.

23 Advanced Bladder Cancer (ABC). Meta-analysis collaboration neoadjuvant chemotherapy in invasive bladder cancer - a systematic review and meta-analysis. Lancet 2003; 361: 1927-1934.

24 Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924.J Clin Oncol 2001; 19(10): 2638-2646.

[25] von der Maase H, Hansen SW, Roberts JT et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin and cisplatin in advanced or metastatic bladder cancer: results of a large, randomised, multinational, multicentre, phase III study. J Clin Oncol 2000; 18(17): 3068-3077.
[26] Splinter TA, Scher HI, Denis L, et al. The prognostic value of the pathological response to combination chemotherapy before cystectomy in patients with invasive bladder cancer. European Organization for Research on Treatment of Cancer - Genitourinary Group. J Urol 1992; 147(3): 606-608.
[27] Sternberg CN, Pansadoro V, Calabro F, et al. Neo-adjuvant chemotherapy and bladder preservation in locally advanced transitional cell carcinoma of the bladder. Ann Oncol 1999; 10(11): 1301-1305.
[28] Shipley WU, Winter KA, Kaufman DS et al. A Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of RTOG 89-03 J Clin Oncol 1998; 16: 3576-3583.
[29] Tester W, Caplan R, Heaney J, et al. Neoadjuvant combined modality program with selective organ preservation for invasive bladder cancer: results of RTOG phase II trial 8802 J Clin Oncol 1996; 14: 119-126.
[30] Sternberg CN, Pansadoro V, Calabro F, et al. Can patient selection for bladder preservation be based on response to chemotherapy? Cancer 2003; 97(7): 1644-1652.
[31] Huddart RA, Birtles A. Selective organ preservation in muscle invasive TCC of the bladder: a biological approach. BAUS Annual Meeting 2005: abstract 112.
[32] Zietman AL, Sacco D, Skowronski U, et al. Organ-conservation in bladder cancer treated by transurethral resection, chemotherapy and radiation: results of urodynamic and quality of life study on long-term survivors. J Urol 2003; 170: 1772-1776.
[33] Shipley WU, Kaufman DS, Zehr E, et al. Selective bladder preservation by combined modality protocol treatment: long term outcomes of 190 patients with invasive bladder cancer. Urology 2002; 60: 62-68.
[34] National Institute for Clinical Excellence. Guidance on Cancer Services: Improving outcomes in Urological Cancers - The Manual. NICE September 2002.
[35] Donovan JL, Hamdy FC, Neal DE et al. Prostate Testing for Cancer and Treatment (ProtecT) Feasibility Study. Health Technol Assess 2003; 7(14): 1-42.
http://www.ncchta.org/project.asp?PjtId=1079
[36] Ozer H, Armitage JO, Bennett CL et al. 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. JCO 2000; 20(15): 3558-3585.
[37] PDR Physicians' Desk Reference 54 Edition 2000. Medical Economics Company Inc, at Montvale, JH 07645-1742. Product Information: Gemzar®, gemcitabine hydrochloride. Eli Lily and Company. Indianapolis, IN.
[38] Bairatil, Meyer F, Gelinas M et al. Randomised trial of antioxidant vitamins to prevent adverse effects of radiation therapy in head and neck cancer patients. J Clin Oncol 2005; 23: 5805-5813.
[39] Camphausen K, Citrin D, Krishna MC, et al. Implications for tumour control during protections of normal tissues with antioxidants. J Clin Oncol 2005; 23(24): 5455-5457.
[40] Zietman AL, Grocela J, Zehr E et al. Selective bladder conservation using transurethral resection, chemotherapy, and radiation: management and consequences of Ta, T1, and Tis recurrence within the retained bladder. J Urol 2001; 58(3): 380-385.
[41] Sanchez-Martin FM, Palou Redorta J, Regalado Pareja R et al. BCG and radiotherapy: the compatibility of 2 conservative treatments for cancer of the urinary bladder. Arch Esp Urol. 1999; 52(7): 749-58.
[42] Palou Redorta J , Sanchez-Martin FM, Rasales A et al. Intravesical bacille Calmette-Guerin in the treatment of carcinoma in situ or high-grade superficial bladder carcinoma after radiotherapy for bladder carcinoma. BJU Int. 1999; 83(4): 429-431.
[43] Pisters LL, Tykochinsky G, Wajsman Z et al. Intravesical bacillus Calmette-Guerin or mitomycin C in the treatment of carcinoma in situ of the bladder following prior pelvic radiation therapy. J Urol. 1991; 146(6): 1514-1517.
[44] Robins J, Tsiatis A. Correcting for non-compliance in randomised trials using rank preserving structure failure time models. Communications in Statistics – Theory and Methods 1991; 20: 2609-2631.
[45] Branson M, Whitehead J. Estimating a treatment effect in survival studies in which patients switch treatment. Statistics in Medicine 2002; 21: 2449-2463.
[46] http://www.wma.net/e/ethicsunit/helsinki.htm

A1. APPENDIX 1 – TNM Staging and RECIST Criteria

TNM Staging

- **Primary tumour (T)**

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Ta Non-invasive papillary carcinoma
Tis Carcinoma *in situ*: "flat tumour"
T1 Tumour invades subepithelial connective tissue
T2 Tumour invades muscle
  T2a Tumour invades superficial muscle (inner half)
  T2b Tumour invades deep muscle (outer half)
T3 Tumour invades perivesical tissue
  T3a microscopically
  T3b macroscopically (extravesical mass)
T4 Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
  T4a Tumour invades prostate, uterus, vagina
  T4b Tumour invades pelvic wall, abdominal wall

- **Regional Lymph Nodes (N)**

Regional lymph nodes are those within the true pelvis; all others are distant lymph nodes
NX Regional lymph nodes cannot be assessed
N0 No regional lymph metastasis
N1 Metastasis in a single lymph node, 2 cm or less in greatest dimension
N2 Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
N3 Metastasis in a lymph node more than 5 cm in greatest dimension

- **Distant Metastasis (M)**

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

RECIST Criteria

* Complete Response (CR):	Disappearance of all target lesions.
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

A2. APPENDIX 2 – Expected Gemcitabine and Cisplatin toxicities

The following list of expected toxicities is taken from the electronic Medicines compendium (http://emc.medicines.org.uk)

A2.1. Gemcitabine toxicities

The following table of undesirable effects and frequencies is based on clinical trial and post-marketing spontaneous reports.

A2.1.1. Blood and Lymphatic System Disorders

Very common (>1/10):

- Leucopenia
- Thrombocytopenia
- Neutropenia
- Anaemia

Common (>1/100,<1/10):

- Febrile neutropenia

Very rare (<1/10,000):

- Thrombocythaemia

A2.1.2. Immune System Disorders

Very rare (<1/10,000):

- Anaphylactoid reaction

A2.1.3. Nervous System Disorders

Common (>1/100, <1/10):

- Somnolence

A2.1.4. Cardiac Disorders

Very rare (< 1/10,000):

- Myocardial infarct
- Congestive heart failure
- Arrhythmia - predominantly supraventricular in nature

A2.1.5. Vascular Disorders

Rare (>1/10,000, <1/1,000):

- Hypotension

Very rare (<1/10,000):

- Clinical signs of peripheral vasculitis and gangrene

A2.1.6. Respiratory, Thoracic, and Mediastinal Disorders

Very common (>1/10):

- Dyspnoea - usually mild and passes rapidly without treatment

Uncommon (<1/100,>1/1,000):

- Bronchospasm - usually mild and transient but may require parenteral treatment

Rare (>1/10,000, <1/1,000):

- Adult respiratory distress syndrome (ARDS)
- Interstitial pneumonitis together with pulmonary infiltrates - symptoms may be relieved with steroid treatment
- Pulmonary oedema

A2.1.7. Gastro-intestinal Disorders

Very common (>1/10):

- Nausea
- Vomiting

Common (>1/100, <1/10):

- Stomatitis and ulceration of mouth

- Diarrhoea
- Constipation

A2.1.8. Hepatobiliary Disorders

Very common (>1/10):
- Elevation of liver transaminases (AST and ALT) and alkaline phosphatase

Common (>1/100, <1/10):
- Increased bilirubin

Rare (>1/10,000, <1/1,000):
- Increased gamma-glutamyl transferase (GGT)

Very rare (<1/10,000):
- Serious hepatotoxicity, including liver failure and death - in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs

A2.1.9. Skin and Subcutaneous Tissue Disorders

Very common (>1/10):
- Allergic skin rash often associated with pruritus
- Alopecia - usually mild with minimal hair loss

Rare (>1/10,000, <1/1,000):
- Vesicle formation and ulceration
- Scaling

Very rare (<1/10,000):
- Severe desquamative and bullous skin eruptions

A2.1.10. Renal and Urinary Disorders

Very common (>1/10):
- Haematuria
- Proteinuria

Rare (>1/10,000, <1/1,000):
- Renal failure, aetiology unknown
- Haemolytic uraemic syndrome

A2.1.11. General Disorders and Administration Site Conditions

Very common (>1/10):
- Oedema/peripheral oedema - reported in approximately 30% of patients. A few cases of facial oedema have been reported. The reaction is not associated with signs of cardiac, hepatic, or renal insufficiency and is usually reversible after stopping treatment.
- Influenza-like symptoms - the most commonly reported symptoms include fever, headache, back pain, shivering, muscle pain, asthenia, and anorexia. Cough, rhinitis, malaise, perspiration, and sleeping difficulties have also been reported.

Common (>1/100, <1/10):
- Fever
- Asthenia

Rare (>1/10,000, <1/1,000):
- Injection site reactions - mainly mild in nature

A2.1.12. Injury and Poisoning

- Radiation toxicity

A2.2. Cisplatin toxicities

A2.2.1. Nephrotoxicity

Renal toxicity has been noted in about one third of patients given a single dose of cisplatin when prior hydration has not been employed. It is first noted during the second week after a dose and is manifested by elevations in plasma urea and serum creatinine, serum uric acid and/or decrease in creatinine clearance.

A2.2.2. Gastrointestinal toxicity

Nausea and vomiting occur in the majority of patients, usually starting within 1 hour of treatment and lasting up to 24 hours. Anorexia, nausea and occasional vomiting may persist for up to a week.

A2.2.3. Ocular Toxicity

There have been reports of optic neuritis, papilloedema and cerebral blindness following treatment with cisplatin. Blurred vision and altered colour perception have also been reported

A2.2.4. Ototoxicity

Ototoxicity has occurred in up to 31% of patients treated with a single dose of cisplatin 50 mg/m^2.

Unilateral or bilateral tinnitus, which is usually reversible, and/or hearing loss in the high frequency range may occur.

A2.2.5. Haemotoxicity

Myelosuppression is observed in about 30% of patients treated with cisplatin. Leucopenia and thrombocytopenia are more pronounced at higher doses. Anaemia (decreases of greater than 2 g% haemoglobin) occurs at approximately the same frequency.

A2.2.6. Anaphylaxis

Reactions possibly secondary to cisplatin therapy have been occasionally reported in patients who were previously exposed to cisplatin. Patients who are particularly at risk are those with a prior history or family history of atopy. Facial oedema, wheezing, tachycardia, hypotension and skin rashes of urticarial non-specific maculopapular type can occur within a few minutes of administration.

A2.2.7. Serum Electrolyte Disturbances

Hypomagnesaemia, hypocalcaemia, hyponatraemia, hypokalaemia and hypophosphataemia have been reported to occur in patients treated with cisplatin and are probably related to renal tubular damage. Hypomagnesaemia and hypocalcaemia may result in tetany. Inappropriate antidiuretic hormone syndrome has also been reported.

A2.2.8. Neurotoxicity

Usually characterised by peripheral neuropathies and paresthesia in both upper and lower extremities. Peripheral neuropathy, while reversible, may take a year or more to recover. Loss of taste and seizures have also been reported. Neuropathies resulting from cisplatin treatment may occur after prolonged therapy; however, neurological symptoms have been reported to occur after a single dose.

A2.2.9. Hyperuricaemia

Hyperuricaemia occurring with cisplatin is more pronounced with doses greater than 50 mg/m^2.

A2.2.10. Other Toxicities

Vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents have been reported rarely. These events may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (haemolytic uraemic syndrome) or cerebral arteritis. Other toxicities reported to occur infrequently are cardiac abnormalities including tachycardia and arrhythmia.

Local soft tissue toxicity has been reported rarely following extravasation of cisplatin. Infiltration of solutions of cisplatin may result in tissue cellulitis, fibrosis and necrosis.

A3. APPENDIX 3– Quality of Life Study

A3.1. Background

The primary outcome of the feasibility study is recruitment rate. The primary outcome of the main trial is overall survival with health-related quality of life (HRQL) as a secondary endpoint. Patient-based outcomes using HRQL measures are relevant to this study because evidence from the literature has shown that radical cystectomy has a substantial negative impact on HRQL during the first post operative year that subsequently recovers except for on going reduction of sexual function.[1] Bladder preservation therapy, however, has a different spectrum of early impact on HRQL (problems related to radiotherapy) and patients experience more gastrointestinal dysfunction.[2] Assessment of HRQL in this trial is therefore essential because if survival is equivalent in each arm of the trial then HRQL outcomes will determine treatment options. If the trial demonstrates a clear survival advantage in one arm, 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 radical cystectomy and selective bladder preservation 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 cystectomy and bladder preservation. Following major surgery it is expected that reduction in physical and social function and more problems with fatigue and pain will be reported. Problems with sexual function and continence may occur and also psychosocial issues related to coping with an ileal conduit. Many of these symptoms and functional issues will improve with recovery and as patients adapt to the sequelae of major surgery.[3 -4] At present, less is known about the HRQL impact of bladder preservation treatment although a recent literature review has concluded that most patients undergoing bladder preservation retain good urinary function, but some experience distressing bowel dysfunction and possible altered sexual function.[5]

A3.2. Hypotheses

It is hypothesised that patients undergoing radical cystectomy will report more generic HRQL issues within the first six months after treatment than patients undergoing bladder preservation treatment. Physical and role function and fatigue and pain scores are expected to be worse in the surgical arm of the study. It is hypothesised that the long term gastrointestinal side effects of bladder preservation will be worse than in patients undergoing surgery, but that these patients will experience better sexual function than patients undergoing radical cystectomy.

A3.3. Quality of life measures

Quality of life will be assessed with the EORTC Quality of Life Questionnaire (QLQ-C30) version 3.[6] This 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. This questionnaire lacks some dimensions that are relevant to HRQL in patients with T2/T3 bladder cancer and these will be assessed with a disease specific module. The EORTC Quality of Life group has designed a site-specific module that is specific to patients with muscle invasive bladder cancer (EORTC QLQ-BLM30).[7] This includes scales assessing urinary symptoms, stoma issues, gastrointestinal symptoms, sexual function and body image. This instrument has been widely used, although formal validation data are not yet published.

A3.4. 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. Patients 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. Patients entered in the

feasibility study will be included in the analysis of the main trial therefore HRQL will be assessed in these patients.

A3.5. Timing of data collection

Patients will be asked to complete HRQL questionnaires within 14 days prior to randomisation whilst in the hospital for a scheduled visit for neo-adjuvant chemotherapy. 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. Post-treatment questionnaires will be completed 6 weeks after cystectomy or 6 weeks after completion of radical radiotherapy and will also be administered by the centre. Further assessments will be sent to patients' homes by the ICR-CTSU at 9, 12, 24, 36, 48 and 60 months after D1 Cycle 3. This will total eight HRQL assessments per patient. The time windows for eligible follow up will be +/- two weeks of the scheduled follow-up assessment.

A3.6. 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 9 months post day 1 cycle 3 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 investigated at each time point.

A3.7. Statistical considerations

Data will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual.[8] All scales and single items are scored on categorical scales and linearly transformed to 0-100 scales where: a high score for a symptom scale or item represents a high level of symptoms or problems, a high score for a functional scale represents a high or healthy level of functioning and a high score for the global health status/QL represents high QL.

The sample size of the main trial has been calculated based on overall survival. It is not expected that all patients entered into the main trial will complete HRQL assessments. The following table illustrates the standardised difference that could be detected (if a normally distributed variable) depending on sample size. All illustrations are based on 90% power and type 1 error of 0.01. The type 1 error chosen allows, to some degree, for the multiple testing involved in analysing individual sub-scales of the QL questionnaires.

Standardised Difference	Patients completing HRQL assessments
0.35	490
0.30	670
0.27	820 (i.e. approx 80% of all patients)
0.24	1020

A3.8. References

[1] Shipley WU, Zietman AL, Kaufman DS et al. Selective bladder preservation by trimodality therapy for patients with muscularis propria-invasive bladder cancer and who are cystectomy candidates - the Massachusetts General Hospital and Radiation Therapy Oncology Group experiences. Semin Radiat Oncol 2005; 15: 36-41.

[2] Herman JM, Smith DC, Montie J et al. Prospective quality-of-life assessment in patients receiving concurrent gemcitabine and radiotherapy as a bladder preservation strategy. Urology 2004; 64: 69-73.

[3] Hardt J, Filipas D, Hohenfellner R et al. Quality of life in patients with bladder carcinoma after cystectomy: first results of a prospective study. Qual Life Res 2000; 9: 1-12.

[5] McGuire MS, Grimaldi G, Grotas J et al. The type of urinary diversion after radical cystectomy significantly impacts on the patient's quality of life. Ann Surg Oncol 2000; 7: 4-8.

[6] Zietman A, Skinner E. Quality of life after radical treatment for invasive bladder cancer. Semin Radiat Oncol 2005; 15: 55-59.

[7] Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality of life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85: 365-376.

[8] Blazeby JM, Sprangers MAG, Cull A, Groenvold M, Bottomley A. EORTC Quality of Life Group - Guidelines for Developing Questionnaire Modules. 2001.

[9] Fayers P, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. EORTC QLQ-C30 Scoring Manual. 3rd, 0-86. 2001.

A4. APPENDIX 4 – Qualitative Study – Patients' Experience of Recruitment

This sub-study has now closed to recruitment, having reached its target sample size.

A4.1. Background

Recruitment is a particularly difficult challenge in the context of randomised trials and especially so when strategies are complicated.[1] Many important trials are not implemented because recruitment is thought to be 'impossible' in such contexts. When trials are established, recruitment is often much lower than anticipated[2] and barriers well known to both clinicians and patients have now been documented.[3] Until recently, methodological issues had been conducted by statisticians and epidemiologists and few have confronted the myriad effects of research conduct or demands put on both participants and the trialists themselves.[3] Evidence suggests that the improvement in design and conduct of randomised trials comes about by embedding them in qualitative research.[3]

The ProtecT trialists[3] randomised participants in a multi-centre study to see a specialist nurse or urologist for an 'information' appointment. Participants were given details about the treatments and the need for a randomised trial and were asked to consent to randomisation. Subsequent in-depth audio-taped semi structured interviews were held with men after their diagnosis to a) explore interpretation of study information and experiences of the study including treatment preferences; b) to perform a detailed examination of recruitment ("information") appointments and follow up interviews to examine the delivery of information by recruiters and its interpretation by patients, and c) to carry out a detailed examination of other information appointments (all audio-taped) to investigate reasons for different levels of recruitment between centres, and over time, in an effort to gain insight into the problems encountered.

The concepts of equipoise and presenting treatments equally were found to be difficult to explain, partly because participants misinterpreted their terminology and partly because clinicians found the concept of equipoise difficult to impart in a confident way. These findings led to changes in content and presentation of information which in turn led to an emphasis on equivalence; utterances that were likely to be misinterpreted were avoided; the non radical arm ('watchful waiting') was redefined and presented as 'active monitoring'; and randomisation and equipoise were presented in a clearer way. Recruiters were encouraged to elicit patients' views and then discuss differences with the ProtecT study information. They were asked to explain that randomisation offered a way of resolving the dilemma of treatment choice and an attempt to randomise was made before the end of the information appointment. However, patients were informed that they could have time to consider whether the allocated treatment was acceptable. Patients and all recruiters were told that recruiters must be genuinely uncertain about the best treatment on offer; that they believed that the patient was suitable for all treatments on offer; and that they were confident in their beliefs. This approach led to a 40% increase in acceptance of randomisation to 70%, all treatments became acceptable and the design of the study was changed to include three arms that included monitoring as an option for patients.

Early findings were implemented initially in one centre. Findings and recommendations for changes to the content and presentation of information were circulated in documents to recruiters, and a training programme was developed and delivered to recruiters. Subsequent 'information' appointments were investigated in order to evaluate the impact of the documents and training. Recruitment rates (consent to randomisation and acceptance of allocation) were calculated regularly.

The SPARE trial is likely to encounter similar difficulties to those experienced in ProtecT[3] and other studies. Recruiting patients into an endeavour is complicated on all levels: the medical aspects of the trial may be difficult to comprehend, the ways in which information is imparted may be erroneous and the timing of randomisation equivocal. Moreover men and women may

have differing reasons for accepting or rejecting aspects of this trial, the results of which may include an impact on sexual activity and other factors.

Based on the ProtecT approach, a patient advisory group meeting that included four bladder cancer patients (who had received cystectomy) and one bowel cancer patient met to discuss the best way for the SPARE trial to proceed, including the best timing for randomisation to take place and the best ways to impart information to participants. Written comments were also provided from two bladder cancer patients who were unable to attend the meeting. It was proposed by the group that randomisation to the treatment arms (cystectomy or selective bladder preservation) should take place as early as possible. Although these patients are not directly comparable to patients actually going through the trial, they have alerted the SPARE Trial Management Group to some of the difficulties that patients may encounter and have helped to inform them as to the best ways to proceed at this stage, underpinning the ethics and thus the *quality* of the SPARE feasibility study. A qualitative interview study will elicit patients' views on trial procedure during the actual feasibility trial (see below).

A4.2. The Qualitative Study

Qualitative research methods are increasingly used in health services research, usually as an 'add on' to help interpret quantitative results or understanding of trials.[4, 5] The ProtecT trial has diverged from this approach by embedding the qualitative study within the randomised trial. This has enabled each to inform the other regarding randomisation and procedures including the giving of information. We propose to follow a similar approach.

This qualitative study will be researching *actual* trial patients, enabling us to make further changes to the protocol if necessary in readiness for the SPARE trial to proceed in the next stage. Importantly an expert in the field will always verify any changes in order to avoid the giving of overly optimistic views[6] which will, in the longer term, help to eliminate coercion and preference bias.[6]

A4.3. The Patient Sample

The SPARE feasibility study aims to recruit 110 patients who have muscle invasive T2/T3 transitional cell carcinoma of the bladder. A total of thirty (30) English speaking patients will be asked to give consent to enter the qualitative substudy. They will be:

a) patients who have agreed to randomisation (20); and
b) patients not agreeing to participation (10).

A representative sample will initially be studied but a targeted study may also be initiated in centres with lower than expected acceptance of randomisation. As men are likely to outweigh women with the disease, purposeful sampling may take place, i.e. if there is an imbalance of the sexes purposeful sampling[4] (recruitment of the 'missing' sex will take precedence) will be carried out.

A4.4. Methodology

A4.4.1. Procedures

Early recruitment is preferable in the first instance, since any changes in randomisation procedures or the giving of information will have to be conveyed in time for changes to take place well before the end of the feasibility study. This early recruitment process will also help to eliminate memory bias.

Patients who have agreed to randomisation

Consent to be contacted by the Qualitative Researcher (QR) will be obtained at the time of consent to randomisation. Patients will be given the Qualitative Study PIS by the site staff and asked to complete contact details at the back of this information sheet. These details will be sent to the ICR-CTSU. This initial consent does not bind the patient to participation in the Qualitative Study. A consecutive number of those who consent will be contacted by the QR (after notification to the QR by the ICR-CTSU). If the patient is willing, an interview will be

arranged by the QR. Informed consent will be obtained prior to the interview commencing, and all patients will be reminded that they may withdraw at any time. Patients not selected for interview will be contacted by the QR when the sample collection is completed, according to the protocol.

Approximately ten patients who have finished treatment will be asked to give consent to a further interview so that a longer term view can be assessed. Patients will be asked at their first interview if they would be willing to participate in a second interview. If the patient is willing they will be telephoned by the Qualitative Researcher after their treatment is complete and a second interview may be arranged.

Patients not agreeing to participation

Patients declining entry into the SPARE study will be asked if they are interested in participating in the Qualitative Study. Patients will be given the Qualitative Study PIS by the site staff and asked to complete contact details at the back of this information sheet. These details will be sent to the ICR-CTSU This initial consent does not bind the patient to participation in the Qualitative Study. A consecutive number of those who consent will be contacted by the QR (after notification to the QR by the ICR-CTSU). If the patient is willing, an interview will be arranged by the QR. Informed consent will be obtained prior to the interview commencing. This group is particularly important and often ignored in research. It is essential that we investigate the possible negative reactions of patients who decline participation if we are to gain knowledge regarding trial procedures. It will always be made clear that refusal will be respected and that this will not jeopardise their treatment. Patients not selected for interview will be contacted by the QR when the sample collection is completed, according to the protocol.

The Interview

Patients will be invited to participate in a semi-structured, audio-taped interview, carried out by a researcher who is familiar with qualitative work and the rudiments of the trial, in a place of the patient's choice. All interviews will be transcribed verbatim and analysed. The right to refuse entry to or exit from the study will be accentuated. A contact number of a consultant and researcher will be given to all participants. In the event of the study provoking anxiety or other psychological 'events,' counselling will be offered either through talking with a clinician or a counsellor according to the appropriateness of the situation.

A4.4.2. Analysis

A 'framework analysis'[7] will be carried out to analyse the data collected. Framework analysis is a method used by health service researchers who are undertaking qualitative work that has an a priori list of questions that are to be answered. These questions have been informed by the literature (in this case the literature provided by ProtecT and other trials) that in turn is both theoretical and substantive. The SPARE qualitative study seeks to answer specific questions, although it must be stressed that participants will have time and encouragement to add their own thoughts and experiences regarding the question in hand, during the interview.

Framework analysis functions in much the same way as other qualitative methods in the 'doing' of analysis. The transcribed tapes will be read line by line. First line face value coding (or 'open' coding) will take place to illuminate the words and sentences of the participants; a higher level of coding will move into a more abstract level of analysis. Themes will be extracted from these higher levels. Field notes will be written that will inform the ways in which the themes are interpreted. Interpretation will also rely on the literature, on comparing and contrasting each manuscript, and in highlighting and discussing 'deviant' cases..

Validity will be sought through patients' own reading of their transcripts and through a reading of the final report (with their consent) and through other work that has been carried out in this area of medicine.

A4.5. Time frame

This substudy will commence at the same time as the feasibility trial. It is estimated that recruitment into the study will take approximately six months. The interviewing of 30 people will take approximately six months. A further two months will cover the second interviews. Transcribing and analysing will take approximately six to eight months to complete.

A4.6. Ethical considerations

Patients agreeing to be randomised in the feasibility study will be asked for their consent to be contacted regarding the qualitative study. Consent for the qualitative study will be sought separately to consent for the feasibility trial. Each patient will be given an information sheet. Informed consent will be obtained prior to the start of the tape recorded interview. Each patient will also be asked to stipulate his or her wish to see the transcribed interview and to critically review it if that is what they wish.

Confidentiality will be adhered to at all times. Patients will be given a study number and no name will appear on any document. Patients will be told that their utterances will be made anonymous at all times. All documentation and tapes will be kept in a locked room and the Chief Investigator (Qualitative Study) will be held responsible for their safe keeping.

A4.7. References

1 Pringle M, Churchill R. Randomised controlled trials in general practice: gold standard or fool's gold? BMJ 1995; 311: 1382-1383.

2 Lovato L, Hill K, Hertert, S. et al. Recruitment for controlled clinical trials: literature summary and annotated bibliography. Control Clin Trials 1997; 18: 328-357.

3 Donovan J, Mills N, Smith M, et al. Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. 2002 BMJ. 325: 766-770.

4 Mays N, Pope C. Qualitative research: Rigour and qualitative research. BMJ 1995; 311: 109 -112.

5 Snowdon C, Garcia J, Elbourne D. Making sense of randomisation: responses of parents of critically ill babies to random allocation of treatment in a clinical trial. Social Science and Medicine 1997; 45: 1337-1355.

6 Little P. Commentary: presenting unbiased information to patients can be difficult. BMJ 2002: 325 770.

7 Ritchie J, Spencer L. Qualitative data analysis for applied policy research in: Bryman A, Burgess R. eds. Analysing qualitative data. London Routledge. 1994: 172-194.

A5. APPENDIX 5 – Qualitative study – Recruitment Processes

A5.1 Background

Recruitment is a particularly difficult challenge in the context of randomised trials and especially so when strategies are complicated.[1] Many important trials are not implemented because recruitment is thought to be 'impossible' in such contexts. When trials are established, recruitment is often much lower than anticipated[2] and barriers well known to both clinicians and patients have now been documented.[3] Until recently, methodological issues had been conducted by statisticians and epidemiologists and few have confronted the myriad effects of research conduct or demands put on both participants and the trialists themselves.[3] Evidence suggests that the improvement in design and conduct of randomised trials comes about by embedding them in qualitative research.[3] The SPARE trial embedded a prospective interview study with both SPARE participants and decliners within its protocol. This study has now completed recruitment. Please refer to appendix 4 for further information about this study.

The ProtecT trialists[3] randomised participants in a multi-centre study to see a specialist nurse or urologist for an 'information' appointment. Participants were given details about the treatments and the need for a randomised trial and were asked to consent to randomisation. Qualitative methods were used to investigate the recruitment process in three main ways:

1. The information ("recruitment") appointments were routinely audiotaped, and subsequently examined in detail to investigate the content and method of delivery of information.

2. In-depth interviews were conducted with some of the men after they had attended the information appointments in order to elicit interpretations of the study information and experiences of the study, including treatment preferences.

3. Interviews were conducted with recruitment staff to understand their perspective and explore their reactions to the men's interpretation of their appointments.

Qualitative analysis of the information appointments and interviews illuminated some key problems with the presentation of information to trial participants. On the basis of these findings, recommendations for change were circulated to recruiters and a training programme was developed and delivered. The impact of the training was evaluated by further scrutiny of subsequent information appointments and by regular calculation of recruitment rates.

The rate of consent to randomisation changed over time as the findings from the qualitative research were introduced, increasing from 30-40% in May 2000 to 70% by May 2001. Moreover, the findings of the ProtecT study indicate increased levels of *informed* consent among the men, as training helped recruiters to present trial information in a more balanced, less ambiguous manner.

It is intended to build on the existing qualitative study by investigating communication and information giving in real time and as it is given by a health professional to the patient. Therefore, given the findings in ProtecT a second qualitative study will be initiated within SPARE to investigate the presentation of SPARE information to potential participants, with the aim of implementing training to overcome any barriers to recruitment which are identified. It is intended that this training will also be informed by the knowledge gained from the qualitative study of patient interviews.

A5.2 Data collection

A5.2.1 Interviews with recruiters

A sample of recruitment staff will be interviewed in depth to elicit views about the purpose of the trial, controversial aspects, the effectiveness and suitability of interventions, and

understanding of randomisation and clinical equipoise. Recruitment staff will be asked to reflect on appointments they have conducted, the adequacy of the discussion, the acceptability of the trial design, satisfaction with the decision reached, recruitment strategies, and why they feel recruitment is proving difficult.

A5.2.2 Audio-taped recruitment appointments

All the recruitment appointments at participating centres will be routinely audiotaped during the research period to avoid bias introduced by knowledge of selective recording. The researcher will concurrently listen to the recordings and read the transcripts of a sample of recruitment appointments. The object of taping recruitment interviews is to record what actually happens without relying on recall or interpretation. Analysing interviews alongside the audio recordings of the actual information appointments aids researchers in identifying unforeseen issues with which either recruitment staff or trial participants have difficulties. The aim is to identify potential problems with the way information is presented and to focus on how key terms are understood by both parties.

A5.3 Procedures

Both newly opening centres and those which have experienced consistent barriers to recruitment into SPARE will be invited to participate in this sub-study. Patient pathways through the centres will be researched to identify the appropriate time for audio-recording to begin.

A5.3.1 Interviews with recruiters

Recruiters will be provided with an information sheet and asked to provide written consent to be interviewed and for their appointments with potential SPARE patients to be audio-recorded. They will be able to withdraw this consent at any time.

A5.3.2 Audio-recording recruitment appointments - patient consent

Patients who are eligible for SPARE will be asked at the beginning of the consultation to provide verbal consent if they are happy for the discussion to be audio-recorded. This consent, if given, will be recorded by the recruiter on a verbal consent form.

At the end of the discussion, the recruiter will provide the patient with a patient information sheet to take home containing more information about the study. Patients will be asked to provide written informed consent for their initial appointment recording to be used and for future appointments to be recorded until the patient's treatment decision has been made. The aim is to collect recordings of consultations discussing potential treatment options with both patients who accept randomisation into SPARE and those who decline.

A5.3.3 Staff training and feedback

Feedback and training will be focused on eliminating the reasons for inefficient recruitment uncovered by the barriers to recruitment sub-study. Findings will be fed back to the recruiters individually and in staff training sessions. The researcher will continue to listen to taped interviews and provide support, feedback and training sessions until recruitment rates improve and remain reasonably constant, or it is found that improvement is not possible.

A5.4 Analysis

Thematic analysis will be used to identify common and emergent themes in the interview data by employing constant comparison techniques until no new themes emerge. Throughout the analysis the perspectives of the recruiters will be paramount. Content analysis will be used to describe the terminology used by the recruiters and compare this with written study information. Discrepancies and areas of controversy will be identified and explored. Conversation analysis will be used to investigate the delivery of information during the recruitment appointments, with a particular focus on the interaction between recruiter and patient (e.g. analysis of patient requests for clarification or places in the conversation where pauses or other utterances disrupt the smooth flow of interaction).

There will be frequent assessments of recruitment rates – both randomisation and rates of compliance with assigned treatment. These will be calculated for each of the centres in which the sub-study is running and across the trial as a whole.

A5.5 Time frame

This substudy will commence in the final year of the feasibility trial. It is anticipated that the audio-recording of patient consultations will begin as soon as ethical approval has been gained. Recruiter interviews will begin as soon as is feasible. Timing of any implementation of training the training programme will be agreed by the SPARE Trial Management Group.

A5.6 Ethical considerations

All participants will be asked to provide informed consent prior to taking part in any aspect of this sub-study. The interviews will be conducted at a time suitable for the recruitment staff, and permission will be sought from participants to audiotape these. All data collected by will be used only for the purposes of improving levels of informed consent and acceptance of randomised treatment within SPARE.

Confidentiality will be adhered to at all times. Transcripts of all audio-recordings will be anonymised, and audiotapes will be labelled with a patient code to protect anonymity. All documentation and tapes will be kept in a locked room and the Chief Investigator (Qualitative Study – Barriers to recruitment) will be held responsible for their safe keeping.

A5.7 References

[1] Pringle M, Churchill R. Randomised controlled trials in general practice: gold standard or fool's gold? BMJ 1995; 311: 1382-1383.

[2] Lovato L, Hill K, Hertert, S. et al. Recruitment for controlled clinical trials: literature summary and annotated bibliography. Control Clin Trials 1997; 18: 328-357.

[3] Donovan J, Mills N, Smith M, et al. Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. 2002 BMJ. 325: 766-770.

A6. APPENDIX 6 – Pathological Study

The SPARE trial seeks to investigate if early therapeutic response to chemotherapy can select patients for conservative treatment. This approach could be further improved if the genotypic correlates which predict for successful conservative treatment were understood. A limited number of genetic changes particularly in genes involved in the G1/S checkpoint (e.g. changes in Rb, p53, p21, p27, XRCC1 expression levels) have been correlated with outcome in patients with invasive bladder cancer treated by cystectomy, chemotherapy and to a lesser extent radiotherapy.[1-6] Work in this area is limited and the potentially complex interactions have not yet been explored. In particular, factors related to therapy response have not been distinguished from factors related to overall prognosis. This study provides an opportunity to examine these factors. By undertaking prospective data collection, the aim is to correlate genetic changes with chemotherapy response, successful radiotherapy treatment and overall outcome. Paraffin tissue will be collected from all consenting patients and used to construct tissue arrays for genomic analyses. Genomic DNA will be collected for pharmaco and radiogenomic studies. Potential future analyses include exploration of the relationship of outcome with variability of DNA repair genes. Samples from the feasibility study will be used to develop genetic correlates with outcome measures and derive prognostic models which will be tested in the subsequent phase III trial.

Specific objectives are:

1. To store tissues (blood, and tumour) for future and related translational studies;
2. To identify germline variations associated with outcome measures (response, toxicity) after chemotherapy and radiotherapy;
3. To identify gene expression patterns in primary urothelial carcinoma which predict response to neo-adjuvant chemotherapy and radiotherapy; and
4. To evaluate gene sets as phenotypic markers on TMA and assess known phenotypic biomarkers of chemotherapy response.

Detailed arrangements for tissue and blood collection, local handling, storage and postage will be discussed with centres individually.

An outline of samples required and procedures for collection is provided below.

A6.1 Tissue Sample Collection

Paraffin blocks from the initial diagnostic surgery will be collected for all SPARE-T participants. Although consent will be sought at trial entry, samples will be collected retrospectively, and centres will be contacted at a later stage to arrange the transfer of paraffin blocks.

Some patients may have undergone a series of tumour resections prior to study entry, in this case the most recent samples will be collected as baseline samples (although earlier resection samples may also be requested).

Samples will also be collected from all SPARE-T participants undergoing cystectomy. The samples sent must have been assessed and confirmed to contain tumour. Research teams will inform the UCL receiving laboratory when patients have undergone cystectomy .The pathology department will then be contacted to request the required paraffin blocks.

Additional samples required:
Patients who develop recurrence following radiotherapy may undergo transurethral resection of the recurrence and or cystectomy. In the event of this, paraffin embedded blocks which are representative of recurrence will be requested from local pathology labs.

A6.2 Blood Sample Collection

Consenting SPARE-T participants will provide a 5-8ml blood sample for genomic testing.,It is recommended that this sample is collected at baseline at the time of routine tests, although samples may be collected at any point during the study if necessary. Kits will be sent to participating centres to enable the collection and transfer of blood samples. A 5-8ml blood sample in an EDTA tube will be collected from each patient using the S-Monovette blood collection system. Once collected, the samples will be posted in pre-paid envelopes to the UCL receiving laboratory.

A6.3 References

[1] Agerbaek M, Alsner J, Marcussen N, Lundbeck F, von der Masse H. Retinoblastoma protein expression is an independent predictor of both radiation response and survival in muscle-invasive bladder cancer. Br J Cancer 2003;89(2):298-304.

[2] Garcia del Muro X, Condom E, Vigues F, Castellsague X, Figueras A, Munoz J et al. p53 and p21 expression levels predict organ preservation and survival in invasive bladder carcinoma treated with a combined-modality approach. Cancer 2004;100(9):1859-67.

[3] Qureshi KN, Griffiths TR, Robinson MC, Marsh C, Roberts JT, Lunec J et al. Combined p21WAF1/CIP1 and p53 overexpression predict improved survival in muscle-invasive bladder cancer treated by radical radiotherapy. Int J Radiat Oncol Biol Phys. 2001;51(5):1234-40.

[4] Rotterud R, Pettersen EO, Berner A, Holm R, Olsen DR, Fossa SD. Cell cycle inhibitors and outcome after radiotherapy in bladder cancer patients. Acta Oncol 2002;41(5):463-70.

[5] Shariat SF, Tokunaga H, Zhou J, Kim J, Ayala GE, Benedict WF et al. p53, p21, pRB, and p16 expression predict clinical outcome in cystectomy with bladder cancer. J Clin Oncol 2004;22(6):1014-24.

[6] Feber A, Clark J, Goodwin G, Dodson AR, Smith PH, Fletcher A, Edwards S, Flohr P, Falconer A, Roe T, Kovacs G, Dennis N, Fisher C, Wooster R, Huddart R, Foster CS, Cooper CS (2004). Amplification and overexpression of E2F3 in human bladder cancer. Oncogene 23: 1627-1630.